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PREFACE

Men's Health and Aging: The 5th World Congress on the Aging Male

BRUNO LUNENFELD

During the past few decades, life expectancy at birth has been prolonged by more than 25 years but men's life expectancy continues to be significantly shorter than that for women in most regions of the world. Moreover, despite the enormous medical progress during the past century, life expectancy at 60 has only been prolonged by a few years; more than 25% of the remaining life span is spent with some disability and the last years of life are accompanied by a further increase of frailty, incapacity, sickness and dependency. The soaring elderly population will raise major health, social economic and ethical issues worldwide and may strain to the limit health services as well as socioeconomic and political infrastructures. The ability to permit men to age gracefully and maintain independent living, free of disability, for as long as possible is a crucial factor in aging with dignity and would furthermore reduce health service costs significantly. To achieve this objective, a holistic approach to the management of aging has to be adopted. The promotion of healthy aging and the prevention of disability in all older people must assume a central role in medical research and medical practice as well as in the formulation of national health and social policies. Effective programs promoting healthy aging will ensure a more efficient use of health and social services and improve the quality of life in older persons by enabling them to remain independent and productive.

This situation prompted the founding of the International Society for the Study of the Aging Male (ISSAM). The objectives and rational of ISSAM was ''achieving healthy aging for men''. This was followed by the ''Weimar Initiative'' [1], The Geneva Manifesto [2] and the report on ''Men, Ageing and Health'', published in collaboration with WHO [3]. The Textbook on Men's Health [4] and the Recommendations for Androgen Replacement Therapy [5] demonstrates ISSAM's involvement in education. The context of the four world congresses and the five regional meetings which preceded this meeting have witnessed our loyalty to our objectives. The increasing number of members, affiliated national and regional organizations, and participants at our congresses are only few examples of the interest ISSAM has raised worldwide.

The impact that ISSAM has already made on the international platform during its short existence can be measured by the immense increase of media interest, and the awareness it has created among various professional organizations and national and international societies. After years of relative lack of interest in ''Men's Health'', Urologists, Andrologists, Endocrinologists and even Gynecologists wish to cater for this relative new field of interest, and this even extends to some national and international societies devoted specifically to women's health, such as the Menopause Society which has recently changed its name to the Menopause and Andropause Society. This increased interest in men's health is timely and welcome, as long as it will lead to interdisciplinary collaboration and not to animosity and negative competition.

This Fifth World Congress on the Aging Male, organized by ISSAM and co-sponsored by the Austrian Society of Urology, European Academy of Sciences and Art, European Association of Urology (EAU), European Federation of Endocrine Societies (EFES), European Menopause and Andropause Society, German Dermatologic Society (DDG), German Society of Applied Endocrinology, International Menopause Society, International Society of Sexual Medicine, Population Council and World Association for Sexology demonstrates that such interdisciplinary collaboration is possible, and can unite all the forces in this relatively new discipline. It truly displays our purpose to comprehensively examine the causes and consequences of male aging and its social and medical repercussions, with the goal being to improve the health status and quality of life of men. The interdisciplinary nature of this field of research is evident from the contents of this program which contains more than 280 presentations by scientists of various disciplines and of more than 40 nations.

The publication of the abstracts and the journal would not have been possible without the continuous help of the contributors, the encouragement of the scientific community, the Organizing Committee, the Secretariat, Taylor and Francis Publishing and the generous contribution of many sponsors.

We hope that the contents of this abstract book will permit those present to better follow and take part in frank interdisciplinary discussions, exchange of results and the development of ideas. For the benefit of those who could not join us, this abstract book should stimulate their awareness of this discipline and motivate them to join us in our next meeting.

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The Aging Male

01

CHALLENGES OF MEN'S HEALTH AND AGING IN THE ASIA PACIFIC REGION

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Aging is dependent on many factors including those of genetics, socio-economics, and geopolitics. Aging impact every single compartment in an integrated manner. For example, from our data, it is clear that tT does not change with age. On the other hand, there is a clear age-dependent increase in SHBG concentrations resulting in significant decrease in fT and BioT with age. Furthermore, subjects with metabolic syndrome have altered SHBG levels which, therefore provides the platform for gonadal-metabolic compartmental interactions. This interaction is further evident by our observations that androgen levels are negatively correlated with the IGF1, IGF2 and insulin levels. In addition, tT is negatively correlated to many of the CVD/artherosclerotic risk factors including body weight, BMI, waist and hip circumferences, waist/hip and waist/height ratios, and percent body and percent abdominal fat. Lifestyle issues also affect the gonadal compartment. Men with sufficient aerobic exercise have higher levels of tT, fT and BioT levels than those who did not. Androgen levels were shown to impact other than the endocrine and metabolic compartments. Low testosterone levels are associated with a higher loss of bone as shown by the negative correlation of tT with NTx. Falling levels of androgens with age are associated with falling frequency of sexual intercourse, increasing incidence of loss of libido, and lower incidence of morning erection and rigidity of this erection. These observations illustrate the complexity and inter-compartmental impact of aging on the human system. Merely looking at the presenting symptom runs a danger of misdiagnosing the primary cause and the administration of inappropriate or incomplete treatment. Therefore, the challenge in managing men's health and aging is to 1) Avoid a simplistic or symptomatic approach to the management of aging, 2) Develop a comprehensive diagnostic paradigm and, 3) Establish an integrated, holistic approach for their management.

02

POPULATION BASED STUDIES ON MEN'S MEDICAL ISSUES IN THE ASIA PACIFIC REGION

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People neighboring around the Pacific Ocean have had a closely relationship since ancient times. Beginning with the 21st century, the economical and cultural exchanges between nations are becoming more and more frequently than ever. In recent years, the aging problem is becoming a serious new topic for the medical and social societies to face. Life expectancy of Asian men has increased tremendously over the last 50 years. However, the health expectancy has lagged behind our Western counterparts significantly. The aging world particularly in Asia where the majority of the countries are in the developing stage is heading towards a bleak future, if prompt measures and advice are not heeded or implemented expeditiously on both the nation and international levels. The socio-economic, financial and medical consequences of the aging population will be more pronounced in Asia where resources are limited. The health of an aging male is the net effect of both current health related factors and factors that prevailed during earlier periods in the life course. The health status of the elderly population has tremendous far reaching consequences to the family, society and their respective countries. Asian countries desperately need to strive for a healthier elderly population to maintain productivity, to reduce healthcare cost and financial burden to the family, community and countries respectively. A multidisciplinary, well concerted effort to refocus and reorientate our thoughts to provide a holistic care for men's health problems is desperately needed, including erectile dysfunction, hormone replacement therapy, osteoporosis, prostate cancer neurological disorders, ADAM, folk medicine and phytotherapy for the aging male. However, the situations of men's health are quiet diversitious. On the one hand, owing to the advancement of public health, life expectancy of human-being is continuing to grow and therefore the elderly comprise the fastest increasing segment of the global population in Japan, Singapore, Korea, Australia, New Zealand and Taiwan. For instance, the mean life-length in male is over 80 years in Japan. Thus, partial androgen deficiency of the aging male (PADAM) has received widespread attention in the popular and medical media in Japan. In these countries, overfed, under-exercised, highly stressed issues are main public problems of men's health. Cerebrovascular and ischemic heart disease, diabetes, cancer, respiratory disease, depression, osteoporosis, Alzheimer's, hepatorenal disease, trauma etc. – the whole spectrum are all prevalent diseases. On the other hand, there are the impoverished millions in some underdeveloping countries, such as India, Laos and Afghanistan. In addition to the usual morbidity associated with the aging process, these men suffer the consequences of nutritional (e.g. calcium deficiency, anemias) and medical deprivation. Consequently, many give up sexual expectations of themselves and their partners in the sixties and beyond. For males, their physical and psychological changes after mid-age need to be well researched, especially in the Asia Pacific Region. The promotion of healthy aging and the prevention of disability in all old people must be assumed a central role in medical research and medical practice as well as in the formulation of national health and social policies. Furthermore, public awareness of medical knowledge needs to be increased; and basic, clinical, socio-economic, as well as epidemiological researches' need to be intensified. These will necessitate a quantum leap in multi-disciplinary and international coordinated research efforts.

03

SYMPTOMATIC LATE ONSET HYPOGONADISM (SLOH) – THE ASIAN PERSPECTIVE

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As Asia is aging more rapidly than the rest of the world, and advancing age is the main cause of androgen decline in an aging male, the prevalence of symptomatic late onset hypogonadism (SLOH) in Asia will increase drastically. Taking a conservative prevalence of 20% for men above 60 years old suffering from SLOH, the number of Asian men potentially having SLOH is enormous, with an estimate of 350 millions based on current demographic data. The figure will escalate by the fact that Asia will experience a 4-fold increase of the aging population (>65 years) in the next 50 years. Hypogonadism is strongly associated with a decrease in sexual interest and deterioration in the quality of erectile function. In Asia, sexual function is viewed as part of ego, strength and success. Preservation of sexual function, therefore, extends beyond the ability to engage in sexual activity. Treating SLOH may help to improve sexual performance, which in turn will improve self image and quality of life of Asian men. The benefits of testosterone replacement therapy in patients with SLOH is well documented. In theory, Asian men with SLOH may benefit greatly from testosterone replacement therapy as there is an increasing demand for a larger and more rigorous workforce in nearly all Asian countries. As most part of Asia is in the midst of rapid economic growth, the male workforce is expected to remain in good health and be more competitive for a prolonged period of time. Thus, Asian male who suffer

from SLOH will benefit from treatment to keep up with the pace of development. Further, the theoretical concern of activating a subclinical prostate cancer is less likely as the overall problem of prostate cancer in Asia is much lower than in the West. In Asia, there are many countries which have their traditional and complementary treatments. Many ongoing researches on Asian herbal treatment have shown potential phytoandrogenic properties. The results of these researches may change the future direction of treatment of SLOH in Asia. The challenge in Asia is to establish the true prevalence of clinically significant SLOH in the aging male population that may benefit from treatment. Other specific Asian issues including establishing Asian normative data on testosterone level, the androgen level associated with appearance of clinical symptoms, and ultimately which preparation can provide optimal efficacy with minimal adverse effects.

04

REMEDIES FOR ERECTILE DYSFUNCTION-ASIA PACIFIC EXPERIENCE WITH ALTERNATIVE THERAPIES

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These herbals are found throughout Asia. Testosterone Releasers help andropause and energizers like ginseng help the tired and asthenic males. Deer horn improves nocturnal erections. ''Penis Soup'' and cobra blood is famous in Surabaya. Examples Chinese Yam: a tonic to the reproductive system, Eucomnia: treats impotency and fatigue Ginseng: improves potency. Deer Antlers: invigorate impotency and fertility Gingko Biloba: equilibrates body systems Tribulus terrestris: for sexual deficiency Gambih: application for prolonging erection and retarding PE. Muira Puama: increases libido and penile hardness Yohimbe: for dual aphrodisiac function Epimedium Extract 'horny goat weed'. L-Arginine: for male infertility and sexual wellness. Maca Root: increases strength, libido and sexual function Oat Straw: restores energy in sexual asthenia. Catuaba: to combat sexual weakness. Oyster Meat: for men's reproductive health and endurance. Nettle Leaf: for prostate health. Animal Testicles: orchic substance from bulls/wild boars increases testosterone and sperm counts. Testis soup popular in parts of China and Japan. Zinc: essential mineral for male sexuality. Cayenne: increases blood penis. Astragalus: stimulates energy and strengthens immunity and increases semen. Wild Oats: heightens sexual awareness, increases sexual thoughts and orgasms. Sarsparilla: aphrodisiac and sexual stimulant. Licorice Root: overall health at cellular and hormonal level. Pumpkin Seed: Improves prostate health, Boron. Citrate: maintains integrity of hormones. Dadder seed: for deficient kidneys manifested as impotence, nocturnal emissions, premature ejaculation. Gecko: for impotence due to kidney deficiency. Also used with Ginseng, Pilose antler and pimedium. Cordyceps: for deficient kidneys causing impotence, seminal emissions. The myths and realities concerning these and other village remedies will be fully discussed.

05

CHALLENGING TRENDS IN MANAGING METABOLIC DISORDERS IN THE ASIA PACIFIC REGION

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The past century has witnessed a transition from a high mortality and high fertility pattern to one of low mortality and low fertility. This change of pattern resulted in a rapidly aging population in most Asian countries. Andropause has received widespread attention in the popular and medical media in the last few years. Partial androgen deficiency of the aging male (PADAM) or symptomatic late onset hypogonadism (SLOH) have been used to designate andropause. Testosterone is a hormone responsible for the secondary sex characteristics that appear at puberty. It has a potent effect on stimulating libido, arousal and erectile function. It is also an anabolic hormone that enhances metabolic processes in muscles, bones, bone marrow, the immune system and the brain (cognition and mood). Thus, reduced testosterone level can cause sexual, somatovegetative and psychological symptoms. It is well known that the serum androgen level declines with aging. This is the main cause of PADAM because it is defined as a biochemical syndrome associated with advancing age and is characterized by a deficiency in serum androgen with or without decreased genomic sensitivity to androgen. The metabolic syndrome also increases with aging. It is a common subtype of obesity characterized by insulin resistance and increased risk of cardiovascular disease and type 2 diabetes and defined as central obesity plus any two of elevated triglycerides, low HDL-cholesterol, elevated blood pressure and impaired fasting glucose or diabetes. In this symposium, we will present our experience of treatment for several metabolic disorders including ED, lower urinary tract symptoms (LUTS), diabetes mellitus, hypertension, PADAM and the metabolic syndrome in aging male.

06

AGING – A CULTURAL EUROPEAN EVENT

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Aging is indeed a cultural event. Due to the enormous endeavours and results in medicine the life span increased in the last hundred years drastically, this trend will continue. Therefore a new environment for aging people is mandatory which are usually long in a very good health condition. While not being able to change human genes, a few simple measures could influence the speed of aging. The most important factor was a proper diet, but also measures such as minimising chronic stress could significantly reduce the risk of illness. From the political site a new change in health care policy should lead to more self-responsible prevention and as most important element the intended the intended holistic health care. A special new trend is given with the new family doctors. In the age there must be a new ability to create social relationships, to be able to rely on friends and family, loneliness and depressions are not to be underestimated in the development of illness in age. The aged can design their own future, where people are overcoming loneliness by creating social contacts, individual autonomy and inner freedom. The aging process is indeed a very cultural event, based to the endeavours of medicine, theology, sociology and retirement systems as well as creating the ideas of overcoming illness, how to deal with illness and finally to think on the end of the life.

07

AN AGING WORLD CHALLENGES AHEAD

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Abstract not available at the time of printing.

Androgens and Aging

08

ANDROGENS AND THE METABOLIC SYNDROME

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The co-existence of visceral obesity, increased blood lipids, hypertension and impaired glucose tolerance is known as the

metabolic syndrome and is an important determinant of morbidity and premature mortality. Total testosterone levels are low in men with metabolic syndrome, diabetes, visceral obesity and coronary artery disease. In a longditudinal study of 702 Finnish men who had neither diabetes nor metabolic syndrome, after 11 years, low total testosterone and SHBG levels independently predicted the development of metabolic syndrome and diabetes, so hypoandrogenism is an early marker for disturbance of insulin and glucose metabolism. In a glucose clamp study to look at testosterone levels, insulin sensitivity and mitochondrial function, low testosterone levels were associated with an adverse metabolic profile, with low insulin sensitivity and impaired mitochondrial function. In another study, higher testosterone and SHBG levels in ageing males were independently assocviated with higher insulin sensitivity and a reduced risk of the metabolic syndrome, independent of insulin levels and body composition measurements, suggesting that testosterone may protect against the development of the metabolic syndrome. Rapid weight loss with successful weight maintenance in abdominally obese men with the metabolic syndrome, brings about a sustained increase in free testosterone levels. Interestingly, the polymorphic number of CAG repeats within the androgen receptor is inversely associated with the transcriptional activity of the target genes, and a low number of CAG repeats is independently associated with low body fat mass, plasma insulin and low HDL levels, suggesting a role for this polymorphism in modulating androgen effects on cardiovascular risk factors. Interventional studies to correct hypogonadism show a decrease in abdominal fat mass and reversal of glucose intolerance. Testosterone may have a role in the pathogenesis of metabolic syndrome.

09

ANDROGENS, THE PROSTATE AND SAFETY OF TESTOSTERONE TREATMENT

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Introduction: for patients taking testosterone supplementation, clinical concern relates to the progress of undiagnosed prostate cancer or its development with advancing age. The historical basis for concerns of prostate cancer will be considered in relation to contemporary clinical practice and concepts of prostate cancer biology, both of which have advanced considerably within the PSA era. The role of androgens and androgen signalling pathways in the normal prostate, and changes acquired with benign hyperplasia or malignant transformation will be discussed. Methods: An updated analysis from the UK Andropause Study (UKAS) of 1,650 men on testosterone treatment for up to 15 years, will be presented. All patients underwent at least annual monitoring by digital rectal examination (DRE) and PSA; abnormal findings or rising PSA were further investigated by transrectal ultrasound and prostate biopsy. Results: 13 cases of prostate cancer were diagnosed by prescreening (0.5%), and 12 new cases occurred during 2,300 man-years of treatment, all being clinically localized. Irrespective of the hormone preparation, no significant effect on total PSA, free PSA or total/free PSA ratio was detected. Similarly, there was no significant change in urinary symptoms or renal function, in spite of wide variations in endocrine profiles with different testosterone preparations. Conclusions: Prostate cancer is an uncommon but important diagnosis in men recieving androgen replacement therapy. Before commencing treatment, patients should be advised of the interaction between undiagnosed prostate cancer and androgens, as well as the increasing risk of developing prostate cancer with advancing age. Men at risk of androgen deficiency should have prostate monitoring, as several lines of evidence suggest that reduction of physiological androgen activity within the prostate may increase the risk of a more aggressive phenotype. This study confirms the importance of PSA testing and screening for prostate cancer, and assuring prostate health in men recieving testosterone replacement.

10

AN APPRAISAL OF METHODS TO ASSESS COMPLAINTS ASSOCIATED WITH ANDROGEN DEFICIENCY

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Several questionnaires have been used to collect symptoms or complaints of patients with androgen deficiency (AD), but very few are sufficiently validated. The requirements for a state of the art validation will be reviewed with examples. Such a scale should be able to (a) compare relevant symptoms, (b) evaluate the severity of complaints over time, and (c)measure changes pre and post androgen replacement therapy. One example of a validated scale is the AMS scale which is internationally well accepted (translated into 20 languages). Reliability measures (internal consistency and test-retest reliability) were found to be good across countries. Acceptable validity data were also published. The internal structure of the AMS in healthy and in androgen deficient males, and across countries, was sufficiently similar to conclude that the scale really measures the same phenomenon in different cultures. Experience in France demonstrated that the scale similarly measures values in younger age groups, below 40 years. This is important for investigations in young hypogonadal men. In addition, population reference values for the AMS results, seem to be pretty similar across countries. Clinicians usually consider validity as utility for outcome measurement. This can be shown for the AMS scale. For more details: www.aging-males-symptoms-scale.info. The comparison of the AMS with two established screening instruments for androgen deficiency (ADAM Scale, Morley et al. and the screening instrument of Smith et al.) showed sufficiently good compatibility despite conceptual differences among the scales. Recent publications and new data have shown that the AMS scale together with other data, such as age and BMI, gives an efficient screening tool for AD. A proposal for a mass screening via an open acess website will be demonstrated, and future steps discussed.

11

ANDROGENS AND GENETIC VARIATIONS IN MEN WITH ALZHEIMERS

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We were the first to show that low testosterone (T) levels are associated with Alzheimers Disease (AD), but it remains unclear wether this is a co-morbid effect due to cachexia, subclinical hyperthyroidism or other morbidity co-existing with AD. The biological plausibility for potential protective effects of T on brain functions is substantial. In addition, higher levels of gonadotrophins found in older cases with AD, suggest that low levels of T are not due to brain degeneration and that the hypothalamic-pituitary-gonadal (HPG) axis is still intact. In fact, there may be a role for elevated gonadotrophin levels in promoting AD pathology. Data from the Oxford Project To Investigate Memory and Aging, showed that men genetically at risk for AD were also already found to have lower levels of T. Other genetic polymorphisms associated with T metabolism were not deviant. However, despite having lower levels of T, women do not show accelerated cognitive decline when compared to men. in addition, castration has not necessarily shown a decline in cognitive functions. Some studies even found improvement of memory recall. Age may be an important factor when assessing optimal levels of T, and several studies suggest that free or bioavailable T may be a better marker than total T levels when investigating associations of androgen activity with cognitive function. Small-scale T intervention trials in elderly men with and without dementia, suggest that some cognitive deficits may be reversed, at least in part, by short term T supplememntation. Age and prior hypogonadism may play an important role in therapy success, and these factors should be investigated in more detail in future, large scale, randomised, controlled studies.

12

SEASONAL COLD AND CLIMATIC FACTORS IN CARDIOVASCULAR AND DIABETIC PATIENTS

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There is a widespread belief in the UK that large numbers of older people suffer death from hypothermia in the winter months. This is not borne out by the statistics which show rather that there is an excess of winter deaths due largely to respiratory and circulatory disease, such as heart attack and stroke. Several studies have now established that there is a relationship between these deaths and seasonal reductions in temperature but the nature of this relationship is unclear. Many European countries with more severe winters than the UK suffer much lower winter mortality and though indoor temperatures in the UK have improved over the years, the number of excess winter deaths caused by circulatory disease shows little decline. There is a trend towards fewer winter respiratory deaths. Recent studies examining the way in which populations are exposed to cold stress have indicated that outdoor excursions and the degree of cold protection involved, as well as the indoor climate, may play a role in the causation of winter deaths. This review will therefore examine the relationship between cold stress and the health of older people, with particular reference to circulatory disease and diabetes. Patho-physiological mechanisms will be considered including endocrine responses to season and cold. The role of physical activity will also be considered. Recent evidence indicates that physical activity in older people may in fact be raised in the winter and may contribute to the effects of cold stress in provoking higher blood pressure, a known risk factor for thrombotic disease.

13

THE LIMITATION OF ANDROGEN ASSAYS

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In 2003, in an editorial on Clinical Chemistry, Herold and Fitzgerald suggested that testosterone assays could be considered random number generators. These investigators were commenting on the performance of assays under controlled experimental conditions. In the laboratory there are a number of factors that could cause even worse performance. Recent papers on the measurement of testosterone raise a series of questions. These include: 1. Do testosterone assays have adequate precision and specificity to give the clinician confidence in the results they recieve for their patients? 2. How good is the agreement between different assays? If a patient's sample is sent to a laboratory using method A, will there be a similar result from another laboratory using method B? 3. What factors such as drugs, concentration of proteins, and other constituents in the sample influence the result? 4. Does it matter what sample tube is used and when the sample is taken? 5. Should we be measuring free testosterone as well as, or instead of, total testosterone? If so, is an androgen index (testosterone/SHBG) as good as free testosterone determination? This talk will address each of theses issues showing recent data on the limitations of testosterone assays.

14

AN ANDROGEN RESISTANCE SYNDROME (ARS) IN THE ADULT MALE?

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There are many theoretical parallels, as well as biochemical links, between the insulin resistance seen in mature onset diabetes and metabolic syndrome, and androgen resisitance. As with insulin, the resistance to androgens may vary between tissues, and determine the physical, mental and pathological expression of their actions throughout life. The mechanisms of androgen resistance in the adult male can be considered as follows: Receptor Polymorphism: The androgen receptor gene is the most mutated in the human body, and shows marked individual and racial differences, giving different responses to testosterone treatment and hormonal contraception. Longer CAG repeats make men more resistant to the action of androgens, and are linked with obesity and insulin resisitance. Longer GGN repeat lengths can also be linked to androgen resistance, and may be the cause of 'Testicular Dysgenesis Syndrome' which includes testicular maldescent, hypospadias, testicular cancer and infertility. Age-related Receptor Changes: With age, the number of androgen receptors can decrease, and down-regulation occur. Protein Binding: Free testosterone can vary between 1% and 3% of the total, depending on the amount and affinity of its binding proteins. Sex Hormone Binding Globulin (SHBG) increases with age, hyperthyroidism, cirrhosis, and low carbohydrate, high fibre diets. Certain drugs, notably anticonvulsants, can raise SHBG and precipitate androgen deficiency symptoms. The binding affinity of SHBG is affected by metabolites such as free fatty acids, and environmental factors, such as xenoestrogens and antiandrogens. Endocrine Factors: Variations in 5 alpha-reductase activity can be due to genetic polymorphism, dietetic or pharmacological factors. Similar factors apply to aromatase activity, which may also vary with age. Other counter-regulatory factors include increased catecholamines and glucocorticoids, or growth hormone deficiency. Summary: These factors can combine to make resistance to the action of androgens as important as insufficient production in relation to the symptomatology and pathology of androgen deficient states.

15

LONG TERM EXPERIENCE OF MORE THAN 8 YEARS WITH A NOVEL FORMULATION OF TESTOSTERONE UNDECANOATE (NEBIDO) IN SUBSTITUTION THERAPY OF HYPOGONADAL MEN

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Objective: A reliable form of androgen substitution therapy in terms of favorable kinetics and tolerance as well as effective restoration of androgenicity is paramount in hypogonadal men. A feasible modality is the intramuscular injection of the long-acting ester testosterone undecanoate (TU). Design: We report data from 22 patients (15 with primary and 7 with secondary hypogonadism) aged 30 to 65 years (mean 43.8 ± 8 years) who received injections of 1000 mg of TU (4 ml – ampoules) for over 8 years. Results: The medication was well tolerated and local irritation of the injection site was moderate and did not exceed a duration of 3 days. Serum trough levels of testosterone were generally within the low normal range, indicating sufficient substitution. Individual dosing intervals ranged from 10 to 14 weeks. In accordance, patients reported restoration of sexual functions and convenient changes in mood patterns, e.g., gain of vigor and loss of depressiveness. In contrast to short-acting testosterone esters, sensation of fluctuations in androgen concentrations was rarely reported. If this was the case, it was within the last 2 weeks before the next injection as loss of androgenic psychotropic effects. Hemoglobin concentrations and hematocrit were markedly elevated under treatment but remained within the normal range. Prostate size as assessed by transrectal ultrasound remained below 30 ml in all patients and PSA concentrations did not exceed 2.0 μg/l. Bone density as determined by quantitative computer tomography of the lumbar spine or phalangeal ultrasound generally improved in all patients. Conclusion: In summary, intramuscular injections of testosterone undecanoate represent a feasible, safe and well tolerated modality of androgen substitution in hypogonadal men.

16

MONITORING THE SAFETY AND EFFICACY OF INTRAMUSCULAR TESTOSTERONE UNDECANOATE IN ELDERLY HYPOGONADAL MEN

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Currently, physicians have a wide choice of testosterone (T) preparations for the treatment of hypogonadism. One of the newer delivery forms is T undecanoate which allows intramuscular (IM) administration at intervals of 10 to 14 weeks. This feature decreases patient inconvenience and may increase compliance. The issues of safety and efficacy, as anticipated in a new delivery system, are not yet fully established. Safety. Concerns have been expressed by some, mostly, in relation to prostate safety. Hematological issues have also been raised. I believe these to be unjustified for several reasons: 1. A medical society recommended annual prostate specific antigen (PSA) (no digital rectal examination!) but hematocrit and lipids every 6 months. Others recommended both DRE and PSA on a quarterly basis (that is every 12 weeks) for the first year. 2. Let's assume, for the sake of argument, that there is a rapid increase in PSA at the first treatmenht (that is 12 weeks after the injection of depot-T). The knowledgeable physician would stop T therapy and proceed with biopsy of the prostate. If cancer is found, curative treatment can be instituted. The literature is very clear (and most urologists would agree) that a delay of a few months in treatment of prostate cancer (regardless of Gleason grade and probably T levels) is not detrimental to prognosis. Would it be different if we are talking of hematocrit or lipids? I don't think so. 3. 'Transdermal applications imitate the circadian production of T'. This is true. I am not aware, however, of a study indicating that the maintenance of such circadian rhythmicity in any way diminishes the beneficial effects of T or enhances its potential adverse effects. 4. Furthermore, the blanket repudiation of long acting T preparations dismisses the fact that hypogonadal men are on treatment chronically. What could be wrong in instituting long-acting T treatment in a man who is stable on short acting preparations and prefers the long-acting ones? Efficacy. One would expect a drug class efficacy for T as long as sufficient serum (and most importantly) tissue levels are achieved. As a newer T preparation, long-term (years) of efficacy studies are not available for the Injectable undecanoate. The early evidence, however, shows maintenance of adequate levels of serum T and a satisfactory clinical response. Conclusion: Available evidence indicates that long-acting IM preparations of T (cypionate, enanthate and undecanoate) are safe and effective within the parameters of other T delivery formulations. Warnings and restrictions apply to all of them.

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17

COMPARISON OF KINETICS, EFFICACY AND SAFETY OF THE LONG-ACTING TESTOSTERONE UNDECANOATE FORMULATION WITH STANDARD TESTOSTERONE ENANTHATE

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Here we report on the long-term results in an open-label, randomized, prospective clinical trial investigating a novel long-acting intramuscular testosterone undecanoate (TU) formulation, in 40 hypogonadal men. During the first 30 weeks, patients were randomly assigned to receive either standard treatment with 250 mg testosterone enanthate (TE) i.m. every 3 weeks ($n = 20$) or 1000 mg TU i.m. every 6 to 9 weeks ($n = 20$). After the comparative study, a one-arm follow-up study was started and all men received 1000 mg TU every 12 weeks. This regimen resulted in stable mean serum trough levels of testosterone (from 14.9 ± 5.2 to 16.5 ± 8.0 nmol/l) and estradiol (from 98.5 ± 45.2 to 80.4 ± 14.4 pmol/l). Hemoglobin and hematocrit levels significantly increased over the observed 30-week comparative study period (hemoglobin: from 14.4 ± 1.0 g/dl to 15.7 ± 1.2 g/dl [TU] and from 14.7 ± 0.8 g/dl to 15.9 ± 1.1 g/dl [TE]; hematocrit: from $43.4 \pm 3.0\%$ to $46.8 \pm 3.3\%$ [TU] and $44.4 \pm 2.2\%$ to $47.8 \pm 3.0\%$ [TE]). During prolongation of the study, hemoglobin and hematocrit remained stable. Total serum cholesterol concentrations declined from 235.3 ± 46.7 mg/dl to 215.3 ± 36.8 mg/dl (TU) and from 235.5 ± 54.0 mg/dl to 220.9 ± 55.7 mg/dl (TE); LDL- cholesterol concentration from 158.8 ± 45.4 mg/dl to 148.6 ± 39.1 mg/dl (TU) and from 158.7 ± 51.0 mg/dl to 153.4 ± 54.3 mg/dl (TE). Total and LDL-cholesterol concentrations decreased further under long-term therapy with TU (to 202.4 ± 35.7 mg/dl and to 134.9 ± 35.7 mg/dl). In both treatment groups, serum PSA levels rose slightly after 30 weeks to levels of 0.6–0.7 mg/l remaining stable during long-term administration of TU. In summary i.m. TU administration every 12 weeks is a safe and efficient therapy for male hypogonadism.

18

LONG-ACTING TESTOSTERONE ESTER INJECTION AS A SECOND LINE THERAPY IN HYPOGONADAL PATIENTS WITH ERECTILE DYSFUNCTION

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Objective: To assess the impact of long-acting testosterone injection alone to restore the erectile function in hypogonadal men. Material and methods: Assessing 771 ED patients, resulted 141 men (18.2%), (mean age: 56 yr.) with hypogonadism. 122 of subjects were prospectively evaluated for a mean of five months (3–11 months) under long-acting testosterone injections. Lab included total testosterone, DHT, lipid profile, blood sugar and HBA1c, as well as prostate specific antigen. Time average for ED 3.6 years. Physical and sonographic examination for prostate were performed besides waist circumference three-monthly. Sexual function assessment performed, using the International Index of Erectile Function (IIEF) at baseline and after 12 weeks. Baseline Testosterone level varied between 1.9 ± 0.5 ng/ml. Patients received i.m. long-acting testosterone injections at day 1, after six weeks and thereafter three-monthly. Results: 71 patients reported significant improvement in the sexual desire domain (main value 4.5 to 8.0). Erectile function domain from 12 to 25, following treatment for 12 weeks. No patient was excluded from study in this period of time. No patient reported irritation or pains in the gluteal injection areas or any other adverse events. The remaining 51 patients who suffered from ED longer than 7 years reported an improvement of sexual desire but no significant improvement in erectile function domain, despite their testosterone values were normalized (4.6 ± 0.5 ng/ml). All subjects are under follow-up. No alteration in prostate parameters was noticed so far. Conclusion: This encouraging result suggests that a testosterone therapy alone could have restored the erectile function in the majority of the hypogonadal patients of this group. It could be considered as second line therapy after PDE-5 inhibitors and before the combination with them. Further evaluation in comparison with control group will enlighten the influence of testosterone alone. For patients in rush, early combination with PDE-5 inhibitors is recommended.

19

HOW TO SELECT THE RIGHT PATIENT?

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The main indication for testosterone use is replacement therapy of male hypogonadism (for review: Nieschlag E, Behre HM, eds. Testosterone – action, deficiency, substitu-

tion. 3rd edition. Cambridge University Press, Cambridge, 2004). In secondary hypogonadism, hypothalamic or pituitary disorders result in decreased LH secretion and therefore insufficient testosterone production by testicular Leydig cells. In primary hypogonadism, the testis is unable to produce sufficient amounts of testosterone despite increased LH levels. Patients with primary and, if no fertility is desired, secondary hypogonadism require appropriate testosterone substitution to maintain androgen dependent functions. Late-onset hypogonadism (LOH) in males has become a topic of increasing interest and debate throughout the world. Recently, recommendations of the International Society of Andrology (ISA), the International Society for the Study of the Aging Male (ISSAM), and the European Association of Urology (EAU) have been published on investigation, treatment and monitoring of LOH in males (Nieschlag et al. Aging Male 2005;8:56–58). These recommendations provide clear statements on the indication for TRT in aging males with androgen deficiency. TRT should only be initiated if careful monitoring can be guaranteed, e.g., by patients' well-being, hematocrit and prostate function including PSA levels.

20

WHICH PATIENTS WITH SEXUAL DYSFUNCTION ARE SUITABLE FOR TESTOSTERONE REPLACEMENT THERAPY?

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While in women sex steroids substantially fluctuate as a function of ovarian cyclicity, in men testosterone (T) is relatively constant and high, allowing the male to be always ready to take advantage of sexual opportunities. Male sexual activity is characterized by a T-driven synchronization of sexual desire, arising in the brain, and its transmission to the periphery, allowing penile erection. The most important pathway underlying the penile erection is the nonadrenergic/noncholinergic signalling, which through the release of nitric oxide (NO), leads to an intracellular increase of cyclic GMP (cGMP), the main secondary messenger mediating tumescence in the penis. Interestingly, both cGMP formation and degradation are affected by testosterone (T). In fact, beyond to the well-known role of T in regulating sexual desire and NO release, recent experimental evidences, from our and other groups, showed that T also regulates the expression of phosphodiesterase type 5 (PDE5), the hydrolytic enzyme involved in cGMP breakdown. This antithetic role of T seems to be the main way through which the peripheral hormonal regulation of penile erections occurs. Because T positively controls both the initiation (NOS) and the end (PDE5) of the erectile process, its net effect on erection is null. Hence, erections are still possible in hypogonadal conditions where a decreased cGMP formation, due to impaired NO production, is counterbalanced by a reduced cGMP hydrolysis. The main action of T is therefore to timely adjust the erectile process as a function of sexual desire, therefore finalizing erections to sex. Restoring by TRT normal androgen levels in hypogonadal subjects has the main effect to transform a still possible erection in a sexual act. Another important aspect of TRT is to positively regulate penile PDE5 expression, the main target of PDE5 inhibitors (PDE5i), an obligate step for their efficacy. Without PDE5, PDE5i are almost ineffective.

21

TRT – WHO IS BENEFITING AND WHO IS AT RISK?

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There has been a dramatic increase in the use of testosterone replacement therapy (TRT) in aging men over the last several years, despite multiple concerns raised in medical and lay publications. Several benefits of TRT are well established, such as improvements in libido, body composition, and bone density, whereas other areas have yielded promising results that bear further investigation. Concerns are frequently raised regarding the possibility that TRT may increase the risks of prostate cancer and heart disease, yet to date these concerns have not been supported by existing research. There is considerable room for further standardization in the field, and further research is required to help guide clinicians in the optimal management of symptomatic men with testosterone deficiency.

22

THE AGING MALE

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The interest of the medical community in age-related endocrine deficiencies is increasing in parallel to the ageing population. With ageing, men experience a gradual reduction in bioactive circulating testosterone that worsens with the increase in SHBG. Illness begins when the low androgen level results in impairment of the androgen sensitive systems or functions. Estimates from the Massachusetts' Male Aging Study gave a crude prevalence of 12.3% and a crude incidence of 12.3% for LOH in men aged 48–79 years. These data show that, in addition to the estimated 2.4 million prevalent cases of androgen deficiency in American men between the ages of 40 and 69 years, approximately 481,000 additional cases can be expected annually in this population. The ubiquitous impact of androgens explains the variety of possible manifestations. The severity of one manifestation does not necessarily match that of others, nor do they need to be present simultaneously. Sexual and mood disorders are prominent features. A relationship exists between decreased testosterone levels and symptoms of depression. Memory loss and attention disorders appear as frequent signs. Changes in body composition affect soft tissues and bone, with a decrease in muscle mass and strength which can jeopardize balance in the oldest people, an increase in visceral fat mass and a decrease in bone mineral density. Some co-morbid conditions like visceral obesity and type 2 diabetes, which are the main features of the metabolic syndrome, are considered as risk factors for LOH and all other causes of premature mortality. Epidemiologic data are consistent with the negative impact of LOH on the quality of life of ageing males. Whether androgen supplementation, with its classical major contraindications represented by prostate and breast cancers, would influence cardiovascular risk factors and mortality, type 2 diabetes, fracture and frailty risks remains a subject of debate which can only be addressed by large, long term randomized studies.

23

IDENTIFYING THE LOH MAN

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The burgeoning interest in treating androgen deficiency against the background of the age-related decline in circulating testosterone in middle-aged and elderly men has outpaced the accrual of an adequate evidence base on causation, natural history, and accuracy/validity of diagnosis. The relevance of age-related hormonal changes in the somatotrohic and adrenal axes are currently also unclear. Fuelled by the increased choice of androgen preparations and heightened patient expectation, clinicians are put under increasing pressure to prescribe without an assured diagnosis. A number of questionnaires have appeared that claim to improve the detection of symptomatic hypogonadism in elderly men – these have not been validated against clinical outcomes. Best practice interim recommendations have also recently been proffered from many quarters in attempts to rationalise management of ageing men suspected of being androgen deficient. The most important principles underpinning these guidelines include are the pre-requisites of clinical features supported by consistent biochemical evidence of testosterone deficiency

and exclusion of recognisable reversible pathologies. How these principles can be applied in practice will be discussed. It must be emphasised that any current practice recommendations should be revised in the light of new and more substantial evidence from future research.

24

TREATING THE MEN WITH LOH

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Late-onset hypogonadism (LOH) is a clinical and biochemical syndrome which results in significant detriment in the quality of life and adversely affects the function of multiple organ systems. The evidence of androgen treatment in hypogonadal men on multiple target organs was demonstrated during the last decades and recent studies show that short term beneficial effects of testosterone in older men are similar to those in younger men. A clear indication based on a clinical picture together with biochemical evidence of low serum testosterone should exist prior to the initiation of testosterone substitution. The absolute contraindications are the suspicion or the presence of a carcinoma of the prostate or breast; apart from this, age is not a contraindication to initiate testosterone supplementation. Most of the available preparations of testosterone, intramuscular, transdermal, oral and buccal preparations are safe and effective. However, short-acting (transdermal, oral, buccal) preparations should be preferred over long-acting (intramuscular, subdermal) depot-preparations, since the possible development of a contraindication during treatment (as prostate carcinoma) requires rapid discontinuation of testosterone substitution. The preparations avoiding supraphysiological concentrations and releasing steady testosterone levels should be preferred. It will be the case with the new generation of testosterone matricial patches which will come on the market soon (Testopatch®, Pierre Fabre Medicament company). In all the cases, the selection of the preparation should be a joint decision between the patient and the physician. Prostate health has to be checked prior to the treatment, by the determination of serum prostate-specific antigen (PSA)associated to digital rectal examination (DRE). This baseline measurement should be repeated at quarterly intervals for the first 12 months and yearly thereafter. Transrectal ultrasound-guided biopsies of the prostate are indicated only if the DRE or the serum PSA levels are abnormal. Testosterone therapy provides benefits to elderly men as improvements in mood and well-being, increasing libido and erectile function (replacing or in combination with phosphodiesterase 5-inhibitors), muscle mass and prevention of osteoporosis. Larger-scale and longer-term data are needed on the effects of testosterone treatment in the older population to confirm safety on specific risk data on the prostate and cardiovascular systems.

25

PRACTICAL USE OF A TESTOSTERONE GEL FOR THE TREATMENT OF HYPOGONADISM

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The treatment of hypogonadsim is defined by low blood levels of testosterone and appropriate symptoms of androgen deficiency. The most commonly quoted level of total testosterone under which a deficiency may be diagnosed is 10.4 nmol/l (300 ng/dL). Newer guidelines from ISA, ISSAM and EUA, state that an area of deficiency might be considered between 8–12 nmol/l (231–346 ng/dL). The treatment modality varies according to the patient's personal preference and satisfaction. Long-acting injectable testosterone esters have been used for decades. Supraphysiological levels achieved are a concern for side effects. The oral testosterone, methyltestosterone, was abandoned due to liver function abnormalities and liver tumors. The newer oral testosterone undecanoate is quite safe but requires multiple daily doses and may have erratic blood levels because of the requirement of lymphatic absorption after a fatty meal. Testosterone patches delivered bioidentical testosterone, and the blood levels remained fairly constant in the eugonadal range, but the high incidence of skin irritation limited its acceptance. Buccal pellets were recently tried but were cumbersome to use and require bid dosing. Testosterone gels have recently dominated the market, at least in the USA. The levels of testosterone remain quite stable in the eugonadal range and only require a once-a-day application. Skin irritation is rare. There are two major gel products and they differ in the transdermal enhancers used, the time for absorption, and the blood levels achieved. Like any other method of testosterone delivery to hypogonadal men, safety issues are important. Blood levels of testosterone should be checked after one or two months. Adequate and frequent follow-up are important, especially rectal examinations, and measurements of PSA and hemoglobin. The same potential risks are present with gels than with other modalities, but like other therapies, no definite cause and effect relationship has been established with prostate cancer.

26

TESTOSTERONE AND HIS BRAIN

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A decline of cognitive abilities as well as adverse mood shifts are observed in aging men, and hormonal effects on cerebral functions are a focus of interest. Androgens are especially important, as many men experience age-related alterations within the hypothalamic-pituitary-gonadal axis leading to late-onset hypogonadism. Several aspects have to be considered in this field. Firstly, a multitude of subdimensions exist concerning cognitive functions: memory has verbal and visuospatial properties, acute task-solving abilities comprise visuomotor capacities as well as processing visuospatial input, performing constructional tasks and verbal functions relate to fluency of recognition and output. Secondly, the associations of deteriorating cognitive functions with declining androgen concentrations, which are described by cross-sectional or longitudinal observation studies, have to be corroborated by interventional trials. Thirdly, testosterone undergoes aromatization to estradiol, which has properties of modulating cerebral functions on its own. Indeed, observations and intervention trials in younger and aging hypogonadal men demonstrate that testosterone is directly and indirectly required for proper cerebral functioning. In regard to spatial cognition, functional neuroimaging demonstrates an androgen-induced activation of a distributed cortical network, the ventral processing stream. Spatial cognition in its various subdimensions is directly augmented by replenishment of androgen resources in hypogonadal men of any age, also shown by the experimental regimen of additional aromatase-inhibitors. Verbal abilities of these patients, as measured by tasks of memory and output fluency, experience an improvement during testosterone substitution as well; this process is most likely estrogen-mediated. Testosterone levels and depressive disorders have been associated frequently: psychological symptoms of depression are observed in hypogonadal men and depressive patients often exhibit low androgen concentrations. Correspondingly, testosterone substitution can attenuate symptoms of depression in both groups of patients. In conclusion, in hypogonadal men, testosterone substitution will contribute to improve the overall quality of life by positively affecting cognitive abilities and emotional well-being.

27

TESTOSTERONE AND HIS BODY FUNCTIONS

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Testosterone is one of the prerequisites for male differentiation during embryonic development. Physiologic serum testosterone levels are also necessary for many organ and cell functions by stimulatory effects on bones, bone marrow,

muscles, liver, skin with sebaceous glands and melanocytic cells, hair, spermatogenesis, prostate gland, penis and renal erythropoietin producing cells. Treatment of male patients with coronary heart disease has been shown to improve clinical and ECG parameters. Testosterone was found to be effective in the treatment of diseases associated with hypogonadism such as AIDS and rheumatoid arthritis. In addition, data from clinical studies have demonstrated a reduction of body weight, body fat and erectile dysfunction in patients with type-2 diabetes but without clearly defined hypogonadism. However, the main indication of testosterone substitution is the treatment of hypogonadism in adult men leading to an improvement in bone mineral density, quality of life, muscle mass, libido and mood. The majority of studies in aging men has shown positive effects on visceral fat mass, blood pressure, insulin resistance and the symptom complex related to partial androgen deficiency of the aging male. Testosterone substitution causes significant increases of hematocrit and hemoglobin and induces growth of the prostate gland until the size of that of age-matched eugonadal controls. Long-term treatment of older hypogonadal men with testosterone has not been associated with increased risk of prostate gland cancer or hepatotoxicity. Inconsistent changes of serum lipid levels have been observed during testosterone therapy, with increase, decrease or no changes of total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. In addition to the intramuscular injection of testosterone esters, oral, buccal, and transdermal substitution therapy or implantation of pellets has been established. In case of side effects or new contraindications, testosterone serum levels will decrease within very short periods after discontinuation of oral and transdermal testosterone treatment.

28

HIS MIND, HIS BODY, HIS SPIRIT, HIS TESTOSTERONE THERAPY: TESTOSTERONE AND HIS ERECTILE PHYSIOLOGY

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Testosterone is important for libido, energy, sense of well being, as well as for integrity of muscle and bone. The Adam questionnaire, however, recognizes erectile dysfunction as a major symptom of hypogonadsim. Testosterone is indeed important in erectile physiology itself. This basic model has been shown by Traish and others. It is comprised of stimulating the pelvic nerve of an animal and monitoring the erection produced. A castrated animal will not respond, but replacing the testosterone will restore the function. This group further showed that giving a PDE5 inhibitor to a castrated animal will not achieve a significant erection. It is known in humans that these drugs lose their potency in the presence of hypogonadism. Rajfer reported that testosterone affects the endothelial cell by showing that nitric oxide activity decreases in castrated animals, only to be restored with testosterone replacement. This group also showed that dihydrotestosterone is the active hormone in penile physiology. Lewis reported that by blocking endothelial function biochemically, erections are inhibited after pelvic stimulation in castrated animals. Under these conditions, testosterone administration produces a moderate erectile response, indicating an endothelial independent pathway. There is also evidence by Wingard and others that testosterone may affect adrenergic penile tone. Clinically, we have shown that men with erectile dysfunction and low testosterone levels have a decreased responsiveness to sildenafil. Aversa reported that men who had hypogonadsim, and who failed sildenafil, responded again when testosterone was replaced, a study that was confirmed by Shapsigh. Jain, in a meta-analysis, found five crossover studies that studied the effect of testosterone therapy on erectile dysfunction. The response rate for erectile improvement was 65.4%, over 16.7% for placebo. We found a 75% improvement in erectile function when testosterone levels were raised in men with secondary hypogonadsim.

29

TESTOSTERONE AND HIS QUALITY OF LIFE

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Aging, eventually associated with a decrease in quality of life (QoL) of the global population, will become one of the major public health issues in the near future. Over the past decades, life expectancy has considerably increased, mainly in western populations. Recent WHO data have reported a worldwide total of 600 million people aged 60 and older in the year 2000, a figure estimated to double by 2025 and to reach virtually 2 billion by 2050. Rather than aiming simply to live longer, people are also aspiring to undergo 'active ageing' with an emphasis on their QoL. Significant advances in the understanding of the physiology and pathophysiology of the aging male population, as well as substantial efforts to measure related QoL, have been achieved over the past years. As a result, it is now well established that aging in healthy men entails an age-related decline in serum testosterone (ST) production. After the age of 50, testosterone levels decline by 1% per year, and over 60 years 1 in 5 men lives with ST levels below the range for young males. Although a great inter-individual variation exists among elderly men in the decline of ST levels, a large body of evidence suggests that decreased ST levels contribute, at least in some men, to age-associated physiological processes that may affect the function of multiple organ systems. Although so far less conclusive, there is progressively more evidence indicating that decreased ST levels are involved in a significant detriment in the quality of life of the aging male. More consistent evidence exists on the benefit, in terms of signs and symptoms, of normalizing ST levels by testosterone substitution. However, there is also an increasing interest in assessing the impact of androgen substitution therapy on the restoration of QoL in older men with age-related decline in ST levels. In particular, several comparative studies using testosterone substitution have shown very promising results in improving QoL of the aging male.

30

SYMPTOM-SPECIFIC THRESHOLDS FOR TESTOSTERONE DEFICIENCY MODULATE COMPLAINTS AND METABOLIC RISK IN 434 AGING MEN

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Objective: The structure of psychological and somatic complaints of aging male patients in relation to sex hormone patterns and metabolism has not been fully elucidated, especially in regard to late-onset hypogonadism. Methods: We investigated the nature of complaints in 434 consecutive patients aged 50–86 years attending our andrology unit and their association with physical characteristics, life style habits and sex hormone levels. Results: Three independent symptom complexes could be identified by cluster analysis: 1. psychosomatic complaints, 2. metabolic disorders and 3. lower urinary tract symptoms. Erectile dysfunction was assigned to both complexes 1 and 2. Levels of total testosterone (T) <12 nmol/l were seen in 48% of the men. Regression models revealed concentrations of T to be inversely associated with psychological complaints such as "feeling sad" ($p = 0.006$), loss of libido ($p < 0.001$), loss of vigor ($p < 0.001$), lack of concentration ($p = 0.01$), hot flushes ($p = 0.004$). The overall presence of diabetes mellitus ($p = 0.001$), arterial hypertension ($p = 0.02$) and obesity (body mass index ≥ 30 kg/m^2, $p < 0.001$) was associated with lower T concentrations. The relation of symptoms and metabolic risk factors to T was non-linear, causing respective prevalence to increase below specific cut-off levels (>8, >10 or >12 nmol/l). Obese men were more likely to present with diabetes mellitus in case of lower T levels ($p = 0.02$). Erectile dysfunction in non-smokers was associated with decreased T concentrations ($p = 0.02$) while the overall presence of

erectile dysfunction was associated with cigarette smoking and age, but not with T. Lower urinary tract symptoms were mainly dependent on prostate size but also on advanced age and higher T concentrations. Conclusion: Psychosomatic complaints, behaviour and metabolic risk of older men are interdependent and relate to T in a non-linear, symptom-specific manner. In individual patients, occurance of symptoms related to late-onset hypogonadism may have specific thresholds of T levels.

31

DOES A PATIENT'S BIOCHEMICAL PROFILE LEAD TO CONFUSION IN THE DIAGNOSIS OF LATE-ONSET HYPOGONADISM?

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Objectives: Various biochemical measurements are recommended for the diagnosis of late-onset hypogonadism (LOH) including low total testosterone (T), bioavailable testosterone (bioT), calculated free testosterone or free androgen index. However, there is a wide variation of the reference ranges for T (10–35 nmol/l) and bioT (3–12 nmol/l) among clinical laboratories in our region. Therefore, we examined the distribution range of biochemical profiles according to these reference ranges. Patients and methods: Between June 2002 and August 2005 approximately 300 males with complaints of hypogonadism or erectile dysfunction underwent hormonal biochemical profiling. All patients had early morning measurement of T, bioT, FSH, LH, prolactin, CBC, PSA, and sex hormone binding globulin (SHBG) in a smaller cohort. Results: Age ranged 30 to 90 years. The overall T and bioT were 13.46 ± 5.72 nmol/l and 4.13 ± 1.72 nmol/l, respectively. At least 80% of the cohort had a T between 6 and 18 nmol/l and bioT 2 to 6 nmol/l. There was no difference in T when it was stratified by age decade. However, there was a decrease of bioT of about 0.33 nmol/l per age decade from 4.71 ± 1.11 to 2.71 ± 0.98 ($p = 0.003$). There was no difference in PSA according to T or bioT levels (cohort PSA $= 1.36 \pm 1.25$ ng/ml). As bioT increased from <2 to >8 nmol/l, hemoglobin increased 14.2 to 15.5 g/dl ($p = 0.06$), FSH decreased 15.5 to 4.3 IU/l ($p = 0.05$), and LH decreased 9.5 to 4.8 IU/l ($p = 0.16$). Conclusions: The reference ranges of T and bioT provided by clinical laboratories may be an inaccurate way to stratify patients leading to confusion in determining which patients are truly ''hypogonadal''. Further laboratory tests are needed to examine the actual end-organ response to testosterone in LOH with less dependence on traditional parameters. Thorough clinical history and physical examination remain important in the decision algorithm for testosterone replacement therapy.

32

SYMPTOMS OF LATE ON-SET HYPOGONADISM IN 15,920 FINNISH MIDDLE-AGED MEN

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Background: The aging in men is associated with subjective and objective biological changes, which can display as symptoms of decreased physical, mental and sexual performance. It is not known whether these symptoms are associated to late on-set hypogonadism or simply aging itself. Methods: To all the men aged 40–70-years ($n = 28.622$, year 2000) in the city of Turku, Finland was sent a questionnaire including issues of general health and Aging Male Symptoms (AMS) scale. The aim was evaluate these findings and their association to each other. Results: 15.920 men returned the questionnaire (56%). In both AMS and general health questionnaire an increasing incidence of symptoms and illnesses was observed with increasing age. The criteria for significant ''andropausal'' symptoms (AMS score higher than 36) were fulfilled in 30.0% of the respondents on average. The increase in these symptoms was most clearly seen between the 50–60 years of age and the overall age-dependent increase of symptoms was most clearly seen in sexual functions. Subjective health correlated significantly with healthy life style e.g. the amount of exercise, non-smoking and low alcohol consumption. In addition, when all chronic illnesses and health behavioural variables were adjusted, there was still a significant (approx. 15–25%) proportion of men suffering from these symptoms. Conclusions: There is an increasing symptom profile measured by AMS scale observed among aging men with increasing age. According to this study the symptoms are independent from medical conditions as well as other confounding factors.

33

COMPARATIVE ASSESSMENT OF THE INFLUENCE OF ANDROGEN DEFICIENCY ON QUALITY LIVE MIDDLE-AGED IN MEN WITH DIABETES AND WITHOUT DIABETES

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Introduction: The symptoms of andropause usually occur of the age of fifty. The aging process man is accompanied by a loss of libido, impotence, feeling of tiredness, sleep disorders and depression. Material and methods: Life quality was evaluated in 200 men with diabetes mellitus. The clinical study was based on: International Index of Eractile Function (IIEF-5), International Prostate Symptom Score (I-PSS) and Test of Quality Life (QoL), andrological and sonographic examinations. Laboratory test included basic blood tests and hormonal tests. The evaluation of qality life was estimated in three groups depending on type of diabetes and also in three age groups. Results: The degree of erectile dysfunction below 16 points occurred: Gr.A (diabetes type 1) – in 93%, Gr.B (diabetes type 2) – in 74% and Gr.C (without diabetes) – in 59% men. Dysuria symptoms were respectively: Gr.A-21.2, Gr.B-19.4 and Gr.C-15.1 points. The average testosteron level in blood serum was respectively: Gr.I (40–49 age) – 9.4 ng/ml, Gr.II (50–59 age) – 6.1 ng/ml, Gr.III (60–69 age) – 3.2 ng/ml. The average volume of prostate was in Gr.I – 24.2 ml, in Gr.II – 28.8 ml, in Gr.III – 40.1 ml. Conclusions: Quality of sexual life in men with diabetes regardless to the diabetes type is significantly lower than in men who do not suffer from this disease. Dysuria symptoms and decrease of life quality were significantly higher in a group of older men (Gr. III). Decrease of testosterone level, progressing with age, influences on life quality, therefore it should be an indication to hormonal substitute therapy.

34

COMPARISON OF SERUM TESTOSTERONE, ADAM QUESTIONNAIRE AND IIEF-5 SCORES IN ANDROPAUSE SCREENING IN KOREA

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Introduction and objective: Andropause is a clinical and biochemical syndrome characterized by a decline in levels of serum testosterone, and results in various physical and mental disabilities in aging males. We aimed to investigate the epidemiology of andropause, as well as the relation between serum testosterone level and andropause symptoms by ADAM

questionnaire and IIEF-5 scores in aging males in Korea. Methods: We examined ADAM questionnaires and IIEF-5 for clinical symptoms, and serum total testosterone levels for biochemical diagnosis. Results: The mean age of the 272 men was 59.9 (40–86) years, and the mean serum testosterone level was 457 ± 164 ng/dl. According to age, the serum testosterone level was 484 ± 173, 454 ± 173, 469 ± 159, and 422 ± 141 ng/dl in the 5th, 6th, 7th, and 8th decades, respectively. Among the men, there was a 85.3% positive response on the ADAM questionnaire. The mean IIEF-5 score was 12.52 ± 6.13. The percentage of patients whose serum testoterone was less than 350 ng/ml in a positive ADAM questionnaire was 25.7%. The mean serum testosterone level in a positive or negative ADAM questionnaire was 441 ± 157 or 482 ± 160 ng/dl: there was not a difference ($p > 0.05$). The mean serum testosterone level according to the IIEF-5 scores was 432 ± 144, 456 ± 146, 458 ± 168, 490 ± 201, and 419 ± 112 ng/dl in score 1–7, 8–11, 12–16, 17–21, and 22–25, and there was no relation between them. Conclusions: Among men over 40 years of age, 25.7% met the both of clinical and biochemical diagnostic criteria for andropause in our study. There was no relation between serum testosterone level and andropause symptoms.

35

HYPOTHALAMIC-PITUITARY-TESTICULAR AXIS SENSITIVITY IN AGING MALE

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As the term ''Andropausa'' is inappropriate one we've already suggested the term ''Hypoandria involutiva''. The decrease in serum testosterone in men with involutive hypoandria seems to be a result of primary testicular changes and altered neuroendocrine regulation of Leydig cell functions. AIM of this study was to test the sensitivity of hypothalamic-pituitary-testicular axis in aging male. Subjects: I group: 30 men, 52.7 ± 2.4 yr old, BMI = 27.0 ± 4.6 kg/m^2. II group: 30 men, 62.6 ± 7.2 yr old, BMI = 28.3 ± 3.7 kg/m^2. Methods: Blood samples for FSH, LH, prolactin, testosterone, estradiol, SHBG were taken at 8 am. LHRH test (FSH and LH were measured before and 20 & 60 min after LHRH administration) and HCG test (testosterone was detected before and 3 days later after Pregnyl amp. a 5000 ij per day was administered) were performed. Hormone analysis were measured by RIA. Statistics: Spearman, Mann Whitney test, ANOVA. Results: Significant difference were found for LH in 20.min (18.0 ± 14.8 vs. 26.1 ± 12.9 IU/l, $p = 0.03$) and LH AUC (982.4 ± 742.9 vs 1397.7 ± 614.6 IU/l/min, $p = 0.03$). The positive correlation was found for testosterone prior to and after HCG test (19.5 to 32.0 vs. 14.4 to 30.6 nmol/l, $p = 0.0021$) and the negative correlation was found for testosterone and BMI ($p = 0.02$). Conclusion: The slight decrease of testicular activity is associated with the modest LH increase inadequate to compensate T decrease due to reduced mean LH pulse amplitude and altered GnRH secretion. Despite the slight endocrine changes sensitivity of the gonadal axis is preserved in aging men.

36

ANTHROPOMETRIC, METABOLIC, AND HORMONAL CHARACTERISTICS OF MEN WITH OBESITY AND WITH METABOLIC SYNDROME

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In this study we investigated 85 men of age 19–50 years with obesity (body mass index, BMI 27–42 kg/m^2). The control group consisted of 20 age-matched healthy men. In 64 obese men we found metabolic syndrome (MS). The frequency of MS was associated with obesity duration: MS was found in 28% of patients with obesity duration 1–4 years, in 60% of patients with obesity duration 5–10 years, and in 77% of patients with obesity continuance above 25–30 years. A strong inverse relationship exists between androgens secretion and abdominal fat mass. In healthy men the concentration of total testosterone (TT) was 21 ± 7 nmol/l, and the concentration of free testosterone (fT) – 375 ± 69 pmol/l; in obese men the level of TT was 16 ± 7.4 nmol/l, and fT – 313 ± 122 pmol/l; in patients with MS the level of TT was 11.7 ± 3.9 nmol/l, and fT – 179 ± 117 pmol/l. Insulin concentration in blood of MS patients was approximately 2 times higher as compared with healthy individuals, and blood glucose level was also statistically significantly higher. Lipid profiles in patients with MS had typical character for this disease, particularly we registered high concentration of triglycerides, 2.9 ± 1.7 mmol/l, whereas in patients with obesity without MS it was 1.4 ± 0.8 mmol/l. Leptin level correlated positively with BMI, it was as high as 27 ± 19 ng/ml in patients with MS. Glucocorticoid function of adrenals (as judged by cortisol level) remained unbiased in all studied patients, and reduced dehydroepiandrosterone sulfate concentration was found only in patients with MS. Role of androgens in the evolution of insulin resistance and transformation into MS is discussed, as well as the perspectives of replacement therapy with androgens in patients with MS.

37

LOW SERUM BIOAVAILABLE TESTOSTERONE LEVELS ARE ASSOCIATED WITH MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE IN CHINESE OLDER MEN

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Introduction: The serum testosterone level, particularly the bioavailable testosterone level, decreases with advancing age. However, there was no previous report on the relationship of serum testosterone levels, cognitive impairment and Alzheimer's disease in the Chinese elderly. Objective: The objective of the present study was to investigate the associations of serum total and bioavailable testosterone levels with mild cognitive impairment and Alzheimer's disease. Methods: This was a cross-sectional study. 94 Chinese older men aged ≥60 were assessed by a detailed clinical, laboratory and neuropsychological assessment as well as fasting morning blood serum total and bioavailable testosterone levels. We established the diagnosis of dementia by the DSM-IV criteria, Alzheimer's disease (AD) by the NINCDS-ADRDA criteria and mild cognitive impairment (MCI) by the Petersen's criteria. Results: 51, 28 and 15 of the subjects had normal cognitive function (N), MCI and AD respectively. The mean serum bioavailable (but not the total testosterone) levels showed a statistically significant difference between the N, MCI and AD groups {mean(sem) serum bioavailable levels were 1.49(0.13), 0.95(0.11) and 0.91(0.12) nmol/l respectively for N, MCI and AD groups, $p = 0.003$, 1-way ANOVA}. Significant differences were present between the N and MCI as well as the N and AD subjects in the subgroup analysis (post-hoc, Bonferroni). Among all the potential confounding variables, only the fasting glucose level and age showed significant differences in univariate analyses ($p < 0.05$ for both, 1-way ANOVA). Adjustment of these two confounders by analysis of covariance (ANCOVA) showed that the serum bioavailable testosterone levels remained statistically significant in the corrected ANCOVA model for the N, MCI and AD groups (between groups: $F = 3.95$, $df = 4$, $p = 0.005$). Conclusion: Low serum bioavailable testosterone levels were significantly associated with mild cognitive impairment and Alzheimer's disease in Chinese older men.

38

EXPERIMENTAL STUDY OF ALLOGRAFT LEYDIG CELLS TRANSPLANTATION ON AGED SD RAT (ANIMAL MODEL OF PADAM)

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Objective: The leydig cell of the testis producing most of circulating testosterone is reduced much not only in number but also in function in PADAM. By the way setting up before, we can obtain pure leydig cells without immunogenicity, and remove all another cells having immunogenicity. This study is to investigate the feasibility and side effect of leydig cell transplantation in aged rat(the animal model of PADAM). Method: Ten aged SD rat with significantly decreased serum total and free testosterone were selected as the model of PADAM. leydig cells of adult rat testes were cultured in vitro and transplantated into the vastus medialis of the aged SD rat. The serum total and free testosterone were monitored 1 day before transplantation and 2, 7, 12, 17, 22, 27 days. Results: (1) The plasma level of total testosterone is 321.4 ± 175.6 ng/dl and 87.4 ± 28.2 ng/dl in young SD rat and aged SD rat respectively. ($P < 0.01$) The plasma level of free testosterone is 7.0 ± 2.9 pg/ml and 2.4 ± 1.7 pg/ml in young SD rat and aged SD rat respectively. ($P < 0.01$). (2) Before transplantation, the plasma level of total and free testosterone is 87.4 ± 28.2 ng/dl and 2.4 ± 1.7 pg/ml. But after the transplantation, the plasma level of total and free testosterone increased greatly. In the 12th day of transplantation, the plasma level of total and free testosterone is 315.88 ± 89.05 ng/dl and 7.31 ± 2.11 pg/ml, and this level can maintain for a long time. Conclusions: After the allograft leydig cells transplantation, both of the total and free testosterone of aged SD rat are increased greatly, and can reach the mean level of young SD rat.The transplanted leydig cells can work properly and maintain their testosterone secretary ability for a long time without any immunosuppressant drugs.

39

MOLECULAR ASPECTS OF DECLINING SPERM MOTILITY IN AGING MEN

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Objectives: In contrast to the female, male reproductive functions do not cease abruptly, but may continue lifelong. However, a distinct decrease in the concentration of free testosterone and sperm motility has repeatedly been described. Therefore, this study aimed at investigating molecular reasons for decreased sperm motility in aging men. Methods: More than 3900 patients were analyzed for sperm concentration, ejaculate volume, motility, normal sperm morphology, abnormally blue stained flagella (in the Shorr stain), testosterone, FSH and LH. In addition, 90 ejaculates were analysed for sperm concentration, motility, sperm velocity parameters, normal sperm morphology and the percentage of abnormally blue stained flagella. Moreover, in these patients the flagellar zinc content was measured by means of atomic absorption spectrometry. Results: Age was significantly negatively correlated with ejaculate volume, motility, normal sperm morphology and different velocity parameters and testosterone. Sperm concentration, percentage of abnormally stained flagella, flagellar zinc concentration and serum FSH concentration showed positive relationships. Highly significant negative correlations were found between the percentage of abnormally blue stained flagella and motility ($P < 0.0001$). The concentration of testosterone was positively correlated with motility ($P = 0.0123$) and sperm concentration ($P = 0.0033$). The percentage of abnormally stained flagella with flagellar zinc concentration was also positively correlated. On the contrary, the correlations between the percentage of abnormally stained flagella and motility ($P < 0.0004$) and the velocity parameters, respectively, were negative ($P < 0.005$). Conclusion: Since flagellar zinc is positively correlated with age but negatively correlated with motility, this sheds light on epididymal sperm maturation and on the functions of the outer dense fibres. During spermiogenesis, zinc is actively incorporated in these substructures but removed again during epididymal maturation. As epididymal function is obligatory testosterone-dependent, it appears that the removal of zinc from the sperm flagella is also hormone-dependent. Thus, while aging the epididymis seems to become dysfunctional resulting in poor motility.

40

EFFICACY AND SAFETY OF A NEW TESTOSTERONE-IN-ADHESIVE MATRIX PATCH APPLIED EVERY 48 HOURS FOR TWO YEARS TO HYPOGONADAL MEN

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Objectives: To evaluate the long term efficacy and safety of a new matrix patch, in which testosterone (T) is dissolved in a non-alcoholic drug solvent to limit skin irritation. Methods: Randomized, open label, multicenter European 2-years study. 224 hypogonadal patients were included (mean age 41.8 (12.4) yr). 188 patients received 2 patches of 60 cm2 every 48 hours and 36 patients had IM testosterone enanthate injection every 3 weeks. T, bioavailable T (BT), DHT, E2, LH, FSH and SHBG and clinical symptom scores (AMS and MSF-4) were assessed at 3, 6, 9, 12, 18 and 24 months. Among the 159 patients who completed the study, 115 accepted to enter the 1-year study extension and 97 patients completed the 1-year study extension. Results: The percentage of normalized patients increased up to 73.6% after one year of treatment, and then was maintained around 70% over the extension period (71.4% at 18 and 68.6% at 24 months). BT, DHT and E2 levels were restored within physiological range; the patch avoiding the supra-physiological T levels observed after IM injection. A significant correlation was found between T and the MSF-4 changes, the 7 points decrease was in accordance with the improvement observed for the sexual sub-score of the AMS questionnaire. Serum PSA values showed a little (SD) increase from baseline of 0.15 (0.36) ng/mL over the two years. The patch was well tolerated with no impact either on lipid profile, or red blood cells. The most common adverse events were administration site reactions (redness barely perceptible) in 35 patients (18.8%). Conclusion: Two 60 cm^2 patches, delivering 4.8 mg of T daily, allowed constant physiological levels of testosterone over time in >2/3 of hypogonadal men. This new patch was well tolerated, easy to use, and displayed a good adhesiveness.

41

PROFILE OF SERUM TESTOSTERONE AND FREE TESTOSTERONE LEVELS AFTER APPLICATION OF TESTOSTERONE OINTMENT (GLOWMIN) IN HEALTHY MEN AND LATE-ONSET HYPOGONADISM PATIENTS

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Objective: To clarify the hormonal effects of Glowmin (GL) (testosterone ointment produced in Japan), serum

testosterone (T) and free testosterone (FT) levels were investigated in healthy volunteer men and late-onset hypogonadism patients. Methods: (1) T and FT were estimated from 4 healthy volunteer men after application of 2 cm in length GL (3 mg of testosterone) on scrotal skin, and compared with their circadian rhythm. (2) The profiles of T and FT were observed from 4 late-onset hypogonadism patients after 3 mg of Gl on the scrotal skin. (3) Fifty late-onset hypogonadism patients were treated with 3 mg of GL twice a day on scrotal skin (6 mg per day) for 12 weeks. Afterward, T and FT levels just before GL application were compared with those at 1 hour after GL treatments. Results: (1) The maximum T and FT were observed after 1 hour and not elevated beyond the physiological levels, then returned to circadian rhythm after 4 hours in healthy men. (2) In late-onset hypogonadism patients, the highest T and FT levels were also obtained after 1 hour, and maintained within normal range for 6 hours. (3) After 12 weeks of GL treatments, T and FT just before GL were 2.5 ± 1.1 ng/ml and 8.1 ± 4.3 pg/ml, respectively, which were not significant different from the pre-treatments data. However, T and FT at 1 hour after GL were 5.5 ± 2.4 ng/ml and 13.3 ± 6.1 pg/ml, respectively, which were significantly increased, and revealed the same good responses as the initial GL administration. As adverse reactions, 2 complained difficulties on urination and 1 had seborrhea, which were not serious at all. Discussion: GL is a short acting testosterone ointment with mild elevation of T and FT. GL might be useful as androgen replacement.

42

THE ASSOCIATION OF SEX-HORMONES AND ERECTILE DYSFUNCTION. CROSS-SECTIONAL RESULTS FROM THE MASSACHUSETTS MALE AGING STUDY (MMAS)

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Prevalence of erectile dysfunction (ED) increases as men age. At the same time, there are considerable age-related changes in male endocrine functioning. However, the precise role of endocrine function in ED is not well-established. We examined the association between ED and total testosterone (TT), bioavailable testosterone (BT), sex-hormone binding globulin (SHBG), and luteinizing hormone (LH). Data were obtained from the baseline examination of the Massachusetts Male Aging Study (MMAS), a population-based prospective cohort study of 1709 men aged 40–70 years at baseline. Self-reported ED was dichotomized as "moderate" or "severe" vs. "none" or "mild". TT (ng/dl), BT (ng/dl), and SHBG (nmol/l) levels were grouped into quintiles of their distribution, while LH (mIU/ml) was categorized into three groups: 1–4, 5–8, and ≥ 9. Odds ratios (OR) and 95% Confidence Intervals (95%CI) were used to assess the association between sex-hormone levels and ED. Multiple logistic regression models were used to adjust for potential confounders including age, BMI, smoking, partner availability, physical activity, depression, diabetes, and heart disease. Analyses were conducted using data from1519 men with complete information on ED, hormone measurements, and all potential confounders. No meaningful association was observed between TT and ED. Moderate associations between ED and BT and SHBG did not hold after adjusting for potential confounders. On the other hand, increasing levels of LH were associated with an increased risk of ED with adjusted OR of 1.55 (95%CI: 1.15–2.09) and 2.24 (95%CI: 1.39–3.62) for LH levels of 5–8 m IU/ml and ≥ 9 mIU/ml respectively compared to LH levels of 1–4 mIU/ml. Consistent with results from some previous studies, we found no association between TT, BT, and SHBG with ED. In addition, the increased risk of ED with higher LH levels may be indicative of a relationship between decreased testicular function and ED independently of testosterone levels.

43

LEYDIG CELL SENSITIVITY DURING INVOLUTIVE HYPOANDRIA

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As the term "Andropausa" is rejected, the term "Involutive hypoandria" can be appropriate one. The challenge was to determine Leydig cell response during involutive hypoandria. Two different groups of patients were compared. Each group was consisted of 30 men. In first group patents were 52.7 ± 2.4 and in the second 62.6 ± 7.2 years old. BMI in I group was 27.0 ± 4.6 kg/m^2, and in the II 28.3 ± 3.7 kg/m^2. Blood samples for FSH, LH, prolactin, testosterone (T), estradiol and SHBG were taken at 8 a.m. Test with human chorion gonadotrophin (HCG) (5000 ij. i.m/day, 3 days) was performed in all patients. Testosterone and SHBG were measured prior to and after the test. Hormone analysis: RIA. Statistics: Spearman correlation test. I group FSH = 5.4 ± 2.9 IU/l; LH = 4.2 ± 3.5 IU/l; T before the test = 19.5 ± 8.2 nmol/l; PRL = 222.9 ± 132.9 mlU/l; estradiol = 0.1 ± 0.1 nmol/l; SHBG = 64.3 ± 106.5 nmol/l; T after the test = 32.5 ± 13.5 nmol/l; SHBG after the test = 30.6 ± 11.6 nmol/l. II group FSH = 7.8 ± 5.2 IU/l; LH = 5.4 ± 3.5 IU/l; T before the test = 14.4 ± 7.5 nmol/l; PRL = 240.8 ± 80.1 mlU/l; estradiol = 0.2 ± 0.3 nmol/l; SHBG = 37.4 ± 15.1 nmol/l; T after the test = 30.6 ± 18.0 nmol/l; SHBG after the test = 30.0 ± 13.8 nmol/l. Positive correlation was found between testosterone and SHBG before HCG test ($p = 0.023$), ($t = 3.41$). On the other hand, negative correlation was obtained for testosterone and BMI ($p = 0.02$), ($t = -2.3$) prior to test indicating that obese men have lower testosterone levels. Finally, positive correlation in testosterone levels before and after the test was confirmed, ($p = 0.0021$), ($t = 3.43$). Although the slight decrease in serum testosterone is detected in aging men, the responsiveness of Leydig cell to HCG is preserved in older group indicating no changes in Leydig cell number, receptor sensitivity and testicular steroid metabolism.

44

SEASONAL VARIATION IN TESTOSTERONE AND OTHER STEROID HORMONE LEVELS IN MEN

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Attempts to identify seasonal variation in testosterone and other steroid hormones in men have provided mixed results regarding the timing of maximum and minimum levels, and whether hormones vary seasonally at all. Wide variation in sample size among studies and the use of cross-sectional designs, which are subject to bias from inter-individual differences, in several studies may have contributed to the heterogeneous results. We present a longitudinal investigation of seasonal variation in testosterone (total, free, and bioavailable), DHT, SHBG, LH, DHEA, DHEAS, estrone, estradiol and cortisol in 134 community-dwelling men, 30–80 years old, from Boston, Massachusetts, USA. Randomly selected subjects were recruited over 12 months. Two blood samples were obtained two days apart at study entry, and again 3 and 6 months later (6 total samples per subject). All samples from each subject were assayed in the same batch to exclude inter-assay variation from intra-individual variation. Linear models were employed to test for seasonal variation in hormone levels. As of 30 September 2005, all subjects had completed the first two visits, 126 had completed the first four and 103 had completed all six. Eight subjects dropped out or were removed from the study, most because they began taking medications that altered hormone levels. Assay results are available from the first 90 subjects, including 82 subjects who completed all six visits. Sample collection will end in December 2005. Analysis of results from the first 90 subjects provided no evidence of seasonal variation in any of the hormones considered ($p > 0.10$ for each hormone). Assuming

there is one peak and one nadir per year, this sample size is sufficient to provide > 80% power to detect seasonal variation if peak hormone levels are at least 15% above nadir levels. Thus, seasonal variation, if it exits, is of very limited amplitude.

45

ASSOCIATION OF TESTOSTERONE DEFICIENCY AND SYMPTOMS WITH HYPERTENSION: A SUBSET ANALYSIS FROM THE HYPOGONADISM IN MALES (HIM) STUDY

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Introduction and objectives: Hypogonadism (Total testosterone [TT] <300 ng/dL) is associated with signs and symptoms that include erectile dysfunction, bone mineral density loss, and decreased quality of life. The goal of this study was to estimate the prevalence of hypogonadism in men presenting to primary care practices, focusing on those with a history of hypertension. Methods: Men recruited at 95 primary care centers were eligible to participate if they were aged ≥45 years and provided written informed consent (regardless of reason for visit). Eligible patients underwent testosterone assessment (TT, free testosterone [FT] and bioavailable testosterone [BAT]) by a blood draw obtained between 8 am and noon. Patients were asked about common symptoms of hypogonadism including sexual dysfunction, fatigue/weakness, and mood changes. Prevalence rates were estimated for the total sample and the subset with a history of hypertension. Results: of 2162 men enrolled with evaluable TT, 1226 had a history of hypertension. The crude prevalence of hypogonadism (based on TT) for all patients was 38.7%. Similar trends were observed with FT and BAT. Of these, 80 were receiving testosterone treatment. For the patients not receiving testosterone, 756 (36.3%) had TT <300 ng/dL; in those with a history of hypertensive patients, the relative risk of hypogonadism was 1.84 (95% confidence interval (C1), 1.53–2.2). Decreased ability/frequency to perform sexually was the most common symptom of hypogonadism among these men, reported by 55.8% ($P = 0.014$ vs eugonadal group). Conclusions: Men presenting to the primary care office with a history of hypertension have a higher crude prevalence of hypogonadism than men without a history of hypertension. The decrease in ability/frequency to perform sexually was statistically significant in Hypogonadal versus eugonadal hypertensive men. Based on these results, it may be prudent to obtain blood testosterone concentration in hypertensive men.

46

AGE-ASSOCIATED PREVALENCE OF HYPOGONADISM AND RELATED SYMPTOMS: DATA FROM THE HYPOGONADISM IN MALES (HIM) STUDY

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Introduction and objective: The goal of this study was to estimate the prevalence rate of hypogonadism (total testosterone [TT] <300 ng/dL) among men in a primary care practice setting. Methods: Men aged ≥45 years presenting themselves for care at any one of 95 primary care centers and who provided written informed consent were eligible for the study. Patients underwent testosterone assessment (TT, free testosterone [FT], and bioavailable testosterone [BAT]) by a single morning blood draw (8:00 AM-noon). Patients were queried for common symptoms of hypogonadism, including sexual dysfunction, fatigue/weakness, and mood changes. Prevalence rates were estimated for the total sample and age subsets. Results: of 2162 patients enrolled in the study with evaluable testosterone levels, 836 were Hypogonadal. The crude prevalence rate of hypogonadism was 38.7% (based on TT). Similar trends wee observed with FT and BAT. The table presents the prevalence rates of hypogonadism in patients grouped by age. More Hypogonadal patients ≤64 years reported decreased ability/frequency to perform sexually ($P < 0.001$), decreased sexual desire/libido ($P < 0.001$), and decreased physical exhaustion/lacking vitality than did eugonadal men of the same age range ($P = 0.015$). More Hypogonadal men ≥65 years experienced a decline in general sense of well-being than did eugonadal men aged ≥65 years ($P = 0.005$). Conclusion: In patients presenting to primary care offices, approximately 40% of men age ≥45 had low TT concentrations. Younger (age 45–64 y) Hypogonadal men experienced a greater number of symptoms than older (age ≥65 y) Hypogonadal men compared with eugonadal men.

Age (y)	Hypogonadal Prevalence Rate, n (%)	Eugonadal Prevalence Rate, n (%)
45–64	537 (36.9)	915 (63.0)
≥65	299 (42.1)	411 (57.9)

47

CALCULATION OF BIOAVAILABLE AND FREE TESTOSTERONE IN MEN; A COMPARISON OF FIVE PUBLISHED ALGORITHMS

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Estimating serum levels of free or bioavailable testosterone by calculation is cheap and appears to be uncomplicated. We compared the results obtained using five published algorithms, applied to samples from 399 men aged 40 to 80 years. Levels of testosterone and SHBG had been measured, levels of bioavailable (bioT) and free testosterone (FT) were calculated using the algorithms described by Sodergard et al. (bioTS and FTS), Vermeulen et al. (bioTV and FTV), Emadi-Konjin et al. (bioTE), Morris et al. (bioTM) and Ly et al. (FTL). Mean bioavailable testosterone was highest for bioTS (10.4 nmol/l), followed by bioTV (7.99 nmol/l), bioTM (5.39 nmol/l) and bioTE (3.87 nmol/l). Mean free testosterone was highest for FTS (0.41 nmol/l), followed by FTV (0.35 nmol/l) and FTL (0.29 nmol/l). For bioavailable testosterone levels Pearson's coefficient of correlation was highest for the association between bioTS and bioTV ($r = 0.98$) and lowest between bioTM and bioTE ($r = 0.66$). FTL was significantly associated with both FTS ($r = 0.96$) and FTV ($r = 0.88$). Pearson's coefficient of correlation for the association between FTL and bioTM almost reached 1.0. The fractional deviation from the mean bioavalable testosterone level ranged from –35 to +92% for bioTM versus bioTE, 43 to 122% for bioTS versus bioTE, 12 to 40% for bioTS versus bioTV, 43 to 75% for bioTS versus bioTM, 31 to 94% for bioTV versus bioTE and 3 to 64% for bioTV versus bioTM, 21 to 69% for FTS versus FTL and –6.9 to 60% for FTV versus FTL. BioTM, bioTE, bioTV and FTL were all significantly associated with SHBG levels. We conclude that algorithms to calculate bioavailable or free testosterone cannot be transferred to other users unless a careful re-validation in the local setting is performed. Without prior validation, one risks over- or under-estimating free or bioavailable testosterone and potentially introduces confounding by SHBG.

48

EXPERIMENTAL STUDY OF CHANGES IN MICROSCOPIC CHARACTERISTICS AND ABILITY OF SECRETING TESTOSTERONE OF AGED SD RAT LEYDIG CELLS

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Objective: To research the changes in microscopic characteristics and ability of secreting testosterone between aged

SD rat Leydig cells and young SD rats Leydig cells. Methods: The total and free testosterone levels of serum both young aged rats were examined; The changes in microscopic characteristics between young and aged rat Leydig cells were observed under microscope and electron microscope; The testosterone secreted by both group cultured Leydig cells were examined. Results: A significant difference was found in both total and free testosterone level between young and old rats ($P < 0.05$); Aged SD rats Leydig cells were observed smaller in volume and more deeply stained than young ones; The secreting ability of aged rats Leydig cells was found decline than that of young rats Leydig cells with or without HCG and Forskolin stimulation ($P < 0.05$). Conclusion: The secreting ability of aged SD rats Leydig cells is worse than that of young rats Leydig cells both in vivo and vitro, and the reason is the system of synthesizing testosterone is arrested.

49

VARIABILITY IN DAY-TO-DAY CONCENTRATION OF TOTAL TESTOSTERONE IN MEN

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We previously confirmed in a single 24-hour study in 18 men the marked diurnal variation in total testosterone and demonstrated that this is maintained into the 7th decade. To assess day-to-day variability we have measured total serum testosterone concentration in 8 normal men between 0900h and 1000h and between 1600h and 1700h on the same day on at least 6 days within a 1-month period. We also compared total testosterone concentrations 23.5 hours apart in 18 normal men. In one subject, testosterone was measured between 0900h and 1000h at random time intervals on 22 occasions over an 8-year period. All sera were frozen at -20° after separation and measured batchwise in a DPC Coat-a Count immunoassay, each subject's samples being assayed in the same batch. Between-batch precision between 6.0 nmol/l and 29.0 nmol/l was <10%. The mean difference in peak to nadir concentrations in AM samples was 30% (12.6%–48%) and in PM samples was 37.4% (15.3%–49%). A difference of up to 33% was observed in samples taken 23.5h apart. In one subject concentrations ranged from 13.5 nmol/l to 35 nmol/l over an 8-year period with no correlation between testosterone and age. Our results suggest that in normal men serum total testosterone concentration in samples collected under strict conditions may show a marked day-to-day variability both in the morning and the evening. As some of these subjects displayed concentrations below the lower limit of normal on one day while being well into the reference range on another day, it may be prudent to measure total testosterone (along with other relevant hormones) on more than one occasion when results initially might indicate hypogonadism.

50

BODY FAT MASS, WAIST CIRCUMFERENCE AND WAIST-TO-HIP-RATIO IN HYPOGONADAL MEN: RESPONSE TO SUBSTITUTION WITH TESTOSTERONE ENANTHATE (TE) AND LONG-ACTING TESTOSTERONE UNDECANOATE (TU, NEBIDO)

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In an open-label, randomized, prospective clinical trial we investigated body fat mass, lean body mass, and waist-to-hip-ratio in 40 hypogonadal men during 90 weeks of androgen replacement therapy. For the first 30 weeks (main study), patients were randomly assigned to receive either standard treatment with 250 mg testosterone enanthate (TE) i.m. every 3 weeks ($n = 20$) or a novel testosterone formulation, i.e. 1000 mg testosterone undecanoate (TU, Nebido) i.m. every 6 to 9 weeks ($n = 20$). After the comparative study, a one-arm follow-up study started, and all men received 1000 mg TU every 12 weeks. The former TE patients switched to TU every 12 weeks starting with an interval of 8 weeks between the first two TU injections, allowing testosterone levels to achieve steady state conditions more quickly. We assessed testosterone levels every 3 weeks, waist-to-hip-ratio at baseline, 12, 30, 54, and 90 weeks, body fat mass and lean body mass using dual-energy X-ray absorptiometry at baseline, 54, and 90 weeks of therapy. Substitution with testosterone led to significantly higher trough levels of serum testosterone in men receiving TU than TE (16.3 ± 5.7 nmol/l versus 8.3 ± 4.0 nmol/l) after 30 weeks of therapy. T substitution yielded a decrease in total body fat mass (TE: $30.3 \pm 9.8\%$ at baseline to $27.6 \pm 8.3\%$ after 90 weeks, TU: $31.3 \pm 6.5\%$ to $27.9 \pm 7.1\%$), waist circumference (TE: 96.8 ± 19.7 cm at baseline to 97.6 ± 14.0 cm after 90 weeks, TU: 101.9 ± 13.6 cm to 96.2 ± 11.3 cm), and waist-to-hip-ratio (TE: 0.91 ± 0.08 at baseline to 0.89 ± 0.06 after 90 weeks, TU: 0.95 ± 0.09 to 0.91 ± 0.07). Lean body mass remained unchanged. We conclude that testosterone therapy is closely associated with reduction of body fat mass, waist circumference, and waist-to-hip-ratio, showing that i.m. administration of TU every 12 weeks offers a safe and efficient treatment modality for testosterone therapy in male hypogonadism.

51

STABLE TESTOSTERONE LEVELS ACHIEVED WITH SUBCUTANEOUS TESTOSTERONE INJECTIONS

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Objectives: The preferred technique of androgen replacement has been intramuscular (IM) testosterone, but wide variations in testosterone levels are often seen. Subcutaneous (SC) testosterone injection is a novel approach; however, its physiological effects are unclear. We therefore investigated the sustainability of stable testosterone levels using SC therapy. Patients and methods: Between May and September 2005, we conducted a small pilot study involving 10 male patients with symptomatic late-onset hypogonadism. Every patient had been stable on TE 200 mg IM for >1 year. Patients were instructed to self-inject with testosterone enanthate (TE) 100 mg SC (DELATESTRYL 200 mg/cc, Theramed Corp, Canada) into the anterior abdomen once weekly. Some patients were down-titrated to 50 mg based on their total testosterone (T) at 4 weeks. Informed consent was obtained as SC testosterone administration is not officially approved by Health Canada. T levels were measured before and 24 hours after injection during weeks 1, 2, 3, and 4, and 96 hours after injection in week 6 and 8. At week 12, PSA, CBC, and T levels were measured however; the week 12 data are still being collected. Results: Prior to initiation of SC therapy, T was 19.14 ± 3.48 nmol/l, hemoglobin 15.8 ± 1.3 g/dl, hematocrit 0.47 ± 0.02, and PSA 1.05 ± 0.65 ng/ml. During the first 4 weeks, there was a steady increase in pre-injection T from 19.14 ± 3.48 to 23.89 ± 9.15 nmol/l ($p = 0.1$). However, after 8 weeks the post-injection T (25.77 ± 7.67 nmol/l) remained similar to that of week 1 (27.46 ± 12.91 nmol/l). Patients tolerated this therapy with no adverse effects. Conclusions: A once-week SC injection of 50–100 mg of TE appears to achieve sustainable and stable levels of physiological T. This technique offers fewer physician visits and the use of smaller quantity of medication, thus lower costs. However, the long term clinical and physiological effects of this therapy need further evaluation.

52

SAFETY AND ABSORPTION OF 1% TESTOSTERONE GEL (TESTIM®) WHEN APPLIED TO DIFFERING APPLICATION SITES

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Introduction: Testosterone (T) gel had become the treatment of choice for hypogonadism. One such gel (Testim®) has shown superior blood levels; however, its application data is limited to the upper arms/shoulders. The objective of this study was to compare the serum T level achieved when the gel was applied to three different application sites. Safety was assessed across specific safety parameters including prostate specific antigen (PSA) and hemoglobin (Hb). Methods: Twenty-one hypogonadal men (total T <10 nmol/l) applied Testim® for one month, in rotation to onto three sites: arm and shoulder (A), lateral chest and abdomen (C), and calves (L). One-half tube of gel was applied to each side of the body each day. Parameters measured at baseline and after each month: total testosterone (TT), calculated free testosterone (CFT, using Sodergard equation), PSA, and Hb. Results: The mean age of the subjects was 56.9 years. TT increased from a baseline of 227 ng/dL 548 (A), 440 (C), and 398 (L). CFT increased from a baseline of 193 pmol\L to 535 (A), 406 (C), and 380 (L). Baseline and post-treatment PSA values remained consistent (1.1 vs. 1.05, respectively) and mean Hb increased from a baseline of 14.66 to 15.49 g/dL. In terms of Hb, 4 subjects experienced a correction in anemia (i.e., Hb levels increased from below 13.5 to greater than 13.5 g/dL). Conclusions: Mid-normal levels of TT and CFT were achieved whether Testim® was applied to the arm and shoulder or chest and abdomen. Low-normal levels were achieved when applied to the calves. The safety of Testim® remained consistent regardless of application site. Data from this study support standard PSA and Hb follow-up recommendations (monitor at 3, 6, and 12 months) and the dosing of Testim® across multiple application sites.

53

SERUM FREE TESTOSTERONE IS THE MOST PREDICTIVE MARKER FOR AGING MALES' SYMPTOMS IN HEALTHY JAPANESE MALES

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Objective: The relationship between serum androgen levels and symptoms of aging males in the general population is still controversial. The aim of this study was to clarify whether the serum testosterone levels correlate with aging males' symptoms in healthy Japanese males. Subjects and methods: for this study, 125 males aged from 20 to 77 years who visited to hospitals for health checkups were recruited after giving informed consent. Aging males' symptoms were evaluated by Heinemann's Aging Males' Symptoms rating scale (AMS). Serum total and free testosterone (T) were measured using commercially available radioimmunoassay kits. Calculated bioavailable testosterone (CBT) was estimated by total T, albumin and sex hormone-binding globulin (SHBG). This study was approved by the institutional review board of our hospital. Results: Serum free T ($r = -0.422$, $p < 0.01$) and CBT ($r = -0.228$, $p < 0.05$) were significantly correlated with aging. No correlation was detected between total T and age ($r = -0.131$). The total AMS score was significantly correlated with serum free T ($r = -0.264$, $P < 0.01$) and CBT ($r = -0.215$, $p < 0.05$). In particular, serum free T was significantly correlated with the somatic subscale ($r = -0.254$, $p < 0.05$) and sexual subscale ($r = -0.279$, $p < 0.01$) of AMS. No correlation was shown between total T and the total AMS score and any subscale. The psychological subscale of AMS did not have a correlation with any androgen. Of men in their 50s, 23.1% had a low free T level (less than 8.5 pg/ml) and symptoms of aging males (37 or more in AMS rating scale), as did 36.8% in their 60s and 50% in their 70s. Conclusions: Serum free T is suspected to be the most appropriate value to predict aging males' symptoms in the general population. Serum free T might be useful to decide the indication for androgen replacement treatment in aging males.

54

EFFECTS OF HYPOTENSIVE THERAPY ON PITUITARY-TESTICULAR AXIS IN MEN WITH ARTERIAL HYPERTENSION

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Objective: The aim of this study was to determine the level of the insulin, main steroids and pituitary hormones in men with arterial hypertension (AH) treated with hypotensive therapy. Background: The role of hyperinsulinemia in pathogenesis of low androgens level in PADAM syndrome, which contributes in the diseases accompanied with insulin resistance (AH, diabetes mellitus) are under discussion Methods: We studied 91 previously untreated hypertensive male patients. Serum free testosterone (FT), dehydroepiandrosterone-sulfate (DHEAS), estradiol, cortisol, LH, FSH, prolactine were measured both before and after 30 days of therapy with calcium channel blockers (CCB), ACE inhibitors or β-blockers (BB). Results: After 30 days of treatment men who were treated with CCB or ACE inhibitors demonstrated a reduced insulin level, increased concentrations of serum FT and DHEAS. The BB treatment was associated with an increase in serum fasting insulin, decrease in main androgens. The levels of gonadotropic hormone, estradiol and cortisol were unaffected after the treatment, and their concentrations were the same in all groups of patients. Hormonal changes in treated male patients correlated with the presents of AH positive family history. Conclusions. These findings evidence that insulin acts as a physiological regulator of androgens metabolism and lowers circulating FT and DHEAS concentrations in men with AH. The CCB and ACE inhibitors induced reduction in circulating insulin was also accompanied by rising of androgen level. The BB treatment resulted in opposite changes.

55

LONG-ACTING INTRAMUSCULAR TESTOSTERONE UNDECANOATE (TU, NEBIDO®) IN TREATMENT OF AGING MALES WITH HYPOGONADISM

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Introduction: Over the last five years testosterone therapy in men became more safer, efficient and 'patient-friendly' with the introduction of new testosterone preparations. Testosterone gels are in widespread use, but they are associated with the risk of interpersonal transfer and need daily application. Recently, injectable testosterone undecanoate (TU, Nebido®) has become available in Europe. Long term data of aging males with long-acting testosterone esters are limited. Specific risk data on the prostate and haematological parameters are not available. Patients and methods: 33 hypogonadal men with primary, secondary or late-onset hypogonadism between the age 45–79 years (mean: 59.2 ± 7.3 years; $x \pm SE$) were treated with TU. 29 patients were pre-treated,17 patients with T-gel, 12 patients with intramuscular testosterone enanthate. Two patients assessed tolerability of intramuscular injection as "very poor" and dropped out. 21 patients received TU for more than 6 months. Patients were assessed before the first injection and in 6-weekly intervals over the treatment period of 30 weeks. At each consultation, sexual function, mood, quality

of life and skin reactions were monitored. Hematology, clinical chemistry, Total Testosterone, SHBG, Dihydrotestosterone (DHT), Estradiol, LH, FSH and prostate specific antigen (PSA) were measured prior the next injection. Results: Testosterone levels increased from 2.6 ng/ml ($\pm$1.09; x $\pm$ SE) [range 2.3–6.00 ng/ml] at baseline to 3.9 ng/ml ($\pm$1.35; x $\pm$ SE) after 6 weeks and to 4.73 ng/ml ($\pm$1.85; x $\pm$ SE) after 30 weeks of treatment. DHT levels increased from 286 pg/ml ($\pm$141; x $\pm$ SE) [range 310–1463 pg/ml] to 905 pg/ml ($\pm$299; x $\pm$ SE). PSA levels fluctuated minimally in the normal range. In two patients the length between two injections could be prolonged from 12 to 14 weeks. Conclusion: Treatment with TU is a safe and efficacious option for the hypogonadal aging male. Regular clinical and laboratory control is mandatory.

56

INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN3 (IGFBP-3), NOT INSULIN-LIKE GROWTH FACTOR-1 (IGF-1), IS RELATED WITH METABOLIC SYNDROME IN ELDERLY MEN

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Objective: Low plasma levels of Insulin-like growth factor-1 (IGF-1) have been implicated in the pathogenesis of arthero-sclerosis and cardiovascular disease. The bioavailability of IGF-I is regulated by with IGF binding protein-3 (IGFBP-3). We report the relative contributions of IGF-1, IGFBP-3 to the occurrence of the metabolic syndrome. Design and methods: From March 2000 to February 2005, 1756 men after age of 50 who coming at health promotion center, were included in this study. We measured plasma IGF-1, IGFBP-3, high density lipoprotein (HDL), triglyceride (TG), fasting blood sugar (FBS), and Weight circumference(WC), blood pressure (BP). The metabolic syndrome was defined according to the National Cholesterol Education Program Adult Panel III (NCEP-ATP III). Results: For the highest quartile groups of IGFBP-3, WC, TG, FBS, BP were higher and HDL were lower than the lowest quartile group of IGFBP-3 ($P < 0.05$). Logistic regression, adjusted for age, smoking, alcohol intake, physical activity, demonstrated a 2.49-fold increased odds ratio for the metabolic syndrome in the highest IGFBP-3 quartile group (odds ratio 2.49 [1.78–3.49], $P = 0.00$). For IGF-1 quartile group, we had no significant results. Conclu-sions: The high IGFBP-3 results in a increase in an individual's risk of having the metabolic syndrome in elderly men. We suggested that Increased circulating IGFBP-3 increase the risk of cardiovascular disease in elderly men.

57

THE EFFICIENCY AND SAFETY OF HUMAN CHORIONIC GONADOTROPIN (HCG) THERAPY ON LOW URINARY TRACT SYMPTOMS (LUTS) IN MEN WITH BENIGN PROSTATIC HYPERPLASIA (BPH)

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Aim: To study the influence and safety of HCG therapy on LUTS in men with BPH. Materials and methods: We studied 23 men with secondary late-onset hypogonadism (LOH) and BPH without symptoms of infravesical obstruction, who were receiving HCG (1000–2000 IU i.m. 1 time in 4 days) during 12 weeks. We examined International Prostate Symptom Score (IPSS), total PSA level, transrectal ultrasound of the prostate before the treatment, on the 12 and 24 week after the treatment. During the study all the patients were divided into two groups by age: 1 group – mean age 55,5 [45;59] years ($n = 9$) and 2 group mean age 67 [60;72] years ($n = 14$). Statistical analysis was made using Friedman and Wilcoxon tests. Results: The most frequent complaints were of weak urinary stream, frequent urination and frequently awakening at night to urinate. All the patients reported the improvement in urination: increase in stream strength and decrease in quantity of urinations, including night awakening, this effect maintained after the end of the treatment. We revealed significant decrease in IPSS-score in both groups (1 group from 10.8 to 2.1, $p < 0.001$; 2 group from 13.8 to 6.9, $p < 0.001$), while there was no significant difference in prostate volume ($p > 0.05$) and US-structure or PSA-level ($p > 0.05$) before and after the treatment. Conclusion: HCG has a positive effect on LUTS in men with BPH and secondary LOH. Testosterone level restoring has a positive effect on urinary bladder wall.

58

THE SAFETY OF HUMAN CHORIONIC GONADOTROPIN (HCG) THERAPY OF LATE ONSET HYPOGONADISM (LOH) ON THYROID GLAND FUNCTION

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HCG consists of two polypeptide chains – alpha and beta subunits. Alpha-subunit is the same for HCG and hypotha-lamic hormones (LH, FSH, TSH), beta-subunit is specific for each hormone. It is supposed, that HCG can effect thyroid gland function (1). Aim: To study the safety of HCG therapy of LOH on thyroid gland function. Materials and methods: We studied 20 men with secondary LOH, mean age 52 [45; 55] years. Including criteria were: clinical symptoms of LOH, AMS-score >26, decrease in total testosterone level and decrease in LH level. We examined total testosterone, TSH, free T4 levels before and 1.5 years after the treatment. 18 patients received HCG 1000–2000 IU i.m. 1 time in 4 days, 2 patients received HCG 5000 IU i.m. 1 time in a week. Statistical analysis was made using Wilcoxon test. Results: There was a significant increase in total testosterone level in all patients up to the normal range (from 6.74 to 21.88, $p < 0001$). There was no significant difference in TSH ($p = 0.60$), free T4 levels ($p = 0.55$) before and after the treatment. Conclusion: HCG therapy in men with secondary LOH significantly increases total testosterone level. HCG therapy is safe in relation to thyroid gland function.

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59

AGING MALE SYMPTOMS AND SERUM TESTOSTERONE LEVELS IN HEALTHY JAPANESE MIDDLE-AGED MEN

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Objective: To evaluate the usefulness of the ADAM ques-tionnaire and aging males' symptoms' (AMS) rating scale for Japanese middle-aged men, we analyzed the results of these tests. We also examined the range of serum testosterone levels of these individuals. Material and methods: Answers to these tests were obtained from 202 healthy Japanese men (from 46 to 64 years old) who visited for medical check-up in January 2005. Serum total (TT) and free (FT) testosterone were also examined, and calculated free (cFT) and bioavalable (cBT) testosterone levels were obtained. Result: According to the ADAM questionnaire, 155 (76.7%) men were judged to be PADAM. Mean AMS total, psychological, somatovegetative, and sexual symptom scores were 30.0, 7.6, 13.2, and 9.2, respectively. Although 39 (19.7%) men had more than moderate symptoms on AMS total score, 131 (66.2%) men complained of more than moderate sexual symptoms.

In contrast, the testosterone levels of these people were not always low. Mean values of TT, FT, cFT, and cBT were 5.4 ng/ml, 14.8 pg/ml, 115.4 pg/ml, and 290.7 ng/dl, respectively. None of these testosterone levels was significantly correlated with age or AMS score. Only sexual symptom score among AMS subscales was significantly correlated with age. Conclusion: The borderlines for the ADAM questionnaire and AMS rating scale appear too stringent for healthy Japanese middle-aged men. The sexual activity of Japanese middle-aged men appears less than that of Westerners. Criteria of these tests in Japanese middle-aged men, especially sexual function, should be changed.

60

MEASURES OF SALIVARY TESTOSTERONE AND THEIR RELATIONSHIP WITH 'THE AGING MALE SYMPTOMS' SCALE (AMS) IN ELDERLY MEN

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Objectives: Androgen production declines with age in men. Circulating testosterone (T) is comprised of several different forms. On the other hand, salivary testosterone (Sa-T) exists mainly in an unbound state and its measurement is noninvasive. The decrease of serum testosterone is thought to increase complaints such as depressive mood, erectile dysfunction. The aim of the study was to determine the relationship between the serum testosterone fractions and salivary testosterone. Moreover, we studied the relationship of male climacteric symptoms as assessed by 'the aging male symptoms' scale (AMS). Patients and methods: The study included fifty-two patients who visited our clinic. The age range was 30–73 (mean 54.5 ± 9.7, median 57). Saliva and serum samples were collected in the morning. Bioavailable T (Bio-T) is determined by separation of the SHBG bound steroid. Levels of non-SHBG-bound T, free T and Sa-T were measured by LC-MS/MS. AMS questionnaire is consisted of 17 item-scale. Three factors of symptoms are identified: psychological, somatovegetative and sexual factors. The study was analyzed each symptom factors. Results: The range of serum free-T, Bio-T, and Total T were 4.2 to 17.9 pg/ml (mean 9.7 ± 3.2, median 9.75), 305.8 to 1703.0 pg/ml (mean 850.0 ± 365, median 782.0), and 1.68 to 18.8 ng/ml (mean 4.74 ± 2.71, median 0.42), respectively. The range of Sa-T was 23.1 to 107.0 pg/ml (mean 50.1 ± 21.4, median 45.1). There was significantly correlation between free-T and Sa-T ($r = 0.709$, $p < 0.01$), Bio-T and Sa-T ($r = 0.591$, $p < 0.01$). However, there was no correlation between total T and Sa-T ($r = 0.188$, $p = 0.18$). On the other hand, there was no significant association of Sa-T with psychological ($r = 0.84$), somatovegetative ($r = 0.14$) and sexual factors ($r = -0.16$) of the AMS scores. Conclusion: Free-T and Bio-T correlated with Sa-T. None of the three AMS factors significantly correlated with Sa-T.

61

INTRAVENOUS ADMINISTRATION OF EMBRYONIC PLURIPOTENT PROGENITOR CELLS (EPPC) RESTORES THE REPRODUCTIVE FUNCTION IN OLD STERILE RAT MALES

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Introduction: We examined the concentration of sex hormones in blood, qualitative and quantitative characteristics of spermatogenesis with estimation of a reproductive success to study a possible restoration of reproductive function in old sterile rat males with the help of intravenous EPPC administration in mega doses. Methods: EPPC were administrated into old males, which fertility was fixed through the placing to them of 5 different sexually mature females for a month and repeated this procedure within 3 months. In blood plasma we determined the content of testosterone and biological active luteinizing hormone (LH), in testis–activity of 3-beta-hydroxy-Δ5 steroiddehydrogenase (SDG). We determined the weight parameters of testis, appendages and counted the amount of spermatozoons in epidermis. We placed females to the males in 6 months to study the reproductive success. Results: Intravenous administration of EPPC in mega doses facilitates the restoration of reproductive function in old sterile males about this fact testifies an increased content of testosterone and LH in blood, increased SDG activity, spermatogenesis activation, formation in testis of Leidig cell adenomas and healthy posterity in females. Conclusions: Intravenous administration of EPPC in mega doses restores the sexual function and reproductive success in old sterile males.

62

THE EFFECT OF TESTOSTERONE ON POTASSIUM CHANNELS IN HUMAN CORPORAL SMOOTH MUSCLE CELLS

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Purpose: The role of testosterone in penile erection remains unclear. Recent studies have showed that testosterone administration induced a significant increase in arterial inflow to cavernous arteries and a significant improvement in erectile function. Although the data support the role of testosterone in the preservation of libido and nocturnal erectile function, its effect on reflexogenic erection is less clear. To define the cellular mechanism of testosterone in regulating the tone of the corpus cavernosum, we investigate the effect of testosterone on potassium channels activity in human corporal smooth muscle cells. Materials and methods: The conventional patch-clamp technique was applied to short-term cultured smooth muscle cells of human corpus cavernosum. Single-channel currents (cell-attached configuration and inside-out patches) and whole-cell currents were recorded. Results: The application of testosterone (200 nM) significantly increased whole cell $K+$ currents by $443.4 \pm 83.4\%$ (at $+60$mV; $n = 11$), and this effect was abolished by TEA (1mM), blocker of calcium-activated potassium (BKCa) channels. Consistent with the whole cell results, testosterone increased the single channel activity. With pretreatment of cells with vardenafil (1nM), testosterone produced a markedly stimulating effect on BKCa channels activity. Testosterone also, induced glibenclamide-sensitive currents at -60mV. ATP-sensitive $K+$ channel (KATP channels) could be activated in the same patch by testosterone and pinacidil. Testosterone increased cGMP levels in corporal smooth muscle cells in a concentration-dependent fashion but showed no effect on cAMP. These finding indicated that testosterone induced relaxation of corporal smooth muscle predominantly by activation of potassium channels. Conclusions: The present study is the first to report the testosterone induced the activation of potassium channel (BKCa and KATP channels) in human corporal smooth muscle cells and this response was mediated by accumulation of cyclic GMP. The activation of potassium channel by testosterone can be one of mechanisms in regulating the tone of the corpus cavernosum.

63

IS THERE A RELATIONSHIP BETWEEN CIRCULATING ANDROGEN LEVELS AND UROLOGIC SYMPTOMS? RESULTS FROM THE BOSTON AREA COMMUNITY HEALTH (BACH) SURVEY

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Introduction and objective: Pelvic floor muscles are androgen sensitive yet there is little data from adequately powered, population-based surveys on the association of hormone levels and urologic symptoms in men. Accordingly, we determined whether there is a relationship between circulating androgen levels and urological symptoms in men, using data from the Boston Area Community Health (BACH) Survey. Methods: BACH used a multi-stage stratified cluster approach to randomly sample 5506 adults aged 30–79 from the city of Boston. Anthropometric measures, lifestyle and psychosocial factors, comorbidities and urological symptoms were obtained during an interviewer administered questionnaire. Serum testosterone (T), sex hormone binding globulin (SHBG) and dehydroepiandrosterone sulfate (DHEAS) levels were measured in 1899 men (538 African Americans, 651 Hispanic, 710 Caucasian). Bioavailable T (BT) was calculated from total T and SHBG concentrations. Urological symptoms included IPSS/AUA symptom score, lower urinary tract symptoms (LUTS) (AUA 8 or higher) and self reported weekly urinary incontinence (UI), dribble and hesitancy. Regression was used to investigate the relationships between androgen levels and urological symptoms. Results: Accounting for survey weights, 19% of men reported LUTS; 6% UI; 9% dribble and 4% hesitancy. Before covariate adjustment, T, BT and DHEAS values were inversely related to AUA score; SHBG values and AUA scores were positively correlated ($p < 0.0001$ for each). After controlling for age, physical and mental health scores, depression, socioeconomic status and urinary tract infections, T, BT, SHBG and DHEAS were not significant predictors of AUA score ($p = 0.83$, 0.43, 0.13, 0.23). No hormones were associated with LUTS, UI, dribble or hesitancy after covariate adjustment. Conclusions: Testosterone levels are not statistically significant predictors of urologic symptoms in men after controlling for age, health and lifestyle factors. These data are consistent with the notion that pathophysiology of LUTS in men is complex and includes factors other than circulating testosterone levels.

64

CIRCADIAN RHYTHM OF SEX HORMONE LEVELS IN PADAM

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Background: The levels of serum testosterone in healthy men are declining with aging. Circadian rhythm of serum testosterone level tends to be less prominent with aging, too. It has not yet been known whether patients with PADAM maintain circadian rhythm of serum testosterone level. Purpose: The purpose of this study was to demonstrate the circadian rhythm in sex hormone levels of the patients with PADAM. Subjects and methods: The study included 19 men with PADAM symptoms who had been untreated before. We evaluated their symptoms with Aging Males' Symptoms Scale (AMS). Serum levels of LH, Testosterone, free testosterone and cortisol were examined at 6:00, 12:00, 18:00 and 21:00. Results: The median age of patients was 53. The median value of AMS was 58. The median ranges (Max-Min) of lutenizing hormone, total testosterone, free testosterone, cortisol were 2.8 IU/l (min-max: 0.8–7.5), 114.9 ng/dl (34.3–263.8), 4.2 pg/ml (1.1–13.2), and 13.1 mg/dl (6.1–23.4), respectively. Age was significantly correlated with the AUC and the range of LH and with the AUC of serum free testosterone. Total score of AMS was not associated with hormonal parameters. Conclusion: The levels of LH and free testosterone were correlated with aging in PADAM patients. This age-related decrease in circadian rhythm of testosterone level was not significantly associated with the severity of PADAM symptoms.

65

THE EFFICACY OF 'AGING MALE QUESTIONNAIRE' (KUMAMOTO) FOR JAPANESE PADAM PATIENTS

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Background: Aging males' symptoms scale (AMS) is used widely for the diagnosis and evaluation of PADAM symptoms. Kumamoto in Japan developed 'Aging Male Questionnaire' (AMQ) that consists of 18 questions related to psychological, somatic and sexual symptoms of PADAM based on a community-based QOL study. Purpose: We evaluated the efficacy of AMQ for Japanese PADAM patients by comparing with that of AMS. Subjects and Methods: Sixty-one patients who visited the PADAM clinic of Teikyo University Hospital from November, 2003 to September, 2004 were included in this study. Patients' symptoms were evaluated by AMS and AMQ. Factor analysis was conducted in the individual questions of AMS and AMQ. Results: Total score of AMS and AMQ was correlated significantly in individual patients. In AMS, significant independence of three subgroup domains: psychological, somatic and sexual symptom, was not achieved. Questions of AMQ were successfully classified into three independent domains. Conclusion: Considerable mutual dependence of questions in AMS might make it difficult to analyze patients' symptoms in subgroup domains. Thus the total sum of AMS was considered as suitable for the evaluation of the severity of symptoms. For the analysis of subgroup domains, AMQ might be more useful for Japanese patients.

66

THE EFFECTS OF TESTOSTERONE REPLACEMENT THERAPY ON LATE ONSET HYPOGONADISM: TESTOSTERONE UNDECANOATE VERSUS TRANSDERMAL TESTOSTERONE GEL

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Objective: Testosterone undecanoate (Andriol®) and transdermal testosterone gel (Testogel®) have been widely prescribed to increase serum testosterone level and improve symptoms of PADAM. We evaluated the changes of serum testosterone level and effects of these medicines. Method: The patents with symptoms of PADAM and who had an initial serum testosterone level of < 2.55 ng/mL were enrolled. Andriol (Group I) or Testogel (Group II) were randomly offered. In group I, 2 tablets of Andriol were given at first. In case of the follow-up serum testosterone level was not increased enough, the dosages were gradually increased upto 6 tablets. In group II all the patient rubbed one pack (5 gm) daily without dosage adjustment. Statistical analysis was done to identifying the correlation among age, baseline/final follow-up aging male's symptoms (AMS) scale of Heinemann, baseline/peak/final testosterone level. Results: Mean ages of Group I ($n = 111$) and Group II ($n = 51$) were 53.4 ± 14.5 and 55.2 ± 11.9, respectively ($p > 0.05$). The initial and final testosterone levels were not significantly different between groups. However, the peak level during the treatment was significantly higher in Group II ($p < 0.05$). The maximal increment (peak – initial level) was also significantly higher in Group II. The final serum levels were not significantly different after adjustment of dosages in Group I. The AMS scales were significantly decreased in both groups. Although initial AMS scores were not different between groups, the final

score of Group II were significantly lower than Group I. Conclusion: Both Andriol and Testogel improved serum testosterone level and symptom score of late onset hypogonadism. for a final conclusion, large prospective studies are required to assess the precise role of testosterone replacement therapy.

67

TREATMENT FOR CLIMACTERIC DISORDER IN MALE PATIENTS

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Objectives: To describe our therapeutic experience for climacteric disorder in male patients in the Kobe University School of Medicine. Recently, the number of patients visiting urology departments with the main complaint being these symptoms is increasing. In our hospital, the outpatient department for male climacteric disorder has been open since May 2005. Methods: A total of 43 male patients (age; 38–68, mean; 54) who visited the outpatient departments of Kobe University School of Medicine were investigated. The symptoms of male climacteric disorder were measured by the aging males symptoms (AMS) rating scale made by Heinemann et al. Depression was measured by the Self-Rating Depression Scale (SDS), and blood androgen by free testosterone (FT). First line treatment was drug treatment such as antidepressants and herbal medicine, and counseling. Hormone replacement therapy (testosterone enantate depo 250 mg/2–3 weeks) was given to the patients for whom first line therapy did not work. Results: Twenty-four of forty-three (56%) patients were classed as psychological patients because of their hospital experience in the department of psychosomatic medicine and SDS measurements. In twenty-three of thirty-three (70%) patients who could be measured after first line therapy, the symptoms of male climacteric disorder improved. In these patients, the mean FT was 8.5 ± 2.4 pg/ml. Hormone replacement treatment was given to six patients with PSA < 2.5 for whom the first line therapy did not work. In five of these patients, the symptoms of male climacteric disorder improved and blood androgen increased. The mean FT in these six patients was 6.6 ± 1.1 pg/ml before hormone replacement. Conclusion: Some patients showed the symptoms of male climacteric disorder without any blood androgen decrease. Other treatments are considered to be important and we experienced cases for whom hormone replacement therapy worked effectively, although the number was small. Further studies with more cases are required.

68

METABOLIC SYNDROME (MS): DIAGNOSIS AND ASSOCIATED DISORDERS IN THE MIDDLE AGE AND AGING MALE: OUR EXPERIENCE IN LUANDA, ANGOLA

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The MS is based upon several metabolic changes due to insulin resistance. The aims of this study is to determine the frequency of diagnosis criteria variables, and other associated disorders in men with MS. We studied all diabetic men aged 40 yr or more that consulted in Endocrinology at CIMECA during 28 months; 71/203 (31%) were identified with MS according WHO rules. Personal history and physical examination were completed with lab tests and ECG. Patients were divided in three groups according to age: A) 41–50 yr ($n = 30$), B) 51–60 yr ($n = 28$) and C) +60 yr ($n = 13$). Chi-square, Yates and student Tstatistics tests were used where indicated. Severe obesity were lower in group C, but no significant differences were observed in body mass index. Frequency of high triglycerides and central obesity were lower in group C (p lower than 0.05), whereas hypertension increases with age. Low HDLc tended to be more frequent in older men but no statistics differences were observed. Mean values of HDLc, triglycerides (Tg) and total cholesterol (Ct) were lower in the older group; Tg also were lower in group B than in group A. Common associated disorders were high Ct, high LDLc and high uric acid, as well as abnormal ECG and cardiovascular abnormalities in thorax X-rays. Age groups differences were demonstrated only for ECG and thorax X-rays with incresing prevalence with age. In summary, these results suggest that MS characteristics, in this population, could change during aging of the human male, mainly lipids profile.

69

CHANGES IN EXPRESSION PATTERN OF LH SUBUNIT GENES IN RAT TESTIS AND EPIDIDYMIS DURING THE AGING PROCESS

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Background: Recently we found that LH subunits were expressed in the rat testis, epididymis and vas deferens. Sperms in seminiferous tubule and epididymis also expressed the LH genes. Objective: In this study, we investigated the age-related changes in the expression of LH subunit genes in pituitary, testis, epididymis, and vas deferens of the Sprague Dawley rats. Materials and Methods: Semi-quantitative RT-PCRs and LH radioimmunoassay, and immunohistochemistries were employed to measure the transcripts for LH subunit genes and their translated products. Results: The expression of alpha subunit gene in the testis and epididymis were significantly decreased in the aged (20 months) compared to those in the adult (6 months) rats. The expression of beta subunit gene in the testis and pituitary were not changed while the expression in epididymis was increased in the aged (20 months) compared to those in the adult (6 months) rats. Imunohistochemical study showed considerable decrements of sperm numbers and LH-immunoreactivity in seminiferous tubules and epididymis from aged rats, Conclusion: Our findings suggest that the aging process might induce changes in the transcriptional activities of LH genes in testis, epididymis and sperm in the rat.

70

TESTICULAR HYPERTHERMIA AFFECTS LEYDIG CELL STEROIDOGENESIS IN OLD RAT

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Purpose: The aim of this study was to investigate the effects of testicular hyperthermia on the Leydig cell steroidogenic capacity in old rat. Materials and Methods: Twenty Sprague-Dawley young rats (12 weeks) and 20 old rats (20 months) were divided into control and hot bath groups in each. The hot bath group was assigned to the hot bat h (41–43°) for 10 minutes and then exposed to the room temperature(23–24°) for 3 minutes. Each procedure was repeated twice daily and 3 days a week for 4 weeks. Each animal was sacrificed after 4 weeks of treatment. Serum testosterone, serum luteinizing hormone and intratesticular testosterone were measured. The expressions of StAR and P450c17 were examined by Western blot. Testis was processed for histology with H&E stain and electron microscopy. Results: Serum testosterone and luteinizing hormone levels were not significantly changed after hot bath in both young and old rats compared to the control. However, intratesticular testosterone level showed significant decrease in the old hot bath group compared to the old control group($p = 0.01$). And the expressions of StAR and P450c17 decreased in the old hot bath group compared to the control group($p < 0.05$). Conclusions: The testicular hyperthermia affected the steroidogenic capacity in old rats. These results imply that the negative effect of frequent hot bath on testicular steroidogenesis needs to be considered in aging men.

71

SERUM BIOAVAILABLE TESTOSTERONE: ASSAYED OR CALCULATED?

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Introduction: In human, testosterone (T) is tightly bound to Sex Hormone Binding Globulin (SHBG) and weakly to albumin. The free T-fraction accounts for only 1 to 2% of total testosterone (T) serum concentration. Bio-available testosterone (BT) refers to non-SHBG-bound T (including free and albumin-bound T) and is considered to be the biologically active fraction. Methods: Several methods are described to determine BT, either by mathematical derivation calculated from T and SHBG concentrations, or by direct methods as equilibrium dialysis, or steady state gel filtration, or after precipitation of SHBG-bound T with ammonium sulphate. During the development of a new matricial testosterone patch (Testopatch®), serum SHBG and BT concentrations have been measured (n = 548) by radio immunoassay and TR-FIA (time resolved fluoro-immunoassay) respectively. Results: Important variations in SHBG levels were found (from 0.5 to 15 mg/mL). When the BT/T ratio was expressed as a function of SHBG level, the ratio decreased from 90% to 10%. Between calculated BT (CBT) and assayed BT (ABT), a good correlation R = 0.972 was found but mean ratio CBT/ABT (m) was equal to 1.58. To overcome this pitfall, the association constant of testosterone for Albumin of 3.6×104 in Vermeulen's equation has been reset to 1.1×109; then: R = 0.979 and m = 1.02. Thus, the association constants for albumin and/or SHBG, in Vermeulen's equation (Vermeulen A, JCEM 1999 84 3666–72) have to be adjusted to match assayed BT. At least 30% of the results of the CBT, differed from assayed ABT of more than 20% at least, in spite of good correlation coefficients (0.98) between ABT and CBT. Conclusions: In addition to the determination of serum testosterone and PSA levels, measurement of SHBG should be a prerequisite before initiating testosterone treatment, since SHBG concentration determine the amount of testosterone needed for hypogonadal men, to restore physiological testosterone level.

72

PHARMACOKINETIC STUDY OF A NEW TESTOSTERONE-IN-ADHESIVE MATRIX PATCH APPLIED EVERY TWO DAYS TO HYPOGONADAL MEN

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Introduction: Pharmacokinetic testosterone (T) time profile after single 48 hours application of 3 different strengths of a new matrix testosterone patch (30, 45, 60 mg for a size of 2×30, 2×45, 2×60 cm^2) and dose proportionality, have been assessed. Methods: This open study was a single dose, 3-period, crossover trial with a randomized treatment sequence in twenty four hypogonadal men. Each period consisted in a single 48-hr application of 2 patches on the lower back, separated by a 5-day washout. Blood samples were collected over the 48-hr patch application, and 1 and 3 hrs after patch removal. T concentrations were determined by a GC/MS method, developed and validated at CEPHAC. Dose proportionality was assessed on baseline corrected dose normalized parameters for AUC(0 48), Cav and Cmax. Owing to the high inter-individual variability, the range for concluding linearity was set to [0.7–1.43]. Results: From a baseline value of 1.3 ng/mL, T concentrations rose during the first 9hrs following patch application. The mean T concentration was maintained above 3 ng/mL for 42, 44 and 45 hours with the 2×30 cm^2, 2×45 cm^2 and 2×60 cm^2 doses, respectively. Mean Cav were 3.39 ng/mL, 4.03 ng/mL and 4.58 ng/mL, respectively. At the end of patch application (48 h), mean testosterone concentrations were 2.98, 3.90 and 4.19 ng/mL respectively; AUC(0 48), Cav and Cmax were dose dependent with 90% confidence intervals of point estimates for 2×30 vs 2×45, 2×30 vs 2×60 and 2×45 vs 2×60 cm^2 mean ratios within the (0.70 1.43) interval. Conclusion: A plateau of T concentration was obtained 9 hrs after patch application; then, mean T concentrations were sustained over 3 ng/mL until the end of the 48-hr patch exposure. A dose linearity has been demonstrated between the 3 different patch sizes (30 cm^2, 45 cm^2 and 60 cm^2).

73

THE EFFICIENCY OF HUMAN CHORIONIC GONADOTROPIN (HCG) THERAPY ON SECONDARY LATE-ONSET HYPOGONADISM (LOH) AND ITS INFLUENCE ON THE PROSTATE

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Aim: To study the efficiency of HCG therapy on secondary LOH and its influence on the prostate. Material and methods: We studied 55 men with secondary LOH, who were treated with HCG (1000–2000 IU i.m. 1 time in 4 days) for 12 weeks. We examined clinical signs of androgen deficiency (AMS), total testosterone, LH and total PSA level, transrectal ultrasound of the prostate before the treatment, on the 12 and 24 week. During the study all the patients were divided into two groups by age: 1 group – mean age 52 [45;55] years (n = 34) and 2 group mean age 66 [60;72] years (n = 21). Statistical analysis was made using Friedman and Wilcoxon test. Results: We revealed the improvement in laboratory and clinical symptoms of androgen deficiency in men with secondary LOH (the positive effect of HCG therapy): increase in total testosterone level (1 group from 9.8 to 18.0 nmol/l, $p < 0.001$; 2 group from 8.5 to 15.0 nmol/l, $p < 0.001$), decrease in AMS-score (1 group from 39.4 to 24.7, $p < 0.001$; 2 group from 46.5 to 27.7, $p < 0.001$). There were no pathological changes in transrectal ultrasound of the prostate, prostate volume ($p > 0.05$) or PSA-level ($p > 0.05$) after the treatment. Conclusion: HCG is an effective therapy of secondary LOH. Therapy with HCG has no negative effect on the prostate in men.

74

ESTIMATION OF PROLONGED ANDROGENTHERAPY SAFETY IN PATIENTS WITH FEMALE-MALE TRANSSEXUALISM

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Background: Observation of the prolonged androgentherapy safety in patients with female-male type of transsexualism being treated with prolonged androgenic testosterone ether drugs. Materials and Methods: Fifty-two patients with female-male transsexualism were included into the trial. They were administered substitution hormonotherapy (Sustanon-250, Omnadren-250) once per 1–3 weeks with individually adjusted doses. To evaluate cardio-vascular system safety we applied instrumental examination algorithm, which included ECG and Holter monitoring. To evaluate hepatic function in all patients, blood biochemical analysis, including AST and ALT estimation was performed. Venous blood glucose level and immunoreactive insulin level were defined to evaluate carbohydrate metabolism. Besides, 13 patients underwent echocardiography with ultrasonic multifunctional scanner VIVID-7 GI US with multifrequency transducer (3.5 MHz), with main hemodynamic values estimation and evaluation of blood lipids (levels of total cholesterin, triglycerides, HDL, LDL). Statistical analysis were performed with non-parametric methods usage. Results: Median age was 28 [23;34] years, therapy length was 4 [2;7] years. Cardio-vascular status of all patients was appropriate to the age standard in the socially

adapted age population. There were no significant arrhythmias and segment ST fluctuations. Carbohydrate metabolism was normal in all examined patients glucose and immunoreactive insulin levels (n = 9) were in normal values limits. None of patients had increased levels of AST or ALT. Eleven of 12 examined patients total cholesterin and LDL were 5.4 [5.3;5.8] and 3,7 [3.6;3.9] mmol\l, respectively and exceeded levels of normal values, whilst levels of HDL and triglyceride were 1.30 [0.99;1.47] and 1.3 [0.8;1.5] mmol\l, respectively, and were in levels of normal values. Found data are unable to indicate hyperlipidemic effect of androgentherapy, as increased levels of totall cholesterin and LDL were not significant ($p >> 0.05$). Conclusions: Results showed safety of the extended androgentherapy regarding cardio-vascular system, carbohydrate metabolism and impact on hepatic function.

75

RELATIONSHIP BETWEEN BONE MINERAL DENSITY AND TESTOSTERONE IN KOREAN MEN WITH PURE KLINEFELTER'S SYNDROME

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Objectives: A reduced bone mineral density (BMD) is frequently observed in hypogonadal males. Therefore we evaluated the relationship between BMD and testosterone in patients with pure Klinefelter's syndrome. Methods: Total 46 patients with pure Klinefelter's syndrome were enrolled in this study. Serum testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were measured by radioimmunoassay. BMD at lumbar spine (L2–4), femoral neck and Ward's triangle were determined by dual-energy X-ray absorptiometry Results: In our study that is 11 with normal serum testosterone (>3.46 ng/ml) and 35 with a low serum testosterone (<3.46 ng/ml). A statistically significant linear correlation was found between BMD of spine and baseline testosterone ($r^2 = 0.251$, $p = 0.02$), Z-score of Ward's triangle and baseline testosterone ($r^2 = 0.129$, $p = 0.034$) in low testosterone group with Klinefelter's syndrome. Conclusions: We found relationship between lower BMD and testosterone in patients with pure Klinefelter's syndrome. These findings suggest that low testosterone levels cause inadequate bone development and low BMD in pure Klinefelter's syndrome. Therefore, testosterone replacement may be necessary to prevent bone mineral deficiency and future risk of fractures in pure Klinefelter's syndrome with low serum testosterone level. Key Words: Klinefelter's syndrome, bone mineral density, testosterone.

76

HOW LONG DO ELDERLY MEN ADMINISTER TESTOSTERONE SUBSTITUTION?

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Testosterone (T) serum levels in men decline gradually with age. It is generally accepted that substitution should be recommended when symptoms of T deficiency in combination with low endogenous T level are present. We attempted to obtain information on the duration of T therapy in our elderly patients. In the database of our laboratory we identified 4463 results of hormone analysis of 2770 patients between Jan. 1997 and Dec. 2003. Among them, 378 patients older than 50 years with T levels <3.0 ng/ml were identified. 84 of the patients were seen in the department, in 49 of them T substitution was prescribed. Of these, 16 patients were prescribed T-enanthat, 12 patients T patch, 17 patients T gel, and 4 patients T undecanoate. 14 patients did not present for a second time. 3 patients did not use T, 13 patients administered T up to twelve months, 19 more than twelve months. PSA levels remained low in these patients. The duration of treatment did not depend on the T levels at the time of examination, it was not related to the age or significantly related to the mode of application. The longest treatment continuitation was observed in patients using T-gel. Also in the literature authors prescribing T gel were convinced that T-gel is best accepted by their patients. In general, most investigators agree with short-term safety of T substitution, but also potential risks are mentioned. The main concern of T supplementation in the elderly man is that about prostatic diseases. At time the risk appears to be moderate.

77

IMPROVEMENT OF QOL EVALUATED BY SF-36 IN PADAM PATIENTS RECEIVING ANDROGEN REPLACEMENT THERAPY

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Objectives: This study was designed to investigate the time course of change in scores of the SF-36 (a comprehensive health-related QOL scale) in PADAM patients who received hormone replacement therapy. Subjects: The subjects of this study were 36 males who visited the PADAM Clinic of the Kansai Medical University Hospital to receive androgen replacement therapy between September 2002 and May 2005. The mean age of the subjects was 57.7 years (range: 37–75 years). The total testosterone and free testosterone (RIA) levels at the first visit were 290.8 ng/dl (110–517 ng/dl) and 6.9 pg/ml (3.3–11.6 pg/ml), respectively. Methods: Each subject received intramuscular injections of testosterone enanthate (250 mg/dose) at intervals of 3–4 weeks. The SF-36 scores before the treatment, at the end of treatment, and 3 months after the end of treatment for 6 months were recorded and analyzed after conversion based on mean scores for Japanese individuals. Results: When the SF-36 scores at the end of treatment were compared with those before treatment, significant differences were noted in 2 summary scores and 2 subscales. However, no scores differed significantly between evaluation at the end of treatment and that 3 months later. When evaluation before treatment was compared with that 3 months after the end of treatment, significant differences were noted in the summary score and 2 sub-scales for physical health ($P < 0.05$), and the summary score and 5 sub-scales for mental health ($p < 0.01$). Discussion: These findings suggest that the improvement in QOL achieved by hormone replacement therapy is maintained even after this therapy is discontinued.

78

HUMAN CHORIONIC GONADOTROPIN (HCG) IN LATE-ONSET HYPOGONADISM (LOH) TREATMENT

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Aim: To prove the possibility of using Human Chorionic Gonadotropin (HCG) in late-onset hypogonadism (LOH) treatment. Materials and methods: 150 patients in the age of 50–70 with diagnosis of LOH were included in this study. Inclusion criteria were clinical signs of androgen deficiency, AMS scale >26, serum total testosterone <12 nmol/l. The levels of LH and FSH were measured. All patients were undergoing a HCG stimulation test (2000 U i.m., 3 injections every other day) under total testosterone level control, because all the patients had no increase in LH level. Statistical analysis was made using Student's t-test. All data are presented as mean (mean root square deviation). Results: The results of patients' examination (n = 150) before stimulation test were the following: LH = 3.8(1.1) U/l (normal range 2.5–10.0); FSH = 4.2(0.8) U/l (normal range

1.2–5.0); total testosterone 9.8(3.2) nmol/l. HCG significantly ($p < 0.01$) stimulated secretion of total testosterone up to 17.2(3.8) nmol/l (normal range 13–33). Low serum testosterone was not accompanied by high gonadotropin levels, which is the evidence of secondary cause of androgen deficiency. Moreover, 20% of patients had low serum total testosterone levels together with even low LH levels. HCG stimulation therapy increased the level of testosterone, which also indicate the secondary origin of LOH. Conclusion: Our data demonstrate a secondary cause of LOH. The positive results of HCG test allow to use HCG as one of the possible methods for LOH treatment.

79

DETERMINANTS OF SHBG IN HEALTHY ELDERLY MEN: A CROSS-SECTIONAL AND LONGITUDINAL STUDY

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Introduction: Ageing in men is accompanied by a progressive decline of total serum testosterone (T) levels and by a steeper decline of free (FT) and bioavailable T (bioT). Sex hormone binding globulin (SHBG) is known to increase with age. However, the factors responsible for the increase of SHBG with age are not fully understood. Methodology: A cross-sectional and longitudinal study (over 4 years) included a population of $n = 209$ elderly, healthy, community-dwelling men aged 71–86 yr (mean 75.2 yr) at inclusion. Hormonal and anthropometric data were evaluated. Results: Serum total T and Oestradiol (E2) were positively correlated with SHBG, after adjusting for age and BMI. Insulin, E2/T – reflecting aromatase activity-, IGF-1 (Insulin-like growth factor 1), IGFBP-3 (Insulin-like growth factor binding protein 3), body weight, body mass index (BMI), total body fat mass (FM), total body fat percentage and total lean mass (LM) were negatively correlated with SHBG ($p < 0.05 - p < 0.01$). After adjusting for age and BMI, E2/T and IGFBP-3 remained significantly negatively correlated with SHBG. There was no significant increase in SHBG between 1996 – 2000 in this group of elderly men (mean 45.6 vs 47.1 nmol/l, $p = 0.47$). The predictors of longitudinal changes in SHBG were FE2 and IGFBP-3 at baseline ($p < 0.05$). In linear regression analysis BMI emerged as an independent, negative determinant of SHBG in 1996 and 2000 and changes in BMI accounted for 9.73% of changes in SHBG. IGF-1 or IGFBP-3 were independent, negative determinants of SHBG both in 1996 and 2000. Conclusion: In ambulatory healthy elderly men BMI and changes in BMI were independent, negative determinants of (changes in) SHBG over a 4-year follow-up period. Moreover, IGF-1 or IGFBP-3 were found to be independent, negative determinants of SHBG, irrespective of body composition.

80

THE EFFECTIVENESS OF GLOWMIN, TESTOSTERONE OINTMENT FOR THE TREATMENT OF HYPOGONADAL MEN

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Purpose: The aim of the study was to evaluate, in hypogonadal men, the effectiveness of GLOWMIN (Daitou Pharmaceuticals, Yamanasi, Japan), Testosterone (T) ointment. Materials and Methods: Fifty hypogonadal men, average age, 55.5 years-old (34 to 81 years-old) with total T level < 2.7 ng/ml or free T level < 10.0 pg/ml at our PADAM clinic were included. They were assessed by AMS, SF-36 and IIEF. Blood samples were collected in AM and measured T and free T before and one hour after the treatment at 12 weeks. They received GLOWMIN, twice/day, on the scrotal skin (6 mg of T per day) for 12 weeks. Results: Their scores (mean $\pm$ SD) of mental domain, physical domain and sexual functional domain in AMS questionnaire before and after the treatment were 12.4 ± 4.8, 10.9 ± 5.0, 18.7 ± 4.9, 16.4 ± 5.1, and 14.5 ± 4.6, 13.1 ± 4.4 respectively and decreased significantly. Four (domains of Role-physical, Social functioning, Role emotional and Mental health) of eight domains in SF-36 QOL questionnaire, raised 7.4, 5.0, 8.1 and 3.2 points respectively, significantly after the treatment. Scores of full-IIEF and IIEF5 before and after the treatment were 38.5 ± 20.0, 42.1 ± 20.5 and 12.8 ± 7.8, 14.8 ± 7.5 respectively and rised significantly. Two (domains of erection and sexual satisfaction) of 5 domains in full-IIEF raised 2.3 and 0.8 points respectively, significantly. T (ng/ml) and free T (pg/ml) levels before and 1hour after the treatment raised 2.5 ± 1.1 to 5.5 ± 2.4 and 8.1 ± 4.3 to 13.3 ± 6.1 respectively, significantly. The side effects were not serious. Liver dysfunction or the elevation of PSA was not seen. Conclusion: GLOWMIN raised T and free T levels to within the normal range in hypogonadal men and effective against the symptoms associated with hypogonadism and was a safe and well tolerated. In Japan, GLOWMIN is considered a useful alternative for androgen replacement.

81

LONG-ACTING TESTOSTERONE ESTER INJECTION DOES NOT ALTER THE DIHYDROTESTOSTERONE LEVEL

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Objective: To evaluate the impact of long-acting testosterone injection on DHT level in serum in our clientele comprising 122 patients under long-acting testosterone ester injection i.m. Material & Methods: A retrospective analysis of 122 patients under long-acting testosterone ester injection i.m. Patients received injections according to therapy protocol on day 1 and week 6 and then three-monthly. Three patients with primarily elevated DHT level over 600 ng/l (DHT normal range: 40–575 ng/l, Architec, Abbott), Were intensively controlled. One took 5-alpha reductase inhibitor for prostate safety issue, the other two refused under signed consent. All patients underwent blood controls including also total testosterone, DHT and PSA in week 6 and week 18 and later on every three months under therapy. Results: Levels of total testosterone were within the normal physiological values in all subjects in the whole control intervals, between 4.8 ± 1.5 ng/ml (Architec Abbott). DHT level in these patients showed no alteration and varied between 86 and 511 ng/l (normal range: 40–575 ng/l, Architec Abbott). The two patients with primarily elevated DHT who signed consent forms refusing therapy with 5-alpha reductase inhibitor for prostate safety issue, surprisingly showed normalization of DHT level under therapy respectively. No alteration was found in prostate safety parameters so far Conclusion: In this therapy period (3–11 months) we did not notice any alteration in the DHT level exceeding the physiological threshold. The interesting data about the 2 patients with primarily elevated DHT and then normalizing under testosterone ester injection are subject to follow up. At the moment we are not able to clarify this interesting data. It may be hypothesized that in the complex regulation of hormonal balance involving feedback mechanisms, normalizing testosterone levels can lead to also improve the balance of its metabolites.

82

RESTORING OF VENO-OCCLUSION IN PATIENTS WITH METABOLIC SYNDROME/ HYPOGONADISM, PENILE VENOUS LEAKAGE AND ED BY LONG-ACTING TESTOSTERONE INJECTION

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Objective: Evaluating the impact of long-acting testosterone ester injection on the venous leakage/cavernosographic changes in patients with obesity and metabolic syndrome. Material & Methods: We selected 23 hypogonadal patients with severe ED, metabolic syndrome or DM who didn't respond neither to PDE-5 nor to 20 μg intracavernosal injection with Alprostadil. Testosterone level was in hypogonadal range 1.07–3.3 ng/ml (normal: 4–8.6 ng/ml). Penile cavernosography was performed and showed venous leakage in nine cases. Average age: 57 years (47–72). Two subjects with DM Type I, three with DM Type II. Other comorbidities: metabolic syndrome, hypertension. Cavernosography re-evaluation followed in these 9 patients after three months under long-acting testosterone ester 1.000 mg i.m., day one, week 6 and quarterly according to therapy protocol. Results: Lab control showed significant improvement to 4.3 $\pm$ 0.31 ng/ml 6 weeks after first injection. Three patients with DM Type 2 and/or metabolic syndrome, reported improved sexual function within 9 weeks under therapy. Another patient with severe hypogonadism and Peyrounie's disease reported similar results. A fifth patient whose primary testosterone level was at 1.07 ng/ml, reported remarkable but partial improvement in sexual desire and function after 5 months therapy. His control cavernosography showed no venous leakage in profound veins, but only slight leakage in superficial veins. In all patients sexual desire domain increased from 4 to 8, erectile function domain from 10 to 24. Remaining four patients with persistent leakage (therapy 3–7 months) still under follow-up. Conclusion: These results suggest that testosterone has positive impact on haemodynamic process and veno-occlusive properties in penile trabecular tissues. Disappearance of venous leakage in these five from nine cases is encouraging treatment with testosterone in hypogonadal ED-patients and subjects with metabolic syndrome, to improve penile resilience and veno-occlusive features. These clinical results are correlating with data of basic research in animals and humans.

83

IS LOW TESTOSTERONE A FLIGHT SAFETY RISK?

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The cost of human error and poor performance resulting in accidents and low productivity has major consequences for society in both human and economic terms. Nowhere is this impact more apparent than in the aviation industry. Medical assessments of worker fitness are commonplace today, however, little if any attention is paid to the effect of hormone balance on fitness and safety. The effects of hormone deficiency on safe perormance are ignored at our peril. The published medical literature increasingly links low serum testosterone to impaired cognitive performance such as short term memory loss and impaired visual and visuo-spacial ability, as well as behavioural changes that are key contributors to human error and performance problems. Studies of testosterone effects on cognitive behaviour are discussed and details of the limitations of serum assays of hormone levels outlined. The significance of assessing hormone status in evaluating the fitness of safety critical personnel is discussed with particular reference to flight safety and its broader implications for limiting cost to the community and enhancing corporate profitability.

Metabolic Disorders

84

METABOLIC SYNDROME, DEFINITION AND CLINICAL IMPLICATIONS

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The metabolic syndrome is a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, dyslipidemia (high triglycerides, low HDL, small dense LDL), high blood pressure and hypercoagulability. From a pathophysiological viewpoint, the metabolic syndrome is largely identical with the insulin resistance syndrome. The global prevalence is 25% in adults. In those with metabolic syndrome, type 2 diabetes risk is fivefold higher, heart attack and stroke morbidity is threefold higher and mortality is doubled compared with subjects without the metabolic syndrome. Up to 80% of the 200 million people with diabetes globally will die of cardiovascular disease. This puts metabolic syndrome and diabetes way ahead of HIV/ AIDS in morbidity and mortality terms yet the problem is not as well recognised. Earlier diagnosis is needed to stop this global threat. The new International Diabetes Federation (IDF) Worldwide Definition of the metabolic syndrome provides physicians with the tools to quickly identify those at risk and also to compare the impact across nations and ethnic groups.

85

THE POSSIBLE ROLE OF DHEA IN PREVENTION THE METABOLIC SYNDROME

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The prevalence of the metabolic syndrome, characterized by obesity, insulin resistance, dyslipidemia and hypertension, is steadily increasing in the countries of the Western hemisphere and strategies for prevention are urgently needed. Based on epidemiological data it has been suggested that the decline of adrenal DHEA secretion contributes to the development of the metabolic syndrome. Experiments in rodents support this view: animals treated with DHEA showed reduced visceral fat, improved insulin sensitivity, and a less atherogenic lipid profile. However, rodent adrenals do not physiologically produce DHEA and most reported studies employed highly supraphysiological DHEA doses. Despite this fact, DHEA is broadly marketed as an anti-aging drug in the United States, where it is freely available as a food supplement. In the last decade, an increasing numbers of clinical trials studied the effects of DHEA administration in humans, also assessing features of the metabolic syndrome. Two recent studies reported significant improvements in insulin sensitivity and fat mass, respectively. One reported a significant decrease in visceral fat and increased insulin sensitivity in 56 persons with a physiologic, age-related decline in circulating DHEA after receiving 50 mg DHEA daily for 6 months (1). In another randomized trial 28 hypoadrenal women were treated with 50 mg DHEA daily for 12 week, resulting in improved insulin sensitivity and improved serum lipid profiles (2). These two randomized trials suggest that DHEA replacement could have a potential impact on improving surrogate markers of the metabolic syndrome in certain subgroups of patients. However, the number of treated patients is far too low to draw any final conclusion on this topic and importantly, women with excess amounts of androgens suffer from polycystic-ovarysyndrome, which carries an increased risk of type 2 diabetes and arterial hypertension. Larger studies are needed to clarify the role of DHEA within the metabolic syndrome. 1) Villareal et al. JAMA 2004, 2) Dhatariya et al. Diabetes 2005.

86

CAN TESTOSTERONE PROTECT AGAINST CARDIOVASCULAR DISEASES?

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The adverse affection of arterial endothelium is a pivotal step in atherosclerosis and closely linked to the metabolic syndrome, a complex disorder with a high prevalence in developed countries and an increasing prevalence in less developed regions. Abdominal obesity, dyslipidemia, insulin resistance and other factors contribute to a symptomatology which progressively leads to the manifestation of diabetes mellitus type 2 and cardiovascular diseases. Cross-sectional and longitudinal epidemiological studies show that low testosterone levels are more common in patients with the metabolic syndrome, cardiovascular diseases, or diabetes type 2 than in the normal population. Studies in obese men reveal that these persons, whether in good or impaired general health, have lower testosterone levels than non-obese controls. Adiposity is closely related to the development of type 2 diabetes mellitus by fostering insulin resistance. In this clinical entity, high levels of insulin promote atherosclerotic events by adverse effects on the vessel wall and facilitating high cytokine concentrations. Interestingly, type 2 diabetes mellitus impairs the hypothalamic-pituitary axis, resulting in secondary hypogonadism. Several smaller intervention studies in patients with visceral obesity, cardiovascular diseases, and diabetes type 2 suggest that the normalisation of testosterone levels reduces fat mass and inflammatory markers, increases lean body mass and shows an overall improvement of the risk factors for the metabolic syndrome and cardiovascular diseases. Nevertheless, also adverse effects of testosterone on HDL-cholesterol concentrations and arterial vasoreactivity have been reported. It remains to be elucidated by larger long-term studies whether testosterone substitution can decrease the incidence of cardiovascular events.

87

SEX HORMONES AND METABOLIC SYNDROME – NEW DATA

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Sex hormone levels in men change during aging, while the health status gradually deteriorates, and chronic disease incidence, like type 2 diabetes and heart disease, increases. These changes in sex hormone levels may be associated with insulin sensitivity and the metabolic syndrome. In this talk, data regarding circulating sex hormone levels and insulin sensitivity and metabolic syndrome will be discussed. Data of the presenter indicate that increasing levels of testosterone, bioavailable as well as total testosterone, SHBG, and DHEAS are related to a lower prevalence of the metabolic syndrome. Higher testosterone is also related to increased insulin sensitivity. When the associations were further adjusted for insulin levels, they all attenuated, suggesting that the biological mechanism for the protective effect is (partly) trough insulin. However, an independent effect of sex hormones was still observed. It will also be discussed what can be expected of testosterone supplementation with regard to metabolic syndrome and insulin resistance.

88

EFFECTS OF TESTOSTERONE REPLACEMENT ON BODY COMPOSITION AND ITS POTENTIAL ROLE IN THE METABOLIC SYNDROME

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Male ageing is associated with a 1–2% annual decline in serum total testosterone levels beginning in the fourth decade. Parallel changes in body composition are seen with a doubling in percent body fat and a 20% decrease in fat free mass (FFM). As similar changes in body composition occur in hypogonadal young men and are reversible with testosterone therapy, it has been proposed that testosterone treatment of ageing men may (partially) reverse age-related sarcopaenia and prevent or reverse gains in fat mass (FM). Placebo-controlled trials of testosterone therapy report approximately 2–3 kg gains in FFM and more modest, approximately 1–2 kg, decreases in FM. Baseline testosterone levels, body composition (specifically FM), and the dose and duration of testosterone treatment all influence the magnitude of the observed responses. Treatment effects on regional fat distribution are less well studied but our data, and that of others, suggest that visceral fat may be preferentially lost, particularly in abdominally obese men. Visceral FM, reflected clinically by waist circumference, is an integral component of the cluster of adverse cardiovascular risk factors known as the metabolic syndrome. Strategies to decrease visceral FM are likely to improve insulin sensitivity and lipid profiles thereby favourably influencing the metabolic risk profile of the increasing number of aging men now exhibiting this phenotype. The increasing recognition of low serum testosterone levels in ageing men with the metabolic syndrome, and preliminary evidence suggesting beneficial effects of exogenous testosterone on key components of the metabolic syndrome, provide a rational basis for urgently needed interventional studies in men with established metabolic syndrome and in those with visceral obesity who are at particular risk of its development.

89

EPIDEMIOLOGY – TESTOSTERONE AND THE METABOLIC SYNDROME

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Low levels of testosterone, hypogonadism, have several common features with the metabolic syndrome such as disturbances in glucose metabolism and insulin secretion, overweight and abdominal fat distribution, dyslipidemia and hypertension. In the Tromsø Study, a population-based health survey, we found that testosterone levels were inversely associated with anthropometrical measurements. The lowest levels of total and free testosterone were found in men with the most pronounced central obesity, measured as waist circumference. Total testosterone was inversely associated with systolic blood pressure, and men with hypertension had lower levels of both total and free testosterone. Furthermore we found that men with diabetes had lower testosterone levels compared to men without a history of diabetes, and an inverse association between testosterone levels and percent glycosylated hemoglobin was found. Our results are in harmony with other epidemiological studies, which in addition have reported a positive relationship with HDL-cholesterol and a more favorable lipid profile. In a recent publication from Finland, low concentration of total testosterone and to a lesser extent free testosterone predicted the development of the metabolic syndrome in middle-aged men. It was also suggested, in another publication from the same Finnish group, that the metabolic syndrome itself could be a cause of low total and free testosterone levels and hypogonadism. Thus, lifestyle intervention in men with or at risk for the metabolic syndrome may prevent not only diabetes but also hypogonadism.

90

IS THERE A ROLE FOR TESTOSTERONE IN TYPE 2 DIABETES MELLITUS?

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Several epidemiological studies have demonstrated a higher prevalence of low serum testosterone levels in men with Type 2 Diabetes Mellitus. Recent work has shown that the majority have symptomatic hypogonadism and is not wholly attributed to a low level of sex hormone binding globulin. The major cause of morbidity and mortality in diabetic patients is coronary heart disease, which in turn is also associated with low levels of serum testosterone. Insulin resistance is a major risk factor for atherosclerosis. Diet, exercise, insulin sensitisers such as metformin and thiazolidenediones has been shown to improve vascular risk factors. Treatment of insulin resistance has also been shown to reduce carotid artery intima media thickness. Animal studies have demonstrated that testosterone enhances insulin sensitivity. There is a strong association between insulin resistance and visceral obesity. The potential mechanism by which testosterone acts as an insulin sensitiser will be discussed including the role of the adipocyte and the androgen receptor. We have recently completed a clinical trial on the effect of testosterone replacement therapy in hypogonadal men with type 2 diabetes. This study showed that insulin resistance, glycaemic control, waist-hip ratio and total cholesterol all significantly improved. Larger clinical trials will be required to investigate this further to determine whether or not TRT should be used routinely in hypogonadal diabetic men. For review: Androgens, insulin resistance and vascular disease in men. Kapoor D et al., Clin Endocrinol 2005,63;239–250.

91

PATHOGENESIS OF THE METABOLIC SYNDROME: THE INTERPLAY BETWEEN OBESITY AND ANDROGENS

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The metabolic syndrome is a common metabolic disorder which is closely linked to a generalized metabolic disorder called insulin resistance in which the normal actions of insulin are impaired. The syndrome is associated with increased risk for type 2 diabetes mellitus and cardiovascular disease, and its pathogenesis is multifactorial. Obesity and sedentary lifestyle are major components; however, recently it has been demonstrated that in males reduction of endogenous sex hormone levels is importantly linked to the occurrence of the metabolic syndrome. Interestingly, obesity and type 2 diabetes are frequently associated with low testosterone levels in men, and few studies have addressed the issue of the mechanism of this reduction. The decline of testosterone levels occurring in obese or diabetic men, as well as in older males, usually it is not accompanied by a compensatory rise in gonadotrophins; for this reason, in a rather simplistic way, the hypogonadism of diabetics has been often labeled as exclusively hypogonadotropic. However, there is a number of publications showing that this phenomenon has a combined etiology, central and peripheral. More important, in obese and insulin resistant subjects the frequently described hypogonadism may have a prevalent peripheral origin. It has been shown that aging is associated with a defective LH signal transduction in Leydig cells, and it has been demonstrated that in male obesity the defect in Leydig cells testosterone production correlates with insulin resistance and it is not the consequence of a chronic alteration in the hypothalamic-pituitary function. Finally, we found that in adult obese men, Leydig cell output is progressively reduced with increasing adiposity, and that adipocyte derived products, such as leptin, are likely to be involved. Since higher testosterone is associated with a higher insulin sensitivity and a reduced risk of the metabolic syndrome, it is conceivable to hypothesize that testosterone may exert a protective role in the development of the metabolic syndrome and insulin resistance in aging and obese men.

92

AN ENDOCRINE APPROACH TO ADDRESS THE CLUSTER OF RISK FACTORS ASSOCIATED WITH DEVELOPMENT OF TYPE II DIABETES IN MEN

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A cluster of riskfactors including hypertension, hyperlipidemia, glucos intolerande and insulin resistance are prevalently observed in men and women with increased accumulation of intra abdominal fat. This cluster of symptoms is commonly referred to as the metabolic syndrome although the interrelationship between the different perturbances has not been clarified. In men, these symptoms are also associated with a high prevalence of low testosterone levels and it has been suggested that low testosterone levels facilitate development of the metabolic syndrome, Furthermore, changes in testosterone levels influence insulin sensitivity and a decrease in testosterone levels decreases insulin sensitivity. It has also been suggested that testosterone therapy reverses some of the symptoms of the metabolic syndrome, including the abdominal fat accumulation. In a recently concluded randomized placebo-controlled double blind study with testosterone therapy to men with advanced stages of type 2 diabetes and abdominal obesity we could demonstrate significant metabolic changes and changes in body composition with a moderate increament (40%) in circulating testosterone levels. It was also evident that testosterone therapy also caused a decrease in liver steatosis, possibly indirectly achived by a decrease in abdominal fat mass.

93

AGING, OBESITY, METABOLIC SYNDROME AND DIABETES MELLITUS

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The rapid increase of the percentage of the elderly population, of the prevalence of obesity and of diabetes mellitus, are among the many problems with which will face this century. Aging, obesity and diabetes are interrelated. Aging is associated with a decrease of T levels, with an increase in BMI and body fat and with an increase of insulin resistance and diabetes. Obesity is accompanied by decreased T levels, with insulin resistance leading frequently to the metabolic syndrome and diabetes mellitus. NIDDM, the prevalence of which increases with age, is accompanied by decreased T levels, and generally, increased BMI. Whereas it could be expected that the correlation of T levels with insulin resistance might have as common denominator the increase in BMI, it is surprising that this correlation appears to persist after correction for BMI: higher T and SHBG levels in aging males have been reported to be independently associated with increased insulin sensitivity. Moreover low T levels appear to predict the development of NIDDM, even after correction for BMI or WHR. Hypoandrogenism has been considered an early marker of disturbances in insulin and glucose metabolism, possibly contributing to the development of the metabolic syndrome and NIDDM. Several hypotheses have been advanced to explain this BMI independent decrease in T levels, which appears to have both a hypothalamo-pituitary as well a peripheral, testicular origin. As cardiovascular disease is by far the most frequent cause of death in NIDDM, one may question the role of T in atherosclerosis and coronary ischemia, Contrary to a general belief, all data show that endogenous T is not atherogenic and, at least in cross-sectional studies, low T levels appear to be associated with increased prevalence of coronary stenosis. Several authors observed in short term studis (<3 months), that androgen treatment improves the ECG and has favorable clinical effects in patients with coronary ischemia. Moreover, T has favorable

effects of several risk factors of CAD, such as total cholesterol, LDL-C, fibrinogen, plasminogen-activatior type 1. It might be tempting therefore, to administer T to prevent or treat CAD in diabetics. Sofar only one small, non controlled, study reports beneficial effects of T treatment on HgBA1c (Boyanov 2003), but at present, no reliable, placebo controlled data are available which could justify T treatment of NIDDM, in the absence of evident, laboratory confirmed hypogonadism.

94

TESTOSTERONE DEFICIENCY AND DIABETES: A SUBSET ANALYSIS FROM THE HYPODONADISM IN MALES (HIM) STUDY

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Introduction and Objective: Hypogonadism (total testosterone [TT] < 300 ng/dL) may be associated with sexual dysfunction, bone mineral density loss, fatigue, and decreased quality of life, many of which occur in men with diabetes. The goal of this study was to estimate the prevalence rate of hypogonadism in men presenting to primary care practices (PCPs). A subset of those with a history of diabetes is also presented here. Methods: Men aged ≥45 years providing written informed consent at 95 PCPs had a single blood draw for assessment of TT, free testosterone (FT), and bioavailable testosterone (BAT) between 8 am and 12 pm to estimate prevalence rates. Patient characteristics including medical history and symptoms often associated with hypogonadism (sexual dysfunction, fatigue, and mood changes) were also collected. Results: of 2162 men enrolled with evaluable TT, 495 (23%) had a history of diabetes. The crude prevalence rate of hypogonadism for all enrolled men was 38.7%. Similar trends were observed with FT and BAT. Of the 836 men who were Hypogonadal, 80 were receiving testosterone. For the men not receiving testosterone, 756 (36.3%) had TT < 300 ng/dL. In patients with a history of diabetes not receiving testosterone (n = 237), the prevalence rate of hypogonadism was 50% and the relative risk of hypogonadism was 2.09 (95% confidence interval, 1.70–2.58). Diabetes was also a significant risk factor for hypogonadism. Decreased ability/frequency to perform sexually was the most common symptom of hypogonadism among these men, reported by 55.8% (P = 0.014 vs eugonadal). Conclusions: Men presenting to the primary care office with a history of diabetes have a higher prevalence of hypogonadism than non diabetic men. A decrease in ability/frequency to perform sexually was statistically significant in Hypogonadal versus eugonadal men with diabetes. Based on those results, it may be prudent to obtain blood testosterone concentrations in men with diabetes.

95

BODY COMPOSITION, LIPID METABOLIC PARAMETERS, AND VMAX IN HYPOGONADAL TYPE II DIABETIC MALE PATIENTS

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Introduction: Type II diabetes are well known disease in aging male patients along with change of body compositions. Hypogonadism also close related with metabolic syndrome in aging male, especially diabetic patients. We hypothesis diabetic male patients who are low testosterone may be changed their body composition and related metabolic parameters, and exercise tolerability. Method: We analysis 36 diabetic male patients about BMI, body composition by DXA, BP, triglyceride, total cholesterol, HDL-cholesterol, and Vmax. Result: Total fat mass are increased in diabetic hypogonadal man compare with diabetic eugonadal man (23.3% vs 21%), central fat is more prominent (8.57% vs 7.1%). TG levels are higher in hypogonadal male dibetic patients (193.3 mg/dl vs 160 mg/dl) but total cholesterol and HDL-cholesterol are not comparable. There is no significant difference lean body mass and Vmax in both hypogonadal and eugonadal diabetic male patients. Conclusion: Even hypogonadal diabetic male patients are increased the fat mass and related TG level. But Vmax, exercise tolerability, and lean body mass are independent testosterone level.

96

INFLUENCE OF INTRAUTERINE CONTRACEPTIVE DEVICES ON GLYCAEMIC CONTROL AND LIPOPROTEIN METABOLISM IN PERIMENOPAUSAL WOMEN WITH TYPE 1 DIABETES

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Objective: To evaluate the effects of modern IUDs (copper- and levonorgestrel-releasing) on glycaemic control and lipoprotein metabolism in perimenopausal women with Type 1 diabetes during 12 months. Study Design: A total of 44 women with Type 1 diabetes (mean age 44.3 years) were assigned to equally large groups, each composed of 22 women, in whom the copper- or levonorgestrel -releasing IUD was inserted. 20 women with Type 1 diabetes of comparable age not using some form of contraception constituted the control group. Evaluation was performed before and at 3, 6, 9 and 12 months after insertion using nonparametric statistical methods. Results: HbA1c levels, body mass index, 24-hour insulin requirements did not change significantly. Lipid profile was not impaired in women with HbA1 levels; 7% and was impared in women with HbA1 levels >7% (increased levels of total cholesterol, low-density lipoprotein cholesterol and decreased levels of high-density lipoprotein cholesterol were observed). Conclusion: IUD use (copper- and levonorgestrel-releasing) does not influence negatively glycaemic control and lipoprotein metabolism in perimenopausal women with Type 1 diabetes. Diabetes control have greater influence on lipid profile than composition of intrauterine contraceptive.

97

THE PREVALENCE OF HYPOGONADISM IN PATIENTS WITH DIABETES MELLITUS TYPE 2 (DMT2)

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Aim: To study prevalence of hypogonadism in men with DMT and the influence of hypogonadism on the compensation of DMT2. Materials and methods: We studied 82 men with DMT2. We examined sexual function (IIEF-5 score), clinical signs of hypogonadism, AMS-score, level of HbA1c, total testosterone and SHBG. Free testosterone level was calculated by method of Vermeulen. Statistical analysis was made using Mann-Whitney U-test, Fisher exact p-test and Speerman correlation test. Results: Median age of the patients was 53 [47;61] years. The prevalence of hypogonadism, based on total testosterone levels – was 68.3%, on free testosterone levels – 83%, and on AMS – 76.8%. There was no significant correlation between AMS-score and the levels of total and free testosterone ($r = -0.2$; $p = 0.07$ è $r = -0.15$; $p = 0.17$, respectively). Total testosterone level in patients with hypogonadism was 6.8 [4.3;8.6] nmol/l (n = 56), without hypogonadism – 15.0 [12.1;17.5] nmol/l (n = 26). The prevalence of hypogonadism, based on total, free testosterone levels and AMS-score increased with aging. Median diabetes duration among the patients was 5 [2;9] years, and there was a tendency to the increasing of hypogonadism prevalence with the increasing of diabetes duration. The compensation of

diabetes in patients with hypogonadism was statistically ($p = 0.04$) worse (HbA1c level 7.2% [6.4;9.1]), compare with patients without hypogonadism (HbA1c level 6.8% [6.4;7.0]). The prevalence of sexual disorders was significantly higher in patients with hypogonadism compare with patients without hypogonadism: decrease libido – 96% vs. 20% ($p < 0.001$) respectively, and erectile dysfunction 72.6% vs. 45% ($p = 0.03$) respectively. Conclusion: The prevalence of hypogonadism among patients with DMT2 is about 70%, increasing with age and the duration of diabetes. Hypogonadism negatively effects the compensation of diabetes and sexual function in men with DMT2. Testosterone level should be checked in every patient with DMT2.

98

EFFECTS OF ANDROGEN DEPRIVATION ON GLYCEMIC CONTROL AND ON BIOCHEMICAL CARDIOVASCULAR RISK FACTORS IN MEN WITH DIABETES

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Introduction and objective: Treatment of prostate cancer by androgen deprivation may result in loss of bone mass, changes in body composition, and a deterioration of arterial stiffness. The present study monitored the effects of administration of GnRH agonists to 29 men with insulin-dependent diabetes on glycemic control and on biochemical cardiovascular risk factors. Methods: 29 patients from a urology practice were included. All men had insulin-dependent DM prior to being diagnosed with prostate cancer. In a retrospective analysis, levels of fasting glucose, HbA1c, total cholesterol, HDL-C, LDL-C, triglycerides, fibrinogen, PAI-1, tPA, C-reactive protein as well as insulin requirement on 5 to 8 occasions (depending on survival time) over a period of up to 24 months were evaluated. Results: After 5 measurements (all 29 men), glycemic control worsened substantially with increases of serum glucose (from 143.2 to 187.3 mg/dL) requiring increases in insulin dosages (from 26.1 to 48.2 units). HbA1c levels rose from 6.3% to 9.3% indicating impaired glycemic control. All biochemical cardiovascular risk factors deteriorated: CRP from 1.3 to 2.3 mg/dL, total cholesterol from 252.0 to 322.3 mg/dL, HDL-C from 31.4 to 20.9 mg/dL, LDL-C from 184.5 to 229.1 mg/dL, triglycerides from 207.4 to 283.9 mg/dL, fibrinogen (data from $n = 13$) from 3.0 to 13.0 g/l, PAI-1 (data from $n = 6$) from 36.9 to 69.0 μ/l, and t-PA (data from $n = 6$) from 124.9 to 185.7%. Conclusion: In men with (insulin-dependent) diabetes, androgen deprivation may have profound negative effects on their glycemic control and aggravate the biochemical risk profile of cardiovascular disease to which diabetics are predisposed. This observation is in agreement with the emerging role of low levels of testosterone in the metabolic syndrome and insulin resistance.

Sexual Dysfunction

99

DEBATE: IS AGE BY ITSELF A RISK FACTOR FOR ERECTILE DYSFUNCTION?

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The classic work by Kinsey suggested that aging is a key risk factor for the development of male erectile dysfunction (ED). In his work the prevalence of ED increased with age from 0.1% at 20 years of age to 75% at 80 years of age. A half century later, the Massachusetts Male Aging Study (MMAS) showed the same trend. The prevalence of ED increased from 39% in men in their 40's to 67% for men in their 70's. Using the same questionnaire as used at the MMAS study, a cross-national epidemiological study was conducted in four different countries with varying cultures; Brazil, Italy, Japan and Malaysia. The results confirmed the findings of the MMAS with an age-dependent increase in the prevalence of ED in these different countries. Although all epidemiological studies have shown a strong correlation between ED and aging, there are many indications that diseases and risk factors associated with aging play a major role in the pathogenesis of ED. The prevalence of diseases and risk factors such as cardiovascular disease, diabetes, metabolic syndrome, hypogonadism, depression, smoking, obesity, sedentary lifestyle and others increases significantly with aging. However, each of these diseases and risk factors remains an independent risk factor for ED. Furthermore, ED is an early warning symptom of these important men's health conditions. Therefore, there is a sound rationale that screening for ED and associated risk factors should be an integral part of care of the aging male.

100

DEBATE: DOES TESTOSTERONE DECLINE PLAY A ROLE IN AGING MALE'S SEXUAL DYSFUNCTION?

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The answer is definitely 'YES'. Decline in testosterone plays a role in aging male's sexual dysfunction. The backgrounds for the answer are as follows; 1. Libido is essential to any kind of sexual activities, which is a first step in sexual contact. There is no objection to the fact that testosterone increases intensity of libido. 2. There has been increasing evidences that testosterone enhances the effect of 5-PDE inhibitors in the patients with hypogonadism. From the finding, testosterone may have effect, to some extent, on erectile function. 3. If general condition is well, aging male is more frequently interested in having sex. Testosterone supplementation in the aging male can improve general condition, producing numerous beneficial effects on whole body systems. Considering these two situations, testosterone contributes to sexuality of the aging male.

101

SEXUAL DYSFUNCTION AND LOW URINARY TRACT SYMPTOMS: MORE THAN JUST A COINCIDENCE?

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Erectile Dysfunction – defined as the consistent inability to obtain and maintain an erection of sufficient quality to enable satisfactory sexual relations – is a very prevalent disease in men aged over the 40s. The MMAS Study showed a prevalence of 52% of men aged from 40 to 70 with some degree of ED – two thirds of them with moderate or severe ED. Many studies around the world showed – and this is well known – that ED increases with age. Compared to the age 40, men aged 50 have a 2.1 higher odds ratio of having ED and this number increases to a fivefold increased odds ration in their 60s. Benign Prostatic Hyperplasia (BPH) is an histologic benign proliferation of the prostate often associated with increase of urinary symptoms. It is also associated with aging. In autopsies it was found in 8% of men aged 31 to 40 years, in 50% between 51 and 60, in 70% between 61 and 70 and in 90% in those over the 80s. Lower Urinary Tract Symptoms (LUTS) occur in micturition dysfunction and normally are: increase in urinary frequency, urgency, urge incontinence, dysuria, nocturia, decreased urine flow rates, hesitancy and incomplete emptying of the bladder. It is also related to aging. LUTS has been found to occur in 8–58% in men in the 60s and in 26–90% in men over 80s. The Omsted County Study

showed a decrease in the urinary peak flow by 2 mL/s each decade. The relationship between ED and LUTS have received increased attention recently because they coexist in the same age group, they are highly prevalent and affects significantly the quality of life. Many studies correlate the presence of LUTS and ED. The Krimpen study showed that LUTS has a strong relationship with the increasing risk of ED, in a dose response curve. They reported an increase of the relative risk of ED from 1.8 to 7.5 depending on the severity of LUTS. The Multinational Survey of the Aging Male (MSAM-7) provide a strong evidence of the relationship between age, LUTS severity and ED. They demonstrated that for each decade of age the percentage of men with moderate or severe LUTS increase and, for each LUTS severity groupe (mild, moderate, severe) the frequency of sexual activity decline and the prevalence of ED increase. But is aging the only common factor between these conditions? Are they only a coincidence? ED increases only because of the botheration of LUTS affect quality of life? Or are there biological and pathophysiological common factors leading to both conditions? There are some theories trying to elucidate this: 1) Nitric oxide synthase (NOS)/ Nitric oxide (NO) pathway It is based in the concept of the reduced production of NOS/NO in the pelvis – including the penis and prostate. It is known that decreased NO can promote ED. In the BPH the production of NOS/NO in the prostate is reduced (transition zone) when compared to normal prostate tissue. This could lead to reduction in the prostatic tone relaxation resulting in an altered neurogenic influence on voiding function: LUTS. Another support for the LUTS-ED:NOS/NO theory is the presence of Phosphodiesterase (PDE) type 5 – normally related to decrease of NO in the corpora cavernosa – and PDE 11A in the prostate evoking the possibility of the use of PDE 5 inhibitors in the treatment of LUTS. 2) Autonomic hyperactivity and Metabolic Syndrome effects on LUTS and ED This theory proposes that the Metabolic Syndrome – Increased BMI (obesity), hyperinsulinemia, increased age, decreased physical activity – increases the autonomic hyperactivity. This increased sympathetic tone increase BPH growth, develop LUTS and increase vasoconstrictive factors that results in ED. 3) Alpha 1 adrenoreceptors Alpha 1 adrenergic receptors are known to play an important role in mediating the tone of smooth muscle cells in various tissues, including in the lower urinary tract. The theory is that LUTS causes a high sympathetic status in the pelvis in this state leads to contraction of the prostatic smooth muscle via alpha adrenergic receptors. This state also promotes increase in the local norepinephrine levels which act in the on the alpha receptors in the penile cavernous smooth muscle inducing its contraction – as also vascular contraction – and promoting a flaccid state, maybe contributing to ED. 4) Rho-kinase Activation Rho-kinase promotes smooth muscle contraction and is probably involved in the mechanism of the flaccid state of the penis: in animal studies inhibition of Rho-kinase induces erections. LUTS may also be affected by the Rho-kinase action. In animal studies the Rho-kinase pathway maintain the force and the impaired relaxation of the bladder muscle. Men with LUTS have a chronic exposure to procontractile endothelins and alpha receptor agonists and this up-regulates the Rho-kinase pathway that increases the contraction and impairs the bladder muscle relaxation, contributing to LUTS. 5) Pelvic atherosclerosis This theory links ED and LUTS through the ischemia caused by diffuse artherosclerosis of prostate, penis and bladder, that leads to loss of smooth muscle cells and replacement of collagen deposition and fibrosis. 6) Sex Hormones Dihydrotestosterone (DHT) – which levels increase with aging – is predominantly produced peripherally from testosterone via 5 alpha reductase and has a high affinity for androgen receptors. Androgen receptors which are present in both the stroma and the epithelium of the prostate may play a role in their interaction. Age related changes in circulating hormone levels may contribute to the pathophysiology of BPH and ED. It is well known that there is an epidemiological relationship between ED and LUTS and that the huge negative impact that LUTS has in the quality of life causes ED. We now have some strong evidences of the biological link between ED and LUTS, but further studies are needed to stablish the exact correlation between these two very different but often together conditions.

102

SEXUALITY OF THE AGEING COUPLE

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Today ageing does not mean any more end of the sexual life. In 1988 Bretschneider and McCoy already reported that 82% of men and 64% of women more than 80 years old maintained at least some sexual activity, even if it did not involve vaginal penetration every time. Several recent surveys have confirmed that sex remains important for 73% of men and women 40 to 80 years old across the world, and that respectively 82% and 64% of such men and women had had intercourse during the preceding year. of course the frequency of sexual activity declines with age, more in women than in men, in single than in married, in diseased than in healthy persons, due to a decrease in sex drive, as well as a decrease in the number or available sexual partners, specially for women, and an increase in the prevalence of several Sexual Dysfunctions(SD): mainly Erectile Dysfunction (ED), lack of sexual desire, ejaculatory dysfunction and anorgasmia in men, and trouble with lubrication in women. The SD of an individual often results in SD in his/her partner. Especially ED damages the quality of the sexual life of the woman, as well as female inhibited sexual desire, lack of sexual pleasure, and even more dyspareunia impact male sexual function. Hence it is often the couple that is dysfunctional, and not just one individual. Ignoring the female aspects of a couple's SD like ED often leads to failure of a potentially effective pharmacotherapy. Even if he is not prepared to take care of the female or couple problems, any physician attending patients with male SD must inquire about the sexual attitudes and characteristics of the female partner, as well as the level of communication in the couple, in order to leave them in a sexologist's care if the marital interactions impede the success of the pharmacological therapy, while he does not feel able to take himself care of these aspects.

103

HORMONES AND SEXUAL FUNCTION

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Sexual function is influenced by many factors: physical, hormonal, medical, medication, and psychosocial. Sexual arousal is initiated when there is psychic and/or tactile stimulation. To translate this stimulation into a sexual response, both emotionally and physically, requires the availability of a a reasonably functional and balanced hormonal milieu. The hormones primarily (although not exclusively) involved either in a facilitory or inhibitory role, depending on blood concentrations, are: testosterone, estradiol, prolactin and thyroid hormones. In addition, diabetes mellitus may impact on sexual responsiveness by way of several mechanisms. Testosterone is largely a libido enhancing agent in both men and women although it does participate to some extent in formation of erections. Chronic hyperprolactinemia inhibits sexual responsiveness in both men and women while dopamine agonists (which suppress prolactin secretion) facilitate erections, and enhance sexual drive and the quality of orgasms. Less is known about the effect of estrogens on sexual function but evidence suggests it has an enhancing role. There is little information about thyroid hormones in sexual arousal. The hormonal mix, and hence extent of sexual arousal, will vary from individual to individual depending on state of health, medications and other substances being taken, as well as psychosocial factors.

104

THE MULTIDISCIPLINARY APPROACH TO THE MANAGEMENT OF ANDROPAUSAL SYMPTOMS IN THE AGEING MALE

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We will present a multidisciplinary model for the management of Andropausal symptoms in the ageing male. In recent years, clinicians have come to understand that 'andropause' is a complex phenomenon tied up in the process of ageing in a way we are just beginning to understand. The clinical symptom pattern may be due not only to organic, or hormonal elements but also to psychological causes, both primary and secondary. In addition, depression, thyroid abnormalities, and other endocrine abnormalities, medical conditions, and life situations may all contribute to the symptom complex and sexual and social interaction of the patient and his partner (where there is one). The West Island Sexual Dysfunction Clinic and Wellness Clinic has adopted a multidisciplinary approach to the ageing male patient. The clinic includes a urologist, an endocrinologist, a sexologist, a social worker, dietician and nurses. The therapeutic approach is individualised for each patient based on the assessments made by the team. The aim of this presentation is to outline the benefits of this on-site approach to the management of these patients. We will also review the benefit of combining psychosexual strategies with medical evaluation, and laboratory testing in the outcomes of management with hormone replacement therapy, PDE-5 inhibitors, or other ED treatments, as well as other therapeutic approaches either individually or in combination. ED by itself, often seen in these patients is a synergism of psychological and physical factors. From this perspective, successful sexual experiences would depend on both the psychological and physiological contributions. The medical model targets the organic component of ED and employs treatments such as various mechanical techniques or drugs to improve a functional erection. In contrast, the psychosexual strategies typically focus upon the contextual as well as behaviour aspects of the sexual experience to initiate a progressive return to normal sexual functioning. The multidisciplinary approach is more likely to evaluate all aspects of the sexual problem in a given individual and his environment. By combining disciplines and therapeutic approaches to the given case, one is more likely to improve sexual desire, arousal, penile tumescence and sexual satisfaction, and return the patient to a normal organic and psychological state. In this presentation we will focus on several clinical cases to illustrate the therapeutic benefits of our integrative approach to the evaluation and management of this population.

105

SEXUAL DYSFUNCTION AND UROLOGIC SURGERY

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Despite all advances in surgical techniques, erectile dysfunction still remains one the important long term complications following pelvic surgery. Meticulous prospective identification and preservation of neuro-vascular bundles during radical prostatectomy will allow preservation of erectile function in a number of men. Other factors such as age, pre-existing difficulty to obtain and maintain a normal erection and the number of bundles preserved at the time of surgery also play an important role in the ability to recover erection following surgery. To further improve the likelihood of recovery in patients where wide resection was dictated by the extent of tumor, sural nerve graft is being investigated in a number of centers. Conflicting results have been reported and larger experience is being gathered in order to fully evaluate this novel technique. Many recent reports also support the ability to promote erectile function recovery using either PDE5 inhibitors or intra-cavernous injection of PGE1 in order to avoid the appearance of non reversible ischemic damage to the corpora cavernosa. Although erectile dysfunction is often associated with pelvic surgery, many strategies can be contemplated to avoid this complication. The impact of erectile dysfunction on patient's quality of life should not be underestimated and multimodality strategies may be required to maximize recovery post pelvic surgery.

106

YOU'RE NEVER TOO OLD FOR A GOOD THING: ED IN THE AGING MALE

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Society often depicts aging as a time of decreased sexuality. Clinicians may decline to discuss or offer therapy to older men based on assumptions of what constitutes 'normal sexuality' in an older couple. As well, concern for overall health or other co-morbid illness may be seen as more important than addressing sexual health. Since ED is a marker of underlying co-morbid conditions and conversely, ED is often more severe in men with diabetes, hypertension and hyperlipidemia, it is important to consider an aging man's sexuality in the context of his overall health. During this session the misconceptions about older men's sexuality will be addressed, and strategies discussed for assisting older men enjoy this period of their sexual lives. In addition, the vital role of the female partner, her attitudes, beliefs and support of his sexual health will be addressed.

107

SEXUAL HEALTH IS THE PORTAL TO MEN'S HEALTH

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This report focuses on a number of specific conditions that are known to be highly prevalent throughout the aging male population worldwide. There are numerous non-cancer, co-morbid disease states have been shown to adversely affect males over the age of 50. Included are problems such as diabetes mellitus (DM), metabolic syndrome, cardiovascular disease (CVD), erectile dysfunction (ED) hypogonadism, depression and benign prostatic hyperplasia (BPH). These conditions are discussed with special attention aimed at highlighting any associated links that might exist between them in the setting of male aging. A literature search was conducted on MedLine and PubMed using the key words aging male, DM, metabolic syndrome, CVD, ED, hypogonadism, depression, BPH, quality of life (QoL) and other related key words. The National Institutes of Health (NIH), Centers for Disease Control (CDC) and World Health Organization (WHO) conference proceedings and other pertinent reports were also reviewed. Much of the research to date has done very little to establish whether a cause and effect phenomenon exists between the above conditions. However, many have shown that a strong association exists. It is known that the pathogenesis of several of these problems, for example CVD, and ED, is similar. This calls attention to the fact that more detailed investigation is needed in this area of male aging in order to better delineate when and where intervention may be necessary. Several studies have shown that symptoms of sexual dysfunction and hypogonadism may be early warning markers of important men's health issues, such as cardiovascular disease, diabetes, metabolic syndrome, depression and benign prostatic hyperplasia. The new and evolving concept of endothelial dysfunction in the setting of these conditions further highlights the need for a comprehensive assessment rather than a singular approach when caring for the growing male population. Symptoms of sexual dysfunction may be the manifestation that presents an opportunity to detect the other disorders and hopefully modify patients' behavior to improve men's health.

108

METABOLIC SYNDROME AND SEXUAL DYSFUNCTION

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Endocrine and other non-endocrine organic factors often simultaneously and mutually interact with other intrapsychic and relational determinants in the pathogenesis of erectile dysfunction (ED). Among endocrine factors, testosterone (T) is one of the best studied, although its role in ED is still questioned. In a consecutive series of almost 2000 subjects with sexual dysfunction, we identified an overt Hypo ($T < 8$ nM) in 5.2% of the sample. In this sample, obesity and type 2 diabetes mellitus (DM) were the most important determinants of Hypo. Because type 2 DM, obesity and Hypo are considered components (or are often associated with) metabolic syndrome (MS), we now reports their interrelationships and psycho-biological correlates in patients with sexual dysfunction. Metabolic syndrome was defined by Adult Treatment Panel III (ATP III) criteria. Patients with ATP-III MS showed a higher cardiovascular risk (as assessed by PROCAM and Framingham risk scores) and worst subjective (SIEDY structured interview) and objective (PDU) erectile parameters than the rest of the sample. The relative risk for Hypo ($T < 8$ nM) was significantly higher in patients reporting 3 or more factors for MS (6.3[1.4–28.7], $p < 0.001$). At logistic regression, considering ATP-III criteria as putative predictors of Hypo, waist circumference and hyperglycaemia were the best predictors of $T < 8$ nM. Among patients with MS, those with Hypo showed higher LH and FSH and lower free T levels, suggesting a primitive origin of the problem. Hypo patients with MS reported a higher prevalence of Hypo-related symptoms, such as higher depression and hypoactive sexual desire and lower frequency of sexual intercourses. In conclusion our data suggest that the prevalence of Hypo is higher in patients with MS. The presence of Hypo can further exacerbate the already MS-compromised penile blood flow, adding the typical Hypo-related symptoms, which, however, can potentially be ameliorated by T replacement therapy.

109

ANDROGEN DEFICIENCY AND HORMONE REPLACEMENT THERAPY

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The age-related decline of serum testosterone is reported in about 20 to 35% of men, and may be due to an increase in sex hormone-binding globulin. For this reason the biochemical diagnosis of androgen deficiency should be confirmed twice along with the measurement of SHBG and, whenever possible, bioavailable testosterone. Ongoing studies suggest that testosterone may have a role as an anti-atherogenic therapy by preserving endothelial and smooth muscle cells integrity. Furhermore, the recent finding that androgen may also directly control the expression and activity of phosphodiesterase type-5 (PDE5) in human genital tissues opens a new scenario for its use in selected patients in whom total testosterone below 10 nmol/l and/or free testosterone below 0.250 nmol/l may directly determine a failure of men with ED in the clinical response to PDE5-inhibitors. The possibility to challenge these men with TRT to improve their erectile function and sexual satisfaction in the absence of contraindications to testosterone administration, may represent a ''salvage'' for subjects that would be otherwise referred for less satisfactory or more invasive alternatives. Because ED shares the same risk factors and may be a sentinel of cardiovascular disease, in the future TRT will offer the potential to enhance men's motivation for prevention and treatment of cardiovascular disease associated with disorders of erection. for present, the beneficial effects of testosterone administration on body composition, bone density and sexual function have been recently reviewed using the powerful techniques of meta-analyses, providing a summary of the known effects that can be expected. Whether such changes justify a trial or a life-long treatment with one of the several androgen preparations now available, should be evaluated individually for each patient by a physician knowledged in the field, in respect of published guidelines, while awaiting for adequate safety data to become available.

110

REGULATION OF PENILE ERECTION BY ANDROGEN-DEPENDENT CELLULAR AND MOLECULAR MECHANISMS

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Erectile function, a complex neurophysiological process, is dependent upon the health of the penile vascular tissues, nerves and the perineal and ischiocavernosus muscles that support the proximal penis. Adequate arterial inflow and trapping of blood within the cavernosal bodies (veno-occlusion) is critical for the development of increasing pressure and volume expansion. In addition to arterial blood pressure, contraction of the perineal and ischiocavernosus muscles enhances penile rigidity. The veno-occlusive mechanism depends on the integrity of neural, vascular and endocrine systems, as well as the fibro-elastic properties of the cavernosal tissue. Animal studies have shown that androgens play an important role in maintaining penile tissue structure and function and androgen deficiency contributes to veno-occlusive dysfunction. Investigation of androgen action on erectile physiology in the animal model suggest that androgens regulate: a) the expression and activity of nitric oxide synthase isoforms, b) the expression and activity of phosphodiesterases, c) the growth, contractility and state of differentiation of smooth muscle cells, d) connective tissue metabolism, e) the differentiation of progenitor stromal cells into myogenic and adipogenic lineages. We conclude that androgen insufficiency produces erectile dysfunction by affecting multiple cellular components, altering cellular signaling and modulating biochemical pathways, thus adversely changing the structural and functional integrity of penile corpus cavernosum.

111

EPIDEMIOLOGY OF SEXUAL DYSFUNCTION IN THE MALE POPULATION

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Among male sexual dysfunctions, erectile dysfunction has been studied most intensely. The Massachusetts Male Aging Study has demonstrated that complete erectile dysfunction increases from about 5% from the age of 40 to about 15% by the age of 70; milder forms are even more frequent. Other community surveys in European countries following this milestone investigation have yielded overall comparable results. Less knowledge is available about disorders of ejaculation (premature or reduced) and orgasm. Sexual desire has been investigated less frequently and appears to be maintained by the great majority of men until old age. Maintaining a satisfying sexuality into old age is mostly dependent on the availability of a stable partnership and mutual sexual communication and desire (Beutel et al. 2002). The purpose of the paper is to review the prevalence of male sexual dysfunction based on representative studies of the general male population and their methodological underpinning. Determinants of sexual dysfunction are discussed along with the clinical significance of the findings.

Reference

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112

ANDROGEN THERAPY AND EFFICACY OF PDE-5 INHIBITION IN ERECTILE DYSFUNCTION (ED)

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An appropriate androgen milieu is essential for the cascading mechanisms driving the penile erectile response. The serum androgen levels for activation of these mechanisms appear to have a relatively narrow range in the lower normal limits for the young but require larger and more unpredictable T concentrations in their older counter parts. The process of erection involves the production of nitric oxide synthase (NOS), the release of nitric oxide (NO) and the augmentation of the synthesis of cyclic guanine monophosphate leading to arteriolar dilatation and relaxation of the corporeal smooth muscle. When a critical low androgen milieu is reached this complex process is blunted or fails altogether. Possible Synergism of T with phosphpodiesterase-5 inhibitors (PDE-5Is. In cases of recalcitrant ED, a multi-pronged pharmacological approach may be more effective that the single agent management. Specifically in cases of ED and hypogonadism, the available evidence is encouraging. Early studies have shown that following a failure of an appropriate course of PDE-5I therapy, a number of patients can be rescued by the addition of T. Further, larger controlled studies of T with other erectogenic drugs (i.e. PDE-5Is, dopaminergic agonists) need to be pursued vigorously. However, it a more sound, productive and beneficial clinical practice to rule out or treat hypogonadism before blindly embarking on the use of peripheral amplifiers of the erectile response, an approach doomed to fail in the presence of an inadequate hormonal milieu.

113

NON-RESPONSE TO PDE5-INHIBITORS: WHAT'S THE STRATEGY?

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The presentation will allow an practical approach to patients with erectile dysfunction and an insufficient response to oral PDE5-Inhibitors. Many patients do not respond appropriatly to PDE5-i since they are using them the wrong way. Therefore, time span before use, number of attempts and general conditions (libido etc) must be checked. Furthermore, it is well documented that hypogonadism is correlated to a poor response to PDE5-i treatment. Thus, a poor response in a patient should stimulate testosterone measurement. If a low morning testosterone is found, testosterone supplementation should be considered and discussed with the patient. Given a normal testosterone, local pharmacotherapy with PGE1 (either IC or MUSE) should be applied after appropriate information of the patient. If these options fail again, a vacuum device may be prescribed. Only if all these strategies fail, penile prosthesis implantation may be discussed with the patient and his partner.

114

WHY DO PATIENTS NOT COMPLY/ABANDON EFFECTIVE ED THERAPY WITH PDE5 ANTAGONISTS

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PDE5 antagonists represent the most popular and frequent form of treatment in erectile dysfunction today.The objective of this paper is to provide an analysis and overview on patient's compliance while using PDE5 antagonists for the treatment of Erectile Dysfunction (ED). The talk will be focussed on mechnisms that underly non-compliance with the treatment strategy, independent from its effectiveness. Reasons for non-compliance are mostly subjective but may be classified into certain distinct groups: Non-compliance because of insufficient effectiveness of the drup, non-compliance because of side effects and adverse events while using the drug and non compliance due to financial or other social reasons. A short overview of drugs will be presented with special regard to social factors of drug intake. Strategies that might help to improve compliance in patients will be discussed.

115

SEXUAL DYSFUNCTION IN OLDER MEN: TREATMENT AND COUNSELING

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Behind every penis hangs a man; behind this man hangs a partner, and in some cases more than one (Berberich). Thus, sexual (dys)function always is psychophysiology of lust and love. Sexual dysfunctions are conditioned by both: biological factors and biograpical events. This paper focuses on psychological factors as typical barriers of sexual satisfaction in older men. It also describes how the medical doctor within the framework of his/her daily practice can integrate a short sexual counseling (of 3 minutes). This counseling is a step by step guidance of the older man as a partner into new life styles of erotic vitality also as relational receipt, even when physical limitations occur. 8 life styles will be described, with typical risks and chances for andropausal men. Satisfying erotic experiences indeed guarantee life long the quality of life, also as quality a human contact.

116

SEXUAL HEALTH AND RESPONSE IN THE AGEING MALE

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The ageing male will have a variable sexual response and often fluctuating interest in engaging in sexual activities. Often there is little change from earlier lifetime patterns of behaviour. for some men there is a lower priority for sex and this may reflect other health problems which may have a direct or indirect effect on sexual function. Whilst certain vascular conditions are common with co-morbid sexual dysfunction, there are other conditions which are not uncommon such as HIV infection and AIDS which has specific psychological and endocrinological sequelae. Approximately 11% of cases of AIDS in the UK are diagnosed in individuals over the age of 50. The ageing process may bring about changes in cognitive function with unwanted, inappropriate or even uncharacteristic sexual behaviours. Within the context of a relationship this may be particularly distressing to the partner and an area where specific counselling is necessary. Additionally where the ageing male is living with their adult children, the whole matter of sexual activity in the parent may cause embarrassment and difficulties within the family context. It is not inevitable the sexual dysfunction will have a negative impact on the ageing male and a thorough assessment of the multiple factors that could influence the sexual lives of the male and his partner is imperative to providing a comprehensive package of care to the patient. for many men and their partners the primary defining feature of any intimate relationship is to have penetrative sexual intercourse and a

failure for this to be possible may trigger significant emotional disturbance and distress. There is some evidence that hesitation to seek assistance for sexual problems is even greater in ageing people than in the younger population and a number of factors may influence this behaviour. The various barriers that may need additional awareness and assistance to disclose such problems is considerable from clinician. The public health consequences constitute a complex social problem for the general well-being and sexual health of the ageing male.

117

ERECTIONS AND SOCIETY

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Once considered a social taboo and a strictly personal physiological phenomenon, erection has become a veritable social phenomenon since the advent of PDE 5 inhibitors in 1998. Hardly a week goes by without erection being the object of media attention – and often banter – so that little by little it has lost its bawdy connotation (but this was difficult indeed!). Erection now receives attention primarily through its negative counterpart, Erectile Dysfunction. Today, men accept at last to talk about their ''absences,'' ''mechanical problems'' or ''distress,'' though rarely openly. SHAME and GUILT are still all too frequent. In France, only 20% of men who suffer from erectile dysfunction consult a doctor. This figure means that they continue to suffer in silence ... but is this really the case? We will come back to this point a bit later. What PDE 5 inhibitors did, was to widen the scope of 'pathology, thus conditioning the medicalization of erectile dysfunction. Impotence has become a recognized pathology with a name, rather than a terrifying experience. This was quite logically followed by an increase in the medical community's ability to deal with the highly symbolic conditions of ''masculine impotence,'' and thus their implication in the sexual pleasure of other people. This element of progress has allowed the patient to elude the causes of impotence and to become the subject of medicalization at the demand of sexual partners, and this transpires in some of the approaches that appear in the media. This creates a problem for 'powerful' doctors, thanks to their (very efficient) medical prescriptions, because they forget that the patient's problem, although directed towards a well-identified pathology, really concerns the patient in his entirety, and beyond this the couple, and can only be understood in terms of demand. This explains why so many men say that they felt that getting a PDE 5 prescription meant that they had failed in some way. In consequence, we should above all avoid the frequent confusion between the penis and the phallus, the latter symbolically pertaining to the whole body filled with desire, and informed by the language that conveys emotions on a sexuality whose veritable center is the brain. It is often all too convenient for the physician to suppress the patient's need to talk with a chemical prescription, not allowing him to surmount his inhibitions and to arrive at the root of his suffering, beyond the cult of performance to which he has been conditioned. But isn't erection a brilliant example of 'non-performance' function.

118

MIDDLE LIFE CRISIS

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The authors consider the différent aspects of the dynamics of the Middle Life Crisis which results generally: – in a clear and sudden awareness of the brevity of life – in a reconsideration of the ambitions of the subject – in a fear not to be sexually up to it in front of the worship of youth and the performances that media convey – in an objective fall of sexual activity more often due to routine This Crisis often corresponds to adolescence of children or their leaving home and to the death of the parents. These quite real losses add to the change of former balances to amplify the phenomenon of Middle Life Crisis and to worsen its consequences among which Depression is not rare. This loss of the reference marks implies a true work of Mourning and the passage towards an other balance. In the event of failure, it will be able to lead to an undergone loneliness. The impact of this event on Sexuality is often negative. On the other hand, this impact can be positive in all the cases (most of them not seen in consultation) who find in this crisis the appropiateness of the awaited change which release them truly. The different aspects in this dynamics will be considered.

119

DIFFICULTIES IN ACHIEVING VERSUS MAINTAINING ERECTION: ORGANIC, PSYCHOGENIC AND RELATIONAL DETERMINANTS

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Introduction and objectives: Achieving and maintaining a penile erection are two essential components of the male sexual response. It has recently been suggested that distinct molecular mechanism could underlie the two disturbances. The aim of the present study is to verify possible clinical differences on pathogenetic factors underlying difficulties of achieving and maintaining an erection. Methods: We studied a consecutive series of 560 patients (aged 51.9 $\pm$ 12.8 years old) reporting erectile dysfunction (ED), using SIEDY Structured Interview. Patients were classified in two distinct categories: those with difficulties in maintaining, rather than achieving, an erection (sample A) and those with main problems in achieving an erection (sample B). A complete physical examination and a series of metabolic, biochemical, hormonal, psychometric, penile vascular tests and nocturnal penile tumescence and rigidity evaluations (NPT) were also performed. Results: Sample B patients showed a higher prevalence of organic conditions related to ED, when compared with sample A as confirmed by higher SIEDY scale 1 scores (3[1–5] vs 1[0.1–3] for sample B vs sample A, respectively; $p < 0.0001$) which explores organic component of ED and higher prevalence of pathological instrumental parameters. No difference among groups was observed for SIEDY scale 2 (relational component) and SIEDY scale 3 (intrapsychic component) of ED. Conclusion: This study shows for the first time that patients with difficulties in maintaining erection are less likely to be affected by organic disturbances interfering with sexual function, when compared with those unable to achieve a valid erection.

120

PSYCHO-BIOLOGICAL CORRELATES OF DELAYED EJACULATION IN MALE PATIENTS WITH SEXUAL DYSFUNCTIONS

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Introduction and objectives: pathogenesis of delayed ejaculation (DE) is rather unknown, although the contribution of

various psychological, marital, hormonal and neurological factors has been advocated. Methods: in this study we systematically investigated the relative relevance of the aforementioned factors in a large sample (1632) of men, seeking medical help for sexual dysfunction. Delayed ejaculation was defined according to Kaplan criteria. In particular mild/moderate DE (MMDE) was diagnosed if ejaculation and climax were still possible, but only with great effort and after prolonged intercourse (mild DE) or possible only with autoerotism, although in the presence of the partner, but not during coitus (moderate DE). Anejaculation or severe DE (ASDE) was diagnosed if orgasm and ejaculation could not be obtained at all (anejaculation) or could be obtained but only with autoerotism conducted in the absence of the partner (severe DE). Results: mild and moderate DE (MMDE) generally recognized different risk factors than the most severe forms (anejaculation/severe DE; ASDE). ASDE was essentially coupled to the presence of neurological diseases or to the use of serotoninergic drugs. Serotoninergic drugs also significantly increase (by at least ten-fold) the risk for MMDE, which, however was also coupled to other relational (impaired partner's climax, patient's hypoactive sexual desire, HSD) or intra-psychic (stress at work) factors. At multiple regression analysis, some organic conditions (such as psychiatric disorders and hypogonadism) were also associated to MMDE. In particular, hypogonadism retained significance for DE even after adjustment for HSD (Adj. OR = 2.08[1.11–3.89]; $p < 0.05$), suggesting other effects of testosterone deficiency on the ejaculatory reflex, besides reduced libido. Conclusions: in conclusion, the present study demonstrates that multiple psychobiological determinants are associated to DE, a still obscure condition which substantially impairs psychosexual equilibrium of the couple.

121

PSYCHO-BIOLOGICAL CORRELATES OF FREE-FLOATING ANXIETY SYMPTOMS IN MALE PATIENTS WITH SEXUAL DYSFUNCTIONS

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Introduction and objectives: Anxiety has a relevant impact on everyday life, including sexual life, and therefore is considered the final common pathway by which social, psychological and biological stressors negatively affect sexual functioning. The aim of this study is to define the psychobiological correlates of free-floating anxiety in a large sample of patients complaining erectile dysfunction (ED) based sexual problems. Methods: we studied a consecutive series of 882 ED-patients using SIEDY, a 13 items structured interview, composed of three scales which identify and quantify organic, relational and intrapsychic domains. MHQ-A scoring from Middlesex Hospital Questionnaire (MHQ) was used as putative marker of free-floating anxiety symptoms (AS). Metabolic and hormonal parameters, nocturnal penile tumescence (NPT) test and penile doppler ultrasound (PDU) examination were also performed. Results: MHQ-A score was significantly higher in patients complaining difficulties in maintaining erection and in those reporting premature ejaculation (6.5 ± 3.3 vs. 5.8 ± 3.3 and 6.6 ± 3.3 vs. 6.1 ± 3.3 respectively; both $p < 0.05$). Moreover, AS were significantly correlated to life stressors quantified by SIEDY Scale 2 (relational component) and Scale 3 (intrapsychic component) scores, as dissatisfaction at work or within the family or couple relationships. Among physical, biochemical or instrumental parameters tested, only end-diastolic velocity at PDU was significantly ($p < 0.05$) related to AS. Conclusions: in patients with ED based sexual problems, AS are correlated to many relational and life stressors. Conversely, organic problems are not necessarily associated with MHQ-A score.

122

PSYCHO-BIOLOGICAL CORRELATES OF SMOKING IN PATIENTS WITH ERECTILE DYSFUNCTION

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Introduction and objectives: warning labels in cigarette packages often links smoking to a severe impairment in sexual health. To evaluate if this is the case, we studied the psychobiological correlates of smoking behavior in 1150 male patients, seeking medical care for erectile problems. Methods: all the patients have been interview using SIEDY, which explores organic, relational and intra-psychic components of erectile dysfunction (ED), and completed a self-administered psychometric test (MHQ). In addition, several biochemical and instrumental parameters were studied in this population, to better clarify the biological components underlying the ED problem. Results: among hormonal levels, we found that current smokers have a higher activation of hypothalamus-pituitary-testis axis (higher LH, testosterone and right testicular volume) and lower levels of both PRL and TSH than never or past-smokers. Hormonal changes were reverted after smoking cessation. Current smokers showed a higher degree of somatised anxiety and were more often unsatisfied of their occupational and domestic lifestyle. Smoking, as part of a risky behavior, was significantly associated with abuse of alcohol and cannabis. Both current and former smokers have the worst subjective and objective (dynamic peak systolic velocity at penile Duplex ultrasound) erectile parameters. This might be due to a cigarette-induced alteration of lipid profile (higher triglyceride and lower HDL cholesterol in current smokers than in non-smokers or past-smokers) or to a higher used of medications potentially interfering with sexual function. Conclusions: our report demonstrates that smoking have a strong negative impact in male sexual life, even if it associated at an apparently more sexual-favourable hormonal milieu.

123

HOLISTIC MANAGEMENT OF ED FOR BEST QUALITY OF LIFE IN AGING MEN

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More than 50% of men over 40 years of age suffered erectile dysfunction (ED). One of three of them has been reported to be hindered with ED (MMAS, 1994) and touching their quality of life (QoL). Adverse results of medication and life habits may cause sexual problems and other co-morbids in later years. A correct approach during evaluation and management of ED is helpful to get the patients confession and treatment. Aging is multi-factorial process, including decline of immune-system, combining and interacting at many levels. They Interfere protein-metabolism, molecules, cells, tissues, organs and entire holistic body system and mind. It is therefore unrealistic that a single preparation can prevent aging and recover ED. Nutritional-food, sexual tonics have been claimed to be effective as anti-aging-drugs or elixir-of-youth. DHEA, GH, melatonin and sex-steroids have also been mentioned to have potentials to rejuvenate and to treat ED. Testosterone substitution in PADAM (Partial-Androgen-Deficiency in Aging Men) might increase sexual arousal. On the contrary PDE-5-inhibitor seems not always helpful for the aging men with ED. Decrease of self-esteem, fear-of-failures are probably results of SLOH (Slow-Onset-of-Hypogonadism). In such case PDE-5-inhibitor alone may fail to treat ED. The combination of testosterone for PDE-5-inhibitor failures have

proven benefits to improve erection in 80% of cases. Our current clinical trial has proven that testosterone enhances other clinical signs of androgen target organs. Muscle strength, aggressiveness, cognitive wellness, self esteem and libido are improved. HRT does not merely recover rigid erection when PDE-5-inhibitors failed, but also reinsured best QoL in the aging men.

124

CHARACTERISTICS OF PATIENTS WITH ERECTILE DYSFUNCTION IN A LARGE EUROPEAN CLINICAL PRACTICE SETTING: RESULTS FROM THE DETECT STUDY

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Objectives: To determine characteristics of patients with erectile dysfunction (ED) in three age groups. Methods: The DETECT study is an ongoing prospective observational study in ED patients initiating or changing treatment to tadalafil. Its objectives are to assess the proportion of patients who continue treatment with tadalafil and to determine factors associated with its continued use at 1, 6 and 12 months. 264 sites from 9 countries enrolled 2081 patients of which 28% were <50 yr (group 1), 35% 51–60 yr (group 2) and 37% >60 yr (group 3). Results: Per age group (1, 2, 3): Mean patient and partner age (yr) were, 42.9 and 38.0; 55.9 and 49.6; 67.7 and 60.5 .ED etiology was organic in: 16, 29 and 34%; mixed in 42, 53 and 56%, psychogenic in 42, 18, 10%.ED severity was severe in 27, 33, 48%, moderate in 26, 25, 22%; mild in 40, 37, 24% and normal in 6, 5, 6%. Mean number of attempts in last 4 weeks were 6.5, 4.8, 3.6. Duration of relationship >10 years was 42, 70, 78% and <1 year, 27, 11 and 7%. There were problems in relationship in 21, 19, 12%. 64% of patients were treatment naïve. Main reasons for changing therapy to tadalafil were 1) lack of efficacy 2) duration of action/time constraints. 72.2% of partners were aware of the consultation. Level of sexual desire was moderate to very high in 79% of patients. It was higher in patients with more sexual attempts and relationship of less than 1 year duration and decreased with ED severity, long relationship and poor health. Prevalence of comorbidities increased with age. Conclusions: Patients characteristics at baseline are different according to age. The study will examine whether these and other factors may influence the continued use of tadalafil.

125

RELATIONSHIPS BETWEEN ERECTILE DYSFUNCTION AND QUALITY OF LIFE IN JAPANESE SUBJECTS, CONSIDERING DEPRESSION/ANXIETY STATUS

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Aims: This study aimed to elucidate the relationships between erectile dysfunction (ED) and quality of life (QOL) in Japanese subjects, considering depression/anxiety status. Methods: Subjects were 1,332 Japanese men aged 40–69 years. ED was assessed by the International Index of Erectile Function 5 (IIEF-5) score (Japanese version), and depression/anxiety symptoms were assessed by the Hospital Anxiety and Depression Scale (HADS) as self-administered questionnaires. The QOL were measured with the short form of Medical Outcomes Study (SF-36) and age-adjusted scores in eight subscale domains were calculated. In this study ED cases were defined as those whose IIEF-5 value was less than 12, and a score of 8 or higher was used to classify a subject as suffering from depression/anxiety, respectively. We analyzed the relationships between ED and QOL, considering depression/anxiety status, using the two-way analysis of variance (ANOVA), by three age groups (40–49, 50–59, 60–69 years). Results: ED was significantly related to low age-adjusted scores in 'physical functioning (FP)' and 'general health perception (GH)'. ($P < 0.05$) However, within same depression/anxiety group, no subscale scores reached statistical significance by the Tukey multiple comparison tests. (alpha $= 0.05$) Conclusion: ED was significantly associated with QOL in Japanese subjects. However, the influence of ED on QOL was strongly affected by depression/anxiety. Our results might be useful in furthering understanding of ED etiology and determining a target population for prevention in ED subjects.

126

CURRENT STATUS IN THE MANAGEMENT OF ERECTILE DYSFUNCTION: SILDENAFIL VS. PENILE IMPLANTS

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Ever since the introduction of Sildenafil in 1998, the management of Erectile Dysfunction has been revolutionized quite precipitatously. The orally effective PDE 5 inhibitors, namely Sildenafil, Tadalafil & Vardenafil act by potentiating the smooth muscle relaxant effect of nitric oxide. All these drugs appear to effective and safe in men with erectile dysfunction in selected cases. However, in certain cases, these drugs are not effective whereby the successful role of penile implant come into the play.

Implantations of penile prothesis have become an increasingly popular and common procedure for the management of organic erectile dysfunction. Penile Implant has undergone rapid evaluation during the last decade in terms of material construction and innovative designs. They provide improved result functionally, cosmetically, sustainability and longevity. However, proper patient selection, ideal penile implant and a perfect surgical technique play an important role.

In this paper, we plan to highlight the various advantages and disadvantages of various PDE5 inhibitors and also give a complete overview of various penile implant – ranging from malleable to inflatable penile prosthesis. We will also emphasis the side effect of the drugs, their correct indication and also the indication for the proper selection of the patient and the type of the penile implant in a particular case with its associated problem and complication.

This will then conclude that in properly selected patients, penile implant could achieve gratifying results, particularly in Sildenafil refractory cases. A definite role of pre-operative counseling and postoperative patient and partner satisfaction will also be highlighted.

127

PATIENT EXPECTATIONS FOR TREATMENT OUTCOME WHEN INITIATING TADALAFIL TREATMENT FOR ERECTILE DYSFUNCTION: RESULTS FROM THE DETECT STUDY

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Objectives: To assess patient expectations for treatment outcomes of erectile dysfunction (ED) in men who have

chosen to initiate or change treatment to tadalafil. Methods: The DETECT study is an ongoing multi-centre, prospective, observational study in 9 European countries. Men with ED (N = 2081) will be followed for one year with data collected at baseline and at 1, 6 and 12 months. Efficacy (IIEF EF domain) and patient satisfaction (EDITS) will be evaluated for their effect on continuation with ED treatment over one year. Patient expectations at baseline were assessed with a 5-point scale by 7 questions assessing the importance that treatment: works quickly (Question 1) and for a long period of time (Q2), that it improves confidence to engage in sexual activity (Q3), that partner is satisfied with treatment (Q4), that erections feels natural (Q5) and hard with treatment (Q6) and can be maintained long enough to complete intercourse (Q7). Fulfillment of patient expectations is considered important for patient satisfaction and continuation of treatment. Logistic regression models were used to assess the association between patient characteristics and their treatment expectations. Results: Expectations for Questions 1–7 were very-quite important for respectively 75.6, 76.1, 88.5, 87.6, 84.3, 92.5, 94.5% of patients; fairly important for 19.2, 18.3, 9.7, 9.4, 12.0, 6.6, 5.0% and not at all-slightly important for 5.2, 5.6, 1.8, 3.1, 3.8, 0.9, 0.4%. Factors as age, frequency of sexual attempts, desire, and duration of the relationship will be analysed for their influence on patient expectations. Conclusions:Hardness and the ability to maintain an erection to complete intercourse were the most important expectations (>92% of patients), followed by confidence, partner satisfaction and naturalness (>84% of patients), and rapid effect and long duration of treatment (>75% of patients).

128

TESTOSTERONE RESTORES DIABETES-INDUCED ERECTILE DYSFUNCTION AND SILDENAFIL RESPONSIVENESS IN TWO DISTINCT ANIMAL MODELS OF CHEMICAL DIABETES

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Hypogonadism is often associated with diabetes and both conditions represent major risk factors for erectile dysfunction (ED). We evaluated the effect of diabetes-induced hypogonadism on ED in two animal models of chemical diabetes: alloxan-rabbits and streptozotocin (STZ)-rats. In both models, hypogonadism was observed, characterized by reduced testosterone (T) and atrophy of androgen-dependent accessory glands. T substitution completely reverted hypogonadism and diabetes-induced penile hyposensitivity to ''in vitro'' (acetylcholine, rabbit) or ''in vivo'' (cavernous nerve electro-stimulation, ES, rat) relaxant stimuli, along with neuronal nitric oxide synthase (nNOS) expression, which was reduced ($p < 0.05$) in STZ-rats. In diabetic animals, T substitution reinstated sildenafil-induced enhancement of both ''in vitro'' nitric oxide-donor (NCX 4040) relaxant effect (rabbit) and ''in vivo'' ES-induced erection (rat). Accordingly, PDE5 resulted reduced in diabetic STZ-rats ($P < 0.05$) and normalized by T. In STZ-rats, intracavernous injection of sodium nitroprusside (SNP) induced a more sustained erection than in control rats, which was no further enhanced by sildenafil. T substitution normalized both hyper-responsiveness to SNP and sildenafil efficacy. In conclusion, in two models of diabetes T deficiency underlies biochemical alterations leading to ED. Normalizing T in diabetes restores nNOS and PDE5, and reinstates sensitivity to relaxant stimuli and responsiveness to sildenafil.

129

EFFECT OF CHRONIC TADALAFIL ADMINISTRATION ON PENILE HYPOXIA INDUCED BY CAVERNOUS NEUROTOMY IN THE RAT

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Radical prostatectomy is an effective therapy for clinically localized prostate cancer. A significant number of men develops post-prostatectomy erectile dysfunction (PPED), due to surgery-related nervous damage. PPED is relatively refractory to PDE5i therapy. In a rat model of bilateral cavernous neurotomy we evaluated whether chronic tadalafil treatment (CTT) could ameliorate anatomical and functional damage to corpora cavernosa (CC). Tadalafil (2 mg/Kg/daily) was added in drinking water in a subgroup of neurectomized rats (CTT). After 3 months, penile tissues were removed and hypoxia and muscular/fibrous ratio revealed using semi-quantitative immunohystochemistry with hypoxyprobeTM and Masson staining, respectively. Endothelin receptor type B (ETB), PDE5, nNOS and eNOS expression and functional activity were also studied. Penile denervation induced massive hypoxia and a decreased muscular/fibrous ratio, which were completely restored by CTT. Functional studies indicated that hypoxic tissues were hypersensitive to the relaxant effect of the ETB agonist IRL-1620, due to the previously described hypoxia-induced over-expression of ETB (Granchi et al., Mol Hum Reprod 8:1053, 2002; Filippi et al., Mol Hum Reprod 9:765, 2003). CTT restored normal sensitivity to IRL 1620, and normalized ETB gene (real-time RT-PCR) and protein (Western) expression. Hypoxic CC were more sensitive to the relaxant effect of the NO-donor sodium nitroprusside (SNP), while they were unresponsive to acute tadalafil (100 nM) amplification of SNP effect. According to these findings, PDE5 mRNA and protein expression were reduced in neurectomized penile tissue. By restoring PDE5, CTT decreased SNP-induced relaxation and rescued sensitivity to acute tadalafil (100 nM). However, in hypoxic CC, CTT was unable to normalize other observed events, as acetylcholine hypo-responsiveness or decreased nNOS and eNOS, at both mRNA or protein levels. In conclusion, CTT restores several (but not all) of the neurotomy-induced penile alterations, including PDE5 expression and in vitro responsiveness to PDE5 inhibitors, such as tadalafil.

130

MEN WITH THE METABOLIC SYNDROME BUT WITHOUT DIABETES MAY HAVE ERECTILE DYSFUNCTION AND PARTIAL ANDROGEN DEFICIENCY COMPARED TO NORMAL CONTROLS

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Men with type II diabetes are well known to have erectile dysfunction (ED). Whether the metabolic syndrome (MS) per se even in the absence of diabetes may be associated with ED is a matter of uncertainty. This study compared serum testosterone levels and self-administered erectile function questionnaires in middle-aged men with features of the MS but without type II diabetes compared to age-matched healthy controls. Twenty-two middle-aged men (mean age 49.2 $\pm$ 5.4 years) with obesity, hypertension and/or dyslipidemia but without type II diabetes were included in this observational study. The NCEP ATP III criteria for

the MS were used. Twenty-two healthy men served as age-matched controls. Symptoms of androgen deficiency and erectile dysfunction were scored by self-administered questionnaires. Serum testosterone levels were measured in a morning blood sample. The MS had a negative effect on erectile function; we found statistically significant reduction in total erectile function scores. Mean serum testosterone was lower than that in the control group but statistical significance was not reached. Features of the MS even in the absence of type II diabetes in middle-aged men may be associated with androgen deficiency and erectile dysfunction. The physiological basis for this association remains to be elucidated.

131

TESTOSTERONE DEFICIENCY IN MEN ON HEMODIALYSIS: EXAMINING ITS RELATIONSHIP WITH ERECTILE DYSFUNCTION AND DEPRESSION

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Rationale: Testosterone is known to effect sexual function and mood. Men on hemodialysis (HD) suffer from sexual dysfunction and depression. These conditions may relate, in part, to hypogonadism. Purpose: 1. To determine the prevalence of testosterone deficiency (TD) in men on HD at our institution. 2. To examine the relationship between the Androgen Deficiency in the Aging Male (ADAM) questionnaire and TD in men on HD. 3. To establish baseline levels of depression, as measured by the Beck Depression Inventory II (BDI II), and erectile dysfunction, as measured by the International Index of Erectile Function (IIEF), in men on HD. Methods: A descriptive study involving male patients aged 18 to 90 on HD was performed. Exclusion criteria included a history of prostate/breast cancer and previously documented TD or testosterone therapy in the past. The questionnaires were administered during HD. Serum levels of bioavailable testosterone (BAT) were obtained. Results: A total of 27 men participated. 30% were hypogonadal based on BAT levels (mean = 3.9 (3.8) nmol/l). 93% of men had a positive ADAM screen. In 82% there was evidence of erectile dysfunction as indicated by the IIEF-Erectile Function (EF) domain score and in 63% there was evidence of depression as indicated by the BDI II score. We used Spearman Rank Correlations to examine the association of BAT to BDI II and IIEF (total and EF domain) scores. The coefficient between BAT and the BDI II score was 0.40 ($p = 0.04$). Between BAT and the IIEF-total and IIEF-EF domain scores, the coefficients were 0.33 ($p = 0.09$) and 0.35 ($p = 0.07$), respectively. Conclusions: TD is common in men on HD. Symptoms of hypogonadism, depression and ED are also common. BAT and BDI II scores were found to be strongly correlated, while BAT and IIEF scores (total and EF domain) were marginally correlated.

132

SILDENAFIL TAKING ON A DAILY BASIS FOR ERECTILE DISFUNCTION WITH NO RESPONDING TO SILDENAFIL TAKING ON DEMAND

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Introduction and Objective: Nocturnal erections occur at all ages and contribute to the maintenance of the morphodynamic and functional integrity of smooth muscle cells within the corpora cavernosa. New study showed taking sildenafil regularly at bedtime may be able to bring about regression of erectile disfunction (ED).This study was aimed at evaulating the effect and safety of sildenafil taking on a daily basis to ED with no responding to sildenafil taking on demand. Methods: 71 patients with no responding to sildenafil taking on demand (100 mg or 50 mg, $^{3}8$ times) were radomly assigned to two groups (group A, $n = 37$, 50 mg or 25 mg sildenafil taken every night at bedtime for 6 months, group B, $n = 34$, 100 mg Vitmin E taken every night). The efficacy measure was IIEF5 score. IIEF5 scores at both the begin and the end were recorded. Results: IIEF5 scores before the study the group A (12.6 ± 6.1) and group B (11.9 ± 5.9) was similar ($p > 0.05$). All patients completed this study. In group A, IIEF5 scores in post-therapy ((18.8 ± 8.9) was improved significantly than pre-therapy (12.6 ± 6.1) ($p < 0.01$), Though having an little improvement but there was no statistically significant difference between IIEF5 scores in post-therapy (13.3 ± 7.8) and pre-therapy (11.9 ± 5.9) in group B ($p > 0.05$). Using IIEF5 scores in post-therapy $^{3}17$ to define success, $^{3}22$ to define normalized erectile function. 22/37(59.5%) in group A but only 2 (6%) in group B ($p < 0.01$) were successed after the treatment,there was also 13/37(35.1%) in group A but no one in group B ($p < 0.01$) had an normalized erectile function in post-therapy. No serious side effect was seen in all patients. Conclusion: This study suggested that sildenafil taking on a daily basis may be an effective way to improve the erectile function even to normalized the erectile function to ED patients with no responding to sildenafil taking on demand, but the final coclusion need more cases and longer time follow up to further explore.

133

MINIMAL CLINICALLY IMPORTANT DIFFERENCE (MCID) OF THE ERECTION QUALITY SCALE

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Objectives: The recently developed Erection Quality Scale (EQS) is a self-reported measure for assessing the quality of penile erections. To clinicians, it is important not only to ascertain validity of the EQS, but also to comprehend the smallest change in EQS score that patients consider important. The objectives are to report the MCID of EQS and the scientific process within which the MCID was estimated. Methods: A randomized, double-blind, placebo-controlled study was conducted to investigate the responsiveness of the EQS. Men age $\geq$18 years with ED for at least 6 months were eligible. Following a 4-week run-in period, eligible subjects were randomized to receive 10 mg vardenafil or matching placebo for 4 weeks. In a subsequent 4-week period, subjects remained on the assigned treatment with an option to titrate the dose to 5 mg or 20 mg. The International Index of Erectile Function (IIEF), the Global Assessment Question (GAQ), Sexual Encounter Profile (SEP), Keep it Simple (KIS) scale, EQS, and anchor question were administered to study subjects. Safety was assessed throughout the study period. Anchor-based methods and distribution-based methods were used to estimate the MCID. Results: 219 men were enrolled in this study, of whom 113 received placebo and 106 received vardenafil. The MCID generated by two distribution-based methods, namely the 1/2 SD and SEM, was comparable and was 5 points. The estimate generated by cross-sectional anchor-based analyses ranged from 4.82 to 16.33 (with ES ranging from 0.66 to 1.16). With longitudinal method, the mean EQS change scores for subjects with 1 point of anchor score change were 8.08 and 8.03 with ES of 1.12 and 1.18, respectively. Applying Cohen's ES criteria ranging from 0.2 and 0.8, the estimated EQS MCID was 5 points with corresponding ES of 0.5. Conclusions: The MCID of EQS is 5 points.

134

ERECTILE DYSFUNCTION IN PATIENTS WITH CHRONIC RENAL FAILURE UNDERGOING HAEMODIALISIS. PRELIMINARY REPORT

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Introduction: The aim of our study was the estimation of erectile dysfunction (ED) in patients with chronic renal failure (CRF) undergoing haemodialysis (HD). Material and Methods: In study were 35 men with CRF and with accompanied by different rate of ED treated by HD. The age of patients was 24–75 years (mean age 52.3 years). The clinical study was based on andrological and sonographic (color Doppler) examination, the questionnaire IIEF-5 score, Body Mass Index (BMI) and index of adequacy of HD (KT/V). Laboratory tests included basic blood tests and hormonal tests: testosterone (T), luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), estradiol (E2). Results: Amoung the patients with CRF were 31 with ED symptoms: 14(45.2%) diabetic and 17(54.8%) non diabetic men. In age groups: Gr.A: 24–45 years old were 11(35.5%) and Gr.B: 46–71 years old were 10(32.6%) men with ED symptoms below 16 points in IIEF-5 score. The ED symptoms bellow 16 points occured in 12(86.0%) diabetic men and in 13(76.5%) non diabetic men. In patients with ED symptoms BMI was 18.4 ± 32 till 37.2 ± 46 (average 26.2 ± 17) and the avarage T, PRL, E2 levels in blood serum were respectively: 6.7 ng/ml, 18.5 ng/ml, 39.2 ng/ml. Three men have vascular-dependent ED. Conclusions: The symptoms of ED were presented in 86% men with CRF regardless of age, time of HD and KT/V. Diabetes does not modify frequency and severity of ED in patients with CRF. The higher awarding of points in IIEF-5 score were in men with high volue of BMI. The quastionnare IIF-5 should be included to diagnostic men undergoing HD programme. In men with CRF treated by HD the plasma prolactin and estradiol levels were significantly raised and testosteron level was either decreased or normal.

135

THE EFFICACY OF TADALAFIL ON INTERCOURSE SUCCESS IN DIABETIC MEN WITH ERECTILE DYSFUNCTION

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Introduction: In Poland are 1.5 mln men above 35 years old with erectile dysfunction (ED). Diabetes mellitus is a risk factor for ED. Materials and Methods: Tadalafil 20 mg were evaluated in randomized studies in 260 men with ED: 90 with diabetes mellitus type 1- group I and 90 with type 2- group II and 80 without diabetes – group III. The men were evaluated in two age groups: A- 39–50 and B- 51–67 years old. Diagnosis was based on andrological and sonographic (color Doppler) examination. Laboratory investigation included: FSH, LH, T, HbA1C, E2, SHBG, DHEA, IGF-1. Efficacy was measured by: The questionnaire IIEF-5 and Sexual Encounter Profile (SEP). Results: The questionnaire IIEF-5 – before the treatment was in gr.I- 8.1, gr.II- 10.6, gr.III- 7.9 points and after was respectively 16.4, 17.9, 24.3 points. The answers into SEP-test after administration 20 mg tadalafil to question 2 (penetration success) and 3 (intercourse success) were respectively: gr.I- 62.3%, 51.4%, gr.II- 66.2%, 53.6%, gr.III- 86.5%, 68.2%. The efficacy of tadalafil after 60 minutes was: gr.I- 75%, gr.II- 69%, gr.III- 81% and after 24–36 hours was respectively 77.5% 74.3%, 80.1%. The influence of tadalafil on erectile dysfunction in age group was: A- 71%(gr.I), 74%(gr.II) and 94%(gr.III), B- 68%(gr.I), 71%(gr.II), 86% (gr.III). Improvement of erectile dysfunction independently of age and time after administration of 20 mg tadalafil was in: gr.I- 68%, gr.II- 71%, gr.III- 86.1%. Conclusions: Tadalafil significantly improve erection and enable the successfully attempted intercourse in 70% men with diabetes mellitus independently of degree glicemia and age of men. In above 78% patients independently on present and type of diabetes mellitus improve of erection and satisfactory intercourse were observed already after 60 minutes. Improvement of the erection and successfully intercourse for both partners are compared in two age groups and was significantly higher (89%) in men without diabetes mellitus.

136

DAILY LONG TERM TAKING SILDENAFIL RESTORES ERECTION IN SILDENAFIL NON-REPONDERS ON DEMAND

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Introduction and objectives: It has been shown that sildenafil taken at bedtime induced a significant improvment in nocturnal penile erection and long term taking sildenafil an a daily basis may lead to regresion of ED (1). The aim of this study was to assess the efficacy of daily long term taking sildenafil regime in patients who were previously sildenafil non-responder on demand regime. Material and methods: In a propective controlled trial 13 patients with ED more than 1 year non-responder on sildenafil taking on demand were included. Average age of patients was 53.4 All patients had normal level of testosterone. Sildenafil was taken in small dose, 25 mg, every night at bedtime for a period of 1 mounth. The efficacy of treatment measured by EF domain score on IIEF questionnaire and arterial reponse by Penile Doppler Ultrasound wich were done before treamtent and 1 mounth later during the treatment. Results: 11/13 patients showed not only improvement the mean score on IIEF (from 9 ± 6 to 14 ± 5, $p < 0.03$) but also improvemenr in peak systolic velocity up to $15.3\% \pm 4$ ($p < 0.04$). Conclusions: In patients non-reponder sildenafil taking on demand long term treatment with sildenafil on a daily basis should be considered. Long term use of sildenafil at bedtime looks like not symptomatic but pathogenic treatment of ED.

137

EFFECT OF SILDENAFIL CITRATE (VIAGRA) ON LOW URINARY TRACT SYMPTOMS

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Objective: To evaluate the effect of sildenafil citrate on low urinary tract symptoms (LUTS) in patients with erectile dysfunction. Methods. We measured SDH and LDH lymphocyte levels and GP, MDA and AOA plasma levels in rats during immobilization before and after sildenafil citrate intake. In 8 healthy volunteers we assessed pCO_2 and pO_2 before and after acute intake of sildenafil citrate 50 mg. Eleven patients with erectile dysfunction and LUTS (pollakiuria, nocturia, urgency) were treated with sildenafil citrate in low dosage (12.5–25 mg once daily before bed) for 2–4 weeks. We used IPSS, IIEF-5 and diary of urinations to assess the efficacy of treatment. Results. Three-hour immobilization has caused significant increase in functional activity of mytochondria and energy metabolism. These changes of cellular metabolism were prevented by sildenafil. In healthy volunteers pO_2 has significantly increased after sildenafil intake. In patients with LUTS continuous treatment with sildenafil citrate in subtherapeutic dosage has improved symptoms and bladder function. Our data show significantly

improvement on sildenafil citrate therapy: IPSS-score (from 16.6 to 7.8, $p < 0.03$, $n = 11$), frequency of urination per day (from 10.1 to 6.2, $p < 0.02$, $n = 8$) and effective bladder volume (from 196.5 to 248.1, $p < 0.001$, $n = 8$). Conclusion. Sildenafil citrate (Viagra) has multiple effects. It powerfully stimulates erection but also reduces the stress associated with immobilization due to moderate peripheral vasodilatation and activation of oxygen metabolism. These effects may explain its positive effects on bladder function and LUTS. In patients with erectile dysfunction and LUTS continuous treatment with sildenafil citrate in subtherapeutic dosage should be considered.

138

HYPNOTHERAPY IN TREATING PREMATURE EJACULATION

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Case Report Patient: male 23 years Diagnosis: premature ejaculation Material Methods: combination of hypnotherapy and behavioural therapy Medication:% Conclusion: Emotions presumably play an important role in a sexual response and dysfunctions in men. Yet, few studies have investigated differences in affect between sexually dysfunctional and functional men or changes in dysfunctional men resulting from successful treatment. In this case report we can see how fast hypnotherapy can 'open up' the patient at an emotional level which is very important during the therapy. Through the work with symbols and metaphors we can approach the symptom on an unconscious level and let the symbols 'make their own story' and resolve the problem. Very important aspects are the exercises from the cognitive behavioural therapy approach which are given in trance to the patient as suggestions. Here the patient gets 'something to do' and his motivation for therapy is increasing, while the source of the problem is being solved through symbol and metaphor work.

139

ERECTILE DYSFUNCTION POST NON NERVE-SPARING RADICAL PELVIC SURGERY: MANAGEMENT WITH SILDENAFIL AND L-ARGININE EVALUATED BY BUKLING-TEST

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Objectives: Radical pelvic surgery may develop sexual dysfunction able to produce alterations of a somatopsychic equipoise often by itself precarious after the 50's age significant oncological risk and moreover at high incidence of benign pathology but however hurtful of sexuality such as diabetics and hypertension besides conditioning handicaps as visus decrease, baldness and others, to which everyone, silent sufferance. MATERIAL-Methods: 116 pts were run in the study (64 prostatectomies and 52 cystectomies) with average age of 65. Oral administration of L-Arginine was four ampules (8gr) daily for three months. L-Arginine HCl is the precursor of nitric Oxide (NO) chemical mediator of erectile sinusoidal dilatation and therefore worthy helper of Sildenafil function that is effective just joint to NO. Sildenafil is an inhibiting drug of type V phosphodiesterase. In physiological state cyclic Guanosin Monophosphate (cGMP) exiting erectile relaxation, is disactivated by the phosphodiesterase that is inhibited by Sildenafil. Its administration was associated to visual sex stimulation and evaluated by Buckling-test (dynamometric validation of erection). Modern engineering researches on penile haemodynamics, emphasize the role of three functions in the achievement of penile axial rigidity: intracavernousal pressure, penile geometry and cavernous tissue features. Clinical application of those rules enabled to evaluate in mg from to 1000 (v.n. more than 500) the cavernous level of Buckling under a testing weight (Buckling-test). Patients were randomised in two groups: Sildenafil and Sildenafil +L-Arginine. Results: The dose of 50 mg was for everyone insufficient (Buckling test $0 = 250$), 100 mg were effective for a significant number of patient: Buckling test more than 500 mg. in 19% of the first group and in 38% of the second. Conclusions: The only treatment were PGE1 injection. If a restricted number of them can obtain a resolutive benefit from the management nevertheless it can offer the less invasive way for a sexual rehabilitation.

140

SEVERITY OF ERECTILE DYSFUNCTION IN MARRIED IMPOTENT PATIENTS: INTERRELATIONSHIP WITH ANTHROPOMETRY, HORMONES, METABOLIC PROFILES AND LIFESTYLE

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Objective: This study was designed to evaluate the effects of risk factors for erectile dysfunction (ED) or cardiovascular disease on the disease severity in impotent men. Methods: A total of 87 men 25 to 75 years old (mean age 53.4) were included in the study. Patients were evaluated with anthropometry, hormones, metabolic profiles and lifestyle. Baseline erectile function (EF) was evaluated using the International Index of Erectile Function (IIEF). The severity of ED was classified into the following five grades based on the six-item EF domain of the IIEF, i.e. severe (6–10), moderate (11–16), mild to moderate (17–21), mild (22–25). Patients were deemed to have metabolic syndrome (MS) if they had three or more of five criteria according to National Cholesterol Education Program, with some modification. Results of 87 patients, 15 patients (17.2%) had mild, 11 (12.6%) had mild to moderate, 33 (37.9%) had moderate and 28 (32.3%) had severe ED. There was no correlation between scores of IIEF or EF domain and continuous parameters. On the multivariate model used, hypertensive patients had 26-fold higher risk (odds ratio, 26.195; 95% confidence interval, 1.463 to 46.072; $p = 0.027$) of severe ED than those without hypertension. Other factors were not significant. Conclusions: The results of the study indicate that MS might not influence the severity of ED in Impotent men. However, our findings suggest that hypertension play a role in the disease severity in these patients.

141

VACUUM ERECTION SYSTEM IN THE TREATMENT OF ORGANIC ERECTILE DYSFUNCTION

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Intracavernosal pharmacotherapy has shown to be a successful initial treatment for organic erectile dysfunction. On the other hand, the occurrence of fibrous nodes and inflammatory complications were observed in a significant number of patients using intracavernosal self-injection therapy during one year period. Other patients refuse this treatment because of their fear of needles or the burden that treatment imposes on them. These problems made us think about extra vacuum devices also known as negative-pressure devices. The aim of research was to provide more effective treatment for patients with erectile dysfunction caused by diabetes mellitus. Fifteen men aged from 35 to 67 years underwent the treatment using vacuum devices. All patients were complaining of being unable to obtain sexual intercourse due to insufficient erection over a period of 9 to 12 months.

The cause of erectile dysfunction was uncontrolled diabetes mellitus. Diagnosis were established according to protocol recommended by European Society of Andrological Urology. Instructions on the use of vacuum method followed by audio-visual presentation were given to each patient. Sixty days later patients were invited for an interview and assessment of therapy results. In 11 (73.33%) patients obtained blood flow into the penis enabled normal sexual intercourse. Four other patients didn't have satisfying penis rigidity. One patient was complaining of severe pain while applying the ring on the base of the penis. Coldness of the penis with subsequent inability to have sexual intercourse and partner's unsatisfaction was present in one patient. Complications in form of petechial bleeding occurred in three patients but these patients didn't hold to 30 minutes duration of sexual intercourse or constriction of the penis. Vacuum device treatment led to: significant improvement in erection quality; higher frequency of sexual relations; improvement in intercourse satisfaction and orgasm; increased self-confidence of patients and evident family relationships improvement.

142

T-SCORE IN PATIENTS WITH ERECTILE DYSFUNCTION (ED) COMPLAINS. IS THE AGE AN IMPORTANT FACTOR? PRELIMINARY REPORT

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Introduction: Bone Mineral Density (BMD) as T-score is currently assessed during the diagnosis of Late Onset Hypogonadism. No regional reports exists of T-score in patients with ED. Goal: To report local data regarding BMD as T-score in Patients with complains of ED, discover the impact of the age in BMD in patients in Chihuahua, MEXICO. Patients and Method: 35 patients with ED complains were studied (IIFE-5 score ≤ 21), all were tested to asses the T-score by Quantitative Ultrasound with Sahara device (Calcaneous). Body Mass Index (BMI) and Waist/hip ratio (W/HR) were assessed. The normal T-score used was the WHO's data as: Normal > -0.9; Osteopenia from -1 to -2.5, and; Osteoporosis < -2.5. All patients signed informed consent. The data was collected in an Excel data base and analyzed using SPSS 10.0 statistic software (95% IC). Results: The age average of patients was 46.7 years SD 14.54 (range 20 to 80). The correlation by Pearson's R (0.18) between Age and T-score was inverted, with a $p = 0.000$ (by Wilcoxon test; $X^2 = 4.09$) statistically significant. Age analized in percentiles the T-score was: 25th $= -1.1$; 50th $= -0.2$; 75th $= 1.2$. Also the BMI was 25.6, 27.4 and 28.9 respectively ($p = 1.0$ by X^2), and the W/HR was 0.9, 1 and 1 by each percentile ($p = 0.013$ by Chi square). Direct correlation between T-score and W/HR was find. Conclusions: It is a paradox to find more often osteopenia in young people with ED complains than in older men. It would be explained after the endocrine asses of the patients. The direct relation between T-score and the W/HR ($p = 0.013$), confirm the thin body build as risk factor of BMD alterations. The endocrine asses of the patients will be subject of a future report. In this series the age did not impact the BMD.

143

PATHOGENESIS OF ORGANIC ERECTILE DYSFUNCTION (ED) IN PATIENTS WITH DIABETES MELLITUS TYPE 1(DMT1) AND 2(DMT2)

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Aim: To study the pathogenesis of organic ED in patients with DMT1 and DMT2. Materials and methods: We studied men with DMT1 (163) and DMT2 (335). We examined sexual function (IIEF-5), clinical symptoms of androgen deficiency (AMS-score), the sensitivity of the penis and doppler ultrasonography (US) of cavernosal arteries. During the study all the patients were divided into two groups by age: 1 group – 30 – 50 years old and 2 group > 50 years old. Statistical analysis was made using Mann-Whitney U-test and Fisher exact p-test. Results: ED was diagnosed in 53,4% and 60,6% of men with DMT1 and DMT2 respectively. Impaired sensitivity of the penis was diagnosed in patients with ED and DMT1 or DMT2 in $> 85\%$ and $> 70\%$ of cases, respectively. Clinical symptoms of androgen deficiency were observed in patients with ED and DMT1 or DMT2 in $> 45\%$ and $> 50\%$ of cases, respectively. The prevalence of cavernosal arteries atherosclerosis was significantly higher in patients with ED of older age groups, comparing with younger age groups: DMT1 (43.5% and 14.3%, $p = 0.007$), DMT2 and ED (51.2% and 27.3%, $p = 0.013$). Patients with cavernosal arteries atherosclerosis had more severe ED. Conclusion: Our data demonstrates the very high prevalence of neuropathy of penis and clinical symptoms of androgen deficiency in patients with diabetes and ED. Cavernosal arteries atherosclerosis is the cause of more severe cases of ED in patients with DMT.

144

VARDENAFIL IMPROVES TREATMENT SATISFACTION AND SEXUAL PLEASURE IN MEN WITH ERECTILE DYSFUNCTION AND THEIR PARTNERS

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Objectives: To assess the influence of vardenafil on sexual quality-of-life and treatment satisfaction in men with erectile dysfunction (ED) and their partners. Methods: This double-blind, multicenter, 12-week randomized trial enrolled 229 men with ED and their partners. Men received placebo or vardenafil 10 mg for 4 weeks, with option to stay on 10 mg, or titrate to 5 mg or 20 mg at 4 and 8 weeks. Primary efficacy variables were the mean per-patient success rate of erection maintenance to intercourse completion (SEP3), and improvement of partner's sexual quality-of-life (modified Sexual Life Quality Questionnaire quality-of-life domain [mSLQQ-QoL]). Secondary efficacy variables included responses to the Treatment Satisfaction Scale (TSS). Results: Mean baseline EF domain of the ITT population (112 placebo and 113 vardenafil patients) was 13.2 and 13.5, respectively (moderate ED). Vardenafil significantly improved overall LS mean per-patient SEP3 success rates vs placebo (67.7% vs 27.8%, $p < 0.0001$), and partner mSLQQQoL (65.8 vs 32.1, $p < 0.0001$, LOCF). Vardenafil significantly improved all TSS domains (mean values at LOCF, all $p < 0.0001$ vs placebo). Relative to placebo, vardenafil improved confidence in the patient (59.7 vs 26.0) and partner (57.6 vs 20.9), erection ease in the patient (61.2 vs 35.0) and perceived by the partner (60.9 vs 30.8), pleasure in the patient (65.2 vs 38.1) and partner (62.7 vs 40.2), erectile function satisfaction in the patient (53.2 vs 10.5) and partner (53.2 vs 16.9), orgasm satisfaction in the patient (60.8 vs 27.8) and partner (61.1 vs 37.2), and medication satisfaction in the patient (53.8 vs 9.2) and partner (53.1 vs 11.1). Vardenafil was generally well tolerated. The most frequently reported adverse events included flushing, nasal congestion, headache, and dyspepsia (each $< 12\%$). Conclusions: Vardenafil significantly improved erectile function, confidence, ease of erection, pleasure, and satisfaction with erectile function, orgasm and medication in men with ED and their partners.

145

VARDENAFIL IMPROVES ERECTION QUALITY ASSESSED BY THE NOVEL ERECTION QUALITY SCALE IN THE BROAD POPULATION OF MEN WITH ERECTILE DYSFUNCTION

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Objectives: To assess the influence of vardenafil on erection quality in men with erectile dysfunction (ED). Methods: This double-blind, multicenter, 12-week randomized trial enrolled 229 men with ED and partners. Men received placebo or vardenafil 10 mg for 4 weeks, with option to stay on 10 mg, or titrate to 5 mg or 20 mg at 4 and 8 weeks. Primary efficacy variables were mean per-patient success rate of erection maintenance to intercourse completion (SEP3), and improvement of partner's sexual quality-of-life (modified Sexual Life Quality Questionnaire quality-of-life domain [mSLQQ-QoL]). Secondary efficacy variables included responses to the Erection Quality Scale (EQS). Results: Mean baseline EF-domain score (ITT population: 112 placebo, 113 vardenafil) was 13.2 and 13.5, respectively (moderate ED). Vardenafil significantly improved overall LS mean per-patient SEP3 success rates vs placebo (67.7% vs 27.8%, $p < 0.0001$), and partner mSLQQ-QoL (65.8 vs 32.1, $p < 0.0001$, LOCF). Vardenafil significantly improved all EQS variables ($p < 0.0001$) vs placebo, including total score (36.1 vs 14.6), ease of getting erection (2.4 vs 0.9); frequency of getting erection easily (2.6 vs 1.1), confidence getting erection (2.3 vs 1.0); satisfaction in ability of getting erection (2.4 vs 0.7); frequency of lasting long enough for penetration (2.8 vs 1.4); frequency of lasting long enough for ejaculation (2.7 vs 1.3); confidence in keeping erection (2.3 vs 0.7); satisfaction with erection duration (2.2 vs 0.4); erection hardness (2.4 vs 1.1); frequency of erections hard enough for penetration (2.8 vs 1.3); satisfaction with erection hardness (2.2 vs 0.5); pleasurable feeling (2.5 vs 1.4); satisfaction with pleasurable feeling (2.6 vs 1.6); frequency worrying about erections (1.9 vs 0.8); overall erection quality satisfaction (2.2 vs 0.4) (LOCF). Vardenafil was generally well tolerated. The most frequent adverse events included flushing, nasal congestion, headache, and dyspepsia (each $<12\%$). Conclusions: Vardenafil significantly improved perceived erection quality and improved partner sexual QoL.

146

SEX AND THE OLDER MAN – DIRTY OLD MAN? EVALUATING THE ERECTILE ENHANCEMENT EFFECT OF ANDRIOL/TESTOCAPS ON SENIOR, IMPOTENT HYPOGONADAL MEN

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Improvement of unreliable erections in hypogonadal senior-aged men has not been adequately assessed. I conducted an open label, six-month study of 64 hypogonadal, impotent men, all over age 65 using supplemental Andriol/Testocaps 80 mg. bid. The primary objective was to evaluate any potential improvement of impotence using Testosterone Replacement Therapy (TRT). Andriol/Testocaps cost is fully covered under Canadian Drug Formulary for seniors, unlike PDE-5 meds requiring cash payments. Sample PDE-5 meds were not used within the first 3 months. Sexual performance was evaluated using SHIM and GAQ. 64 men began TRT, however, 26 men were lost to within the first two months leaving 38 men by Visit #3 (3-month mark). Here 15/38 (39.5%) men reported positive GAQ, with the 23 non-responders adding PDE-5 to TRT regimen. Visit #6 (6-month mark) – 35 returnees: 14/35 (40%) taking TRT, still maintained positive sexual GAQ and had improvement in SHIM score from 14.4 baseline mean to now 25.4. The large initial returnee drop off was unrelated to TRT side-effects ($n = 3$). Rather, men cited: lack of sexual intercourse opportunity from female partners; fear of being labeled 'dirty old man'; knowledge that PDE-5 free sampling was not open-ended, and declining PDE-5 prescriptions due to the high cost. Hypogonadism may be under recognized as an important co-factor in the erectile functioning of aging men. This observation showed 40% of TRT participants having full sexual recovery without PDE-5. Perhaps we should also remove the social construct of 'dirty old man'. From the novel, 'Angelica's Grotto', author Russell Hoban, 1999, 'I sometimes think a dirty old man might be the only kind of old man there is.'

147

PENILE DOPPLER STUDY IN AGING MALE WITH ERECTILE DYSFUNCTION

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Aims: 1) To objectively assess erectile dysfunction in the aging male patients. 2) To compare the various parameters in adult male patients with erectile dysfunction,with the younger age group with erectile dysfunction. 3) To define differences in etiologies if any, between the 2 age groups. Materials and methods: The study was conducted on 110 patients with complaints of erectile dysfunction between July 2003 to September 2004 .The study was conducted using Hewlett Packard Sonos 5500 color Doppler machine with 7.5 MHz Probe using 60 mg of Intra cavernosal Papaverine for stimulation purpose. Informed consent was taken in all cases. The following measurements were noted in all the cases Basal flow velocity, Plateau phase, Peak flow velocity, resistance index, venous leak if any, erectile response. The data was divided in 2 groups, taking the age of 45 as the cut off and then the data was compared and results analyzed. Results: The fore mentioned parameters were studied and compared and will be discussed in the presentation. Based on the observation of this study we have classified probable etiologies in the younger and the aging male. These shall be discussed in detail in the paper. Conclusion: Through this study we conclude that Penile Doppler study is a useful tool in the diagnosis and management of erectile dysfunction in the aging male.

148

CLUSTERING THE AGING MALE BASED ON IIEF FULL SCALE

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Purpose: This study aims to elucidate the characteristics of subgroups derived from cluster analysis based on International Index of Erectile Function (IIEF). Method Subjects were 1,672 Japanese married men, aged 40 to 69 years (average: 51.0 ± 6.5 y.o.), who had history of neither cerebral apoplexy nor ischemic heart disease. These subjects were arranged to five subgroups derived from cluster analysis of IIEF full scale. These subgroups were compared on the prevalence of erectile dysfunction(ED), aging, the anxiety and depression, lifestyle-related diseases such as diabetes and hypertension. In this study ED was defined as subject whose IIEF-5 score was less than 12. Hospital Anxiety and

Depression scale questionnaire was used in this study. Result: The prevalence of ED and the number of subjects on each cluster (Cluster1–5; CL1–5) was 95.24%(CL1, n = 42), 0.00%(CL2, n = 822), 2.78%(CL3, n = 576), 76.74%(CL4, n = 43), 98.94%(CL5, n = 189), respectively. Age of CL 4 and 5 was significantly older compared to those of CL 1, 2 and 3. The anxiety and depression score of CL 4 was significantly higher than other clusters. The prevalence of diabetes and/or hypertension among CL 1 was significantly higher than those among other clusters. Conclusion: CL 1 was characterized as lifestyle related. CL 2 consisted of normal subjects who have not complained ED. CL 3 seems to be reserve subject to ED. CL 4 was considered to be psychological etiology. CL 5 seems to be due to aging. This study indicated the possibility of etiological background of ED from the analysis of IIEF full scale.

149

MECHANISM OF ACTION OF GROWTH HORMONE ON ISOLATED HUMAN PENILE ERECTILE TISSUE

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Objectives: Recently, human growth hormone (GH) has been shown to reverse the adrenergic tension of isolated human corpus cavernosum (HCC) and increase tissue levels of cyclic GMP. Moreover, it was demonstrated that GH rose in the systemic and cavernous blood of healthy males with the initiation of penile erection. Nevertheless, it still remains unclear which intracellular pathways mediate the physiological effects of GH on the HCC. Thus, we evaluated further the mechanisms of GH action on isolated human penile erectile tissue. Material and Methods: Using the organ bath technique, the effects of GH on electrically (EFS)-induced relaxation of isolated HCC in the absence and presence of the guanylyl cyclase inhibitor ODQ and nitric oxide synthase inhibitor L-NOARG (10 μM) were investigated. Effects of GH on the production of tissue cyclic GMP in the absence and presence of ODQ and L-NOARG were also elucidated by means of a radioimmunoassay. In the experiments, sodium nitroprusside (SNP) was used as a reference compound. Results: ODQ and L-NOARG abolished the relaxation of the tissue induced by EFS whereas amplitudes were increased by physiological concentrations of SNP and GH (1 nM – 100 nM). The attenuation of EFS-induced amplitudes by L-NOARG but not ODQ was in part reversed by GH. The production of cGMP induced by 10 nM GH was completely abolished in the presence of 10 μM ODQ. In contrast, the combination of GH (10 nM) + L-NOARG (10 μM) maintained cGMP-production significantly above baseline (0.68 ± 0.36 vs 1.07 ± 0.48 pmol cGMP/ mg protein). Conclusion: Our data provide evidence that GH may act on human HCC by an NO-independent effect on guanylyl cyclase activity.

150

ARE DIABETOLOGISTS, GENERAL PRACTITIONERS, CARDIOLOGISTS, PSYCHIATRISTS AND UROLOGISTS OPEN-MINDED REGARDING ERECTILE DYSFUNCTION IN HUNGARY?

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Background: Erectile dysfunction should be considered like another physycal sympthom. My previous investigation indicated that 92% of males have never been asked about erectile dysfunction by the general practitioner. I could have imagine that also other specialist tend to avoid questions in connection with sexual functions. Aims: To survey if diabetologists, general practitioners, cardiologists, psychiatrists and urologists were open-minded regarding discussion of erectile dysfunction. Material and Method: A questionnaire was administered at the University of Pécs Medical Faculty. The survey involved 55 doctors: 7 diabetologists, 11 general practitioners, 9 cardiologists, 12 psychiatrists, 16 urologists. The Ethical Committee of University of Pécs Medical Faculty has accepted the project. Results: of those surveyed, 76% stated that erectile dysfunction should be treated for life. 96% are aware of the changes of sexual functions accompanying aging. 45% knew that after the age 40 every second male suffers from erctile dysfuntion. 78% had the knowledge that erectile dysfunction can be caused by hypertension, diabetes mellitus and atherosclerosis; 64% knew that erectile dysfunction can be the side-affect of antihypertensives, anxyolitics and major tranquilizers. 42% of responders stated to routinely assess male patients regarding sexual functions and 87% believe that their patient would tell if erectile dysfunction appeared. Despite this, in a year on the avarage only 40 patient complain about erectile dysfunction by the urologist, 17 by the cardiologist, 15 by the general practitioner, 10 by psychiatrist, 12 by diabetologist. 96% think the erectile dysfunction should be treated by urologist, 58% by psychiatrist, 49% general pratitioner, and only 29% by cardiologist. Discussion and Conclusion: Diabetologists, general practitioners, cardiologists, psychiatrists and urologists are aware about the the diseases and drugs causing erectile dysfunction. Only a low proportion of the affected males receive a treatment in Hungary. The communication between patients and doctors needs an improvement.

151

CLINICAL EXPERIENCE WITH LONG-ACTING TESTOSTERONE ESTER (NEBIDO) IN PATIENTS WITH ERECTILE DYSFUNCTION

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Objective: Evaluating the impact of testosterone therapy on erectile dysfunction, also in combination with PDE-5 inhibitors, besides impact on veno-occlusive insufficiency and cavernosographic changes in patients with obesity and metabolic syndrome and ED. Methods: 1) review of literature in terms of Testosterone therapy alone, and in combination with PDE-5 inhibitors in patients with erectile dysfunction. 2) study review of Yassin and Saad, changes in penile cavernography and venous leakage under testosterone therapy in hypogonadal patients with ED ''Case Report'', Int. J of Andrology, Vol. 28, Suppl. 1, June 2005. Results: 1) 56% of the patients in the Greenstein study and 54% in the Yassin/Saad study reported restored erectile function sufficient for sexual intercourse after 10 resp. 12 weeks of testosterone therapy alone. 2) Studies of Shabsigh, Yassin and Kalinchenko, provided the evidence to convert about 63% hypogonadal non-responders to PDE-5 inhibitors alone into responders within 10 to 12 weeks in combination with testosterone. Patients with veno-occlusive dysfunction with Diabetes or metabolic syndrome, and severe ED could improve their sexual function under Nebido. Cavernosography showed dramatic improvement in many subjects within 3 months under Nebido. Conclusion: ED and hypogonadism are prevalent; the population at risk includes those diagnosed with diabetes mellitus, metabolic syndrome, chronic renal failure, and aging. Screening these populations will yield men who can benefit from testosterone therapy. Testosterone plays a key role in the central and peripheral modulation of erectile function. New research in the laboratory and in humans is shaping a refinement of the role of testosterone therapy in ED. Testosterone deficiency induces both biological and structural/functional changes in the trabecular cavernosal tissues. Adipocyte accumulation in penile subtunical area of the corpus cavernosum in orchietomized rabbit emphasized the potential mechanism for veno-occlusive dysfunction in androgen deficiency (Traish et al. 2005).

152

MODULATION OF ERECTILE FUNCTION IN PROSTATE CANCER PATIENTS AFTER NERVE-SPARING RADICAL PROSTATECTOMY

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Objective: To assess and present our own concept to maintain or improve erectile function in patients who underwent uni- or bilateral nerve-sparing radical prostatectomy. Methods: During 1999 till end October 2004, 420 patients who had undergone radical retropubic prostatectomy by organ confined prostate cancer with uni- or bilaterial nerve-sparing were assessed pre- and post-operatively. The pre-operative assessment showed that 42% initially had no interest in sexual activities, 58% (244 persons) were interested. 120 subjects were considered as control group. 124 patients took the ''penile training''. Partner assessment, IIEF, ICI and doppler ultrasound were performed prior to surgery. From the 11th day after surgery we ordered 25 ml Sildenafil 3 times a week or 5 mg Tadalafil twice a week. We additionally prescribed ''penile body building'' with vacuum device at least twice a day. An additional independent parallel control group of 41 patients who underwent bilateral nerve sparing surgery, took the penile training with vacuum device alone for three months. Outcome in terms of erectile function evaluated after 3 months. Results: 18% of control group patients who underwent bilateral nerve-sparing radical prostatectomy had spontaneous erectile function, whereas in the unilateral nerve-sparing group just 8% achieved it. In the therapy group 56% of the patients obtained good erectile function and sufficient for sexual intercourse under PDE-5 inhibitors in uni- or bilateral nerve-sparing procedure. Sildenafil subgroup reported significantly higher satisfaction (78% vs. 64% to Tadalafil subgroup). In the penile training control group(vacuum device), 16 patients (39%) reported satisfactory erection. The majority of non-responders in these groups took ICI with Alprostadil. Conclusion: Early application of ''penile training'' in patients after nerve-sparing radical prostatectomy with sequential application form of low dose PDE-5 inhibitors in combination with vacuum device leads to considerably better results in terms of preserving the erectile function.

Urological Aspects in Aging Men

153

IMPACTS OF LATE ONSET HYPOGONADISM ON THE PSA-TESTIN IN AGING MEN

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There is conclusive evidence that prostate cancer is androgen sensitive and changes in circulating testosterone may either result in an inhibition or activation of the biological activity. Obviously, the exclusion of prostate cancer prior to testosterone supplementation of hypogonadal aging men is essentiell. The combination of PSA and rectal digital examination (DRE) has acceptable positive predictive values and resulted in a significant increase in the diagnosis of early stages of prostate cancer. However, PSA has shortcomings due to low cancer specificity. Further, the expression of PSA is androgen dependent and hypogonadal men may have lower PSA which could mask pre-existing prostate cancer. These specific problems gave rise to discussion on lower PSA cut offs as well as pretreatment biopsies irrespective of PSA levels in hypogonadal men. Continuing PSA- and clinical monitoring prior to the institution of treatment with testosterone and at regular intervals during therapy is important to detect preexisting tumors and to avoid adverse effects of exogenous testosterone. A rise in PSA shortly after the institution of treatment may unmask prostate cancer.

154

POSSIBLE RELATIONS BETWEEN TESTOSTERONE LEVELS AND INCIDENCE, GRADE AND STAGE OF EARLY DETECTED PROSTATE CANCER

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Morgentaler et al. published nearly a decade ago that the incidence of Prostate Carcinoma (PC) is higher in men with low T levels. The prevalence of low serum T levels is different in men with and without PC. In our studies more than 60% of men with Gleason Score >8 had a serum T level <3 ng/ml. Mean Gleason score was higher (7.4 vs. 6.2) in men with a low serum testosterone, PSA-levels were lower (25.3 vs. 31.9 ng/ml). Mean testosterone levels decreased from 4.1 ± 1.7 ng/ml in patients with Gleason scores ≤ 5 to 2.8 ± 2.7 ng/ml with Gleason scores ≥ 8. These men had lower hLH (3.3 vs. 5.9 mIU/ml), hFSH (6.2 vs. 8.4 mIU/ml), and estradiol (18.8 vs. 29.1 pg/ml) serum levels. The fact that gonadotropins were lower in parallel suggests a tumor-mediated suppression of the hypothalamic-pituitary-gonadal hormone axis particularly in men with high Gleason score tumours. We could not find a correlation of T-levels and local stage in our patients. Androgen receptor expression was higher in patients with low serum testosterone ($96.6 \pm 2.8\%$ vs. $84.8 \pm 7.2\%$; $p = 0.03$) as well as tumour vessel density ($63.0 \pm 30.8/0.46$ mm^2 vs. $39.0 \pm 22.9/0.46$ mm^2; $p = 0.007$). The number of CAG repeats within the AR gene showed no correlation with serum androgen levels. After radical prostatectomy, the serum T level increases after 12 months especially in the group with high Gleason Score. The reasons for this phenomena remain still unclear. Numerous studies suspect Inhibin to influence the pituitary gonadal axis by negative feed back mechanism. We looked at Inhibin B in our patients and we could not find any significant difference in serum Inhibin B level in men with normal and low serum T levels.

155

ANDROGEN POLYMORPHISM AND PROSTATE CANCER

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Beside racial risk factor and increasing age, the family history is a accept risk factor for development of PC. The association of genetic polymorphism's and PC risk is much more common. In the MEDLINE, more than 400 articles were found, whereas particularly the genetic polymorphism's of the gens of the testosterone pathway are investigated. (Cytochrom P 450 enzymes, 5 reductase type II gene, Androgen Receptor gene (AR), PSA gene). The role of number of the CAG repeats of the AR is controversially discussed. Some studies have shown that men with PC have shorter CAG repeats than men without PC In addition, African Americans have shorter CAG repeat lengths in the AR gene associated with a higher incidence and mortality from PC. In parallel, several studies have shown, that the PSA G/G genotype is associated with higher aggressiveness of PC Our study group descript a significant influence of the ARE-I PSA polymorphism on PC risk. (A/G and G/G genotype vs. A/A genotype: Odds ratio 0.63; 95% Confidence interval 0.39–0.99; $p = 0.048$). In addition the PSA G/G polymorphism was significantly more frequent in patients with Gleason Score (35.1%, $p = 0.034$). 134 men of the PC group were underwent a serum hormone analysis including T, Luteotropic hormone (LH), Follicle stimulating hormone (FSH). In a multivariate analysis, the PSA G/G polymorphism was associated with a low serum T (T3 ng/ml) level (Odds ratio 2.25; 95% CI 1.04–11.9; $p = 0.04$) and to Gleason Score 7 (Odds ratio 0.21; 95% CI 0.09–0.44; $p = 0.03$). In addition, CAG repeat length < 22 was associated significantly to serum T levels 3 ng/ml, proven by multivariate analysis. Low serum T levels are associated with higher Gleason Score. The raisons for this phenomenon remain unclear, although PSA gene polymorphism and AR gene polymorphism show significant correlation.

156

POTENTIAL RISKS OF ANDROGEN SUPPLEMENTION FOR THE PROSTATE OF AGING MEN

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Possible impacts of testosterone supplementation on prostate cancer risk in hypogonadal aging men is a matter of controversial debate. The incidence of prostate cancer increases with age while testosterone levels decrease continously. The prevalence of prostate rises with age and >60% of men aged between 60 and 79 years present with preclinical cancer rising to almost 80% in men over 80 years of age. Aging men are at high risk for prostate cancer. It has been clearly documented that androgens stimulate cell proliferation in clinical prostate cancer. However, the effect of androgens on the promotion of preclinical into clinical cancer still remains unclear. Previous studies have not shown that men presenting with higher testosterone levels are at higher risk to develop clinical prostate cancer during life time. There are recent reports, however, that low testosterone is associated with the development of more malignant cancer with high Gleason grade. Data available on possible impacts of exogenous testosterone on the incidence of prostate cancer in hypogonadal aging men are inconsistent and were mainly collected from open studies. The majority of these studies present with small numbers of patient and a short follow up. A prospective controlled trial with recruitment of patients numbers to provide adequate power for statistical analysis to clarify this question is necessary to clarify this problem. Careful assessments of the prostate pretreatment and at regula intervals throughout therapy is mandatory to recognize clinical prostate cancer at an early stage. Prostatae cancer detection mainly relies on PSA, DRE and randomized prostate biopsies. There is controversial debate on prostate biopsies before treatment in men with low PSA. However, prostate cancer cannot be definitely excluded by PSA testing and DRE. This supports the idea of pretreatment prostate biopsies in men with low PSA. Administration of testosterone in hypogonadal men with prostate cancer after radical prostatectomy and non detectable PSA has recently been recommended. However, 30% to 50% of men who underwent surgery for localized cancer develop chemical and/or clinical progress within 10 years after radical prostatectomy.

157

THE AGING BLADDER IN MEN

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Lower urinary tract symptoms (LUTS) are highly prevalent among older men and impair quality of life. LUTS are categorized as storage symptoms (urgency, all forms of urinary incontinence, frequency, nocturia), voiding symptoms (slow stream, splitting or spraying, intermittency, hesitancy, straining, terminal dribble), and post micturition symptoms (sensation of incomplete emptying, post micturition dribble). Although LUTS are also highly prevalent in women, their frequent comorbidity with potential prostatic disease in men adds complexity to the management of male LUTS. Male LUTS are often associated in contemporary literature with benign prostatic hyperplasia and bladder outlet obstruction (BOO), but voiding symptoms are poorly correlated with underlying pathophysiology, whereas the storage symptoms that characterize overactive bladder (OAB) syndrome (ie, urgency, urgency urinary incontinence, frequency, nocturia) are more closely correlated with underlying bladder dysfunction such as detrusor overactivity rather than prostatic pathology. Therefore, pharmacotherapies that target the prostate (e.g., a1-receptor antagonists and 5a-reductase inhibitors) often fail to alleviate OAB symptoms in men with BOO, and may not be the most appropriate therapy for men with storage LUTS. Antimuscarinics have been demonstrated to have little effect on detrusor contraction and involuntary detrusor contractions measured during the bladder filling phase and have been shown to improve OAB symptoms in men enrolled in clinical trials. Multiple studies have also demonstrated the effectiveness of antimuscarinic/a1-receptor antagonist combination therapy in men with OAB symptoms and BOO. Although there is some concern that the inhibitory effect of antimuscarinics on detrusor muscle contraction could theoretically aggravate the voiding difficulties of, or cause urinary retention in men with OAB symptoms and possible BOO, little evidence supports this concern. A new treatment paradigm that recommends antimuscarinics alone or in combination with a1-receptor antagonists as a first-line therapy for men with OAB symptoms is proposed based on the contemporary literature.

158

THE AGING PENIS

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Introduction: Erectile dysfunction (ED) is defined as the persistent inability to attain and/or maintain a penile erection sufficient to complete satisfactory sexual intercourse. As the average duration of life has been progressively increasing, a corresponding increase of the number of men reporting ED should be expected. Material and Methods: Analysis of published full-length papers that were identified through Medline search from January 2000 through September 2005. Abstracts published in peer-reviewed journals from the same period were also considered Results: The process of aging may affect all the components in the erectile process, including nerves, arteries, veins, cavernosal tissue and hormones. Atherosclerotic disease of the pudendal and cavernosal arteries has been shown to be a major cause of ED in the elderly patient Major risk factors for atherosclerosis, e.g. hypertension, hypercholesterolaemia, smoking and diabetes, have also been found to be associated with smooth muscle degeneration, e.g. impaired relaxation of vascular smooth muscle. The decreased smooth muscle content of the corpus cavernosum, related to the severity of arterial occlusion, is associated with the impairment of cavernosal expandability and subsequent veno-occlusive dysfunction. Aging has been shown to decrease the frequency, duration and degree of nocturnal erections. Indeed, animal studies have identified the association between veno-occlusive dysfunction of the corpora cavernosa and corporeal fibrosis. The endocrine milieu is significant in regulating erectile function; several hormonal systems show a gradual decline during ageing, represented by a decrease in their bioactive hormone concentrations. Conclusions: In summary, it seems reasonable to hypothesize that the ED associated with ageing is the result of atherosclerosis-induced cavernosal ischaemia leading to cavernosal fibrosis and veno-occlusive dysfunction. Abnormalities in circulating levels of hormones controlling the sexual organs seem to have an important effect, at least in some patients.

159

UPDATE ON PSA IN DIAGNOSIS OF PROSTATE CANCER

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Although prostate cancer mortality has declined slightly in recent years, the incidence of this disease has shown a marked increase in the last two decades. It has been estimated that 679 000 men world-wide were diagnosed with prostate cancer and 221 000 men died of the disease in the year 2002 alone. There is no doubt that PSA screening has revolutionized the diagnosis of prostate cancer since its advent in the late 1980s. A substantial amount of clinical and basic science research over the last two decades has been dedicated to defining the precise parameters and derivatives of PSA that will optimize the sensitivity and specificity of the test. In recent years, there has been a tempering of the initial excitement over PSA and several studies have been published suggesting that the exact role of PSA in prostate cancer detection needs to be redefined. Unfortunately, we are still lacking evidence from well-designed clinical trials to justify the widespread incorporation of PSA

testing into urologic practices that has occurred recently. Nevertheless, PSA screening continues to gain popularity world-wide. Studies performed in recent years have proven PSA testing to be a far-from-perfect screening test. Though PSA levels can estimate the risk of prostate cancer in a given patient, no PSA level exists below which there is no risk of cancer. Even after years of utilisation and study of PSA testing, the urologic community is still unable to agree upon a PSA cut-off which adequately differentiates patients with a high risk of cancer from those in whom risk is low. PSA testing allows for the diagnosis of more cancers, at an earlier stage, than would be possible without screening. Patients with screen detected cancers may then educate themselves about the benefits and possible morbidities associated with various treatment options, and therefore make an informed decision about their own course of treatment. Further research should allow us to identify more effective screening programs and improved methods of interpreting PSA data, which not only identify men with cancer, but differentiate those men with aggressive, potentially fatal disease from those with more indolent tumors.

160

ALTERNATIVES TO SURGERY FOR LOCALIZED PROSTATE CANCER

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Three-dimensional conformal radiotherapy is the technique of reference for definitive radiation therapy. Dose delivery depends on the risk group of the patient groups as defined by D'Amico. Radiation therapy offers comparable survival rates and quality of life than radical prostatectomy. It is debate if high or intermediate risk group patients should receive adjuvant hormonal therapy. Brachytherapy is a validated option for patients presenting with favourable risk factors. In the USA, 5% of the localized PCa patients were treated with brachytherapy in 1990 and they are now 36%. The success rate of brachytherapy in those instances is comparable to the success rate of 72 Gy external beam irradiation. Experimental treatments are oriented to minimally invasive procedures. Cryosurgery is not recommended so far in Europe. Best results are obtained with good prognosis tumours, but long term results are lacking. High-intensity focused ultrasounds (HIFU) has been developed in Europe, but its evaluation remains difficult as few studies have been published. However, if good prognosis tumours seem to be the best candidates, complications rate remains a matter of concerns. Radiofrequency interstitial tumour ablation (RITA) has limited evaluation in PCa but appears to be a seducing option due to its safety, but oncological data are still waited. Even if in phase I-II, phototherapy of PCa (PDT) may gain interest, but its role as single treatment or in combined modalities remains to be determined. Deferred treatment or active monitoring will probably become a major option for localized PCa. Algorithms and nomograms, including stage, Gleason grade, PSA and, more recently, PSA velocity, help to recognise PCa at low risk of progression. Actually, 10 to 24% of ERSPC patients diagnosed with PCa are already managed with deferred treatment.

161

PREVALENCE OF ERECTILE DYSFUNCTION IN MEN WITH ADENOCARCINOMA OF THE PROSTATE BEFORE RADICAL PROSTATECTOMY (RRP)

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Introduction: Erectile dysfunction (ED) affects around 50% of men over 40 years old worldwide. It is very prevalent and has an enormous impact in the couple's quality of life. Aging and the presence of comorbidities are strong predictors of ED. The younger the patient and the presence of normal erectile function before the surgery are good predictors for the maintenance of the erectile function after RRP. Objective: Determine the prevalence of erectile dysfunction in patients with adenocarcinoma of the prostate who will undergo RRP, correlating their age with severity of ED. Patients and Methods: Between September 2003 and March 2004 140 patients with adenocarcinoma of the prostate answered the International Index of Erectile Function questionnaire (IIEF) prior to the RRP. The erectile function domain of the IIEF was analyzed and the patients were classified regarding the severity of ED and correlated with their age. Results: The mean age was 61.5 years old (56–76). The overall prevalence of ED – any severity – was 67.8%. When stratified by age, severe ED was diagnosed in 12% of men between 51–60 years old, in 24.3% in the group between 61–70 years old and in 43% in those older than 70 years. Conclusion: The prevalence of ED prior to RRP was higher than the most common epidemiologic data available in the general population. According to previous data we found a clear correlation between ED severity and age of the patients. These findings may contribute to the high number of patients with ED after RRP.

162

PREOPERATIVE TOTAL AND FREE TESTOSTERONE AND THE GLEASON'S SCORE AFTER RETROPUBIC RADICAL PROSTATECTOMY (RRP): WHAT'S THE CORRELATION?

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Objective: The aim of this study is to look for statistic association between pretreatment different serum levels of Total (TT) and Free Testosterone (FT) and the Gleason's score after RRP in patients with prostate adenocarcinoma clinically localized. Patients and Methods: Serum levels of TT and FT were obtained preoperatively in 100 patients submitted to RRP between July 2003 and May 2004. The patients were stratified in different range groups: 1) TT: <300 ng/dL, 300–599 ng/dL, 600–899 ng/dL and >900 ng/dL; 2) FT: <10 picog/mL, 10–30 picog/mL and >30 picog/mL; 3) Gleason Score: 4 to 6, 7 and 8 to10. Univariated analyses were done utilizing the qui square test searching for statistic association. Results: The medium values found were: age: 63.8 years old (45–77), PSA: 8.3 ng/mL (1.4–25.6), total testosterone: 490 ng/dL (189–1022) and free testosterone: 16.8 picog/mL (1.2–32.9). 85% of the patients presented confined organ disease (pT1 and pT2) after the RRP. There were no significant statistic association between different preoperative levels of TT and Gleason's score ($p > 0.1$) and FT and Gleason's score ($p > 0.25$). Conclusions: In patients with prostate adenocarcinoma clinically localized we didn't find any statistic correlation–using univariated analyses – between preoperative different serum levels of Total Testosterone and and Gleason's score and preoperative different serum levels of Free Testosterone and Gleason's score in pathologic evaluation after retropubic radical prostatectomy.

163

ASSESSMENT OF COLLAGEN I TELOPEPTIDASE (ICTP) AS A MARKER IN DETECTION OF PROSTATE CANCER BONE METASTASES. AN ALTERNATIVE AUXILLIARY DIAGNOSTIC TOOL FOR ELDERLY PATIENTS

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Purpose: Assessment of diagnostic validity of ICTP level in relation to bone metastases. Background: Skeletal involvement is typical, among the others, for advanced prostate cancer. Diagnostic techniques usually used are X-ray or bone scintigraphy. These are time consuming, expansive and joined with some radiation burden. Simple methods have been investigated. There is certain evidence that ICTP assessment seems to be valuable tool. Material and methods: 436 prostate cancer patients were followed up at our department and PSA

and ICTP was regularly checked-up (total 2003 examinations). The known disease stage in each case or suspicion on cancer recurrence was compared with ICTP and PSA level. Results: ICTP level varied between 1.39–43.58 mg/l and PSA average was 21.46 ng/ml (<0.01; 5398>). ICTP results correlated quite well with T and M category as well as with cancer response to therapy, and finally an ICTP elevation may signalized bone metastases in cases were PSA is still low. Therefore ICTP level could be used as an auxiliary tool when indicating skeletal examination (in sense to postpone or accelerate the indication). That is what we consider important merely. in elderly patients. Results are discussed in details.

164

GAGEC1: A TARGET FOR PROLIFERATIVE DISEASES OF THE AGEING PROSTATE?

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Proliferative disorders of the prostate, such as prostate cancer (PCa) and benign prostatic hyperplasia (BPH), represent two of the most common diseases affecting the ageing male. Alterations in stromal cell composition, function and the presence of reactive myofibroblasts are thought to play a key role in BPH and PCa. These myofibroblasts are generated by the pro-inflammatory cytokine transforming growth factor beta 1 (TGF-β1), and support proliferation, angiogenesis and invasion. We previously showed that GAGEC1 (JM27) is up-regulated in trans-differentiated prostatic stromal myofibroblasts induced by TGF-β1. The stromal-specific gene GAGEC1 is also up-regulated in tissues from patients with BPH and prostate cancer. There have been very few biochemical studies of GAGEC1 and the function of the encoded gene product remains unknown. GAGEC1 is related to the GAGE family of cancer/testis assocaited antigens. In normal tissues, GAGEC1 expression is restricted to male and female reproductive tissues, placenta and the prostate. Transiently expressed recombinant GAGEC1 is distributed throughout the mammalian cell with predominant nuclear staining observed in all tumour and prostatic primary cell lines tested. Consistently the highly conserved N-terminus of in silico-identified GAGEC1 orthologues contains a putative nuclear localisation signal. We demonstrate that whilst ectopic expression of GAGEC1 has no effect on cellular proliferation, apoptosis-related mechanisms may be affected. The observation that GAGEC1 is up-regulated in BPH and PCa together with its restricted expression pattern in normal tissues, suggests that GAGEC1 may be a promising target in the diagnosis and/or treatment of proliferative diseases of the prostate. Supported by FWF Austrian Science Fund FSP S93. NDS is a Lise Meitner Research Fellow.

165

CASE FINDING STUDY ON EARLY DETECTION OF PROSTATE CANCER PRO AND CON FOR BIOPSY ARE DISCUSSED. ANALYSIS OF 5744 CASES

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Purpose: To improve selection of candidate for prostate biopsy among elderly men with PSA elevation. Background: TPSA and isoforms are a powerful tools in searching for the asymptomatic prostate cancer. Prostate biopsy is an unpleasant method and in some cases could be dangerous. Also being labelled with ''cancer'' can be devastating to patients, both emotionally and socially with very negative consequences. Materials and Method: Between 1999 and 2002 yrs 5744 pts. were referred to our department from GP's having PSA over 3.5 ng/ml or with some urinary disturbances. All of them underwent diagnostic algorithm consisting of patient medical history, physical examination, PSA tests (TPSA, FPSA), density and velocity calculation, ultrasound. Based on careful evaluation of obtained data an indication of prostate biopsy was taken. Each patient was thoroughly informed what PSA elevation could signalize, how biopsy is done and what follows if cancer is histologically confirmed. Results: Average age was 66.3 yrs with range 40–82 yrs. Average of PSA in the whole group was 3.86 ng/ml with range 0.1-1687 ng/ml. PSA <4 ng/ml was found in 4372 cases, PSA elevation ranging between 4–10 ng/ml was confirmed in 684 cases, and values over 10 ng/ml were detected in 289 men. Prostate size ranged between 10–212 ml with an average 31.82 ml. From 833 biopsies cancer was histologically proven in 486 cases (48%) what means 8.46% of the whole group. Than each cancer was classified by TNM (see Table I).

Table I.

Stage I	79
Stage II	206
Stage III	119
Stage IV	82
Total	486

Conclusion: Elderly men with elevated PSA should be carefully examined before indication for prostate biopsy is recommended. Diagnostic algorithm is described in details with the stress given on the percept ''first, do no harm''.

166

PROSTATE VOLUME, AGE, SERUM PROSTATE SPECIFIC ANTIGEN AND TESTOSTERONE IN PATIENTS WITH BENIGN PROSTATE HYPERPLASIA INDUCED LOWER URINARY TRACT SYMPTOMS

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Purpose: Development of benign prostate hyperplasia (BPH) is considered to aging and testosterone (T). We studied relationships between serum prostate specific antigens (PSAs), total and free Ts, age and prostate volume in patients with BPH induced lower urinary tract symptoms (LUTS). Materials and Methods: One hundred ninety seven men with BPH induced LUTS were evaluated prostate volume with transrectal ultrasonography and serum total and free PSAs, serum total and free Ts were evaluated. Blood samples were obtained at 9 to 11 am. Results: The average age was 61.0 $\pm$ 11.3 years and average prostate volume was 34.2 $\pm$ 16.7 ml. Serum total and free PSAs, serum total and free Ts were 4.4 $\pm$ 9.7 ng/ml and 0.6 $\pm$ 0.9 ng/ml, 5.1 $\pm$ 2.2 ng/ml and 10.5 $\pm$ 3.4 pg/ml, respectively. They showed significant increase in the serum total and free PSAs, prostate volume and decrease in the serum free T with age. Also, they showed significant increase in the serum total and free PSAs and serum free T with prostate volume. Conclusions: The age correlates positively with serum PSAs, prostate volume and negatively correlates with serum free T. The prostate volume correlates positively with serum PSAs and serum free T.

167

ARE SERUM TESTOSTERONE LEVELS ASSOCIATED WITH MEASURES OF BENIGN PROSTATIC HYPERPLASIA IN AGING MALE?

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Purpose: Benign prostatic hyperplasia (BPH) is very common among ageing male and can cause lower urinary tract symptoms which may be bothersome and tends to interfere

with quality of life. Previous studies revealed androgens play an important role in the process of BPH. This study is conducted to evaluate the relationships between serum testosterone levels and measures of BPH in aging male. Materials and Methods: A free health screening for aging male ($\geq$45 years old) was conducted in Kaohsiung Medical University Hospital in August, 2004. Serum testosterone levels (total-, free-, bioavailable-), serum prostate specific antigen (PSA) level, prostate volume and the International Prostate Symptom Score (IPSS) were evaluated. Subjects also completed a health and demographics questionnaire. Pearson's correlation coefficient and multiple linear regression analysis were used to express the strength of the correlations. Results: Total 148 aging men joined this health screening and completed above questionnaire. Age was significantly correlated with prostate volume ($r = 0.268$, $P < 0.01$), IPSS ($r = 0.182$, $P < 0.05$) and serum PSA level ($r = 0.378$, $P < 0.01$). But serum testosterone levels (total-, free-, bioavailable-) were not significantly correlated with prostate volume and IPSS. In multiple linear regression analysis (including age, body mass index, serum sex hormone binding globulin level and total testosterone level), only age was still significantly correlated with prostate volume ($P < 0.001$). Conclusion: In our study, we didn't find any association between serum testosterone levels and prostate volume no matter total testosterone, free-testosterone or bioavailable testosterone was used. Age is still the most important risk factor in the development of BPH and LUTS. Further large studies may be needed to confirm these preliminary results.

168

IS TURP IN BPH STILL A 'GOLD STANDARD' THERAPY?

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The evaluation and management of symptoms related to bladder outlet and urethral obstruction forms a large portion of any given urology practice. BPH refers to a regional nodular growth of varying combination of glandular and stromal proliferation that occurs almost in all men who have testes and who live long enough. The treatment options for BPH are plenty ranging from medical management to minimal invasive and surgical management for the same. TURP has remained the gold standard in the management of BPH. However, many other modalities like – TUMT, TUNA, TUIP, TUVP, HIFU, Laser etc have come forward from time to time in the management of BPH. This study brings about the various modalities, their comparisons, their advantages and disadvantages and relative combination attached to each procedure. Finally it concludes upon the correct mode and the indication for a particular procedure for the management of BPH. Hence, it is important for the practicing urologist and the population at large to know the various modalities in the management of BPH to select the correct methodology for the treatment of BPH as a gold standard.

169

HEALTH-RELATED QUALITY OF LIFE DURING ANDROGEN DEPRIVATION THERAPY IN JAPANESE PROSTATE CANCER PATIENTS

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Objective: Treatment for prostate cancer (PC) has a significant impact on health-related quality of life (HRQOL). We prospectively evaluated HRQOL in Japanese men undergoing androgen deprivation therapy (ADT). Patients and Methods: 56 PC patients who had received ADT were enrolled in this study. Questionnaires addressing disease-specific (UCLA-PCI) and generic (SF-36) HRQOL were measured before prostate biopsy and during ADT. Mean age at diagnosis was 76.0 ± 6.7 years. Mean pretreatment serum testosterone level was 3.90 ± 1.36 ng/ml. Clinical stages were as follows: B, 22 patients; C, 17 patients; D, 17 patients. The analysis focused on comparing each post- with pre- treatment HRQOL score. Wilcoxon signed-rank test was used to study HRQOL over time. Results: During ADT, these patients showed almost the same SF-36 total scores and its eight domains compared to the baseline. In stages B and C, there were also no statistically significances during the first year of ADT in SF-36 total scales and its sub domains, except for a decline of vitality(6, 12 month; $p = 0.021$, 0.027). Meanwhile, stage D patients had significant improvements in bodily pain (3, 12 month; $p = 0.028$, 0.017), vitality (12 month; $p = 0.037$), mental health (3 month; $p = 0.025$) and role emotional (6 month; $p = 0.010$). Urinary function improved after ADT (6, 12 month; $p = 0.016$, 0.047). Urinary bother scores increased (3, 6, 12 month; $p = 0.027$, 0.005, 0.046). Sexual function deteriorated substantially (3, 6, 12 month; $p = 0.006$, 0.0001, 0.0005). In contrast, sexual bother significantly improved after ADT (6, 12 month; $p = 0.026$, 0.006). Conclusions: Generic HRQOL was mostly unaffected by ADT in Japanese patients. As for disease-specific HRQOL, there was a substantial increase in urinary function. The deterioration of sexual function was marked throughout ADT. In spite, patients mostly did not suffer from sexual bother, which is very specific to Japanese population.

170

THE IMPACT OF OVERACTIVE BLADDER, URINARY INCONTINENCE AND ERECTILE DYSFUNCTION ON QUALITY OF LIFE: A PROSPECTIVE LONGITUDINAL STUDY IN MEN AGED 45 TO 103 YEARS

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Introduction: Lower urinary tract symptoms (LUTS) such as overactive bladder (OAB), urinary incontinence (UI) and erectile dysfunction (ED) have been reported to have a negative impact on quality of life (QoL). The aim of the present study was to re-assess in 2003 the relationship between OAB, UI, ED and QoL in a random sample of men who were initially assessed in 1992. Material and methods: In 1992, 10 458 men, aged 45 to 99 years, were selected at random from the Population Register. The men received a postal questionnaire on OAB, LUTS, ED, social, medical and demographic data. The response rate was 74% ($n = 7\,763$). Eleven years later a similar questionnaire was sent to the men, who responded 1992 and who were still alive and available in the register. QoL was assessed with a visual analogue scale (VAS, 0–100) where 0 represented "maximum well-being" and 100 represented "worst possible well-being". Results: In 2003, 4 072 of the 7 763 men who responded to the questionnaire in 1992 were still available in the Population Register and 3 258 men (80%), aged 56 to 103 years, responded. The results of an assessment of QoL by the VAS in the men grouped according to the absence or presence of OAB, UI or ED in 1992 were (means $\pm$ SD): 17.3 ± 21.4, 28.4 ± 26.8 (OAB); 18.7 ± 22.3, 31.7 ± 29.3 (UI) and 19.0 ± 22.9, 31.7 ± 28.6 (ED), respectively. The corresponding numbers for 2003 were: 16.9 ± 22.3, 25.0 ± 26.1 (OAB); 19.4 ± 23.5, 33.3 ± 30.7 (UI) and 19.1 ± 23.4, 33.0 ± 29.2 (ED). Conclusions: The results support earlier studies documenting that OAB, UI and ED had a negative imapct on QoL in men. The negative impact of OAB, UI and ED increased in the same cohorts of men with older age. This underlines the need for effective forms of treament for OAB, UI and ED.

171

A PERSPECTIVE ON 'INFLAMM-AGING' OF THE MALE GENITAL TRACT: AGE-RELATED CHANGES IN SEMINAL PMN-ELASTASE

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Introduction: Genital tract inflammation is a major contributing factor to male infertility. The majority of patients, however, remains asymptomatic, and thus, diagnosis is based on laboratory methods, i.e. semen analysis. Notably, determination of the seminal polymorphonuclear granulocyte elastase (PMN elastase) has been proven a reliable marker of silent male genital tract inflammation. As male aging does not only decrease serum testosterone levels but has also been associated with impaired fertility and inflammatory reactions of the genital tract, we investigated age-related changes in seminal PMN elastase levels. Patients and Methods: The retrospective study included a total of 4,265 patients (age: 17–66 years) attending the andrological outpatient clinic at the Centre of Dermatology and Andrology, University of Giessen. Semen analysis was performed according to WHO guidelines including the number of peroxidase-positive cells and fructose concentrations. PMN elastase was determined in cell-free seminal plasma using an enzyme-linked immuno-absorbent assay. Results: While ejaculate volume, motility and fructose were negatively correlated with age, sperm concentration, PMN-elastase and the pH-value showed a positive correlation. The prevalence of male genital tract inflammation (as defined by PMN-elastase >250 ng/ml) and its severity increased significantly with age. In contrast, PMN-elastase did not correlate with sperm motility. Fructose as a marker of seminal vesicle function showed a significant negative relationship with the PMN-elastase levels, the number of peroxidase-positive cells and sperm motility. Conclusions: Significant increases of PMN-elastase levels as a marker of male genital tract inflammation in older men appear to be indicative of age-related changes in local immunoregulatory mechanisms. In fact, global immunosenescence has been associated with an increased pro-inflammatory status, thus suggesting 'inflamm-aging' of the male genital tract.

172

SHOCK WAVE LITHOTRIPSY (SWL) FOR URETERAL STONES IN ELDERLY PATIENTS

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Introduction: Age was never taken as a factor in the treatment of ureteral stones. Elderly male patients may suffer from concomitant voiding difficulties and musculo-skeletal disorders (MSD). MSD may affect the ability of accurate aiming of the shock wave focus directly to the stone during SWL, obstructing voiding disorders may interfere with post treatment stone expulsion. Our aim of study was to assess the success rate and complications of SWL for large ureteral stones in patients older than 70. Material & Methods: We retrospectively reviewed the charts and radiology films of all patients who had SWL for ureteral stones, following SWL with the HM3 lithotriptor. We compared SWL results of all patients to the results of the group of patients older than 70 years. Results: During 2000–2003, 243 consecutive male patients underwent SWL under regional anesthesia for ureteral stones. Among them a group of 27 patients were older than 70 years. In group 1 including only patients younger than 70 years, the mean age was 45 years. In group 2 including patients over 70 the mean age was 74 years. Stone sizes, location, opacity, and pre operative drainage procedures matched between groups. Overall stone free rate in group 1was 92.6%, compare to 96.6% in group 2. Complications were recorded in 4% of the patients in group1 and 7% in group 2. All patients suffered from febrile urinary tract infection treated successfully with I.V. antibiotics. No treatment related mortality was recorded. Conclusions: Our data show that age itself has no effect on the stone free rates of SWL for ureteral stones. In general SWL treatment showed a high success rate with minimal morbidity and no treatment related mortality.

173

DOES TOTAL TESTOSTERONE PREDICT MORTALITY IN MEN? RESULTS FROM THE MASSACHUSETTS MALE AGING STUDY

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Testosterone (T) levels decline with age in men. A few small clinical studies have suggested that T may predict short-term mortality. We evaluated total T as a predictor of mortality in a population-based prospective cohort (the Massachusetts Male Aging Study (MMAS)). Participants were followed from 1987–89 (age 40–70 yr) until 2002–04 for mortality due to all causes, cardiovascular disease (CHD), and malignant neoplasms. Person-years (pyr) were accumulated from baseline to date of death or last contact. Total T (TT) was measured at baseline by RIA. TT (ng/dl) was divided into 5 categories: <200; 200–409, 410–509, 510–624, and >624 ng/dl. Cox proportional hazards models were used to estimate hazard ratios (HRs) and confidence intervals (CIs), with and without adjustment for age, smoking, alcohol use, physical activity, blood pressure, BMI, and cholesterol. Men with TT 410–509 ng/dl served as the reference group for HRs. There were 331 deaths (112 CVD deaths, 100 cancer deaths, 119 other). TT was not significantly related to CVD mortality. Risks of all-cause and cancer mortality were significantly higher in men with TT $<$ 200 ng/dl (all cause HR $=1.93$, 95% CI: 1.04–3.57 and cancer HR $=3.30$, 95% CI: 1.10–9.92). This all-cause mortality risk among men with low T was not significant after adjustment for covariates (HR $=1.80$, 95% CI: 0.97–3.36), but low T remained a significant predictor of cancer mortality (HR $=3.48$, 95% CI: 1.15–10.48) with such adjustment. Further examination of the cancer deaths showed that men with low TT were significantly more likely to have died from prostate cancer (odds ratio $=43.0$, 95% CI: 3.86–478.64). TT is an independent predictor of cancer mortality but not all-cause and CVD mortality. The findings on low T as a predictor of prostate cancer death are consistent with previous data showing that men with lower T levels have more aggressive cancers.

174

THE EFFECT OF RISEDRONATE FOR PROSTATE CANCER PATIENTS WITH LOWER BONE MINERAL DENSITY UNDER ANDROGEN-DEPRIVATION THERAPY

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Bone loss under androgen-deprivation therapy (ADT) for prostate cancer is a serious problem. 27 patients with prostate cancer who were scheduled to start ADT were divided into two groups; those patients undergoing ADT with risedronate who had lower bone mineral density (BMD) (T score less than -1 either in femoral neck or in lumbar spine), 14 cases, group A, and the others with ADT only, 13 cases (8 cases with T scores not less than -1 and 5 cases who refused to take risedronate), group B. ADT was performed with leuprolide injection w/wo anti-androgens, and risedronate was administered orally by 2.5 mg tablet every day. BMD was examined with DEXA before and 6, 12 months after, and percent change from the baseline was calculated for primary efficacy variable. There was a significant increase in lumber spine BMD in the group A

($3.7 \pm 4.9\%$, 6 months after, $4.4 \pm 5.0\%$, 12 months after) ($p < 0.05$), however BMD in the group B was significantly decreased ($-4.4 \pm 5.5\%$, 6 months after, $-5.0 \pm 8.7\%$, 12 months after) ($p < 0.05$). No significant changes in femoral neck BMD were observed, and the difference between BMD changes in the group A ($-0.5 \pm 4.8\%$, 6 months after, $-0.2 \pm 5.0\%$, 12 months after) and in the group B ($-0.6 \pm 2.8\%$, 6 months after, $-2.1 \pm 5.4\%$, 12 months after) was not significant. BMD changes in total hip were also insignificant, but the changes in the group A ($0.6 \pm 3.0\%$, 6 months after, $0.1 \pm 2.8\%$, 12 months after) were significantly higher than those in the group B ($-2.1 \pm 2.3\%$, 6 months after, $p < 0.01$, $-2.0 \pm 1.3\%$, 12 months after, $p < 0.05$). Risedronate administration seems beneficial for prostate cancer patients with lower BMD values who undergo ADT.

175

INTRATUMORAL INJECTION OF HOLMIUM-CHITOSAN COMPLEX IN PROSTATE CANCER

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166Ho is a potent beta-emitter with short half-life (26.8 hours) and high beta energy (1.85 MeV), and its necrotic effect on solid tumors has been proved. In cases of prostatic cancer, 166Ho can therefore be used for internal radiation therapy. In this study, 166Ho was complexed to chitosan which decreases the distribution of 166Ho into other tissues when applied intratumorally. The purpose of this study is to evaluate the therapeutic and toxic effect of 166Ho-chitosan complex(166HC) on prostatic cancer pathologically. 24 nude mice with subcutaneous prostatic cancer(DU-145 cell line) were divided into four groups. In each group, intratumoral injections were performed when the tumour measured approximately. Group I received 0.5 ml of normal saline per 1 cm^3, group II chitosan 0.5 ml only per 1 cm^3, group III 370 MBq of 166HC per 1 cm^3 and group IV 740 MBq of 166HC per 1 cm^3. Tumor size was measured at a week and 2 weeks after injection. These 24 mice were sacrificed and pathologic examination was done. Main organs were evaluated pathologically to find toxic effect of 166HC. A week after injection of 166HC, tumor volume increase of group IV was smaller than other groups ($p < 0.05$), and two weeks after injection, that of group III and IV was smaller than group I and II ($p < 0.05$). H & E staining of the tumor showed wide central necrosis in group III and IV, but not in group I and II. TUNEL staining showed false positive reactions along the peripheral margin in all groups. Toxic change was not found in liver, kidney, peripheral blood and bone marrow. Intratumoral injection of 166HC appears to be a new, safe and promising alternative radiotherapeutic modality for the local control of prostatic cancer, minimizing toxicities because administered 166HC is retained at the injection site.

176

SIGNIFICANCE OF 'NOCTURNAL HESITANCY' IN THE TREATMENT OF MEN WITH LOWER URINARY TRACT SYMPTOMS

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Objectives: To determine the significance of nocturnal hesitancy in the treatment of men suffering from lower urinary tract symptoms (LUTS). Methods: A total of 123 patients with nocturia were prospectively studied. The nocturnal hesitancy scores ranged between 0 and 5, and were scored according to the International Prostate Symptom Score (I-PSS). The patients were stratified on the basis of their nocturnal hesitancy scores, as group 1 (0–1, $n = 57$), group 2 (2–3, $n = 45$), and group 3 (4–5, $n = 21$). All patients received treatment with an β-blocker once per day, for 4 weeks. Results: Group 3 scored significantly higher on the I-PSS at both baseline and post-treatment than did group 1. The actual number of nightly voids was highest in group 3, and was lowest in group 1 ($P = 0.011$ at baseline and $p = 0.046$ at post-treatment, respectively). The baseline Nocturia Indices were highest in group 3, and were lowest in group 2 ($P = 0.027$). A significant but weak correlation was also noted to exist between the nocturia hesitancy score and the scores for 'voiding symptoms' ($r = -0.234$, $P = 0.021$) and 'total I-PSS' ($r = -0.270$, $P = 0.011$), respectively. In our multivariate analyses, the 'straining' score was a significant determinant of nocturnal hesitancy. Conclusions: Our study reveals that more emphasis should be placed on nocturnal hesitancy in the terminology of LUTS. Further research regarding the pathophysiological mechanisms underlying nocturnal hesitancy, as well as its effects on sufferers, is clearly warranted.

177

PERINEUM-INGUINAL SLING FOR STRESS URINARY INCONTINENCE (I.U.S.) IN MALE

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Introduction: If a man is hardly suitable for urine leakage and pads, the urology is also disappointed because he has very few to offer for cure Physiokinesy doesn't help much, injectables have short time effectiveness Artificial sphincter may be complicated for elderly. ReMeEx device, already experienced in female, proved effective also in male. Implanted by a perineum-inguinal approach. ReMeEx means Externa Mechanical Rgulator, new technology for incontinence made up by a varitensor like an endless screw, moved by a specialmanipulator. The Prolene sutures of the Propylene sling are connected to the varitensor so that they can be stressed or relapsed adjusting the tension of the suspension. Materials and Methods: A soprapubic incision will receive the varitensor and the needles with the sling sutures inserted, by a perineum-inguinal approach. Perineal incision and careful dissection as far as the bulbar-cavernous muscle that is preserved intact on the urethra. The sling is inserted and fixed under the muscle. The sutures are connected to the varitensor and ligated. The day after, the regulation of the tension is performed under phluoroscopy to obtain continence together with an easy micturition without residual or obstruction. The manipulator is removed with easy reinsertion for eventual future regulations. 6 patients with I.U.S. after R.P. underwent the implant (4RRP, 2 RPP), average age 68. Results: 4 patients cured. Complications were: 1 scrotal haematoma, 2 infections of perineal incision, 1 readjustment at 3 months. Urethral Pressure Profile (UPP) is poorly increased perhaps Valsalva Leak Point Pressure (VLPP) is more favourably changed. Conclusion: This implant seems to be effective and safe: it is neither easy nor seriously difficult; it lasts 90 minutes with whatever anaesthesia and need 3 day hospitalisation.

178

OVERACTIVE BLADDER SYNDROME AND SERUM SEX HORMONES LEVELS IN MEN

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Introduction and Objectives: Overactive bladder (OAB) syndrome is defined by the International Continence Society as urgency, with or without urge incontinence, usually with frequency and nocturia. OAB is estimated to affect between 50 and 100 million individuals worldwide, with prevalence increasing with age. The pathophysiology of OAB is complex, and involves both neurogenic and non-neurogenic factors, in fact, the proportion of idiopathic cases is high. The aim of this study was to investigate a possible correlation between the severity of OAB and serum sex hormones levels in men.

Methods: A total of 182 randomly selected men attending our general urology clinic, were assessed by storage symptoms, the sum of International Prostate Symptom Score (IPSS) question 2 (frequency), 4 (urgency) and 7 (nocturia), and serum levels of total and free testosterone (total T and free T), dehydroepiandrosterone sulfate (DHEA-S), luteinizing hormone, follicle stimulating hormone, prolactin, estradiol and growth hormone. The cases with incomplete data, prostate diseases on anti-androgen therapy and androgen deficiency on androgen replacement therapy were excluded. Results: The mean age was 65.8 ± 12.9 (means ± SD) years (range 21 to 82). The storage symptoms were significantly correlated to age, DHEA-S and free T ($r = 0.535$; $p < 0.0001$, $r = -0.423$; $p < 0.0001$ and $r = -0.353$; $p = 0.0005$, respectively). As mentioned above, it appears that the dominant predictor of storage symptoms is the patient's age. However, in the 65–82 years old subgroup ($n = 75$), there was significant correlation between the storage symptoms and DHEA-S ($r = -0.391$; $p = 0.0087$), but no correlation was seen between the symptoms and age, as well as, between the symptoms and free T. Conclusions: These results show that the severity of OAB is correlated to age, serum levels of DHEA-S, and free T in men. Especially in old men, OAB could be affected by serum DHEA-S level.

179

HYPOGONADISM IN PATIENTS WITH ERECTILE DYSFUNCTION (ED) COMPLAINS. DOES THE AGE MODIFY THE TESTOSTERONE(T) BLOOD LEVEL?

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Introduction: Testosterone levels change with aging. No regional reports are available regarding the T levels and age in patients with ED. Goal: To report local data regarding T serum levels in Patients with complains of ED, and discover the impact of the age in T, in this patients in Chihuahua, MEXICO. Patients and Method: 191 files were reviewed, and classified in two groups: Control Group (CG): Fifty patients without ED complain; Problem Group (PG): 141 patients with ED complain were studied. The data collected were age, Total Testosterone, IIFE-5 score, using an Excel data base and analyzed using SPSS 10.0 statistic software with 95% IC. Results: The mean age of patients was: CG 42.9 years SD 14.54 (range 19–79); PG 45.82 years SD 13.16 (range 19–76) ($p = 0.193$ by ANOVA); The mean T level was: CG 492.1 ng/dl SD 178.7 (range 84–910); PG 457.9 ng/dl SD 206.1 (range 18–1270) ($p = 0.299$ by ANOVA); The mean of IIFE-5 score was: CG 20.92 (SD 5.26); PG 11.67 (SD 5.6) ($p = 0.000$ by ANOVA). Only statistically significant difference was find in IIFE5 Score between two groups. Regarding the PG, 30/141 patients (21.27%) shown T levels ≤300 ng/dl. The mean age was 49.2 SD 13.28 (range 21–69); the mean T level was 226.6 ng/dl SD 64.2 (range 38–300); with mean IIFE5 Score 10.7 (SD 6.5). No statistically significant difference was find in the Age of PG between patients with hypogonadism vs. "normal T Levels" $p = 0.64$ (by Chi-Square). Conclusions: In this series no statistically significant differences in Age were find between Patients with and w/o ED Complains ($p = 0.193$), also in T levels ($p = 0.299$). It is interesting to see that the age did not impact the T levels in patients with ED complains ($p = 0.64$).

180

THE PSA LEVELS IN PATIENTS WITH ERECTILE DYSFUNCTION (ED) COMPLAINS ARE MODIFY BY THE TESTOSTERONE (T) BLOOD LEVEL, BUT AGE INDEPENDENT

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Introduction: Prostatic Specific Antigen (PSA) levels are modify by the age. Testosterone levels change with aging. No regional reports are available regarding the T levels, PSA and age in patients with ED. Goal: To find the correlation between PSA, T serum levels and Age in Patients with complains of ED in Chihuahua, MEXICO. Patients and Method: 192 files were reviewed, only 85 patients with ED complains had the information required, and were classified in two groups: Hypogonadic Group (HG): Nineteen patients with T level ≤ 300 ng/dl. Normogonadic Group (NG): Sixty six patients with T level ≥ 300 ng/dl. The data collected were age, Total Testosterone and Total PSA, using an Excel data base and analyzed using SPSS 10.0 statistic software with 95% IC. Results: The mean age of patients was: HG 49.2 years SD 13.2 (range 21–69); NG 45.6 years SD 13.2 (range 19–80).The mean T level was: HG 226.6 ng/dl SD 64.2 (range 38–300); NG 521.3 ng/dl SD 185.9 (range 301–1270). The mean PSA was: HG 4.7 ng/ml SD 10.11 (range 0.40–34.6); NG 1.3 ng/ml SD 1.13 (range 0.2–7.9). Conclusions: The difference of T levels between 2 groups was statistically significant ($p = 0.000$ by Wilcoxon Test). In this series No statistically significant difference was find in the mean Age of patients between both groups ($p = 0.14$ by ANOVA). It is relevant to see highest PSA levels (4.7 ng/ml) in the HG than PSA levels of NG (1.3 ng/ml) $p = 0.032$ by Chi-Square Test. Strong statistically significant difference was find in PSA between two groups, after adjusting the Age ($p = 0.027$ by Spearman's rho Test). We are confirming the previous reports connecting hypogonadism with the probability of Prostate Cancer, also suggesting stronger efforts for discover this disease before hormonal replacement therapy.

Frailty

181

LOW TESTOSTERONE AND THE RISK OF ANEMIA IN OLDER PERSONS

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Objective: Anemia occurs in male hypogonadism and anti-androgenic treatment. We hypothesized that low testosterone in older persons is a risk factor for anemia. Design: Testosterone and hemoglobin were measured in a representative sample of 905 persons aged ≥65 years without cancer, renal insufficiency or anti-androgenic treatments. Hemoglobin was reassessed after 3 years. Results: At baseline, 31 men and 57 women had anemia. Adjusting for confounders, total and bioavailable testosterone were associated with hemoglobin in women ($p = 0.001$ for total and $p = 0.017$ for bioavailable testosterone) and in men ($p < 0.001$ for total and $p = 0.026$ for bioavailable testosterone). Men and women in the lowest compared to the highest quartile of total and bioavailable testosterone were more likely to have anemia (Men, Odds Ratio: 5.4; 95%CI: 1.4–21.8 for total and 13.1; 1.5–116.9 for bioavailable testosterone. Women, 2.1; 0.9–5.0 for total and 3.4; 1.2–9.4 for bioavailable testosterone). Among non-anemic participants and independent of confounders, men and women with low compared to normal total and bioavailable testosterone had a significantly higher risk of developing anemia at the 3-year follow-up (Relative Risk: 2.1, 95%CI: 1.1–4.1 for total and 3.9; 1.9–7.8 for bioavailable testosterone). Conclusions: Older men and women with low testosterone levels have high risk of anemia.

182

THE ROLE OF IGF-I IN MUSCLE FUNCTIONING

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Aging is associated with decline in physical function, leading to loss of autonomy in ADL. Age-related decline in IGF-I levels has been associated with changes in muscle mass, strength and poor physical performance. However, whether IGF-1 may contribute to maintain physical function in older individuals has not been fully investigated. We tested the hypothesis that IGF-1 levels may predict the development of impaired functional status in participants of the InCHIANTI Study. 784 subjects (395 men and 389 women) aged between 24 and 95 years with no ADL disability and Short Physical Performance Battery (SPPB) >10 at baseline, were selected and evaluated after 3-yr follow-up. Participants having SPPB score <10 were defined as frail. The relationship between total IGF-1 and physical performance, assessed by SPPB, was tested in a logistic regression model adjusted for age and other potential confounders such as SPPB evaluated at baseline, BMI, knee extension strength, calf cross-sectional muscle mass, level of physical activity, nerve conduction velocity, number of medications, total cholesterol, liver and kidney function, MMSE score, CES-D scale score, history of chronic diseases, interleukin-6, serum total testosterone and cortisol. Total IGF-1 was measured with reagents by DSL (Webster, Texas, USA). After 3 years follow-up, 137 participants, 53 men and 84 women developed frail condition. Men with lower levels of IGF-1 at baseline had a risk 3 times greater to develop poor physical performance in age–adjusted (OR 2.915, C.I. 1.413–6.016) ($p < 0.05$) and fully adjusted model (OR 2.810, 1.151–6.858, $p < 0.05$). However, in women the relationship between IGF-1 levels and development of poor physical performance did not reach the statistical significance in age (OR 1.454, C.I. 0.838–2.526 $p = 0.07$) and fully (1.823, C.I. 0.937–3.548) adjusted models, respectively. Our findings suggest that in older men lower IGF-1 serum levels may predict the risk of developing poor physical performance.

183

THE HORMONES: BEYOND CHANGES IN BONE MINERAL DENSITY

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Purpose of the study: In a population-based sample of older persons, we studied the relationship between tibial bone density and geometry and factors potentially affecting osteoporosis, such as calf cross-sectional muscle area (CSMA), ankle muscle strength, current physical activity, bioavailable testosterone (Bio-T), dehidroepiandrosterone sulphate (DHEAS), total insulin-like growth factors-1 (IGF-1), 25(OH)-vitamin D and parathyroid hormone (PTH). Methods: of the 1260 participants aged 65 years or older eligible for the InCHIANTI study, 1155 received an home interview and 915 (79.2%) had complete data on tibial QCT scans and other variables used in the analysis presented here. The final study population included 807 persons (372 men and 435 women, age-range 65–96 years) after exclusion of participants affected by bone diseases or treated with drugs that interfere with bone metabolism. Results: In both sexes, calf CSMA was significantly and independently associated with total bone area (tCSA) and cortical bone area (cCSA) but not with trabecular or cortical vBMD. Bio-T was independently associated with both trabecular and cortical vBMD in both sexes. In women, indendendently of confounders, 25(OH)-vitamin D was positively associated with tCSA and cortical vBMD while PTH was negatively associated with cortical vBMD. IL-1 beta was negatively correlated with cortical vBMD in women, while TNF-alpha was negatively associated with the indexes of bone geometry in men. Conclusions: Physiological parameters that are generally considered risk factors for osteoporosis were associated with specific bone parameters, assessed by tibial QCT. Factors known to be associated to increased bone reabsorption such as 25(OH)-vitamin D, PTH, and Bio-T affected mainly volumetric BMD, while factors associated with bone mechanical stimulation such as CSMA affected primarily bone geometry. Our results suggest that pro-inflammatory cytokines might be considered as markers of bone resorption.

184

INSULIN RESISTANCE: A MODEL OF FRAILTY

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Geriatricians often define frailty as a syndrome of decreased reserve and resistance to stressors characterized by a high degree of vulnerability to negative health outcomes such as, disability, comorbidity and mortality. Even though there is still no consensus definition of frailty, some clinical features have been identified as: muscle weakness, poor exercise tolerance, factors related to body composition, sarcopenia, and lower mobility. Up to now, studies have also tried to identify biological markers associated with such features due to the fact that biological changes may be paralleled by important changes in physiological systems. Methods. To address the hypothesis that IR may also play a pivotal role in the frailty syndrome. It is also widely known that the aging process is associated with significant changes in hormonal levels and one can not rule out that different aspects of the frailty syndrome may be linked to such changes. In particular, an age-related change in insulin levels may be a potential biomarker of the clinical aspects associated with frailty. Like frailty, the metabolic syndrome is made up of a constellation of changes and in particular, insulin resistance (IR) plays a central role in the metabolic syndrome. Results. Previous studies taken separately indicate that IR is also associated with the individual components of the frailty syndrome. In particular, diverse data from the InCHIANTI study have underlined the independent associations among: a) IR and chronic inflammation; b) IR and muscle strength; c) IR and cognitive performance. Conclusions: IR may also be a central biomarker of different aspects of the frailty syndrome in older persons.

185

THE 'HORMONAL DYSREGULATION SCORE' AND FRAILTY

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Background: Frailty is a state of high vulnerability associated with high risk of multiple adverse health outcomes. Age-related

alterations in Hypothalamic-Pituitary-Testicular, Hypothalamic-Pituitary-Adrenal and GH-IGF-1 axes and increase in insulin resistance have been associated with frailty single components such as reduced muscle strength, bone strength or poor mobility. However, no study has investigated the relationship between global hormonal dysregulation and frailty. Aim of the Study: We hypothesized that frailty, as defined by Fried's criteria, results from parallel dysregulation of multiple hormones rather than changes in a single hormone. Material and Methods: Testosterone, cortisol, dehydroepiandrosterone sulphate, free insulin like growth factor-1, sex hormone binding globulin, fasting insulin and leptin, were measured in 586 male participants aged 65 years or older living in the Chianti area (Tuscany, Italy). Concentration of free-Testosterone was calculated using the Vermeulen formula. Results: We calculated a hormonal dysregulation score, defined as the number of hormones either in the lower (for hormones that decline with age) or in the upper (for hormones that increase with age) quintiles. After adjusting for age and gender, we found no significant correlation between circulating levels of a single hormone and the presence of Frailty. However, we found a positive association (P-trend <0.001) between the number of ''dysregulated'' hormones and the Frailty criteria. Compared to participants with a hormonal score of 0 or 1, those with a score of 2 or 3 were 2.2 times (95% CI: 1.0–5.1) and those with a score of 3 or 4 were 6.4 times (95% CI: 2.2–18.5) more likely to be frail. Conclusion: Our preliminary data suggest that age-associated dysregulation of a single hormone has little impact on frailty. On the contrary, dysregulation of multiple hormones is strongly associated with frailty. Key Words: hormonal dysregulation, frailty, older men.

186

WEIGHT LOSS IN THE OLDER MAN: SOMETHING TO BE AVOIDED

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Weight loss in older men is associated with nearly a two-fold increase in mortality. Weight loss leads to hip fracture and increased institutionalization. Severe weight loss can lead to protein energy malnutrition, immune dysfunction and anemia. Weight loss is a major factor in the development of frailty. There are four major causes of weight loss, viz. anorexia, cachexia, dehydration and sarcopenia. The major causes of anorexia are depression and medications. The physiological anorexia of aging involves changes in taste and smell, alterations in stomach fundal compliance, increase in cholecystokinin, decline in testosterone and increased leptin. Cachexia involves rapid loss of muscle and fat. It is predominantly due to marked increases in cytokines. There are multiple causes of sarcopenia. Treatment involves correction of the cause, calorie supplementation and in some cases orexigenic drugs.

187

CAUSES AND PREVALENCE OF SARCOPENIA

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Sarcopenia is the excessive loss of muscle. Older persons who develop sarcopenia have an increased disability. Persons with obese sarcopenia or the ''fat frail'' have been shown to have especially poor outcomes. The causes of sarcopenia are multifactorial. It is due in part to the decreased activity that occurs with aging. In some older persons peripheral vascular disease plays a major role in the development of sarcopenia. The decline in testosterone and IGF-1 have both been related to the loss of muscle. Mechanogrowth factor (MGF) plays a major role in the determination of the quality of muscle. It falls with aging and increases with resistance exercise cytokines (tumor necrosis factor $\times$ and interleukin-6) cause loss of lean tissue. Myostatin inhibits muscle growth. At present, management of sarcopenia focuses on resistance exercise and possibly testosterone replacement.

188

THE MOLECULAR BIOLOGY OF SARCOPENIA

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Sarcopenia is a result of multiple molecular mechanisms that ultimately lead to muscle atrophy and reduced ability to hypertrophy and repair damaged muscle. Central to the maintenance of muscle mass is the PI3K-AKT system which stimulates protein synthesis through mTOR and S6KI and phosphorylates FOXO to inhibit ubiqitination and protein degradation. Atrogin-1(MAFbx) & MURF1 act downstream of FOXO to increase ubiqitination. Active FOXO also down regulates cyclin D's causing cell cycle arrest at the G1 phase. FOXO knockout mice show reduced protein degradation. The PI3K/AKT system is stimulated by growth factors such as IGF-1, MGF, insulin and testosterone. Numerous genes involved in cell cycle regulation; cell growth; the ubiquitin cycle; apoptosis; striated muscle contraction; polyamine biosynthesis; amino acid metabolism; fatty acid synthesis & metabolism; G protein, Wnt, MAPK, PI3K & JAK-STAT signaling pathways were reciprocally changed in skeletal muscle of castrated young adult male mice with or without T replacement. Aged (24 month old) male mice and young adult diabetic mice have reduced skeletal muscle weight, muscle strength and serum testosterone levels compared to young adult mice. The regulation of skeletal muscle gene expression in these mouse models will also be discussed. Cytokines also drive FOXO and atrogin/MURF dependent protein degradation and NF Kappa B stimulated apoptosis. Glucocorticoids have been shown to upregulate the expression of MURF-1. The regulation of muscle gene expression in mice exposed to chronic lipopolysaccharide endotoxin will be addressed. Finally, myostatin phosphorylates Smad3 which leads to down-regulation of MyoD and inhibition of myoblast differentiation.

189

NOVEL APPROACHES TO TESTOSTERONE ADMINISTRATION

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Testosterone therapy represents one of the few methods by which muscle mass and strength can be increased in older males and females. At present the available methods for testosterone administration include short acting and long acting injections, testosterone pellets, oral testosterone and decanoate, testosterone patches, testosterone gels and buccal testosterone. Methods under development include nasal testosterone and inhaled testosterone. In addition, a variety of selective androgen receptor molecules are under development. These can be steroids or non-steroids moieties.

190

MEASUREMENT OF TESTOSTERONE LEVELS IN AGING MALES: TECHNIQUES AND PITFALLS

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Most of the current Testosterone determinations are done from serum samples even if they are giving results in the low concentration range like in hypogonadism patients. It is known since the 80th that testosterone secretion shows a significant episodic pattern. Nevertheless still today most of the determinations are done from just one sample. Moreover the measurement of serum concentrations in the hypogonadism

range technically is rather difficult as it recently has been shown in the scientific literature. Also serum measurements only can give the total hormone concentration. Saliva samples are a reliable alternative provided multiple sampling is done. We are recommending to collect 5 or 6 samples within 2 or 3 hours and the successive measurement of one mixed sample. The analytical sensitivity of current commercial saliva tests do allow a reliable and reproducible measurement even in the low hypogonadism concentration range giving results for the free active hormone fraction. Blood contamination of saliva samples can be excluded by visual inspection. The stability of saliva samples is superior to serum samples. Absorption of the analyte might be a problem which can be overcome by selecting proper plastic material for the sampling device. Influence of hormone containing food is similar in serum and in saliva samples. Meanwhile simple commercial ELISA kits are available for the reliable quantitation of free testosterone in saliva even in the low concentration range.

Alternative Medicine

191

COMMON USE OF TRADITIONAL HERBS FOR THE AGING MEN IN THE PAST, PRESENT AND FUTURE

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Significant advancement in plant derived medicines in the last two centuries in such areas as central nervous system, anti-tumour and anti-inflammatory activities has led to the development and identification of active chemicals and understanding of their modes of action. As for man's health related to sexuality, numerous age-old natural products have been historically claimed as 'aphrodisiacs' – a collective meaning, which describes improvement of arousal, libido and/or sexual energy and activity. Some known phyto-agents considered to be aphrodisiacs include Tribulus terrestris, pausinystalia yohimbe (yohimbine), ptychopetalum olacoids (Marapuama), eurycoma longifolia, root of ginseng plant, ginkgo biloba, green oats extract etc. Most of them are androgenic in nature. However, very few of them went through proper scientific methodology in the identification of the constituents and delineation of effectiveness and modes of action. Natural herbal preparations are alternatives to synthetic anabolic hormones. They can be considered as a form of TRT since some of them are shown to stimulate the body to produce natural testosterone and even DHEA. In general, phytoandrogens are weaker than androgens and therefore have lesser side effects. They are also claimed to have minimal feedback inhibition on testosterone biosynthesis. However, this has to be proven. These will be discussed in the light of the current understanding in this area of alternative therapy for male sexual dysfunctions.

192

STANDARDIZED WATERSOLUBLE EXTRACT OF EURYCOMA LONGIFOLIA (LJ199) MAINTAINS HEALTHY AGING IN MAN

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Eurycoma longifolia jack is a plant shrub commonly found along the hilly slopes of the Malaysian coastal region; the root is used as a health tonic for Early studies showed its testosterone elevating effect and SHBG depressing effect. The present study looked into other beneficial effects. Powdered water-soluble extract LJ100 is taken from PHYTES BIOTEK, Malaysia, with a standardized 28% Eurypeptide. This placebo controlled Study used various dose of LJ100: 200 mg, 400 mg and 600 mg. SHIM and AMS Qols were recorded before and during follow-ups. A series of Serological tests were done. Results: SHIM scores elevated scores from the first week. The AMS lowered through the follow-ups. The two Qols results were positive. Full Blood Examination were normal. Liver and renal function tests were normal. HDL raised. Diabetic Screening of Type 2 diabetic showed low the blood glucose. Cortisol raised. PSA normal. IGF-1 high normal. Conclusions: Standardized LJ100 is non toxic to the liver and renal function, hematological profile, lipid profile, body electrolytes and PSA. Overall effects on the various hormones were positive.It increases HDL. The effect on Cortisol is positive with regards to body ''wellness'' (aging). LJ100 may modulates the released of IGF-1. LJ100 is not only as a natural sex stimulant and energizer but may promote healthy aging.

193

ISOFLAVONE (PHYTOGEN) IN THE TREATMENT OF MALE CLIMACTERIC AND PROSTATISM

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Isoflavone had been used in the treatment of female menopause symptoms with remarkable effect. We also did an open labeled clinical study of Isoflavone for 24 aging male with climacteric symptoms and/or prostatism. Isoflavone (Phytogen®) 6 gm was given daily to 22 men, aged 48 ~ 78 years, for 2 months. Periodic examinations of the prostatic size, PSA, uroflow, as well as follow-up questionnaire with subjective screening of the voiding function, sexual function and male climacteric symptoms were done. The results showed that the prostatic size and serum PSA level of all the patients did not change. for the patients with hypogonadism before the treatment (average serum testosterone level 0.74 ng/ml, $n = 8$), Isoflavone could replace the testosterone deficiency after one month (average testosterone level 3.04 ng/mL) or two months (average testosterone level 3.37 ng/mL) treatment. Peak flow rate of the urine flow was also noted to be improved after 2 months Isoflavone (average peak flow rate was increased from 6.17 to 12mL/s). Some of the male climacteric symptoms such as fatigue, general weakness, skin atrophy were found to be diminished by scoring in the group of diseased patients. Generally speaking, as a natural product, Isoflavone was quite acceptable by the aged patients without any adverse effect. Although neither all the patients nor all the symptoms could be responsive to the treatment after 2 months medication in our series, Isoflavone was really benefit to some patients with climacteric symptoms and/or prostatism and might be one of the alternative therapy for the aging males.

194

PHYTO-DHEA FOR THE AGING MEN, ITS BENEFIT OVER THE USE OF CHEMICAL HORMONES

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In the pass aging has clustered to myths that aging is associated with specific diseases. Therefore aging was believed can be avoided by diversities of ''anti-aging'' (rejuvenate) drugs. However current researches have elucidated a new horizon. Age steady progresses and is inevitable because of multi-factorial processes, decreasing the holistic metabolism and immune-body-system, down-graded physical fitness and cognitive-mental health. Current researches are therefore focused on the management of healthy-aging. History has shown that it is unrealistic to expect that life is immortal or can be rejuvenates by 'anti-aging' drugs. Exercise, inborn processes (genetics); several sex-steroid-hormones seem to be responsible for the management of healthy-aging. Studies have shown that with progressing of age several hormone production decreases also. The

decrease serum levels of steroid sex-hormones have been shown to be responsible of aging-process; Androgen deficiency seems causing 'andropause' in men, while decrease estrogen serum levels cause menopause in women, with all their possible co-morbid (osteoporosis, obesity, hypertension, cardio-vascular, metabolic-diseases etc). Further knowledge has proven that other hormone levels (GH, GnRH, DHEA, Melatonine) in aging decreases also, causing and interacting with steroid-sex-hormones causing varieties clinical symptoms mentioned before. HRT therefore has proven benefits and improves in part aging clinical signs, producing better quality of life. However not a single hormone treatment can maximized all health problems, besides there are still many controversial debates for HRT. Phyto-pharmaceuticals such as protodioscin (phtyo-DHEA) is currently clinically proven for the management of aging to substitute the use of HRT that is still debated. Phyto-DHEA as a plant product has the beneficial as vegetable dishes in daily food to have the properties as a hormonal precursor 'in-need. that can be converted into the respective hormones when needed. Hence having the least side-effects, optimalizing benefits to enhance best quality of men over chemical hormones.

195

ASPARTAME AND AGING

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Aspartame is widely used as food additive. It is a low calorie sweetener sold in India under the names, Nutrasweet, Equal, Spoonful, Indulge and Equal Measure. The present study was undertaken to determine the clastogenic effects of low calorie sweetener aspartame. Different doses of aspartame were selected according to the maximum permissible levels for humans (Prevention of Food Adulteration Act, India, 1954; amended in 1980). Different doses of aspartame i.e. 7 gm, 35 mg, 70 mg/kg body weight were fed to the male Wistar albino rats in laboratory for a period of 90 days. The cytogenetic end point scored was chromosomal aberration and micronucleus. Chromosomal damage was studied in the preparation made from bone marrow cells after colchicine treatment to all the rats. The micronucleus was scored in the peripheral blood film. The effect of damage induction by the sweetener was found to be dose dependant. In rats many chemicals, including methanol, accumulate in the cells with age after aspartame doses as there is no liver enzyme for the conversion of methanol into formaldehyde or formic acid. Methanol and other toxins cause oxidative stress. With toxic stress chromosomal breakage occurs, resulting in early senescence. In human a number of leftovers accumulate from Aspartame consumption: methanol, formaldehyde or formic acid. In liver the methanol is converted into formaldehyde or formic acid. The body cannot effectively eliminate formaldehyde so some of it is combined with water and stored in the fat resulting in weight gain or further converted by the liver into formic acid. The poisoning from methanol, formaldehyde and formic acid causes cumulative damage. The present study has shown a significant rise in the chromosomal breakage and micronuclei appearance after higher aspartame dosage. This is probably the result of oxidative stress of the toxins leading to early aging.

196

USING OF HERBAL TEA 'DR. SELEZNEV' IN REJUVENATION

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Within the framework of the ''Male Age Prolongation'' Programme ''Dr.Seleznev'' Herbal Tea #17 was a part of dietary menu, which created favourable conditions for rejuvenation. Ingredients: peppermint, stevia, sage, haw berries, black elder, ashberry, eglantine, flax, Hypericum, milfoil, Origonum, motherwort, thyme, lime, chamomile, calendula. This herbal tea differs from other 38 kinds of ''Dr.Seleznev'' herbal tea as one can add it to different dishes. You can add it to the 1st course dish as a seasoning, to the 2nd course dish as a spice, and use it as the 3d course dish, i.e. instead of normal tea.This herbal tea is sugar free because it has stevia thanks to which this tea has sweet taste. The programme is based on dietary nutrition, which is important for health maintenance and prolongation, and restoration of capacity for work. Herbal tea accelerates regeneration of tissues, improves oxidation and restoration processes, activity of hormones and ferments. The effect is guaranteed by the unique ratio of ingredients, which together make up necessary energetic chord neutralizing organism misbalance. Restoration of normal energetic characteristics of organism is accompanied with aging slowing down 120 males of 40–65 years of age took part in this programme. 3 years of herbal tea ''Doctor Seleznev'' therapy resulted in 5 years of rejuvenation. According to the recommendations of dietary therapy, herbal tea should be taken 1–2 times a day in 3 courses per 120 days each with 1–2 month interval between courses. Herbal tea #17 being a part of dietary menu cures and prevents persons from diseases and influence of harmful factors, which provoke early aging, such as hypodynamia, irrational nutrition, homeostasis mechanism disorders (oxidation and restoration processes, hormonal balance), atherosclerosis, immune system affection, metabolism disorders, overstrain, alcoholism, smoking, drug taking, harmful working conditions, and living in ecologically unfavourable surroundings.

Boston Area Community Health Survey and Ancillary Studies

197

INTRODUCTION TO THE BOSTON AREA COMMUNITY HEALTH (BACH) SURVEY

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The Boston Area Community Health (BACH) survey is an epidemiological study of symptoms of urological disorders in men and women. We are collecting data on symptoms of urinary incontinence (UI), lower urinary tract symptoms (LUTS), benign prostatic hyperplasia (BPH), interstitial cystitis (IC), chronic pelvic pain of bladder origin, prostatitis, hypogonadism, erectile dysfunction (ED), and female sexual dysfunction. BACH used a multi-stage stratified cluster sample to recruit a community based random sample of 5500 (2300 men) respondents approximately equally divided between men and women, three racial/ethnic groups (black, Hispanic, and white), and four age groups (30–39, 40–49, 50–59, 60–79). In addition to urologic symptoms, information was collected on medical history, medications, family history of disease, quality of life, health care utilization, physical activity, depressive symptoms, interpersonal stress, smoking, alcohol use, fluid intake, nutrition, sexual activity, abuse, anthropometrics including height, weight, hip, and waist measurements, pulse rate and blood pressure, and socio-demographics including country of origin, marital status, employment status, and income. We have collected and stored blood samples taken within two hours of awakening from 83% of the men and have obtained hormone information and a lipid profile. BACH has features distinguishing it from most other epidemiologic studies in urology: it is a random community-based sample (not a convenience sample of patients); it is racially and ethnically diverse; it covers a broad age-range (30–79 years); it includes both males and females; it focuses on symptoms of multiple conditions; it is multidisciplinary; it is intended to be longitudinal.

198

PREVALENCE AND CORRELATES OF MALE URINARY INCONTINENCE IN THE BOSTON AREA COMMUNITY HEALTH (BACH)

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The Boston Area Community Health (BACH) survey is an epidemiological study of urological disorders in men and women. A respondent is said to have weekly urinary incontinence (UI) if they involuntarily leak urine with a frequency of at least weekly. The overall frequency of UI in our cohort of 30–79 year old men is 5.44%. UI increases with age ($p = 0.0467$) ranging from 1.97% in 30–39 year olds to 10.40% in 60–79 year olds. Respondents, who have had a heart attack ($p = 0.0105$), have angina ($p = 0.0291$), high cholesterol ($p = 0.0149$), or cancer ($p = 0.0412$) are more likely to have UI than those without these co-morbidities. The prevalence of UI does not appear to be associated with BMI ($p = 0.7796$). UI has an adverse effect on the respondent's quality of life with a decrease of 3.85 points ($p = 0.0247$) on the physical health component score of the SF-12 and a decrease of 4.70 ($p = 0.0018$) points on the mental health component score of the SF-12 after adjusting for age, race/ethnicity, and the presence of diabetes, heart attack, stroke, high blood pressure, arthritis, and cancer. Respondents with UI are more likely to have an increased number of depressive symptoms than those without UI ($p = 0.0126$). UI may overlap with other lower urinary track symptoms, as men with UI score on average 6.4 points higher on the AUA symptom index ($p < 0.0001$) than those without UI. There is an interaction in the association of UI and socioeconomic status (SES) ($p = 0.0013$). For blacks, those with higher SES have a lower prevalence of UI ($p = 0.0048$). For Hispanics, those with higher SES have a higher prevalence of UI ($p = 0.0093$). for whites, there is no association of UI and SES ($p = 0.8815$).

199

DO CIRCULATING ANDROGEN LEVELS VARY BY RACIAL/ETHNIC GROUP? RESULTS FROM THE BOSTON AREA COMMUNITY HEALTH (BACH) SURVEY

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Introduction and Objective: Incidence and mortality rates for prostate cancer, the second most prevalent cancer in United States men, differ by race/ethnicity. As sex hormones regulate prostate epithelial growth and promote growth of metastatic prostate cancer, we investigated whether levels of testosterone (T), dehydroepiandrosterone sulfate (DHEAS) and sex hormone binding globulin (SHBG) varied in African American, Hispanic and Caucasian men enrolled in the Boston Area Community Health (BACH) Survey. Methods: BACH used a multistage stratified cluster sample to randomly sample 5506 adults aged 30–79 from the city of Boston. Anthropometric measures, comorbidities and lifestyle factors were obtained during an interviewer administered questionnaire. Serum T, SHBG and DHEAS levels were measured in 1899 men (538 African American, 651 Hispanic, 710 Caucasian). Bioavailable T (BT) was calculated from T and SHBG concentrations. Log transformed T, BT, SHBG and DHEAS values were treated as dependent variables in multivariate linear regression models. Results: Controlling for age, body mass index (BMI), waist-to-hip ratio (WHR), smoking, physical health from the physical component score of the SF-12 (PCS12) and hours blood taken from awakening (AWAKE), no statistical difference in T by race/ethnicity was found ($p = 0.54$). BT did not differ by race/ethnicity ($p = 0.36$) accounting for age, BMI, PCS12, smoking, cancer, socioeconomic status and AWAKE. No differences by race/ethnicity were found in SHBG ($p = 0.94$) or DHEAS ($p = 0.69$) after covariate adjustment. Conclusions: No statistically significant racial/ethnic differences are found in T, BT, SHBG and DHEAS levels before or after covariate adjustment. Normative ranges for T and BT need not be adjusted for race/ethnicity in clinical assessment of male androgen deficiency and stratification by racial/ethnic group is unnecessary for design of clinical trials involving androgens. To explain racial/ethnic differences in prostate cancer incidence and mortality, mechanisms that regulate tissue androgen metabolism or action and non-androgen-mediated pathways should be explored.

200

RACE/ETHNIC DIFFERENCES IN BONE MINERAL DENSITY IN MEN: RESULTS FROM BACH/BONE

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While there are a number of studies on bone mineral density (BMD) in men, few present racial/ethnic differences by skeletal site. We examined racial/ethnic differences in areal BMD in men with data from the Boston Area Community Health/Bone (BACH/BONE) Survey, a population-based cross-sectional study of skeletal health in a racially/ethnically diverse sample of Boston men aged 30–79 yr. Data are available for $N = 977$ men. Race/ethnicity (black, Hispanic, white) was determined by self-report. BMD (g/cm^2) was measured with a Hologic QDR 4500W. Mean ages were 48.7 ± 1.06 yr (black), 47.6 ± 0.85 yr (Hispanic), and 49.5 ± 0.95 yr (white). BMD was 11.2%, 8.0%, and 4.1% higher at the femoral neck, L1-L4, and radius, respectively, in black vs. white men. BMD at the femoral neck was 3.4% higher in Hispanic vs. white men, and BMD at L1-L4 ($p < 0.05$) and radius ($p > 0.05$) were 4.0% and 0.7% lower, respectively, in Hispanic vs. white men. Cross-sectional estimates of percent change in BMD per year of age at each skeletal site in the cohort overall were as follows: femoral neck $= -0.39\%$/yr, L1-L4 $= +0.09\%$/yr, distal radius $=$ -0.11%/yr. Age-related declines in black and white men were parallel. In contrast, Hispanic men appeared to have a steeper decline in femoral neck ($p = 0.0510$) and L1-L4 BMD ($p = 0.0325$). Our data could explain the difference in rates of hip fracture among black, Hispanic, and white elderly men, where hip fracture show a similar rank ordering by race/ethnicity. Race/ethnic differences likely arise early in life, reflecting differences in the attainment of peak bone mass. Finally, these data suggest a greater increase in vertebral fracture risk with age among Hispanic men. This is of concern given the expected growth of the elderly Hispanic population in the United States.

201

INTRA-INDIVIDUAL VARIATION IN STEROID HORMONE LEVELS IN MEN

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With the absence of reliable estimates of intra-subject variation in steroid hormone levels in men, designing scientifically credible trials of androgen replacement therapy is extremely difficult. The estimates also provide the basis for interpreting clinical measurements of hormone titers. At present, the number of blood samples required to adequately characterize an individual's steady state hormone level is unknown. We present a prospective study of day-to-day and month-to-month variation in the levels of testosterone (total, free, bioavailable and the free androgen index), DHT, SHBG, LH, DHEA, DHEAS, estrone, estradiol and cortisol in 131 community dwelling men, 30–80 years old, from Boston, Massachusetts, USA. Two blood samples were obtained two days apart at study entry, and again 3 and 6 months later (6 total samples per subject). Short term variation was estimated from the differences between hormone levels 2 days apart. Longer term variation was estimated from the differences among pairs of

measurements. As of June 21st 2005, all subjects had completed the first two visits, 95 had completed the first four and 69 had completed all six. Six subjects dropped out or were removed from the study after the first two visits and two after the second two, mainly because subjects began taking medications that altered hormone levels. Sample collection will close in December 2005. The study will characterize intra-subject variation of each hormone and will determine if the level of variation changes with age. Seasonal variation in hormone levels will be examined. Variables that have been associated with inter-subject differences in hormone levels will be considered as predictors of intra-subject variation, including race/ethnicity, smoking, use of drugs and/or alcohol, weight or body composition, diabetes, heart disease, cancer and depression. Finally, we will estimate the relative contributions of assay variation and biological variation to overall hormone variation.

The Skin of the Aging Male

202

ROS IN THE AGING SKIN

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There is increasing evidence that reactive oxygen species (ROS) play a pivotal role in the process of aging. The skin, as the outermost barrier of the body, is exposed to various exogenous sources of oxidative stress, in particular UV-irradiation, but also cigarette smoke, tropospheric ozone or environmental pollutants are powerfull sources of ROS. These are believed to be responsible for the extrinsic type of skin ageing, often termed photoaging. An antioxidant is defined as a substance that is capable of preventing or significantly delaying the oxidation of an oxidizable substrate when present in lower concentrations than the substrate. An oxidizable substrate can be any molecule occurring in biological systems. Therefore, whether a substance can be described as an antioxidant or not depends on what oxidizable target structure and what ROS are being studied. In human skin several low molecular weight antioxidants are present: tocopherol, ubiquinone, glutathione, ascorbate and urate and some of these are detectable in relevant concentrations even in the stratum corneum. Nevertheless, if oxidative stress overwhelms the skin, e.g. exposure to higher doses of UV irradiation, the concentration can decrease with an associated increase in the formation of oxidized cell components. It therefore seems reasonable to try to increase levels of protective low molecular weight antioxidants through a diet rich in fruits and vegetables or by direct topical application. Indeed, various in vitro or animal studies and a few small human studies have shown that low molecular weight antioxidants, especially vitamins C and E, ascorbate and tocopherol, exert protective effects against ROS.

203

SKIN PHYSIOLOGY OF THE AGING MALE

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Ageing skin is characterised by a thinning of all layers of the skin. Within the dermis, fibrocytes are reduced in number and biosynthetic activity. Dermal density of collagen and elastic fibres is decreased due to reduced synthesis and increased degradation by matrix metalloproteinases. An impairment of physiological function and synthesis of intercellular matrix components such as glycosaminoglycans and proteoglycans is also involved in the physiological alterations of aged skin. Genetic and hormonal diversity as well as a variation in liftstyle have a recognized effect on skin physiology. Gender variations of human skin physiology include a thicker epidermis plus dermis, a higher dermal collagen content and a higher collagen density in males compared to females throughout the entire adult life span. With increasing age, male skin reveals a gradual, more or less constant thinning, while female skin thickness remains nearly constant until the fifth decade, before decreasing significantly. Overall sebum secretion is generally higher in men than in women. In maturity sebum production in males often remains nearly unaltered, while it significantly decreases in females. in contrast to dermal thickness, the subcutaneous fat tissue is thinner in males compared to females. Reduction of subcutaneous fat with increasing age, especially in the mid face region, contributes significantly to the typical appearance of older men. Although differences in skin physiology in aged skin between males and females have been studied far from comprehensively, more and more data is gradually evolving. This is partly motivated by the recent strongly increased male demand for skin care products including anti-ageing formulations. Based on the available scientific data, skin care preparations for men should be adjusted to the dissimilar skin physiology of men and women. For the future a more systematic research into the differences in skin ageing mechanisms between men and women is needed.

204

PDT: A NEW TREATMENT OF SKIN TUMORS

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It is a well known fact that precancerous lesions such as actinic keratoses (APK) and epithelial skin cancers, e.g. basal cell carcinomas (BCC), show a steadily growing incidence. Aging of the population in general and changing leisure activities with increasing sun exposure are supporting factors. The sense for beauty and cosmesis is tremendously increasing and patients are looking more and more for innovative non-surgical treatment modalities combining high cure rates with optimum aesthetical outcome. Here, photodynamic therapy (PDT), which had been introduced to the therapy of APK and superficial as well as nodular BCC, offers a promising alternative treatment modality. After almost 12 years of experimental and clinical trial phase in PDT techniques, recently the topical drug methyl-[5-amino-4-oxopentanoate (MAOP)] has been launched for topical PDT. MAOP is applied to the diseased skin. After an incubation period of 3 hours, the treated skin is irradiated by cold narrow band red light, which may be accompanied by little stinging or pain. PDT is followed by a healing period – including inflammation, crust formation, exfoliation, and transient hyperpigmentation. Optimum results are achieved if PDT is repeated within 7–10 days. APK are healed with cure rates of 95–98%. Superficial BCC show comparable response. In addition, PDT is also an excellent technique for nodular BCC, however, a certain experience is required to avoid treatment failure. In addition to this therapeutic tool, photodynamic sensibilisation of skin cancer cells may be used for fluorescence diagnosis (FD) to detect and to demarcate skin tumors. APK und BCC show a bright red fluorescence if treated by MAOP and irradiated with Wood's light. This innovative diagnostic technique is increasingly performed to preoperatively define the borders of an ill-defined tumor or to control the efficacy of any tumor therapy (PDT, cryosurgery, surgery).

205

IMMUNOTHERAPY: ANOTHER NEW TREATMENT OF SKIN TUMORS

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Demographic factors with higher age of people living in industrialized countries and more frequently occurring sun exposure due to life style factors such as travel tours to tropic or subtropic countries during holidays have increased the prelavence of different types of skin cancers. Actinic keratosis, basal cell carcinoma, squamous cell carcinoma and malignant melanoma are predominantly located in UV radiation-exposed skin regions. UV radiation causes neoplastic transformation of epidermal and melanocytic cells and suppresses cell-mediated immunity. Treatment of skin cancer includes

surgery, cryo-therapy, local application of cytotoxic agents (including photodynamic therapy), ablative laser therapy or radiation. A new therapeutic approach has been introduced by imiquimod, an immune response modifier, which stimulates the immune system by activation of Toll-like receptors and induction of cytokine production in the skin. The first approved indication of imiquimod was the treatment of genital HPV-induced warts. However, further studies have shown that imiquimod is also effective in the treatment of superficial basal cell carcinomas. It is usually applicated locally 5 times per week for 6 weeks. During this treatment period erythema, oedema, induration, scaling, crusting, erosion and ulceration may occur. The severity of local skin reactions is correlated with the clinical and histological response to imiquimod. The complete histological response rate was found to be more than 80% after treatment with imiquimod. More than 90% did not show recurrence of basal cell carcinoma within 12 months after treatment. Personal experience with this substance has shown that it is also effective in the treatment of actinic keratosis and superficial squamous cell carcinoma.

206

SKIN REJUVENATION WITH LASER AND OTHER TECHNIQUES

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Ageing skin is thinner, less hydrated and shows more wrinkles. The oldest methods used are chemical peelings. Subsequently, ablative lasers were introduced for skin rejuventation. The thermal action of CO2-lasers prevents bleeding and during the treatment of deeper layers shrinking of the dermal collagen can be observed. Reports show excellent results for wrinkle reduction which is also due to neo-formation of collagen. Er:YAG lasers allow for a 'cold' ablation. There is no collagen shrinking. The procedure is less painful and the skin surface recovers faster. Mostly, fine elastotic wrinkles of the perioral and periorbital region respond favourably to this treatment. Another method is microdermabrasion, a mechanical peeling with salt or aluminium crystals, that are applied onto the skin and removed immediatly by vacuum suction. Dermabrasion by diamond sanding is indicated for deeper wrinkles (mostly perioral) and yields longer lasting results. Skin is removed up to the stratum papillare. All mentioned methods lead to changes that require a minimum of one week abstinence from work, etc.. Therefore, non-ablative laser methods were developed to perform 'lunch time' rejuvenation. The epidermis is spared as dermal action is more important for wrinkle reduction. In contrast to lasers, the intense pulsed light source (IPL) emits a broad spectrum of wavelengths that can be modified by specific filters. The aim of IPL treatment is not primarily the reduction of wrinkles but the correction of clinical signs of sun-damaged skin, such as teleangiectasias and mottled pigmentation with red or brown spots. Other devices used are the Nd:YAG laser Cooltouch^{TM} and the Smoothbeam^{TM}. The maximal temperature is generated in the papillary dermis where collagen shrinking is induced. The non-ablative subsurfacing is improved by a new technique the fractional photothermolysis that is realized in the device Fraxel^{TM} by Reliant. The skin is treated with microscopic laser spots. There are microthermal zones surrounded by healthy tissue. Another new technique is the device Thermage^{TM} by Thermage. Radiofrequency is the agent that heates up the dermal collagen and induces shrinking. New method modalities are being developed constantly and therefore the duration of therapeutic effects requires further investigation.

207

TESTOSTERONE AND WOUND HEALING

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Aging in men is associated with a progressive decline in the production of several hormones, including androgens. The extent to which an age-dependent decline in androgen levels lead to health problems or can affect quality of life remains under debate. Clinical results on replacement therapy due not provide yet a definitive clue on the benefit/risk balance. A sexual dimorphism of the immune system is well established and the differences between female and male immune responses under normal as well as pathological conditions are generally attributed to the influence of estrogens, progestins, and androgens. The suppressive effects of male sex hormones on immune functions have been observed in a wide variety of disease processes and appear to be testosterone-mediated. Endogenous testosterone inhibits skin wound healing response in males and is associated with an enhanced inflammatory response. Although there are no known gender-related differences in permeability barrier function in adults, estrogens accelerate whereas testosterone retards barrier development in fetal skin and male fetuses demonstrate slower barrier development than female littermates.

Russian ISSAM Symposium

208

CLINICAL CONSEQUENCES OF HYPOGONADISM IN NON-GONADAL DISEASE

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We studied 200 men with different somatic pathologies: chronic obstructive lung disease (COLD) – 33%, hypertension – 33%, ischemic heart disease (IHD) – 11%, mixed somatic pathology – 57%, patients with alcoholic visceropathy – 44%. All patients were divided into 3 groups by age: the first group (1) – under 45, the second (2) – 45–55, and the third (3) – after 55. 79,8% of patients had clinical and laboratory signs of hypogonadism with strong correlation to age, type of patology and treatment options. Clinical signs of severe hypogonadism were found in 30.5% of patients in the group 1, in 51.2% of the group 2 and in 82.9% of the group 3. The levels of testosterone were lowered accordingly in 36% of the group 1, 72% in the group 2 and 84% in the group 3. Clinical signs of hypogonadism were more severe in patients with mixed somatic pathology, especially in combination with alcoholism: hypertension + alcoholic visceropathy – 30%, COLD + alcoholic visceropathy – 90%, alcoholic hepatic cirrhosis – 75%. Also we found a correlation between severity of clinical picture of hypogonadism and kind of therapy taken: clinical picture of hypogonadism was present in 92% of patients treated with diuretics, 100% of those who were taken theophyllines and 85.7% of patients treated with beta-blockers. Thus, we conclude, that the age, the type of somatic pathology and the kind of therapy taken correlate with clinical signs of hypogonadism and blood testosterone level. In Russia measuring of testosterone level in serum is not widely available, that is why we consider AMS (aging male symptoms) scale as a sufficient and adequate method for evaluation of androgen deficiency.

209

TESTOSTERONE: BIOLOGICAL EFFECTS AND METHODS OF MODERN METHODOLOGY OF MEASUREMENT IN BIOLOGICAL FLUIDS

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More and more attention of scientists and clinicians is being attracted to the study of male reproductive system, particularly in men of older age groups, in who late-onset hypogonadism is developed. This is characterized by the clinical symptoms, and

by the deficiency of testosterone circulating in blood, primarily of free testosterone fraction (fT), and to some extent of total testosterone (TT). Along with the classic androgen effects such as sexual differentiation, virilisation, maintaining the phenotype, sexual function and anabolic effects, testosterone and its active metabolites 5alfa-dihydrotestosterone and estradiol, exert a number of other anabolic and metabolic effects. Androgenic status assessment is usually made by TT measurement, formerly with RIA technology, and now using direct non-isotopic automated methods, based mainly on enhanced chemiluminescence principle. We compared the performance of 5 automated methods of TT measurement with a standardized RIA technology. Practically all tested methods had poor agreement with RIA, and at ÒÒ concentrations under 10 nmol/l the results can be considered as critical. These findings necessitate bringing into play another more convenient biochemical marker of androgenic status assessment – fT in blood. The kits presently available for direct fT measurement in blood do not measure what they claim to do. We studied the analytical performance of a novel technology of fT measurement in saliva of healthy individuals, employing the chemiluminescence principle (IBL, Hamburg). Free T in blood in the same volunteers was calculated using the mathematical formula described by A.Vermeulen. The levels of fT in blood and in saliva practically matched each other. However this agreement was less true in patients with diabetes and other chronic diseases. Two more advantages of the described technology are: the possibility to recognize androgenic deficiency in women and to study the pharmacokinetics of androgenic drugs used in the replacement therapy.

210

ERECTILE DYSFUNCTION IN DIABETES MELLITUS PATIENTS: THE ROLE OF ALPHA-LIPOICACID IN THE TREATMENT OF NON-RESPONDER TO SILDENAFIL CITRATE

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Erectile dysfunction (ED) is one of the forms of sexual dysfunction in diabetes mellitus (DM) men. Penile erection is a vascular phenomenon. This, in turn, is controlled by autonomic nervous system. ED in diabetic patients is due to failure of NO-mediated smooth muscle relaxation due to autonomic neuropathy and endothelial cells dysfunction. In some cases it leads to a situation, where PDE 5 inhibitors do not work, mainly due to impaired neuronal NO production. Having this in mind we have to think about treatment options, which are able to restore and/or protect nerve function in patients with diabetes. Diabetic neuropathy can be assessed via neuropathic deficits such as decreased temperature sensation, decreased vibration threshold and by electrophysiological measures such as nerve conduction velocity. The neurological impairment in erectile dysfunction can be assessed at the organ itself (method Kalinchenko-Rozhivanov). How can we manage ED? There are vacuum restriction devices, intracavernosal injections and PDE5 inhibitors. It is very important to note that PDE5 inhibitors are just symptomatic treatment approaches. We used a similar treatment scheme for our ED patients, which is recommended for the treatment of diabetic neuropathy. Patients with moderate ED were treated with alpha-lipoic acid (Thioctacid®) for 2 weeks with 1800 mg orally and then shifted to a 2 month maintenance therapy with 600 mg. Patients with severe ED were treated for 2 weeks with 600 mg infusions of alpha-lipoic acid and then shifted to a 2 month maintenance therapy. Results will be discussed. CONCLUSIONS: ED is a typical complication of DM. ÅD is highly prevalent, under-diagnosed and under-treated. Neuropathy plays a significant role in pathogenesis of sexual disorders (erectile and orgasmic dysfunction). Alpha-lipoic acid (Thioctacid®) appears to be a pathogenetic treatment option for ED. Alpha-lipoic acid (Thioctacid®) may sustain PDE5 efficacy in ED treatment.

211

GENETIC DETERMINANTS OF ANDROGEN SENSITIVITY: IMPLICATIONS FOR TESTOSTERONE REPLACEMENT THERAPY

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Testosterone (T) is essential male hormone that is required for induction and maintanance of secondary sexual characteristics and sexual behaviour, as well as exertion of various metabolic and systemic effects. At the cellular level, T acts through androgen receptor (AR) directly or undergoes enzymatic conversions to another potent androgen dihydrotestosterone (DHT) or estrogen estradiol (E2). There are substantial polymorphisms in the genes encoding androgen and estrogen receptors and enzymes for end-organ conversion of T. These polymorphisms might account for variability in biological responses to T. Population studies showed relationship between some polymorphisms in the ESR1 gene encoding estrogen receptor alpha and atherosclerotic cardiovascular disease both in women and men. Certain polymorphisms in AR and SRD5A2 (5 alpha-reductase) genes are associated with increased risk of prostate cancer. This genetic variability must be taken in account when prescribing T replacement treatment. Preliminary results of population studies in Russia are presented.

212

THE ROLE OF SEX AND GENDER IN MIGRAINE

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Women are 2–3 times more likely then men to suffer migraines. The role of estrogens has been proposed for explanation of this female preponderance. What specifies men who suffer from migraine has not been yet explained. Aim: The aim of our study was to explore the role of sex and gender in migraine Methods: 86 females and 24 males with migraine without aura entered the study. We compared clinical, psychological and socio-cultural characteristics of males and females considering their level of masculinity/femininity according to S.Bem Gender Role Inventory. Results: The dominance of feminine patients was characteristic for the investigated group. Female patients showed higher longevity of the disorder, higher frequency and duration of the attacks, higher level of anxiety,etc. Although the decrease in quality of life was equal for both sexes. About ½ of both males and females reported low sexual activity. In men this produced greater impact: males with low sexual activity showed higher decrease in quality of life than sexually low active females. Conclusion: The dominance of feminine type patients in migraine might be the consequence of organizational effects of female sex hormones on the brain of these patients in perinatal period. More pronounced clinical characteristics of female and feminine (female or male) migrainers might be explained by lower set in perinatal period of their perception threshold to different stimulus. Equal decrease in quality of life in males and females might indicate more serious impact of migraine on male well-being. This stresses the necessity to pay more attention to male patients even with modest clinical presentation.

213

LOW BACK PAIN: RISK FACTORS FOR CHRONIFICATION AND TREATMENT PERSPECTIVES

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Low back pain (LBP) is a common problem affecting most adults at some point during their lifetime. At any one time,

around 1 in 5 adults will report symptoms of LBP. Although majority of people who experience an episode of LBP will improve over time, a sizeable proportion experience repeated episodes or recurrences, and some report continuous symptoms for many years. A wide range of factors are linked to the persistence and chronification of LBP. Some studies have related age and gender to LBP, but the link overall is equivocal. Risk factors for chronification of LBP include depression and anxiety, job dissatisfaction. Chronic LBP places large demands on health, social and welfare systems. One of the important mechanisms of chronification of pain is central sensitization, which is very common for neuropathic type of pain. Different pathophysiological mechanisms are thought to operate in chronic LBP. The nociceptive and neuropathic pain components can be distinguished in LBP. Neuropathic pain may be caused by lesions of nociceptive sprouts within the degenerated disc, mechanical compression of the nerve root, or by action of inflammatory mediators originating from the degenerative disc. The most effective in neuropathic pain treatment are antidepressants and anticonvulsants. Therefore we studied the efficacy of gabapentin, a new anticonvulsant, in the treatment of 24 patients with chronic LBP. In 75% the pain relief was obtained. We conclude that gabapentin was effective due to its action on neuropathic component of LBP and reduction of central sensitization. If it is true, the gabapentin could be useful in patients with chronic LBP, when neuropathic component of pain is present. It seems that therapy with anticonvulsants (like gabapentin) may help to prevent chronification of LBP.

Is there a link between obesity, diabetes, erectile dysfunction and cardiovascular disease?

214

IS THERE A LINK BETWEEN OBESITY; DIABETES, ERECTILE DYSFUNCTION AND CARDIOVASCULAR DISEASE?

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Mortality from coronary heart disease increases with age and is at least twice as prevalent in men compared with age-matched women. Female sex hormones were thought to be protective but two large randomised controlled trials have produced negative results for cardiovascular health preservation. What is it about men? There is a natural change in male body shape with age in association with falling testosterone blood levels. Elderly men develop fat re-distribution to the trunkal area. Is this itself an adverse cardiac risk factor? Age is also independently associated with worsening insulin resistance which is a recognised cardiac risk factor. How do trunkal obesity, increasing insulin resistance and falling testosterone levels combine to affect cardiovascular risk? Does male hormone replacement therapy reverse any of this adverse risk profile? In this presentation I will try to answer these important questions by reference to published studies.

Osteoporosis

215

DIAGNOSIS AND TREATMENT OF MALE OSTEOPOROSIS

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Abstract not available at the time of printing.

216

IGF-1 AND CARDIOVASCULAR RISKS

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Adult GH deficiency (AGHD) is characterized by an altered body composition, an atherogenic lipid profile, decreased exercise capacity, and diminished quality of life .GH treatment has beneficial effects on lean and fat body mass, total and LDL cholesterol levels, and diastolic blood pressure. GH treatment could modify the cardiovascular risk in adults with GH deficiency. Age-related changes in GH and IGF-I secretion occur in both men and women and may partially contribute to the body compositional changes of decreased lean body mass, increased adiposity, and increased cardiovascular risk. In addition, there is potential for hGH use in elderly patients in various catabolic states because of its anabolic effects with nitrogen retention. Only patients with IGF-1 deficiency have increased IMT. In humans, on one hand hypopituitarism and GH deficiency (GHD) are believed to constitute risk factors for cardiovascular disease and, therefore, early death. Twin studies have shown, that the inter-individual variability in circulating IGF-1 levels contributes to genetic differences in 38%. The IGF-1 gene contains a region of multiple CAG repeats, approximately 1 kb upstream from the IGF-1 gene promoter. Studies have been shown, which gave evidence, that the number of repeats is related to the transactivation of this gene. The Rotterdam study, analysing population based polymorphism clusters of the IGF-1 gene snp, showed that there is a highly significant relationship between IGF-1 levels and age. The risk of diabetes type II was increased in those carriers, who displayed increased weight and obesity. The risk for obesity is related to the number of CAG repeats. The rel. Risk for previous MI and for MI during follow up showed, that heterozygous carriers of the snp had higher arteriosclerosis risk. (1.6, 95% CI, previous), 2.7(95% CI, 1.5–4.9) for follow up MI. This presentation suggest that IGF-1 has direct cardioprotective effects, possibly reducing myocardial injury in response to ischaemia.

217

PATHOPHYSIOLOGICAL ASPECTS OF SENILE OSTEOPOROSIS IN MEN

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Osteoporosis in ageing men is a major problem of public health because the number of fragility fractures in men increases rapidly. Two principal risk factors of fragility fractures in elderly men have been studied: low areal bone mineral density (aBMD) and low bone size. Decrease in aBMD is associated with an exponential increase in the fracture risk. The low aBMD is determined by low peak bone mass acquired during the growth and accelerated ageing-related bone loss due to the increased bone resorption which is only partly matched by bone formation. The principal risk factors of bone loss in elderly men are hypogonadism, low level of bioavailable 17beta-estradiol, low body mass index, tobacco smoking, corticosteroid therapy and poor health status. In men with prostate cancer, androgen deprivation therapy induces a rapid acceleration of the bone turnover and bone loss which results in the increased fracture risk. Low bone size is associated with an increased fracture risk regardless of aBMD. Specific determinants of low bone size in men are only partly studied. Potential determinants are: genetic factors, nutritional status, low muscle mass, sedentarity, delayed puberty. Low bone size is associated with the lower bending strength which confers higher susceptibility to fractures by bending and torsion. However, several major aspects of the pathophysiology of the osteoporosis in men remain to be elucidated. There is no generally accepted diagnostic

criterion of the osteoporosis in men. T-score = −2.5 used in postmenopausal women captures only a small proportion of fractures in elderly men. The study of association between bone geometry and fracture risk are based on parameters estimated from DXA scans (dual X-ray absorptiometry) and measurements by using peripheral quantitative computerised tomography are needed. Data on the prediction of bone loss and fragility fractures by the biochemical bone turnover markers in elderly men are limited. Interaction of different factors leading to the increased fracture risk by different mechanisms (hypogonadism, vitamin D deficit, muscle mass) need to be studied. Qualitative parameters of bone tissue (trabecular microarchitecture, degree of mineralization, microstructure of type I collagen) and their specific role as determinants of bone strength (or fragility) in elderly men have not been studied.

218

CLINICAL APPROACH TO SENILE OSTEOPOROSIS IN MEN

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Abstract not available at the time of printing.

Phytoestrogens and Human Pheromones in Men

219

EFFECTS OF VARIOUS PLANT DERIVED SUBSTANCES ON HUMAN PROSTATE CANCER CELLS

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In the prostate, as well as in human prostate cancer LNCaP cells, the androgen receptor (AR), both types of estrogen receptors (ER) as well as the aryl hydrocarbon receptor (AhR) are expressed. These nuclear receptors are involved in proliferation of tumour cells and are therefore pivotal therapeutic targets. The use of anti – androgens to interfere with the AR is well established. Recent research is focussing on the ER, in particular the ER ß. Compounds which specifically bind to this receptor may be anti-proliferative via inhibition of cell cycle progression and enhancement of apoptosis. Besides synthetic substances, phytoestrogens of the isoflavone – type like genistein are thoroughly investigated. Recently, anti – proliferative effects of extracts of Silybum marianum (SM) and of Cimicifuga racemosa (CR) on LNCaP cells have been reported. One active compound isolated from SM is the flavolignan Silybinin, which selectively binds to ERß and down-regulates expression of prostate epithelium-derived Ets transcription factor, of telomerase and of prostate specific antigen. The active principle of CR and its mechanism of action on LNCaP cells are still unknown. However, the anti – proliferative effect of CR is achieved at exceptionally low concentrations of the extract indicating, that the active principle(s) is (are) very efficient. Ligand binding assays with ER α or β and AR revealed that CR lacks affinity towards these receptors. In contrast, CR interacts with the AhR, a receptorwhich was initially identified by its high affinity binding of polycyclic aromatic hydrocarbons. In various cancer cell lines, the AhR interferes with the signal transduction of both, AR and ER, causing inhibition of proliferation. Thus, activiation of the AhR may be the molecular basis of the action of CR on prostate cancer cells. Thus, SM and CR appear to be alternative treatments especially for AR – insensitive prostate tumours.

220

EFFECTS OF CIMICIFUGA RACEMOSA AND BELAMCANDA CHINESIS ON TUMOUR GROWTH IN LNCAP CELL TRANSPLANTED NU/NU MICE

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The Cimicifuga racemosa extract BNO 1055 (CR) inhibits proliferation of human prostate cancer-derived LNCaP cells. Therefore we tested the capability of this extract to inhibit formation and/or proliferation of tumors induced by subcutaneous (s.c.) inoculation of LNCaP cells in immunodeficient nu/nu mice. After inoculation of 1 mio cells 12 of 18 animals developed solid tumors while tumor development was seen in only 5 of 18 CR-treated animals of which the size at termination of the experiments 10 weeks after inoculation was significantly smaller than in the control animals. Upon histological inspection the amount of tumor tissue in the control animals was significantly larger than in the CR-treated animals while in the latter connective tissue was predominant. It is concluded that compounds in CR inhibit tumor development, proliferation and dignity of the tumors following s.c. inoculation of LNCaP cells. Hence, the CR extract may prove to be efficient in preventing and treatment of prostate cancer.

221

DIETARY POLYPHENOLS PROTECT AGAINST PROSTATE CANCER

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Prostate cancer is usually treated at time of diagnosis, and chemoprevention is not usually considered until adulthood. However, development of the prostate occurs perinatally and early development is a critical period for cancer susceptibility. Men in their 20's through 40's develop low-grade prostatic intraepithelial neoplasia (PIN), with a frequency of 9% to 26%. In addition, high-grade PIN, the precursor to prostate adenocarcinoma, is in men in their 4th, 5th, 6th, and 7th decades of life at a frequency of 5, 10, 41, and 63%, respectively. We are investigating the potential of polyphenolic chemicals found in food to suppress prostate cancer development. Our laboratory has found that the soy isoflavone, genistein and the phytoalexin stilbene, resveratrol, found in red wine suppress prostate cancer development in animal models. With genistein, we have shown that dietary achievable doses for humans can suppress prostate cancer in a chemically-induced rat model and a transgenic mouse model that spontaneously develops prostate cancer (TRAnsgenic Mouse Prostate adenocarcinoma: TRAMP). Genistein chemoprevention was demonstrated in intact mice and in castrated (androgen independent) TRAMP mice. Also, resveratrol fed to TRAMP mice suppresses prostate cancer development. Timing of exposure studies with these dietary polyphenols reveals that pubertal through adulthood is the most effective period for genistein suppressing PC development, but adult genistein treatment also suppressed prostate cancer. Genistein and resveratrol regulate cell proliferation, apoptosis, and sex steroid and growth factor signaling as mechanisms of chemoprevention.

222

PHYTOESTROGENS IN PROSTATE CANCER

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Prostate cancer is one of the main causes of cancer death in men in Western countries; in contrast its incidence and mortality are low in Asia. This has been attributed to a diet rich in products

containing high amounts of phytoestrogens such as isoflavones. In many model systems these substances, the prototype of which is genistein, inhibit cell proliferation and cell cycle progression and enhance the rate of apoptosis. The molecular mechanisms involve modulation of steroid receptor expression and steroid hormone metabolism, inhibition of growth factor receptor and survival pathways and depend on concentration and cellular context. Estrogen receptors alpha and beta are both expressed at high levels in the human prostate and seem to be involved in regulation of androgen receptor levels, proliferation and apoptosis and a phenomenon, which was termed embryonic imprinting and describes the influence of steroid hormone exposure during embryonal development on adult steroid hormone receptor levels and prostate cancer risk. In the hormone-sensitive prostate cancer cell model LNCaP, genistein, anisoflavone highly contained in soy products, down regulates androgen receptor protein expression via a mechanism involving estrogen receptor beta. Regulation of prostate growth involves interaction of different cell types and the prostatic stroma plays a curical role, mediating hormone effects and stimulating epithelial cells through release of growth factors. A screen for phytoestrogens inhibiting stromal prostate cells identified apigenin as a potent drug. In cultured prostate stromal cells it reduced proliferation and cell cycle progression in a dose-dependent manner acting on cell cycle regulators and the MAP kinase pathway. In conclusion several phytoestrogens are promising substances for use in prostate cancer prevention, treatment and slow-down of tumor progression. They modulate prostate and prostate cancer cell growth by interfering with several pathways and act on epithelial as well as stromal cells in the human prostate.

223

THE HUMAN PHEROMONES – A COMPARATIVE VIEW

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More than thirty years ago, on the occasion of the introduction of the boar pheromone 5α-androst-16-en-3-one into the pig breeding industry, I gave a comprehensive survey of pheromones. At that time the fact was exciting that the olfactory system is responsible for the sensing of odorous chemicals–pheromones – released by animals that act on conspecifics to regulate animal populations and their social interactions. Pheromones elicit programmed neuroendocrine changes and innate behaviours, suggesting a need for a very precise recognition process. Our knowledge of the chemistry and the mode of action of different pheromones in the animal kingdom has increased enormously since that time. In recent years, the discovery of multigene families which encode many olfactory receptors in three distinct classes has provided molecular tools with which to further explore the physiology and pathophysiology of odorants and pheromones. Despite the large body of information about the role of pheromones in mammals, our knowledge about pheromones in humans is still sparse or speculative. This review will focus on what recent studies have revealed about the function and physiological consequences of odour or pheromone sensing in humans. Information about the influence of aging on the secretion or perception of pheromones in males can only be obtained by extrapolation of results from the boar and other male animals to humans.

Third Wave of the Massachusetts Male Aging Study – New Findings

224

INTRODUCTION TO THE MASSACHUSETTS MALE AGING STUDY (MMAS): A LONGITUDINAL INVESTIGATION OF AGING AND HEALTH

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The MMAS is considered a landmark research effort in the fields of aging, endocrinology and urology: • It employs a random sample of community-dwelling men (not a convenience sample of patient volunteers); • Its size permits estimation of even relatively rare phenomena (e.g., hypogonadism); • It is longitudinal (intra-subject variation) not cross-sectional (inter-subject variation) and has successfully followed a cohort from 1987–89 (T1) through 1995–97 (T2) to 2002–04 (T3); • Worldwide, it remains the largest male endocrine database; • It is the first and still the only major longitudinal study of ED; • It is multidisciplinary; • Emphasis has been given to the practical clinical applications of scientific findings. The accompanying figure depicts the design of the MMAS: starting in 1987 with a random sample of 1709 men (ages 40–70 years), subjects have been followed over 17 years to 2002–04, with a fourth follow-up planned for 2008–10. The effort continues to be supported by the National Institute of Diabetes and Digestive and Kidney Disease (National Institutes of Health).

225

ERECTILE DYSFUNCTION AS A PREDICTOR OF CARDIOVASCULAR DISEASE IN AGING MEN: PROSPECTIVE RESULTS FROM THE MASSACHUSETTS MALE AGING STUDY

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Sexual function is reduced in men with CVD. Whether sexual function (specifically erectile dysfunction (ED)) predicts CVD has not been established. We examined whether ED predicts risk of coronary heart disease (CHD) or stroke in men. Data were obtained from a population-based prospective cohort of men (aged 40–70 yr) from the Massachusetts Male Aging Study (MMAS). Participants without self-reported CHD/stroke at baseline (1987–89) were followed until 2004 for the occurrence of CHD or stroke. Person-years (py) at risk were accumulated from baseline to year of event/last contact/end of study. Self-reported ED was measured at baseline. We computed incidence rates (IR) for CHD and stroke in each ED category, and estimated hazard ratios (HR) for CHD and stroke by Cox proportional hazards regression. There were 1,194 and 1,425 men at risk for CHD and stroke, respectively. During 13,896 py of follow-up for CHD, there were 222 CHD events. During 17,096 py of follow-up for stroke there were 99 strokes. Age-adjusted IRs for CHD and stroke were 28.4/1,000 and 10.1/100,000 py. Men with and without ED had similar age-adjusted IRs for CHD (27.6/1,000 vs. 23.8/1,000 py) and stroke (9.1/1,000 vs. 10.4/1,000 py). Stratum-specific models showed no variation in CHD risk associated with ED across strata of common CVD risk factors. However, similar models predicting stroke incidence showed significant ($p = 0.01$) variation in risk of stroke associated with ED by smoking status, with no effect of ED among non-smokers (HR = 0.75, 95% confidence interval (CI): 0.40–1.45), and a strong effect of ED among current smokers (HR = 2.95, 95% CI: 1.33–6.53). Our data suggest that ED does not predict CHD but is a strong predictor of new cerebrovascular events among smokers. The data conform somewhat to the 'artery-size' hypothesis in that ED predicts stroke but not CHD. ED may represent an early warning of stroke among smokers.

226

ERECTILE DYSFUNCTION: PROGRESSION AND REMISSION. LONGITUDINAL RESULTS FROM THE MASSACHUSETTS MALE AGING STUDY

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Understanding the natural course of disease is critical to interventions to slow or reverse its progression. To model the

natural course of erectile dysfunction (ED), we investigated its progression and remission among aging men. We used data from Waves I and II of the Massachusetts Male Aging Study (MMAS), a study of randomly selected men's aging. ED was assessed using a four-point scale (none, mild, moderate, complete). Progression and remission were respectively defined as higher or lower severity at Wave II than at Wave I. Regression analyses examined age-adjusted relationships between severity and potential correlates, including demographics, lifestyle, comorbidities, and availability of a sexual partner. Data were obtained prior to 1998 (i.e., before introduction of PDE-5 inhibitors). of 323 subjects reporting at least mild, but not complete, ED at Wave I, 107 (33%) reported progression at Wave II. of these, the majority (74; 69%) reported complete ED at Wave II. of 401 subjects reporting at least mild ED at Wave I, 141 (35%) reported remission at Wave II. Of these, the majority (114; 81%) experienced total remission. Overall, total remission occurred more frequently among men with mild ED than among those with moderate or complete (32% vs. 23% total remission, $p = 0.04$). Full progression occurred more frequently among those with moderate ED than with mild (32% vs. 20% full progression, $p = 0.02$). Age, BMI and transition from lacking a sexual partner to having one were associated with remission when controlling for other covariates. The presence and severity of self-reported erectile dysfunction have natural transient properties. Initial severity is significantly associated with progression or remission. However, even some men with complete ED may experience total remission, particularly younger men with lower BMI, or who gain a sexual partner.

227

TESTOSTERONE, DEHYDROEPIANDROSTERONE AND PHYSICAL PERFORMANCE IN OLDER MEN: RESULTS FROM THE MASSACHUSETTS MALE AGING STUDY

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This paper examines the relationships of total testosterone (TT), bio-available testosterone (BT), dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) to measures of physical performance in a large, population-based, random sample of men. In the most recent wave (2003–2004) of data collection of the Massachusetts Male Aging Study, 545 men aged 55–85 had measures of physical performance (7-Item Physical Performance Test [PPT], timed chair stand test and grip strength). Initial graphical exploration of outcomes as a function of hormone levels showed clear threshold effects, and regression models were used to estimate thresholds and standardized regression coefficients (''betas'', B) for these effects. All hormones were positively and significantly associated with PPT score below but not above the thresholds. Similarly, DHEA was positively associated with chair stand score below but not above the threshold. None of the hormones studied were significantly associated with grip strength. Up to certain critical concentrations, elevated levels of TT, BT, DHEA and DHEAS are associated with better physical performance as indicated by the PPT and/or chair stand tests. However, levels beyond those critical concentrations, as might be achieved through exogenous supplementation, do not appear to confer any additional benefit.

228

THE RELATIONSHIP BETWEEN HORMONES AND METABOLIC SYNDROME: RESULTS FROM THE MASSACHUSETTS MALE AGING STUDY

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Metabolic syndrome (MetS), characterized by central obesity, lipid and insulin dysregulation, and hypertension, is an important precursor state for cardiovascular disease. This investigation was undertaken to determine whether low serum sex hormones or clinical androgen deficiency (AD) predict the development of MetS. Data were obtained from the Massachusetts Male Aging Study (MMAS), a population-based prospective cohort of 1709 men observed over three data collection waves. MetS was defined by using a modification of the ATP III guidelines. Clinical AD was defined using a combination of testosterone levels and clinical signs and symptoms. The association between MetS and sex hormones or clinical AD was assessed using relative risks (RR) and 95% confidence intervals (95% CI), estimated via Poisson regression models. An analysis of 950 men without MetS at baseline reveals that lower levels of total testosterone (TT) and SHBG are predictive of MetS, particularly among men with $BMI < 25$, who experience proportionate increases of 41 percent (95% CI: 6–87) and 65 percent (12–42) in the risk of incident MetS per standard deviation decrease in TT and SHBG, respectively. An examination of the relationship between AD and MetS revealed similar results. Among men with $BMI < 25$ we estimate a RR of MetS of 2.51 (1.12–5.65) for those with baseline AD versus those without, whereas among men with $BMI > 25$ the corresponding RR is 1.22 (0.66–2.24). These findings suggest that low serum SHBG and TT, as well as the presence of clinical AD, are associated with increased risk of incident MetS, particularly in non-overweight middle-aged men ($BMI < 25$). Low SHBG and/or AD may provide a warning sign and an opportunity for early intervention in non-obese men.

Morning, Noon, and Night – Older Men at Work, Rest and Play

229

ALL WORK AND NO PLAY: VISIONS AND DIVISIONS OF ACTIVE AGEING

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Against all the doom and gloom that surrounds anything to do with demographic ageing, the idea of 'active ageing' stands out like a shining beacon of hope. Rather than the unpalatable choice between burdening the young with skyrocketing social costs or massively cutting existing public pension provisions and extending the working-life late into the 60s, the idea of active ageing seems to promise an attractive alternative. By providing the right types of policies at just the right points in the life cycle, proponents of active ageing policies – not least the European Commission and the OECD – argue that people will stay healthier for longer, retain competitive skills and motivation as well as participate actively in socio-cultural and political life. Best of all, advocates contend, active ageing policies are so sensible as to be virtually uncontaminated by the quarrelsome bug of policy conflict that inflicts other policy responses to demographic ageing: everyone, whether the state, industry or workers themselves, will ultimately profit from active ageing. Looking at ageing policy in Europe, the proponents of active ageing seem vindicated: any observer would be hard pressed to find any substantial criticism of active ageing policies. Why, then, has active ageing policy in Europe not yet got beyond the stage of being 'a really good idea'? This paper traces the socio-economic and political barriers and opportunities for active ageing policies in Europe. In particular, the paper will show that active ageing may mean very different things to different policy actors. If the divisive policy conflict that characterises other policy debates about demographic ageing is to be avoided, this paper argues that active ageing policy-makers will have to begin to address these fundamental divisions about active ageing policy.

230

COULDN'T BOIL WATER? OLDER MEN'S COOKING SKILLS AND HEALTHY EATING STRATEGIES

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In a generation traditionally reliant on women's domestic skills, little attention has been paid to the experience of older men in relation to food and cooking. This paper reports qualitative interviews with men over the age of 65 (n = 40) and examines their attitudes to, desire for and ability in, meal preparation. Half the men lived with partners, and half never had, or had lost, partners. Our results revealed that long term partnered, and long term lone men, reported routine and stability, although there were differences in involvement and competence. Newly alone men generally tended to find the necessity of feeding themselves boring, yet challenging. Nevertheless, some men in all marital status categories had taken enormous pride in acquiring a late life skill. We categorised the men into three principal groups: 'the enthusiasts', 'the reluctants' and 'the resisters'. Interestingly, the four men who had recently established new co-residential relationships, reported that although they had coped well when alone, they had instantly relinquished the kitchen domain to their new partner. However, we found that sharing a meal, whether informally at home, or formally outside the home, was a much more important issue than who prepared the food.

231

AGEING MALES BUYING SEX: A MALTESE CASE STUDY

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Social science literature on prostitution has traditionally focused on sex workers rather than their clients. This neglect of male clients reflects the brunt of sexism where women are perceived as the deviant party despite avocations to the contrary in various feminist publications. Another lacunae is that little is known about older male clients. However, a survey on The World Sex Guide – a website forum in which male clients exchange information about prostitution opportunities – found 34 percent of members to be above the age of 50. This research presentation is precisely an attempt to commence a better understanding of older clients in the prostitution business, carried out through the case study research design in which four informants took part. It seeks to investigate the construction of the sexual lives of older men who take part in prostitution so as understand the peculiar and normal features characterising their life course. The study also seeks to collect data on why these older men pay for sex, how they succeed in locating sex workers, their expectations regarding the act, how they perceive the sexual encounter, and their labelling of themselves as well as their sexual providers. Most importantly, the research will also be analysing the interrelations between the ageing and sex work. Attention will also be given to how these older males interrelate with significant others in the course of their daily lives. Of course, this paper does not claim to be able to promote or generalise any theoretical framework due to the distinctive empirical context and the low number of informants. Yet, it will hopefully act as a catalyst for the further analysis of older male clients of sex work.

232

MEN'S HEALTH AND SLEEP: LESSONS FROM SOCIOLOGY?

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This paper suggests that sleep, whether individually acknowledged or not, is essential for our well-being and is intrinsically linked to health and illness. Lack of sleep can alter liver function and can substantially impair the immune system. As such, it is possible that the sociological literature on masculinities, health and illness may help better inform the sociologically neglected investigation of men's sleep. for example, established wisdom reports that men care and know little about their health, men take more risks with their health, men delay seeking help for ill health and men deny any and all weaknesses. Data for this paper are drawn from an ESRC funded project on couples' sleep. Forty couples were recruited (10 in each of the brackets <40 with children, <40 without children, >40 with children, >40 without children). The protocol involved firstly interviewing the couple together. Immediately following this, each individual was asked to wear a small watch like device which measures movement and to record audio diary entries about their sleep; both for seven consecutive days. Finally, about a month after this, each partner within the couple was interviewed separately. The different ways that the men talked about their sleep could not be explained through redress to their actual sleep. Masculine behaviours, such as risk-taking and denial of illness, did seem to play a part here. for example, key themes within the men's dialogues included ''laziness'', ''function'', ''doing'' and ''disposable resource''. of particular interest, this relationship between masculinity and sleep is threatened as men age. for many men (and women) chronological ageing is accompanied by physiological changes and a reduction in sleep quantity and quality. These changes may result in an acceptance of the sleep problem and a renegotiation of the male's manliness. They may also, however, be denied.

Public Health Issues

233

THE AGING MALE – DOWN UNDER

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In April 2005 the Australian Medical Association released its first-ever formal Position Paper on Men's Health. AMA President, Dr. Bill Glasson said 'The AMA Position Statement is a direct response to the fact that the overall health of Australian men is generally poorer when compared to Australian women, and getting worse. The poor state of men's health is a significant public health problem for Australia'. A rationale of the above statement is briefly discussed. Australia's population, in line with the rest of the world, is aging. By 2020 the Australian Bureau of Statistics projects the aged will account for 25% of the population – an estimated 6 million people with approximately half (49%) being Aged Males. Other demographic references follow. Congress President, Professor Bruno Lunenfeld (in his greeting to colleagues) states 'The health care of males in their aging years has tended to be piecemeal and somewhat uncoordinated'. He continues 'Despite the enormous medical progress during the past few decades, the last years of life are still accompanied by increasing ill health and disability'. Professor Lunenfeld suggests the key to be 'The ability to maintain independent living for as long as possible is a crucial factor of health and aging'. The Professor's statements are viewed in terms of the WHO's Alma Ata Declaration, and engagement within communities is pursued. An Australian point of view is given. The paper concludes with a review of one aspect of aging health in Australia – Suicide. The demographics point to incidence growth in mortality with increase in aging. Many in Australia consider that suicide is a community problem. A brief dissertation on the roll of community and the community's being in partnership with health services is explored.

234

IS THERE A POPULATION LEVEL DECLINE IN TESTOSTERONE LEVELS IN AMERICAN MEN? COHORT RESULTS FROM THE MASSACHUSETTS MALE AGING STUDY

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That androgens decline with age is well established. However, is there also a population-level decline in testosterone (T) levels in American men? Crude comparison of published cross-sectional and longitudinal analyses of T levels provides some evidence that observed longitudinal decline may be steeper than has been observed in cross-sectional analyses, implying for instance that men who are 60 years old today have lower concentrations than those who were 60 years old 20 years ago. To formally investigate the possibility of a secular decline in T levels, we examined data collected over the three waves of the Massachusetts Male Aging Study (MMAS; Wave 1(1987–89), Wave II (1995–97), Wave III (2002–04)), a longitudinal community-based study of randomly selected men's health and aging. 1709 men contributed one or more records to the analysis. Both uncontrolled and controlled evaluation indicate a mild but systematic decline in total serum T concentrations, as measured by radioimmunoassay, among subjects of like age over time. Results are similar for bioavailable T and are consistent over all ages from 55 to 70 years. In this presentation, we summarize this apparent decline via age-specific comparisons of mean T for groups of men of like age at different points in calendar time, and examine the role of internal and external factors potentially contributing to marginal decline in T, as well as the potentially confounding effect of assay drift.

235

HEALTH ISSUES OF AGING MEN: A JAMAICAN PERSPECTIVE

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The emerging need to address the health issues of older men continues to take prominence in family health issues in Jamaica. The reorganization of differences in choices by gender in the areas of physiological, and social preparedness, are emerging as significant issues for consideration in response to rapid population ageing in developing countries such as Jamaica. Methodology: Multiple methods were used to identify the health and social needs of older men. Quantitative methods used were secondary data from Ministry of Health Reports, the Jamaica Survey of Living Conditions, Demographic Statistics and a community based survey of 500 older men were used. Qualitative work included six (6) Focus Groups and four (4) Case Studies of men 75 + years. Results: Not only are older men not attending the Primary Health Care health facilities but in particular they are not utilizing the services provided by the Government Agencies to access specific health benefits such as low cost drugs. The data showed that less than 2% were registered under the government funded Jamaica Drug for the Elderly Programme (JADEP). Yet, these older men (35%) were paying more than 300% above the price available through the government funded programmes. In probing their lack of utilization of existing health services 40% of men who participated in the community survey suggested that encouragement, and accompaniment from spouses helped. It was further reported that when spouses made the appointments they were more willing to attend the doctor/health facility. Conclusion: Older men are not frequent users of Government Primary Health Care Services and they need the support of spouses and the encouragement of Health Professionals as motivators for such action.

236

MENFIT® A NEW MEDICAL CONCEPT FOR MEN'S HEALTH IN GERMANY – FIRST EXPERIENCES

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Menfit Institut for Men's Health, Ulm, Germany

In February 2005 MENFIT®, as a medical institut for men's health was opened up in Ulm, Germany. The medical concept was developed by a team of physicians for more than 18 months and contains the basic elements of men's health, which is prevention, nutrition, sports medicine and sexual medicine. In the mean time there have been 3 other menfit institute founded in Germany operating with our health concept. We have seen in our institute at Ulm more than 800 patients within the last 6 months and feel that there is a big need for assistance in health education of men. As urologists we should cooperate with physicians specialized in sports medicine and nutrition to become real health managers for our patients. For more information see www.menfit.de.

237

ANDROS MEN'S HEALTH INSTITUTE: A DEDICATED CENTER FOR UROGENITAL CARE OF THE AGING MALE

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In September 2004 the first private urogenital men's health institute for the aging male opened its doors in Arnhem, The Netherlands. The objective of this initiative is to provide adequate early diagnosis and treatment of urogenital dysfunctions associated with male aging. Five different programmes are offered all aiming at ensuring better quality of life: (early) Diagnosis of prostate cancer; (early) Diagnosis and treatment of LUTS/BPH; (early) Diagnosis and treatment of ED; (early) Diagnosis and treatment LOH; Lifestyle advice. In the first year of its existence 1715 men with concerns or questions about their urogenital function visited Andros. They all followed the same intake and evaluation programme which consists of 4 questionnaires (IEEF, IPSS, ADAM and SF36 QoL) full blood (including PSA, T and cholesterol) and urine evaluation, physical examination (including DRE and RR), flowmetry, PVR and, in selected cases prostate biopsy, UDO or UCS. Moreover, an extensive urogenital function interview-analysis was performed by a dedicated nurse practitioner. In a two hour one-stop session each client is fully examined and analysed. In 161 (9.7%) men PCa was diagnosed. In 796 (45.2%) men (symptomatic) BPH was diagnosed. ED was the main complaint in 355 (21.3%) men. 23% of our clients suffered from the combination of ED and LUTS whereas in 11.2% of the men LOH was diagnosed. Treatment was only administered according to the guidelines of the EAU (and ISSAM). This first year experience underlines the important role men's health institutes and urologists can play in providing optimal care and advice to prevent, to diagnose and (eventually) to treat at an early stage urogenital dysfunctions in an aging male population allowing for a better preservation and even improvement of the quality of life in this specific category of men.

238

WHAT ARE THE PREDICTORS OF ACUTE HOSPITAL ADMISSIONS AMONG COMMUNITY-DWELLING ELDERLY MEN?

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Introduction: Acute admissions to the hospital carry a significant morbidity and mortality among the elderly. This study aimed to identify the predictors of acute admissions among elderly men in an urban community. Methods: This community survey targeted men aged 50 and above living in an urban area in Malaysia. We randomly selected 500 men using the latest electoral poll. Face-to-face interviews were carried out using self-designed, pilot-tested questionnaires, consisting of acute admission to the hospitals in the past 12 months, socio-demography, self-reported medical conditions and lifestyle. Results: The response rate was 70.2% (n = 351). 12.3% (n = 43) had been admitted to the hospitals in the past 12 months, out of which majority was admitted once (83.7%, n = 36) and for less than a week (88.3%, n = 38). The main reasons for admission were cardiovascular disease (20.9%, n = 9), surgery (18.6%, n = 8), gastrointestinal disease (18.6%, n = 8) and fever (9.3%, n = 4). The following variables were found to be significantly associated with hospital admissions: urinary tract stones ($p = 0.019$), heart problem ($p = 0.005$), coronary artery bypass surgery ($p = 0.011$), diabetes mellitus ($p = 0.007$), cerebrovascular disease ($p = 0.013$), falls ($p = 0.005$), prostate problem ($p = 0.009$), metabolic syndrome ($p = 0.032$), taking medications ($p = 0.036$), self-reported serious medical condition ($p = 0.003$) and number of medical conditions ($p = 0.02$). There were no significant associations between hospital admissions and age, socioeconomic status, and lifestyle. Using binary logistic regression, the independent predictors were: urinary tract stones (OR 2.91, 95%CI 1.01, 8.43), heart problem (OR 2.97, 95%CI 1.28, 6.86), diabetes mellitus (OR 2.34, 95%CI 1.16, 4.73) and falls (OR 3.19, 95%CI 1.07, 9.49). Conclusions: This study highlighted the associations between certain medical conditions and admissions to hospital. It is important to explore how these medical conditions increase the risk of hospital admissions so that preventive measures can be taken.

239

DEPRESSION IN URBAN AGING MEN

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Introduction: Depression is a significant mental health condition affecting the aging population, where it is reported to be under diagnosed. This paper examines the prevalence of depression and its risk factors. Methods: In this cross sectional community survey in an urban setting in Selangor, Malaysia, 351 men age 50 and above participated. Depression was diagnosed using the short form Geriatric Depression Scale (GDS-15). Erectile function was diagnosed using the International Index for Erectile Function (IIEF-5). Quality of Life was assessed using the SF-12. Risk factors (socio-demographic data, self-reported medical conditions, life events, health status) collected from face-to-face interviews were examined in a stepwise multiple logistic regression model. Results: The prevalence of depression was 22.2% (cutoff > 5). Mean GDS score was 3.33 (sd = 3.29) and median was 2. Among those who were depressed, majority were married (91%) and had secondary education (41%), 41% were Malays, 51.3% were working full time and 29.5% were in the professional and senior managerial categories, 61.5% of them were staying with someone, 50% of the men had erectile dysfunction. Depression was significantly and independently associated with loss of job ($p < 0.01$), financial or occupational setbacks ($p < 0.001$), erectile dysfunction ($p < 0.05$), health status ($p < 0.0001$) and race ($p < 0.01$). Age, educational and occupational level, marital status, staying with family members, quality of life, and self-reported medical conditions (hypertension, diabetes, gout, stroke, prostate, kidney and heart problem) were not significantly associated with depression. Multiple logistic regression analysis showed that job loss (OR = 3.01, 95%CI: 1.30–6.98), poor health status (OR = 2.79, 95%CI: 1.58–4.33) and Malay race (OR = 2.39, 95%CI: 1.36–4.22) were predictive of depression. Conclusion: Depression is common among the aging men. Risk factors are important in health care management and in the prevention of depression in the aging population.

240

MICE AND MEN: BODY COMPOSITION, ERGOGENICS AND THE METABOLIC SYNDROME (MSX)

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Null Hypothesis: metformin and supplementary testosterone, vitamins and minerals are only useful for frank deficiency or maturity diabetes. Older people have higher risk body composition (BC) (more fat, less muscle/strength) than the young. We can prevent this dysmetabolism earlier, before disease presents. Should we? Methods: patient measurement; literature search for: BC changes in independent variables. Results: Average mature adults are morbidly adipose. Leaving aside early mortality from the usual suspects, top contributors to diseases of premature ageing include Fatness – excessive calories, Frailty – low exercise -muscle mass (these three account for > 30% of all premature deaths); and Feeding imbalances. Micronutrients Metformin for up to 5 years (in ~15 RCTs in > 5000 overweight adults, reduced new diabetes by up to 70%, adiposity by about 1/2kg/month; and in over 10 000 diabetics for up to 20years, cardiovascular disease, cancer and all mortality by ~40%. Micronutrient (human) multisupplement tested in the 3year McMaster University trial (2003, 2005) trial in laboratory mice, extended health and lifespan by 11% (in the normal mice) to 28% (in the MSx model). Appropriate testosterone replacement gives well-described BC and multisystemic benefits. Conclusion: Earlier onset of adiposity and the related gonadopause are associated with micronutrient imbalance and dysmetabolism. Metabolic measurement and modulation should be prompted at any age by deviant BC, BP, mood and any chronic health problems, long before typical sexual or overt chronic symptoms develop. Delay is negligence: once obesity and DM2 manifest after fifty, disease is far harder to reverse, and metformin alone may then be too late. The combined ergogenic natural multiple micronutrients (including appropriate testosterone and metformin) started at any age profoundly improve BC, health and MSx, reducing major disease and all mortality by possibly half – adding life to years and decades to lifespan.

241

AGING SYMPTOMS IN MALE POPULATION OF RAJASTHAN OF INDIA WITH REFERENCE TO SOCIO-ECONOMIC STATUS AND BIOLOGY

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The male population aging phenomenon observed in last three decades in India has been attributed to an increase in life expectancy, decline in mortality and birth rate. While people are living longer it is not always in state of good physical, mental and social status. Limited financial resources of the Government, changing family structure, retirement, unemployment have also been identified as contributors to the state of India's elderly male population. A total of two hundred elder male people from Bharatpur and Jaipur have participated in this study. Their age ranged from 60 to 95 years with an average of 68.40 and standard deviation of 5.83. The major data gathering instrument employed questionnaire in Rajasthan based on the "aging male symptom" developed by Lother A.J. Heinemann. The score of this scale reveals that persons living good economic condition have good health except those living in good economic condition have good

health except than not so good mostly they are easily upset, moody, feeling aggressive, more than those living good economic condition and having good health except than too talkative. Knee joint problem, asthma, tuberculosis (mainly in Bharatpur district of Rajasthan, India), hypertension, increasing number in diabetes, sleeping problem (difficulty in falling asleep, walking up early) are common physical symptoms of such aging males. Irritability and anxiety are common in both high and low income group as one of the psychological symptoms. Elderly men feel satisfactory on sexual ground, it may be due to family structure of Indian middle class family; 20% are widower whereas from rest 20% sleep separately in different rooms; 30% have been found lacking desire due to lack pleasure in and nonparticipation in sexual act from the spouse. AMS rating scale score more on psychological subscale than the somatic subscale. Sexual desire gets the score in between them.

242

SOCIAL SUPPORT AND HEALTH STATUS OF MALAYSIAN AGING MEN

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Introduction: Social changes affect the health and support systems especially in the aging population. Social support one receives will influence his quality of life and general well-being. This paper investigates social support and health status of men living in the community. Methodology: Data from a cross sectional survey in Klang Valley consisting of 351 men above 50 years old (70.2% response rate) was used. Respondents were randomly selected based on an electoral list. Face-to-face interview were conducted based on self-structured questions on social support and health care utilization, self-reported medical conditions, sexual health, lifestyle, and health seeking behavior. Results: 41% were still staying with spouse at time of interview. Majority were taken care by their spouses when ill. Support given to children was significantly more than those received from children. Major life events were bereavement, financial or occupational drawback and medical conditions. 62.1% of men have two or more medical conditions while 23.5% have one. Hypertension (30.2%), diabetes mellitus (21.4%), gout (12.3%), prostate problems (11.4%), myocardial infarction (9.1%) are the most common chronic diseases while others included joint pain (41.9%), visual problems (35%), memory problems (18.5%), hearing problems (16.8%) and urinary incontinence (15.1%). 26.8% having erectile problem. 41.9% were current and/or ex-smokers while 43.3% consumed alcohol. 57.3% did exercise but out of this, 60.4% did only light walking. 41% men had a physical examination performed in the last one year and 69% had medical check in the form of blood tests. 12.3% of men had been admitted to hospital in the last year. Slightly over half the proportion of the men sought medical treatment from private hospitals. The men had on average sought 3.65 medical consultations per year. Conclusions: Men preferred to be independent and autonomous. They gave more instrumental support to their children than receiving it from them.

243

POPULATION AGING AND THE RISING COST OF PUBLIC PENSIONS IN THE CONTEXT OF INDIA

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With a population of over 1 billion people, barely one-sixth of Indians are covered by pensions when they retire. Yet, government workers, who comprise just 5–6 percent of the working population, take 55 percent of India's GDP in the form of pension benefits. This means that a very small percentage of the Indian population is using more than half of the country's GDP. Tiny elite of 11 per cent of the total population of India is covered by a formal pension scheme. Many people think that the National Pension System (NPS) could not cover the vast number of people who are outside today's pension schemes. The recently released Indian Retirement Earnings and Savings (IRES) database, produced information on 42,000 randomly sampled households in India. In India, Asia's fourth-largest economy, retirement benefits are available to about eleven percent of the working population, about 3.4 million federal government employees. Starting January1, 2005, India made it mandatory for new federal employees to contribute ten percent of their salary to a new pensions scheme, to be matched by the government. The remaining eighty nine percent of the workforce is engaged cash-in-hand with no formal pension scheme. The government wants to cut the pension burden since the pension liability has gone up 21 percent per year on average since the 1990s. Today,together with interest payments, pension payments make up half of India's federal spending. While the government believes the new policy will ease the pension portion of its finances, it could take decades before the benefits of the contributory scheme roll out. Indian politicians need to formulate and implement a new pension scheme whereby everyone has some form of retirement coverage that doesn't completely eat away at the country's GDP. India has a pension problem that needs reform now, not later.

244

COMPARISON OF HEALTH SPENDING COST OF RETIRED AND STILL ACTIVE PERSONNEL AT THE INDONESIAN NAVY

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The increasing number of retired naval personnel at the Indonesian Naval Base in Surabaya would likely influence the increase budget of the entire Navy. Increasing routine budget to pay the pension is not avoidable, security/health care programs and other administrative and insubstantial costs would also burden the still active naval personnel in duty. The quantity and quality of aging co-morbids would be more significant in the retired naval personnel when compared to the health conditions of the still active naval personnel. This study implies the comparison of the spending costs for the health care of retired naval personnel, the still active ones, as well as for any civilian peers working at the naval base in Surabaya. The result of this study may be proposed to formulate in optimizing health care program to manage best quality of life for the retired naval personnel as well as the entire personnel of the Indonesian Navy.

245

SETTING UP A PRIMARY CARE MEN'S HEALTH CLINIC

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The gender-specific approach to health requires attention to men's health just as attention is paid to maternal and child health. Present and projected health indicators for men are poor. In addition, there are knowledge gaps of men's health. These demand urgent attention. The Singapore Men's Health Clinic (SMHC) is a private men-only community primary care practice set up in November 2003. This presentation will examine the rationale and process of setting up such a practice as well as its operation. Central to setting up this practice is an appreciation of the biopsychosocial determinants of men's health. The clinic must reach out to men and address their health needs and issues. Not only must matters of general health be attended to, but also those related to men's reproductive and sexual health. Bearing in mind the impact of ageing, both screening for disease and health promotion are important in the practice. In almost six months from commencement of practice, the clinic saw 200 new patients,

mostly between 30 to 59 years of age. Although most of the patients presented with problems related to sexual health, this provided occasion for opportunistic screening and health promotion. Health screening included that of general health, late onset hypogonadism and prostate health. Some of the initial results shall be presented. Besides healthcare for the individual, the practice has reached out to the community by giving talks on issues related to men's health. Some clinics for men have not been sustained because of lack of funds. Being self-funding as a private practice, the SMHC has been able to sustain itself. With regular audit of the practice as a clinic and as an outreach to the community, the SMHC aspires to acquire experience and knowledge in a primary care approach to healthcare for men from youth to old age.

246

MODEL FOR A MEN'S HEALTH CLINIC

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Introduction: Our purpose is to provide guidelines for the integration of a Men's Health Clinic into a full service Family Practice Clinic. Globally we have general service medical clinics that, given a model to follow,may readily be assisted to practice competent Male Gender Medicine. Model and Methods: For the past eight years this model has been adapted and combined with a traditional Family Practice Clinic into a fully integrated, efficient, successful Men's Health Clinic. The methodology includes history, researh, education, patient and physician training. Building a strong integrated team of medical and ancillary staff is essential as are ethical public relations & adequate signage. Results: Substantial benefits have accrued from our changes. The overall health of the men has improved immensely,which has led to greater health & happiness in families. Men are being more forthcoming with their medical issues. Further we are recognizing the need to treat our women in order to improve their level of wellbeing so that it is commensurate with their partners. The Menopause, as well as the Andropause,must be treated properly. Testosterone was meant to be shared. Conclusion: The changes have benefited both the patients and the physicians. Patients receive up to date medical care and attention. This is a direct result of the increased interest in research & education that is available to the physicians involved. Included in this presentation will be a booklet containing information,pictures and a provisional clinic layout. The foundation for the greatest success is active membership in both a National Association & the ISSAM.

The Aging Brain

247

NEUROPHYSIOLOGIC PREDICTORS OF PATHOLOGIC BRAIN AGEING

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The subject of the study: peak and mean frequency of brain basic activity in normal ageing personsreduction of alpha-rhythm; diagnostic value of peak and mean frequency variability. EEG was performed on 16 channels and analysed in spectral regimen by the use of 'Brainscan' system in 150 persons divided in three groups: I–50 healthy 40–59 year old volunteers, II – 50 healthy 60–75 year old volunteers, III–50 Alzheimer patients (2.5 ± 0.6 years of anamnesis). Psychic and somatic status of examined were studied accurately. Mean frequency (Fmean) of occipital alpha-rhythm in healthy adults was not lower than 9.5 Hz (100%). With the growth of the age (Group II) the progressive decrease of Fmean was noted: in 4% of cases it was lowed to 9.0 Hz. In Alzheimer disease patients Fmean <9.5 Hz was registered in 42%. Peak frequency (Fpeak) values <9.5 Hz among adults were not noted at all. In the group II–only in 2% of cases, meanwhile in Alzheimer disease group–56% of cases. Visual, digital and statistic analysis shows Fmean/ Fpeak values absolutely specific as a diagnostic neurophysiologic signs in pathologic brain ageing. Thus, in EEG-pattern Alzheimer disease patients except standard characteristics there may be the phenomena of Fmean <9.5 Hz or Fpeak <9.5 Hz. Abovementioned signs, revealed in digital electroencephalogram analysis of the persons under 60, should challenge clinicians to look for possible occult organic brain damage.

248

EFFECTS OF TESTOSTERONE AND GENETIC VARIATIONS RELATING TO ANDROGEN METABOLISM ON COGNITIVE FUNCTION IN ELDERLY MEN AND WOMEN

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Low testosterone (T) levels may predispose to Alzheimer disease (AD) but it is unclear whether this is a co-morbid effect due to cachexia, subclinical hyperthyroidism or other co-morbidity. The biological plausibility for potential protective effects of T on brain functions is substantial. In addition, higher levels of gonadotropins found in older cases with AD suggest that low levels of T are not due to brain degeneration and that the hypothalamic-pituitary-gonadal (HPG) axis is still intact. Men genetically at risk for AD were also already found to have lower levels of T. However, despite having lower levels of T, women do not show accelerated cognitive decline with age when compared to men. In addition, castration has not necessarily shown a decline in cognitive functions, some studies even found improvement of memory recall. Age may be an important factor when assessing optimal levels of T and several studies suggest that free or bioavailable T may be a better marker than total T levels when investigating associations of androgen activity with cognitive function. Small-scale T intervention trials in elderly men with and without dementia suggest that some cognitive deficits may be reversed, at least in part, by short term T supplementation. Age and prior hypogonadism may play an important role in therapy success and these factors should be investigated in more detail in future large scale randomized controlled studies. For elderly women, T treatment does not seem to have additional benefits over estrogen treatment for postmenopausal complaints and cognitive decline and may increase cardiovascular disease.

249

SUBJECTIVE REFLEXION OF AGE-RELATED PSYCHOLOGICAL CHANGES IN MALES

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Objective: The biggest increase of European population growth occurs in the aging population. There are a lot of papers which studied the age-dependent somatic development of males. In contrast, the psychological status of males – including the self-assessment of complaints and contentment in different periods of age – are barely investigated. Therefore, the relationship between age and subjective self-assessment was examined. Methods: Eighty-five men between 40 and 65 of age were anonymously interviewed by mail using three questionnaires. In the first one the men described their self-observed alterations, the second one monitored the complaints associated with late onset-hypogonadism, and the third one summarised questions to the subjective life-contentment. The males were subdivided into three groups: group1 between 40 and 47 years ($N=26$), group 2 between 48 and 55 years ($N=33$) and group 3 between 56 and 65 years ($N=26$) of age. Results: Psychological changes in total: 73% of men reported on decrease of concentration, 71% on tiredness, 66% on psychological irritability and 64% on decreased memory

capacity. The age-related somatic complaints mostly included pain of the joints (78%) and of the lower vertebral column (68%), a decreased interest in sexuality (63%) and an increase of body weight (55%). With age all complaints increased as well as the desire for harmonic partnership. An interesting relationship was stated between age and contentment with the current life. There was no significant difference between the groups 1 and 3, whereas, the group 2 (48–55 years old) was less satisfied. Conclusion: At the age of about fifty the men experienced a destabilisation of several aspects of their lives. After this age most of them have managed this critical period, which demands an adaptation to the changed living conditions.

250

PSYCHOLOGICAL AND PSYCHIATRIC CLASSIFICATION OF MEN'S MENTAL HEALTH DISORDERS FROM THE PERSPECTIVE OF FAMILY PRACTICE

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Male Gender Medicine lacks the proper tools to accurately diagnose men's mental health problems. They largely go undiagnosed and are poorly treated. Men have a reluctance to seek medical advice and they mask their symptoms. Routine care and lack of accurate tools impair accurate diagnosis and treatment of important problems. North American statistics reveal that men suffer more severe chronic conditions, having higher death rates for all leading causes of death including mental health disorders.Men die seven years younger than women on average. Key factors contributing to men's loss of health are: 1) fewer check-ups, 2) less likelihood to practice self-care, 3) greater consumption of alcohol and drugs, 4) engagement in more violence and risk taking, 5) fewer social supports and less medical knowledge than women. Men have poorer diets,are more overweight and less physically active than women. Men are less likely to understand ageing, change of life and the importance of testosterone to their health and well-being. The interrelationship between male psychological and psychiatric conflicts, physical symptoms and demographics were examined by multi-variant analysis. Results were discussed both in terms of their theoretical and practical signifiance. A summary of symptoms, diagnosis and treatment of important psychiatric disorders – Alcohol Dependency, Alzheimer's Disease, Attention Deficit Disorder, Hyperactivity Disorder, Bi-polar 1 & 2, Cocaine Dependency, Depression, General Anxiety Disorder, Irritable Male Syndrome, Major Depressive Disorder, Obsessive Compulsive Disorder, Panic Disorder, Post Traumatic Stress Disorder, Schizophrenia Types I–IV follows. In major psychological categories, we cover Anxiety Disorders, Cognitive Disorders, Mood Disorders, Personality Disorders, Sleep Disorders and Substance Abuse. In men, in order of importance, the factors are: Substance Abuse, Depression, Social Phobias, and Panic Disorders. Details of the background for this research will be handed out for validation.

Miscellaneous

251

ASSESSMENT OF LOW AND HIGH DOSE CIGARETTE EFFECT ON VISUAL AND AUDITORY REACTION TIMES AND VARIABILITIES IN YOUNG AND AGED MALES

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There are previous studies about different effects of cigarette on nervous system function in young and old men. Reaction time (RT) is one of the indicators that show brain function and speed of information processing but few studies has done about cigarette effect on RT especially in aged males. In this study, cigarette and its dosage effect on auditory and visual simple RT and choice RT has measured in two senile groups. Furthermore, for the first time smoking effect on variability of RT has measured and compared between both groups. RT series measured three times: Before and after first cigarette, and after second cigarette. Based on previous studies, smoking must increase speed of response: Results analyzed with SPSS and paired t-test showed that first cigarette reduces all RT factors in both groups but group t-test showed that the speeding effect in aged group was smaller than young group. Second cigarette did not make significant changes, in other words, the second one does not speed up responses. For the first time in this study, we showed that smoking reduces personal RT variabilities and that this effect is smaller in aged group ($p < 0.01$). Second cigarette did not make significant changes in this case too. We concluded on the above finding that aged males benefits smoking less than young peoples in the speeding up their reactions and limiting their response variabilities.

252

AGE-DEPENDANT METABOLISM CHANGES IN ERYTHROCYTES OF HEALTHY MEN AND PATIENTS WITH ULCER AND STOMACH CANCER

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Introduction. Functional ability of erythrocytes depends upon the effectiveness of energy-supply and detoxification processes. Key enzymes of these processes are lactate dehydrogenase (LDH) and adenosine deaminase (ADA), activity of which changes upon hypoxia. According to some authors dynamics of erythrocyte functional state can be used to forecast stomach ulcer clinical course. Aim: research the interdependence between metabolic shifts in erythrocytes and pathological processes in stomach mucosa of healthy men and different age patients. Methods: LDH/ADA activity ratio in erythrocytes of 30 healthy men and of 62 patients with ulcer and stomach cancer aged 30 to 70 has been studied by spectrophotometric method. Results. Age-dependant decrease of LDH/ADA ratio in erythrocytes was revealed in healthy men, what proves hypoxia development upon metabolism changes in the course of ageing. LDH/ADA ratio is reliably decreased in men with ulcer compared to healthy men, especially after 50 and depends on disease severity. In men with non-complicated ulcer the ratio is: aged 30–39 – 3.39 ± 0.32, aged 60–69 – 1.91 ± 0.22, while in patients with complicated clinical course they are: aged 30–39 – 1.15 ± 0.29, aged 60–69 – 0.88 ± 0.24, that is close to LDH/ADA ratio in patients aged 60–69 with stomach cancer – 0.66 ± 0.20. Conclusions. The age-dependant LDH/ADA ratio changes revealed by us reflect intensification of negative processes in erythrocytes that reduce their functional abilities upon ageing and correlate with severity of pathological processes in stomach mucosa. This allows using this ratio in diagnostics and evaluation of stomach ulcer treatment effectiveness.

253

RENAL TUMORS SMALLER TO 4 CM - COMPARISON OF PRESENTATION AND OUTCOME FOR MALE PATIENTS OLDER THAN 70 YEARS AND YOUNGER THAN 69 YEARS

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Purpose: Some studies demonstrate that in old patients with small renal masses with co morbid conditions, Watchful waiting may be a reasonable alternative. We compared histological subtypes, pathological features and Outcome of male patients with solid Adrenal tumors who were older than 70 years old vs. younger than 69. Materials and Methods: We conducted a retrospective review in our Institution Nephrectomy Registry from January 1989 to December 2004, and identified 47 male patients with renal tumors smaller to 4 cm. 17 patients Older than 70 years (16 patients with not metastasis tumors) and 30 patients younger than 69 years (28 patients with no metastatic tumors). Only no metastatic tumors were available for analysis. Results: There was no significant difference in the clinical presentation, pathological stage (12.5% PT3a in older patients vs. 17.8% PT3a younger patients), tumor grade, multifocality (12.5% multifocal tumors in patients greater 70 years old vs. 17.8% in patients smaller 69 years old) and histological type between younger patients or older patients. Younger patients had and improved cancer specific survival compared with older patients but this difference was not statistically significant. Globally older patients had worse survival compared with younger patients (in the first group 6 of 16 patients—37.5%—died, but we did not observe deaths by cancer; in the second group 2 of 28 patients died—7.1%—, only one by renal tumor). Conclusions: We did not observe statistically significant differences between the behaviors of the smaller to 4 cm. Renal tumors in male patients older or younger than 70 years old treated by radical or partial nephrectomy. These patients have a very good prognosis in cancer specific survival. Therefore, watchful waiting may be a reasonable alternative in old male patients and high risk cases with small renal tumors and significant co-morbid disease.

254

VITAMINS AND HEALTH SUPPLEMENTS IN AGING MALE

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Introduction: Aging population is consuming more vitamins and health supplements. They perceive these products are able to revitalize them and are void of side effects. This paper investigates the utilization of health supplements in an aging male population. Methodology: A cross sectional survey was conducted on 351 men above 50 years old (70.2% response rate) that were randomly selected from an electoral list. Face-to-face interviews were performed using self-structured questionnaires comprising demographic data, usage of prescribed medications and health supplements and its cost, health care utilization, self-reported medical conditions and sexual health. Results: 61.3% of men were taking vitamins while 45.3% were taking other health supplements such as fish oil, primrose oil, garlic oil, royal jelly etc. 50.1% were currently on prescribed medications. Significantly more money was spent per month on vitamins and other health supplements (mean = RM 419.02, or USD = 105, $t = 17.89$, $p < 0.001$) than prescribed medications (mean = RM 260.36, or USD = 65, $t = 12.33$, $p < 0.001$). There is a strong correlation between money spent on prescribed medications and health supplements ($r = 0.675$, $p < 0.001$). No significant association was found between money spent on prescribed medications or supplements and the presence of medical conditions. Consumption of vitamins is significantly associated with education level, ethnic groups, religion, exercise, having had medical examination (physical & blood examination) in the last 1 year, had bypass surgery, prostate problems and currently on medication. Consumption of health supplements is significantly associated with education level, ethnic groups, religion, having kidney stones and hypertension. Using logistic regression, religion, having had physical examination in the last 1 year, and having prostate problems are predictors of vitamins consumption while education, kidney stones and hypertension are predictors of other health supplements consumption. Conclusions: Ageing men are spending more money on vitamins and health supplements than prescribed medications. Various factors including demographic and medical conditions determine their usage of health supplements.

255

REFRACTORY HAEMATOSPERMIA IN ELDERLY – HARMFUL OR HARMLESS

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Objective: To assess haematospermia in literature compared with results of own study, and to clarify whether this symptom represents a particular or serious case. Material and Methods: Retrospective analysis of our 502 cases within the last 10 years till Mid 2004. Age: 28–71 (med. 52 years), in terms of characteristics, aetiology, pathogenesis and diagnostic procedures (history, DRE, PSA and lab, cytological smears, Tuberculosis-diagnostics, uro-sonography incl. TRUS, bacteriology incl. specimens of ejaculation and cystoscopy). Our data were compared with previous publication by literature review. Results: 22% of the patients were younger than 45 years ($N = 111$), 78% were older. 502 cases of Haematospermia were analysed! About 57% of our group suffered from the idiopathic & refractory haematospermia. Mainly in men over 45 (78%) living sexually abstinent for quite a long time. 66% of the mentioned cases reported of haematospermia directly after masturbations without accompanying resp. secondary symptoms. Most of these cases are complicated by urethral stenoses or prostate stones. Conclusion: Haematospermia is alarming for those affected – but normally harmless. A urological graduation-diagnostic is advisable in refractory haematospermia. The main reason of the refractory cases is masturbation after long sexual abstinence.

256

AGING MALE IN CENTRAL EUROPE – THE STATUS AND THE PROSPECTIVE

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The region 'Central Europe' can be characterised as a region of permanent changes. Perpetual dynamic changes occur in economic, social life as well as in health care sector. Although the majority of those states are members of European Union now, some differences can be found. However, there has been a remarkable progress in 'male focused care' over the last decade. Aging Male and the problem of Late-Onset Hypogonadism (LOH) is nowadays widely discussed. The aim of such care is apparently not only to offer better quality of life but it has strong economy consequences. It can be expected that quality of life has a major impact on labour productivity and lower expenses on medical care (e.g. prevention of osteoporosis) and, hence, on public revenues. With the availability of modern formulations of testosterone therapy, accessibility to modern devices and diagnostic methods that ensure safety of treatment we have cogent arguments for application of this hormonal treatment on symptomatic hypogonadal patients. Are we prepared for such an approach? What is the situation and our short and long term prospective? On the example of Czech Republic, approaches of health care authorities, general practitioners, urological societies and patients will be presented, evaluated and discussed. Data from extensive research of attitudes of different interest groups will be published for the first time. As a part of the session, approach of general practitioners towards late onset hypogonadism treatment, their knowledge and possibilities in communication with other specialised physicians will be discussed.

257

AGING IN MEN: IS THE ANDROGEN DECREASE IMPORTANT?

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Many theories of aging have been proposed. Examples include genetic mutations, cell loss, wear and tear, waste product accumulation, protein cross-linking, free radicals, immune

alterations, defects in repair mechanisms and neuroendocrine alterations. One endocrine change that is now well-established is a decrease in androgens, particularly the free fraction of testosterone in blood with aging. While the age-associated decrease in T levels is well-established, it is relatively modest and does not necessarily occur in every man. Therefore its importance is unclear. Several changes that occur in men as they age are similar to those that occur with hypogonadism in younger men; these include decreased muscle mass and strength, decreased bone mass and increased fractures, increased fat and decreased sexual function. A key question is whether men might be benefited by androgen administration as they age. Many physicians and aging men are going ahead with androgen administration in the absence of clear evidence. of course, potential adverse effects, particularly on the prostate are of concern. A large-scale trial of T administration has been proposed (roughly analogous to the Women's Health Initiative) but has been delayed in part due to the recommendation from the U.S. Institute of Medicine to perform more short-term studies first. Planning for such efforts is underway. To address issues of fracture rates and prostate disease, however, a large-scale trial will be necessary and should be planned.