The Aging Male, December 2006; 9(4): 189–193

informa
healthcare

REVIEW

Testosterone and men's quality of life

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(Received 15 June 2006; accepted 22 September 2006)

Abstract
As the worldwide population ages, the emphasis on having a reasonable quality of life in old-age is increasing. In men, age-associated testosterone decline is one of the major factors that reduce quality of life. In patients and the physicians treating them, decreased energy levels and impairments to sex-life are perceived as the most important effects of hypogonadism. Two quality of life scales, the Aging Males' Symptoms (AMS) and the Age-Related Hormone Deficiency-Dependent Quality of Life (A-RHDQoL) scales, have recently been developed to specifically assess this patient population, and the A-RHDQoL found that memory, energy and physical capabilities, and sex-life were the factors most adversely affected by low testosterone levels. Unfortunately, there are limited data on the effects of testosterone on the quality of life of men with hypogonadism, but the information that exists suggests that testosterone can improve the quality of life significantly (to the same level as men with normal testosterone levels) and the more severe the symptoms before treatment, the greater the benefits of testosterone replacement. These promising early results need to be confirmed in more detailed quality of life studies.

Keywords: *Testosterone, hypogonadism, quality of life*

Introduction

As is often highlighted, the elderly population is increasing worldwide and recent data from the World Health Organization predicts that by 2025 the population of over 60 year-olds will have doubled to 1.2 billion and this will increase to 2 billion by 2050 [1]. The aim for this population is not simply to live longer but it is also to undergo 'active aging' with an emphasis on quality of life (QoL).

Significant advances in the understanding of the physiology and pathophysiology of the aging male population, as well as substantial efforts to measure QoL, have been achieved over the past few years. As a result, it is now well-established that aging in healthy men involves an age-related decline in serum testosterone levels. The annual decrease in testosterone levels has been estimated at around 1 to 2% [2], and 1 in 5 men over 60 years of age have testosterone levels below the normal range for young males. As discussed in the other chapters of this supplement, this decline in testosterone levels has a major impact on age-associated physiological processes that affect the function of many different organ systems. Functions of the brain and the central nervous system can be affected, bone, muscle, fat and other factors that make up the body composition are detrimentally affected, and sexual dysfunction is common.

In addition to the detrimental effects that testosterone deficiency can have on the body, there is increasing evidence that decreased testosterone also reduces the QoL of the aging male. This has led to an increasing interest in assessing the impact of androgen substitution therapy on the QoL of aging men. The importance of QoL in hypogonadism was highlighted recently when the joint 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) included mention of QoL in its definition of late-onset hypogonadism (Table I) [3].

Therefore, if the aging male population is to achieve its aim of active aging, testosterone deficiency is one of the factors that need to be tackled. Here we look at the effects of testosterone deficiency on QoL and discuss the potential benefits of testosterone replacement therapy.

Impact of hypogonadism on quality of life

Although the impact of testosterone deficiency on QoL has not been well established, it is clear that

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ISSN 1368-5538 print/ISSN 1473-0790 online
DOI: 10.1080/13685530601003180

Table I. ISA, ISSAM and EAU definition of late-onset hypogonadism [3].

Definition of late-onset hypogonadism (LOH): A clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels. It may result in *significant detriment in the quality of life* and adversely affect the function of multiple organ systems.

late-onset hypogonadism has a negative effect on physical, mental and social functioning and therefore on QoL. When experts and men suffering from hypogonadism were questioned, seven key QoL domains were identified as being affected by low testosterone [4]:

- Energy.
- Emotional functioning.
- Social functioning.
- Social emotional.
- Mental functioning.
- Physical functioning.
- Sexual functioning.

Of these, both patients and physicians believed that decreased energy levels and impaired sexual performance were the aspects of hypogonadism that had the greatest impact on QoL [4]. In addition, perhaps due to embarrassment, many men with the symptoms of hypogonadism are reluctant to discuss these symptoms and delay seeking medical advice. As such, the prevalence of late-onset hypogonadism is probably under-estimated.

Further evidence of the effects of androgen deficiency on QoL comes from a study in men undergoing primary androgen deprivation therapy for prostate cancer. A total of 431 men with newly diagnosed prostate cancer received primary androgen deprivation therapy with either orchiectomy or luteinizing hormone-releasing hormone (LHRH) [5]. Using the short form-36 (SF-36), the health related QoL was low after androgen deprivation therapy mirroring a general reduction in, for example, sexual functioning. The 'vitality' domain scores of this questionnaire were particularly low along with the 'physical' domain scores, which confirms that lack of energy is a particular issue in the quality of life of men with low testosterone levels [5].

Clearly, more accurate and detailed information on the QoL of men with hypogonadism is needed, and one of the main reasons that this has not been gathered to date is the lack of relevant questionnaires. The most widely used questionnaire to assess general health-related QoL is the SF-36 [6], but this is very general and does not focus on the issues that affect QoL in men with low testosterone. Other QoL scales therefore need to be considered when assessing men with late-onset hypogonadism.

Quality of life scales

The Aging Males' Symptoms (AMS) scale is the most frequently used scale to measure health-related QoL in aging males. This scale has many advantages such as its availability in most languages and the fact that it has good psychometric characteristics – i.e., reliability in terms of consistency and test-retest stability in different countries [7]. The AMS scale also appears to be valid (it measures the same phenomenon in different countries and in healthy or androgen deficient men), and provides results that are consistent with other health-related QoL scales including the generic SF-36. However, the AMS scale was not originally designed to evaluate QoL before or after testosterone replacement therapy, but was initially used with diagnosis in mind.

A newer, Age-Related Hormone Deficiency-Dependent Quality of Life questionnaire (A-RHDQoL) has therefore been developed specifically for older men with late-onset hypogonadism [8]. The questionnaire is similar to the HDQoL questionnaire used for patients with adult growth hormone deficiency, and contains 24 domains, but only 21 of these are relevant to older men [8]. These domains include 'family', 'social', 'working' and 'sex-life' domains, physical aspects such as 'physical capabilities', 'appearance', 'stamina', 'sleep' and 'pain', and psychological aspects such as 'confidence' and 'motivation'. In addition, the A-RHDQoL contains domains on 'health', 'fertility', 'concentration', 'house-hold tasks' and 'society's reaction'. At the end of the questionnaire there is a 'free comments' section in which respondents can include other ways they perceive QoL issues that are affected by hormone levels. Each domain item is scored for impact on life from -3 to $+3$, with -3 representing the most positive answer and $+3$ the most negative answer (i.e., having the maximal negative impact upon QoL) [8]. In addition, each domain item is rated for importance with a score from 0 (not at all important) to 3 (very important), and the weighted domain score is calculated by multiplying these two scores together. In addition, the patient can indicate that a particular domain item is not applicable and an overall weighted impact score can then be calculated by summing all applicable domain scores and dividing by the number of domains applicable to the individual [8]. The questionnaire is therefore individualized by taking into account the relevance of each domain for the individual.

The A-RHDQoL was used to assess the QoL of 128 men aged 65–80 years who had been recruited into a clinical trial of growth hormone and testosterone replacement therapy [8]. The questionnaire had high internal consistency and reliability, and the fact that participants in this trial were recruited by three different methods had no effect on the reliability of the questionnaire. In addition, it was as a result of testing the A-RHDQoL in these men that 3 domains

from the original 24 were excluded ('fertility', 'finances' and 'depend') for a number of reasons such as them being perceived as unrelated to age-related hormone decline or being perceived as not important. The mean weighted impact of the 21 domains showed that the domains most severely (and negatively) impacted by age-related hormonal decline were 'memory', 'energy', 'sex-life', 'physical stamina', 'physical capabilities' and 'concentration' (Figure 1). Interestingly, the overview item 'present QoL' was correlated with total testosterone levels in this population (deteriorating QoL was correlated with decreasing testosterone levels).

Because the A-RHDQoL is a questionnaire that is completed by the patient and measures their own perception of the effects of hormonal decline on QoL, it may be inappropriate for men in the general population who are not aware of the hormonal decline that accompanies aging, and who would therefore be unable to give informed answers on the possible effects of this decline. It is probably best suited to older men participating in trials of testosterone replacement therapy. The QoL factors most severely affected by hormone-deficiency, as identified by the A-RHDQoL, are therefore aspects of QoL that testosterone replacement therapy should aim to improve, and these can now be assessed with this questionnaire.

Improving quality of life with testosterone replacement therapy

The most important QoL targets for testosterone replacement therapy (identified from the A-RHDQoL study outlined above [8]) are vitality and energy, physical stamina and capabilities, sex-life, memory and concentration, and physical appearance and self-confidence. As it happens, the positive impact of testosterone replacement therapy on many of these aspects and symptoms has been demonstrated in clinical trials.

For example, energy and physical capabilities, as well as self-confidence, will clearly be improved by the increase in lean body mass and decrease in fat mass that is observed in hypogonadal men receiving testosterone replacement therapy. One recent example of this is the significant changes in body composition observed after 6 and 12 months of treatment with 1% testosterone gel – a 2.2 kg increase in lean body mass and 1.8 kg decrease in fat mass after 12 months (Figure 2) [9]. Similarly, significant improvements in sexual life, including sexual activity and number of spontaneous erections ($p < 0.001$) [9], with testosterone replacement therapy will, almost by definition, improve the patients' perception of their sex-life and therefore improve their QoL.

In the few studies of QoL changes with testosterone replacement therapy, the symptomatic improvements do indeed appear to result in QoL improvements. Using the SF-36, transdermal testosterone treatment for 36 months in men over 65 years of age improved the patients' perception of physical functioning compared with placebo (1.9 point improvement with testosterone compared with an 8.0 point decrease with placebo; $p < 0.05$) [10]. The lower the testosterone levels before treatment, the greater the benefits on perceived physical functioning. However, none of the other domains on the SF-36 were significantly better with testosterone than with placebo [10]. Energy and sexual function parameters were numerically superior in patients treated with testosterone than in patients receiving

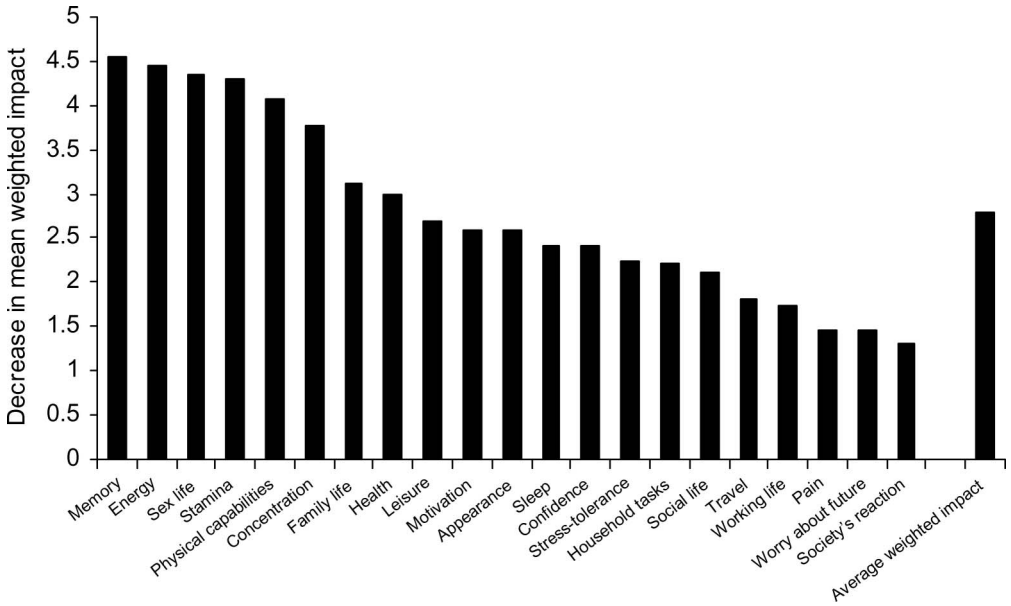

Figure 1. Mean weighted impact scores of A-RHDQoL domains in 128 men aged 64-80 years, when asked to rate the impact of hormonal decline [8]. Used with permission © 2003 McMillan et al.; licensee BioMed Central Ltd, article available from http://www.hqlo.com/content/1/1/51.

placebo but this did not achieve statistical significance. Furthermore, other studies have failed to show QoL improvements with testosterone replacement therapy using the SF-36 [11,12]. These studies may simply emphasize the fact that the SF-36 is too general and not particularly suitable for assessing QoL in this patient population – in addition, despite being described as such, these scales are not measures of QoL but are measures of health status and well-being [8].

Despite not being originally designed to assess changes in QoL before and after treatment, the AMS has been successfully used for this purpose. In over 1000 men with androgen deficiency (QoL data available for 700 men), the AMS was used to assess QoL before and after treatment with testosterone for 12 weeks [7]. The total AMS score was decreased by 15 points after treatment with testosterone – indicating a 32% improvement from the score before treatment (Figure 3). The AMS was therefore capable of detecting treatment effects. This study also showed that the more severe the symptoms of hypogonadism were at baseline, the greater the improvement in QoL according to the AMS (Figure 4). These improvements in QoL resulted in patients having a similar level of QoL after testosterone replacement therapy as healthy men with normal testosterone levels [7].

The study by Daig et al. [7] is the only study to use a specific QoL scale to assess the effects of testosterone replacement therapy in men with low testosterone, and it suggests, as would be expected

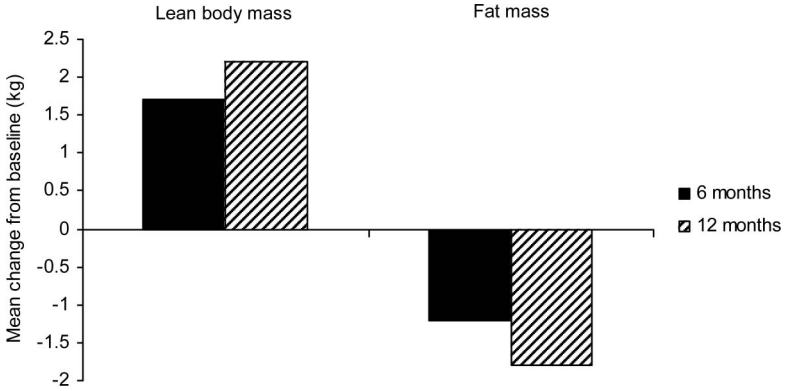

Figure 2. Increased lean body mass and decreased fat mass with testosterone gel treatment after 6 months and 12 months will have a positive impact on QoL [9].

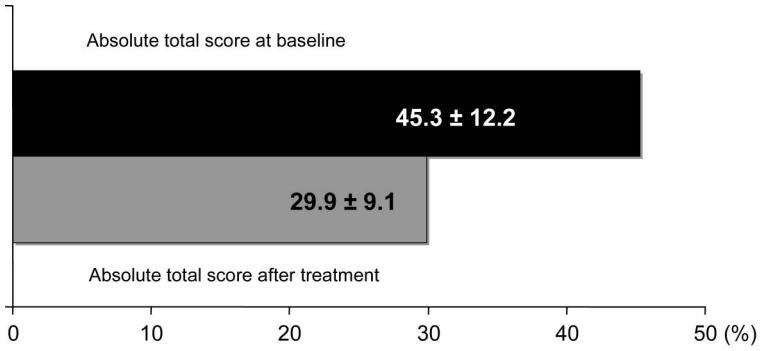

Figure 3. Improvement in QoL in hypogonadal men receiving testosterone replacement therapy for 12 weeks, measured by the mean AMS total score [7]. Used with permission © 2003 Daig et al.; licensee BioMed Central Ltd, article available from http://www.hqlo.com/content/1/1/77.

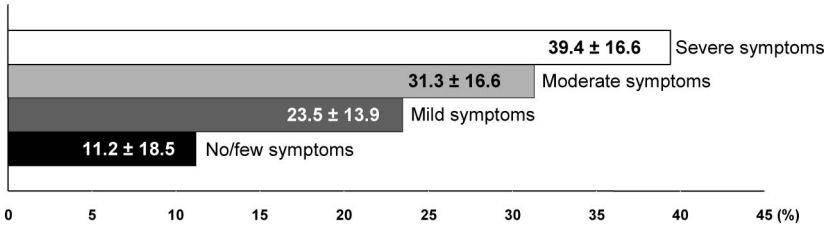

Figure 4. Percentage improvement in QoL in hypogonadal men receiving testosterone replacement therapy for 12 weeks, measured by the AMS and presented according to the severity of symptoms before treatment [7]. Used with permission © 2003 Daig et al.; licensee BioMed Central Ltd, article available from http://www.hqlo.com/content/1/1/77.

from symptomatic improvements, that QoL is improved. In the near future, it would be interesting to evaluate QoL changes with the more specific A-RHDQoL scale and to assess the effects of testosterone replacement therapy on the domains most severely affected by hypogonadism.

Summary

In conclusion, it is clear that late-onset hypogonadism has a negative impact on QoL despite the fact that few well-designed studies have assessed this in detail. One barrier to assessing QoL in late-onset hypogonadism has been the lack of specific scales for this patient population. However, both the AMS and in particular the A-RHDQoL scales are now available and these appear to be valid for assessing QoL in hypogonadism and for assessing the effect of testosterone replacement therapy. Using these scales, the lack of physical capabilities, lack of energy, impaired memory and impaired sex-life all appear to be the most important patient-perceived impairments associated with hypogonadism. Testosterone replacement therapy improves these symptoms, and there is therefore every reason to assume that therapy will improve QoL – the initial evidence appears to confirm this but more work is needed before firm conclusions can be made on the effects of testosterone replacement on QoL. Since changes in QoL are important drivers for patients seeking medical advice and for their acceptance of medication, more studies of QoL in hypogonadism and the effects of testosterone replacement on various aspects of QoL are urgently needed.

References

1. World Health Organization. Men, ageing and health. Achieving health across the life span, 2000.
2. Gray A, Feldman HA, McKinlay JB, Longcope C. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. J Clin Endocrinol Metab 1991;73:1016–1025.
3. Nieschlag E, Swerdloff R, Behre HM, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morley JE, Schulman C, Wang C, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males. ISA, ISSAM, and EAU recommendations. Eur Urol 2005;48:1–4.
4. Novak A, Brod M, Elbers J. Andropause and quality of life: findings from patient focus groups and clinical experts. Maturitas 2002;43:231–237.
5. Potosky AL, Knopf K, Clegg LX, Albertsen PC, Stanford JL, Hamilton AS, Gilliland FD, Eley JW, Stephenson RA, Hoffman RM. Quality-of-life outcomes after primary androgen deprivation therapy: results from the Prostate Cancer Outcomes Study. J Clin Oncol 2001;19:3750–3757.
6. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–483.
7. Daig I, Heinemann LA, Kim S, Leungwattanakij S, Badia X, Myon E, Moore C, Saad F, Potthoff P, Thai DM. The Aging Males' Symptoms (AMS) scale: review of its methodological characteristics. Health Qual Life Outcomes 2003;1:77.
8. McMillan CV, Bradley C, Giannoulis M, Martin F, Sonksen PH. Preliminary development of a new individualised questionnaire measuring quality of life in older men with age-related hormonal decline: the A-RHDQoL. Health Qual Life Outcomes 2003;1:51.
9. Dean JD, Carnegie C, Rodzvilla J. Long-term effects of Testim 1% testosterone gel in hypogonadal men. Rev Urol 2004;6(Suppl. 6):S22–S29.
10. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ, Strom BL. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab 1999;84:2647–2653.
11. Reddy P, White CM, Dunn AB, Moyna NM, Thompson PD. The effect of testosterone on health-related quality of life in elderly males – a pilot study. J Clin Pharm Ther 2000;25:421–426.
12. Kenny AM, Bellantonio S, Gruman CA, Acosta RD, Prestwood KM. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci 2002;57:M321–M325.