Original Paper

Hormone Research

Horm Res 2003;60:21–28
DOI: 10.1159/000070823

Received: October 23, 2001
Accepted after revision: March 3, 2003

Osteoporosis in Male Hypogonadism: Responses to Androgen Substitution Differ among Men with Primary and Secondary Hypogonadism

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Key Words
Testosterone · Male hypogonadism · Bone mineral density · Osteoporosis

Abstract

Background: No randomized study exists comparing the effects of different modes of androgen substitution on bone mineral density (BMD). ***Methods:*** We performed a prospective, randomized, trial assigning 53 hypogonadal men to the following treatment groups: mesterolone 100 mg p.o. daily, testosterone undecanoate 160 mg p.o. daily, testosterone enanthate 250 mg i.m. every 21 days, or a single subcutaneous implantation of 1,200 mg crystalline testosterone. The BMD was determined by peripheral quantitative computed tomography. ***Results:*** At baseline, men with secondary hypogonadism (n = 33) had a lower BMD (–1.52 ± 0.23 SDS; Z-scores) than men with primary hypogonadism (n = 20, –0.87 ± 0.23 SDS, $p < 0.01$). In men with primary hypogonadism, the BMD increased dose dependently (crystalline testosterone +7.0 ± 1.3%, testosterone enanthate +4.8 ± 0.2%, testosterone undecanoate +3.4 ± 2.5%, mesterolone +0.8 ± 1.6%) after 6 months of therapy. Only secondary hypogonadal men treated with testosterone enanthate experienced an increase of the BMD. ***Conclusions:*** In primary hypogonadal men the BMD responds dose dependently to testosterone substitution, whereas in secondary hypogonadism only testosterone enanthate treatment significantly increased the BMD.

Introduction

Testosterone deficiency leads to osteopenia and osteoporosis in men and is associated with an increase in fracture rates [1–4]. Despite the widespread assumption that testosterone substitution increases the bone mineral density (BMD) in male hypogonadism, evidence is based on very small patient numbers [5–7], not unanimously [8], and a recent review concluded that an anabolic effect on bone is not obvious from the available data [9]. Furthermore, so far no study exists investigating the effects of different modes of androgen substitution on the BMD.

Therefore, we retrospectively analyzed data on BMD in 53 hypogonadal men from a prospective, randomized, open-label clinical study, investigating the effects of four different modes of androgen substitution [10, 11].

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Table 1. Anthropometric and endocrine data of the patients (mean ± SEM)

	TU	MES	TE	TPEL
n	13	11	14	15
Primary/secondary hypogonadism	4/9	5/6	4/10	7/8
Cortison/*L*-thyroxine	1/2	1/1	1/2	2/2
Age, years	34.5 ± 3.9	31.6 ± 3.4	31.9 ± 2.5	35.8 ± 2.7
BMI, kg/m^2				
Day 0	25.71 ± 0.79	24.01 ± 0.99	24.80 ± 0.91	25.65 ± 0.76
Day 300	26.20 ± 1.01	24.65 ± 1.06	25.15 ± 0.80	26.58 ± 0.69

The body mass index (BMI) was determined before (day 0) and after androgen substitution (day 300).

Patients and Methods

Patients

Fifty-three men with primary and secondary hypogonadism and serum testosterone concentrations <3.6 nmol/l (normal >10 nmol/l) on two separate occasions, free from neoplastic, inflammatory, renal, or metabolic disorders, and not taking any medication known to influence lipid or androgen metabolism participated in the study (table 1). Non of the men received growth hormone (GH), calcium, or vitamin D. Previous testosterone medication (testosterone enanthate or oral testosterone undecanoate; see below) had been suspended at least 3 months prior to study begin. Men with secondary hypogonadism due to pituitary insufficiency were euthyroid and kept on constant doses of cortisone or *L*-thyroxine throughout the study period. None of the subjects received GH substitution. All men had given written informed consent.

Study Design

In this open-label randomized study, patients with clinically and biochemically confirmed androgen deficiency (serum testosterone <3.6 nmol/l on at least two occasions) were randomly (using the SAS package) assigned to 1 of 4 treatment protocols: mesterolone (MES – Proviron®; Schering, Berlin, Germany) 100 mg/day, testosterone undecanoate (TU – Andriol®; Organon International, Oss, The Netherlands) 160 mg/day, testosterone enanthate (TE – Testoviron Depot®; Schering) 250 mg i.m./21 days, or testosterone pellets (TPEL – TestoImplant®; Organon International) as a single subcutaneous implantation of six TPELs, each containing 200 mg crystalline testosterone [10]. On days 0, 21, 42, 63, 84, 105, 126, 147, 168, and 189 blood samples were drawn after at least 8 h of fasting, medication handed out, and TE injections administered. The study medication lasted until day 210, and follow-up visits were performed on days 246 and 300. The study was approved by the ethics committee of the University of Essen and followed the guidelines of the Declaration of Helsinki 1975. Other results of this study have been published elsewhere [11, 12].

Laboratory Methods

The hormones were measured by commercially available immunoassays: testosterone, estradiol (E_2), and sex hormone binding globulin (SHBG) by radioimmunoassay (Diagnostic Products, Los Angeles, Calif., USA) and 5α-dihydrotestosterone (DHT) by radioimmunoassay after oxidative destruction of testosterone (Amersham, Braunschweig, Germany). The male normal range for testosterone is 10–35 nmol/l and that for DHT 2–5 nmol/l. The inter- and intra-assay variation was below 8% for all assays, except the DHT assay (17%) [10, 13].

Bone Mineral Density

The trabecular BMD was measured at the nondominant ultradistal radius using the high-resolution scanner Stratec XCT 900 (Stratec-Medizintechnik, Pforzheim, Germany) equipped with a 38.5-kV X-ray tube. The measurement site is located at 4% of the total ulnar length proximal toe distal radius end and is identified by a scout scan with high accuracy and reproducibility [14]. The BMD is expressed in equivalents of hydroxylapatite of calcium per volume (mg/cm^3). The in vivo reproducibility is below 2% [14–17]. Standard deviation scores (SDS; Z-scores) of the BMD were calculated based on a reference database established with healthy German adult men using the same bone densitometer [14]. Since the BMD was not the primary end point of the study [10, 11], we analyzed the data retrospectively. During processing of the data, the cortical BMD values were lost; therefore, only the trabecular BMD is reported here.

Statistics

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Chicago, Ill., USA). The results are reported as mean values ± SEM. Statistical comparisons used paired and unpaired t tests or repeated-measures Anova, as appropiate, with the level of significance set at $p < 0.05$ (Student-Newman-Keuls test). The area under the hormone curve was calculated by the trapezoidal rule. Univariate associations between sex steroids (log-transformed) and BMD were examined with Pearson's correlation and linear regression analyses. Joint effects of multiple predictors of BMD were assessed using partial correlation and regression models.

Results

Hormones

All subjects showed greatly reduced serum androgen concentrations before substitution, thereby confirming true hypogonadism. Substitution of androgens led to a significant increase of serum testosterone and DHT concentrations in the TU, TE, and TPEL groups (fig. 1). The

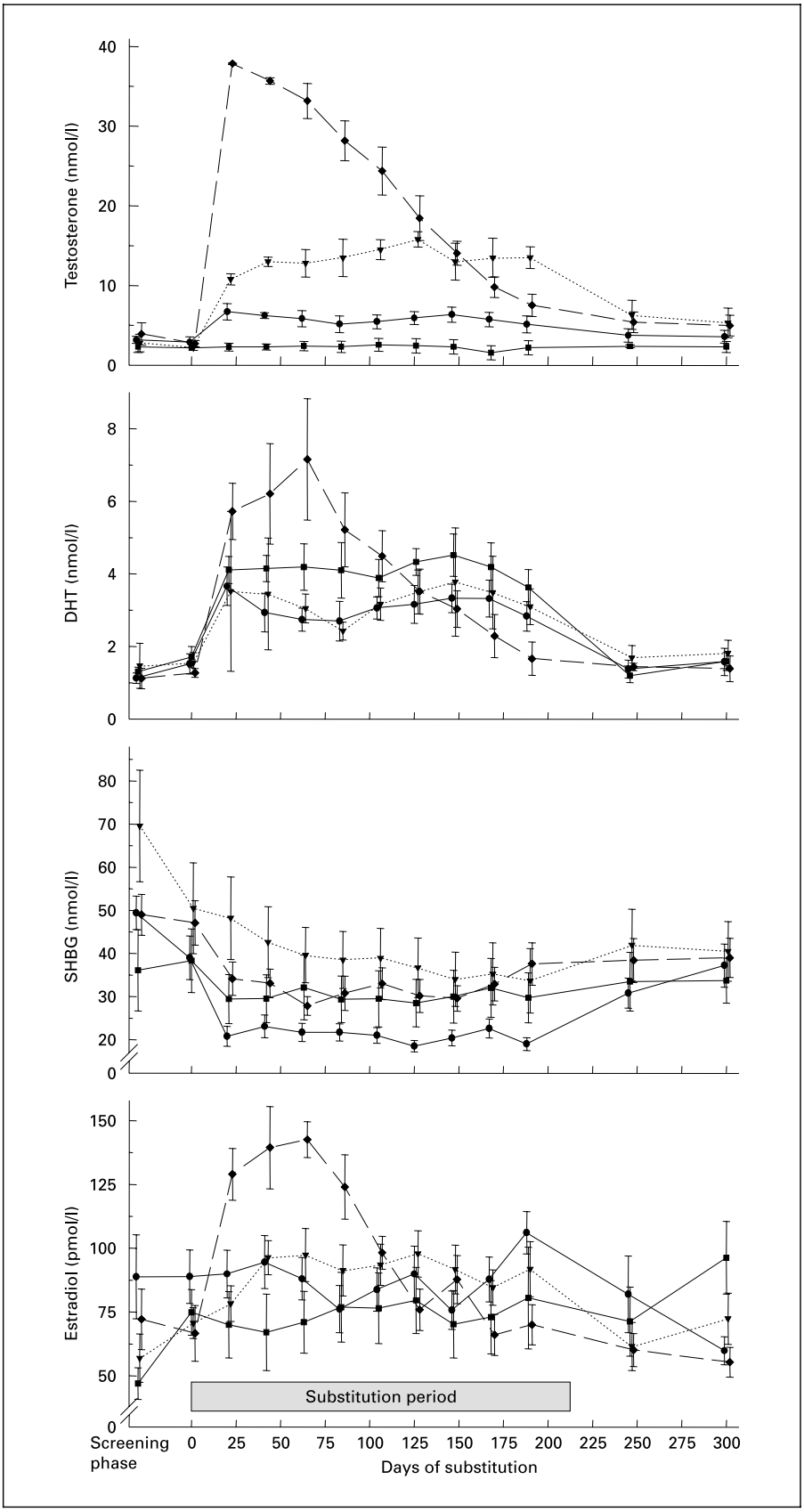

Fig. 1. Serum testosterone, DHT, SHBG, and estradiol concentrations (mean ± SEM) during TU (●), MES (■), TE (▼), and TPEL (◆) substitution therapy.

Table 2. Mean (± SEM) serum concentrations of testosterone, DHT, and estradiol before, during, and after substitution of androgens

Study period	MES	TU	TE	TPEL
Testosterone, nmol/l				
Baseline	2.2 ± 0.5	2.9 ± 0.4	2.2 ± 0.5	2.7 ± 0.4
Substitution	2.5 ± 0.4	5.7 ± 0.3*	13.4 ± 0.8*	23.2 ± 1.1*
Follow-up	2.4 ± 0.5	3.6 ± 0.8	5.2 ± 1.2*	5.0 ± 1.4*
DHT, nmol/l				
Baseline	1.9 ± 0.5	1.8 ± 0.3	2.0 ± 0.5	1.4 ± 0.1
Substitution	4.3 ± 0.3*	3.3 ± 0.2*	4.1 ± 0.5*	5.5 ± 0.4*
Follow-up	1.4 ± 0.2	1.8 ± 0.2	2.1 ± 0.2	1.8 ± 0.2
Estradiol, pmol/l				
Baseline	68.2 ± 6.0	84.7 ± 6.7[a]	66.4 ± 5.5	67.6 ± 7.2
Substitution	69.0 ± 4.1[b]	85.7 ± 3.0	88.7 ± 3.2*	106.0 ± 4.0*, [c]
Follow-up	70.3 ± 9.2	67.2 ± 6.4*	68.4 ± 7.1	58.7 ± 4.6

The mean concentrations for the time periods were calculated by dividing the area under the curve by the time period for the corresponding periods. * $p < 0.01$ (significantly different compared to baseline). Except for the DHT concentrations of the MES and TE groups, all testosterone and DHT concentrations are different between groups during substitution ($p < 0.01$). [a] $p < 0.01$ compared to MES, TE, and TPEL; [b] $p < 0.01$ compared to TU, TE, and TPEL; [c] $p < 0.01$ compared to MES, TU, and TE.

Table 3. Trabecular BMD (mean ± SEM) before and after androgen substitution stratified according to treatment groups and etiology of hypogonadism

Group	n	BMD, mg/cm^3		
		day 0	day 189	difference, %
MES	11	125.27 ± 17.45	126.45 ± 18.26	+0.21 ± 2.62
Prim	5	153.80 ± 32.26	156.60 ± 33.82	+0.75 ± 1.64
Sec	6	101.50 ± 13.21[a]	101.38 ± 13.52[a]	–0.08 ± 5.71
TU	13	154.75 ± 14.54	155.54 ± 14.25	+0.29 ± 3.06
Prim	4	132.38 ± 31.82	141.75 ± 36.23	+3.39 ± 2.49
Sec	9	164.69 ± 15.79	161.67 ± 14.36	–1.21 ± 1.43
TE	14	111.14 ± 12.93	121.36 ± 12.83	+12.21 ± 4.49*
Prim	4	147.50 ± 21.11	154.25 ± 22.16	+4.75 ± 0.23
Sec	10	96.60 ± 14.01[a]	108.20 ± 14.15[a]	+12.0 ± 6.09*, [a]
TPEL	15	154.53 ± 11.45	157.35 ± 10.65	+2.75 ± 2.31
Prim	7	162.86 ± 12.75	173.47 ± 13.20	+6.99 ± 1.25
Sec	8	147.25 ± 18.80	143.25 ± 15.29	–0.96 ± 2.82[a]

Significant differences between treatment groups are denoted by asterik (* $p \leq 0.04$) and within treatment groups between men with primary (Prim) and secondary (Sec) hypogonadism by superscript ([a] $p \leq 0.05$).

largest rise of androgens occurred in the TPEL group, followed by the TE group. TU induced a minor, although significant, increase of testosterone, but did not normalize serum testosterone concentrations. The DHT serum concentrations were raised in all treatment groups.

Comparing the average hormone concentrations during substitution, TPEL raised testosterone, DHT, and estradiol significantly more than the other substitution regimens ($p < 0.001$; table 2). TE increased the testosterone and DHT levels to a considerably lesser extent than TPEL, but still far higher than TU and MES. Neither MES nor TU induced any increase of serum estradiol, whereas TE and TPEL raised the serum estradiol concentrations significantly as compared with baseline values.

Bone Mineral Density

Prior to substitution, 32 men (60%) exhibited a BMD Z-score below –1 and 19 men (36%) one below –2 as compared with a healthy male German control group [14] (fig. 2). Men with primary hypogonadism have significantly higher BMD SDS (–0.87 ± 0.23) than men with secondary hypogonadism (–1.52 ± 0.23; $p < 0.01$).

After 6 months of androgen substitution, the BMD increased in all treatment groups: TU group +0.29 ± 3.06%, MES group +0.21 ± 2.62%, TE group +12.21 ± 4.49%, and TPEL group +4.12 ± 1.72% (table 3). As compared with the baseline BMD, only in the TE-group this increase was significant ($p < 0.01$).

Separate analysis of the BMD in men with primary and secondary hypogonadism revealed a dose-dependent rise of BMD in primary hypogonadism with hardly any increase in the MES group and the most pronounced increase of BMD in the TPEL group (table 3). Men with secondary hypogonadism showed an increase in the BMD only in the TE group. In the other treatment groups the mean BMD of men with secondary hypogonadism did not change significantly. This is reflected by the observation that out of 33 men with secondary hypogonadism, only 16 (49%) responded to androgen substitution with an increase in the BMD. In contrast, 17 of 20 (85%) men with primary hypogonadism demonstrated an increase in BMD. Primary hypogonadal men experienced an increase of the BMD significantly more often than secondary hypogonadal men ($p < 0.01$).

Neither in any treatment group nor when all groups were combined, any correlations were found between sex steroid levels and BMD. A significant negative correlation was observed between change of BMD and age ($r = -0.31$, $p < 0.03$) and baseline BMD ($r = -0.29$, $p < 0.02$). Analysis of multiple variates on BMD, including age, baseline BMD, sex steroid hormone levels during substitution, and etiology of hypogonadism, revealed age ($p < 0.02$) and etiology ($p < 0.01$) as the only significant predictors of BMD after androgen substitution.

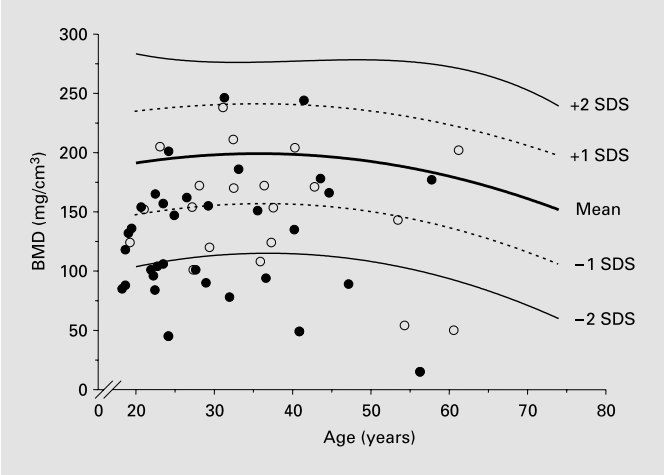

Fig. 2. Baseline BMD of 20 men with primary (○) and 33 men with secondary (●) hypogonadism. The reference range is based on data generated with the same bone densitometer in a healthy male German population [14].

Discussion

This is the first randomized study investigating differential effects of various modes of androgen substitution on the BMD in hypogonadal men. We used peripheral quantitative computed tomography (pQCT) for the assessment of BMD, since it offers the advantage of selective determination of the trabecular BMD with a high reproducibility and a low variability [18–22]. Due to the metabolically higher activity of trabecular bone and the high accuracy of the pQCT in the identification of the measurement site, pQCT is very suitable for short-term repetitive measurements within subjects. Normal values have been established for German men and published in detail [14].

At baseline, over 60% of our patients had a moderately reduced BMD (< –1 SDS), and more than one third had a severely reduced BMD (< –2 SDS). Previous investigations confirm our results not only with regard to the high prevalence of osteopenia but also with regard to the extent of the reduced BMD [7, 23, 24]. The large number of subjects studied permitted stratification according to the etiology of the hypogonadism, revealing a significantly lower

prevalence of osteopenia in men with primary hypogonadism as compared with men with secondary hypogonadism. This might be due to the higher estradiol levels frequently encountered in men with primary hypogonadism [25, 26]. In this study, the baseline serum 17β-estradiol levels were twice as high in primary hypogonadal men as compared with men with secondary hypogonadism (33.6 ± 2.1 vs. 17.1 ± 1.1 pmol/l, $p < 0.001$). Also, accompanying pituitary insufficiency with deficient GH secretion might be responsible for the higher prevalence of osteopenia in men with secondary hypogonadism.

In all treatment groups, the mean BMD showed a slight increase after 6 months of androgen substitution, but a significant effect was observed only in the group receiving TE. 85% of the men with primary hypogonadism responded to androgen substitution with an increase of the BMD, but only 49% of the patients with secondary hypogonadism showed a rise in BMD. Furthermore, in primary hypogonadism a dose-dependent effect of androgen was observed with the lowest increment of BMD in the MES group, which did not experience any significant rise of serum estradiol and testosterone levels, and the highest increase of BMD in the group receiving TPELs, where the largest increase of sex steroids occurred. It should be mentioned that the time point of blood sampling in the TE-group leads to a certain underestimation of the sex steroid levels between two injections.

Neither the better response in primary hypogonadism nor the dose dependency has been reported before, most likely due to the lack of any randomized studies and the small patient numbers studied, hampering any stratification according to the cause of hypogonadism. However, some limitations are also present in this study which might lead to overinterpretation, e.g., the short duration of the study, the small number of subjects in each subgroup, retrospective analysis of the data, and retrospective stratification into the subgroups.

Men with secondary hypogonadism receiving MES, TU, or TPEL unexpectedly did not show any increase of the BMD. This might be due to accompanying pituitary insufficiency, despite adequate substitution of cortisol and *L*-thyroxine, if necessary. However, none of the patients has been treated for GH deficiency which has been shown to cause a low BMD [27–29], and retrospectively GH deficiency cannot be excluded. Isolated GH deficiency or GH deficiency in patients with hypopituitarism seems to increases fracture rates [30, 31]. GH deficiency might partially explain the results found in the present study.

In contrast, secondary hypogonadal men receiving TE demonstrated an extraordinary increase of the BMD. Possibly, the more pulsatile fashion of androgen substitution, as provided by regular injections of TE, is more efficient in the stimulation of BMD than constant high-dose testosterone levels as delivered by TPEL. However, such an effect should be present in men with primary hypogonadism as well. We, therefore, consider it more likely that the lower baseline BMD of the TE-treated group might be responsible for the large increase observed, since men with an initially lower BMD show a higher increase of the BMD during substitution, as shown in this study and others [32].

Analysis of covariates of the treatment effects revealed age and etiology of hypogonadism as the only significant cofactors for the effect on BMD. A recent retrospective observation confirms our results by finding a significant negative correlation between age and increase in BMD of hypogonadal men [32], supporting the notion that hypogonadal men with open epiphyses respond better to androgen substitution than men with fused epiphyses [1]. Our results on the age dependency of the efficacy of androgen substitution on BMD underline the necessity to commence androgen substitution in hypogonadism as early as possible, albeit in adolescence achieving an appropriate final height must be kept in mind. Nevertheless, the results of our study indicate that delayed onset of substitution might not be able to normalize BMD any more, even when androgens are given over extended periods of time [8, 23, 24].

All clinical studies assessing the effect of androgen substitution on bone mineral content, including the present investigation, are hampered by confounding factors beyond the control of the investigation. These include the time since onset of hypogonadism, extent and duration of testosterone deficiency, duration and quality of previous androgen substitutions, and dietary factors such as calcium and alcohol intake prior to the study. In the present study, random assignment and the inclusion of the largest patient group studied so far did not prevent differences in baseline BMD values between the treatment groups. Despite this drawback, we consider the major conclusion of significant differences between the impact of the etiology of hypogonadism on the extent of reduced BMD and the response to androgen substitution valid. All previous studies addressing the influence of androgens on BMD in hypogonadal men have neglected this confounding factor which might explain the paucity of clear evidence for a stimulatory effect of androgens on the BMD [6, 7, 9].

However, there are distinct limitations of the present study. Even though this is one of the largest monocentric studies done so far in male hypogonadism, the numbers of patients in each group are relatively small which might influence the results. Furthermore, the study period is relatively short to determine BMD. The retrospective character of the analysis of the BMD data and the stratification of the subgroups are methodical limitations. Since data on bone maturation are not available in these subjects, the results of the present study could be overstated.

In summary, this is the first study demonstrating significant differences in the prevalence of osteopenia and in the response to androgen substitution between men with primary and those with secondary hypogonadism. Whereas most men with primary hypogonadism respond to androgen substitution with an increase in the BMD, in secondary hypogonadal men a rise of the BMD was observed infrequently, indicating confounding factors, possibly hypopituitarism with GH deficiency. Furthermore, for the first time, a dose-dependent influence of androgen substitution on the increase in the BMD in men with primary hypogonadism was shown. Parenteral application of androgens is more efficient than oral substitution to increase the BMD. Low baseline BMD values, young age, and primary hypogonadism as the cause of androgen deficiency are covariates of a good response to androgen substitution.

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Congress Calendar

04.07.–08.07.2003 **Brussels** Belgium	FEBS 2003, Meeting on Signal Transduction Signal transduction: From membrane to gene expression – from structure to disease	**Contact:** V. Wouters, International Congress & Event Organizer (ICEO) Tel.: +32 2 7795959; Fax: +32 2 75975960; E-Mail: febs@iceo.be; Web: http://www.febs-signal.be
13.07.–16.07.2003 **Aberdeen** UK	Fertility 2003 Joint Meeting of the Society for Reproduction, the British Fertility Society and the British Andrology Society	**Contact:** Victoria Withy, Fertility 2003 Conference Secretariat, BioScientifica, 16, The Courtyard, Woodlands, Bradley Stoke, Bristol BS32 4NQ, UK Tel.: +44 1454 642 219; Fax: +44 1454 642 222; E-Mail: fertility2003@endocrinology.org; Web: http://www.fertility2003.com
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