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Sexual Dysfunction/Male Infertility

Serum Total Testosterone Level and Identification of Late-Onset Hypogonadism: A Community-Based Study

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Purpose: Late-onset hypogonadism (LOH) in aging males is a clinical and biochemical syndrome characterized by a decline in serum testosterone levels. LOH results in various physical and mental disabilities. We evaluated the relationship between serum testosterone levels and symptoms of LOH.

Materials and Methods: During an andropause screening program, we examined responses to the Saint Louis university androgen deficiency in aging males (ADAM) questionnaire and results on the International Index of Erectile Function (IIEF-5) in terms of clinical symptoms and evaluated serum total testosterone levels for a biochemical diagnosis of LOH in healthy community-living volunteers aged over 40 years.

Results: The mean age of the 534 men was 59.1 years (range, 40 to 79 years), and their mean serum testosterone level was 464.1±171.9 ng/dL. The serum testosterone level decreased significantly with age. There was a 92.5% positive response rate to the ADAM questionnaire. The percentage of patients whose serum testosterone level was <350 ng/dL among those with a positive response to the ADAM questionnaire was 25.6% (137 patients). The mean serum testosterone level among patients with a positive or negative ADAM questionnaire was 472.4±198.5 ng/dL and 487.3±165.7 ng/dL, respectively ($p>0.05$). There was no significant correlation between IIEF-5 scores and serum testosterone levels.

Conclusions: Among men over 40 years of age, 25.6% met the clinical and biochemical diagnostic criteria for LOH. There was no relationship between serum testosterone levels and symptoms of LOH.

Keywords: *Aging; Andropause; Testosterone*

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INTRODUCTION

In accordance with improved socioeconomic conditions and advanced medical treatments, the aging of the population has become an issue recently for society overall. Along with a constant increase in the average life span in Korea, the desire for quality of life (QoL) among the elderly population has also increased rapidly compared with that in the past. Aging is accompanied by several age-related symptoms that appear secondary to irreversible and progressive atrophic and degenerative changes as well as intrinsic compositional changes in the body. These symptoms include reductions in happiness, physical capacity, muscle mass, muscle strength, fertility, masculinity, libido, and sexual function. Aging individuals also develop increased body fat, osteoporosis, incontinence, atherosclerosis, cognitive impairment, memory disorders, emotional disturbances, and sleep disorders [1]. In addition, aging may induce changes in endocrinological function, such as that of testosterone. In the Massachusetts Male Aging Study (MMAS), Gray et al. [2] found that total testosterone decreased by 0.4% annually. Furthermore, 7% of 40- to 60-year-old males, 21% of 60- to 80-year-old males, and 35% of >80-year-old males had a total testosterone level under 350 ng/dL, which

is below the normal range. Werner [3] defined such endocrinological changes in males as late-onset hypogonadism (LOH), similar to climacteric changes in females. Multiple subsequent studies reported that symptoms such as hot flashes, nervousness, depression, organic brain dysfunction, and reductions in libido and erectile function were associated with decreased testosterone. Unlike climacteric symptoms in females, the decrease in testosterone is neither involved in drastic changes nor is a common phenomenon among all males. Not all aging males are prone to the reduction in testosterone induced by endocrinological dysfunction. In addition, whether the symptoms related to LOH are proportionally associated with the reduction in testosterone remains unclear. Therefore, there are different perspectives on the diagnosis, treatment, management, and follow-up of LOH in males. In fact, the relationship between the symptoms of LOS in aging males and the testosterone level is important for not only the diagnosis of LOH, but also in terms of the theoretical rationale of testosterone replacement therapy for management and evaluation of treatment results. To our knowledge, however, few studies on this topic have been carried out in Korea. Therefore, the objective of this study was to investigate the relationship between the symptoms of LOH and testosterone levels in aging males.

MATERIALS AND METHODS

1. Subjects

The present study was performed from July 2004 to August 2012 with 534 men aged >40 years and <80 years who were residents in Busan. An andropause screening program was carried out six times (26–30 July 2004, 4–8 October 2004, 29 November–2 December 2004, 20–24 February 2006, 23–26 October 2008, and 7–11 August 2012). A public health lecture on LOH was given to the residents, and willing participants completed laboratory testing and a questionnaire. All participants clearly understood the content of the questionnaire and the purpose of the study and agreed to participate. Approval for this study was obtained from the Institutional Review Board of Busan National University Hospital.

2. Methods

The symptoms of LOH were measured by using the Korean version of the Saint Louis University androgen deficiency in aging males (ADAM) questionnaire [4] established by Morley et al. [5] and the 5-item version of the International Index of Erectile Function (IIEF-5) [6]. The serum total testosterone level was measured between 0800 and 1100 and then analyzed according to age. The relationship between the serum total testosterone level and the symptoms of LOH was evaluated by comparing the rate of positive answers to each item on the ADAM questionnaire according to a 350-ng/dL serum total testosterone level and IIEF-5 score.

The ADAM questionnaire contains 10 questions regarding the most common symptoms observed with age-related decline in androgens. All questions are answered "yes" or "no". A positive questionnaire result, indicating an androgen-deficient state, is defined as a "yes" answer to question 1 or 7 or any 3 other questions. The questionnaire was assessed at baseline and after 6 months of supplementation.

3. Statistical analysis

A linear regression model was applied to the analysis of serum total testosterone level according to age and IIEF-5 score. The ADAM questionnaire responses according to serum total testosterone level were compared by use of Student t-test, which is a parametric test. Statistical significance was considered at $p < 0.05$. All statistical analyses were performed by using PASW ver. 18.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Clinical characteristics of the subjects

The average age of the subjects was 59.1 years (range, 40 to 79 years). A total of 93 (17.4%), 183 (34.3%), 188 (35.2%), and 70 subjects (13.1%) were in their 40s, 50s, 60s, and 70s, respectively.

2. Incidence of symptoms according to ADAM questionnaire responses

In the ADAM questionnaire, 375 (70.2%), 411 (77.0%), and 424 patients (79.4%) gave positive responses to question 1, question 7, and question 1 or question 7, respectively. A total of 402 patients (75.3%) gave positive answers to the other three questions, excluding questions 1 and 7. Symptoms of LOH were exhibited by a total of 494 patients (92.5%, Table 1).

3. Serum total testosterone level

The average serum total testosterone level of the 405 subjects was 464.1±171.9 ng/dL. Subjects in their 40s, 50s, 60s, and 70s had average serum total testosterone levels of 470.7±196.1, 464.6±176.4, 474.3±169.8, and 440.5±146.2 ng/dL, respectively, indicating that the serum total testosterone level was reduced significantly as subjects aged (r^2=0.009, p=0.04) (Fig. 1).

4. Serum total testosterone level according to responses on the ADAM questionnaire

A total of 137 patients (25.6%) in the positive ADAM questionnaire response group had an average serum total testosterone level of <350 ng/dL. The serum total testosterone levels were 472.4±198.5 and 487.3±165.7 ng/dL when the symptoms of LOH as indicated by the ADAM questionnaire were present and absent, respectively, but no statistically significant difference existed. Significant differences were also not observed for any specific question, including questions 1 and 7 (Table 1).

TABLE 1. Prevalence (%) of positive responses to the 10 items on the ADAM questionnaire in the total sample and in men with a total testosterone level below or above 350 ng/dL

Item	Question topic	Total (n=534)	<350 ng/dL (n=137)	≥350 ng/dL (n=397)	p-value
1	Libido	70.2 (375)	70.8 (97)	70.0 (278)	0.873
2	Energy	60.9 (325)	63.5 (87)	59.9 (238)	0.547
3	Strength endurance	68.0 (363)	70.8 (97)	67.0 (266)	0.49
4	Height	39.7 (212)	46.0 (63)	37.5 (149)	0.152
5	Enjoyment of life	45.1 (241)	44.5 (61)	45.3 (180)	0.84
6	Sad/grumpy	48.8 (261)	51.1 (70)	48.1 (191)	0.528
7	Erections	77.0 (411)	75.2 (103)	77.6 (308)	0.635
8	Playing sports	58.4 (312)	56.2 (77)	59.2 (235)	0.499
9	Sleeping after dinner	44.9 (240)	48.2 (66)	43.8 (174)	0.389
10	Work performance	60.0 (320)	56.9 (78)	61.0 (242)	0.401
Q1 or Q7		79.4 (424)	77.4 (106)	80.1 (318)	0.557
Any other three questions		75.3 (402)	75.9 (104)	75.1 (298)	0.973

Values are presented as percentage (number).
ADAM, Saint Louis University androgen deficiency in aging males questionnaire.

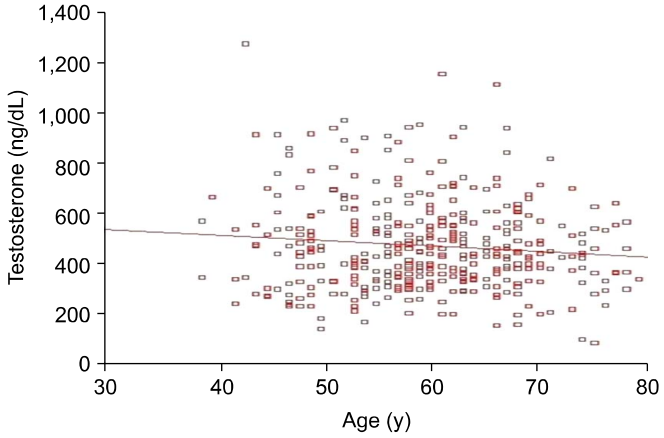

FIG. 1. Serum total testosterone level according to age. r^2=0.009, p=0.04.

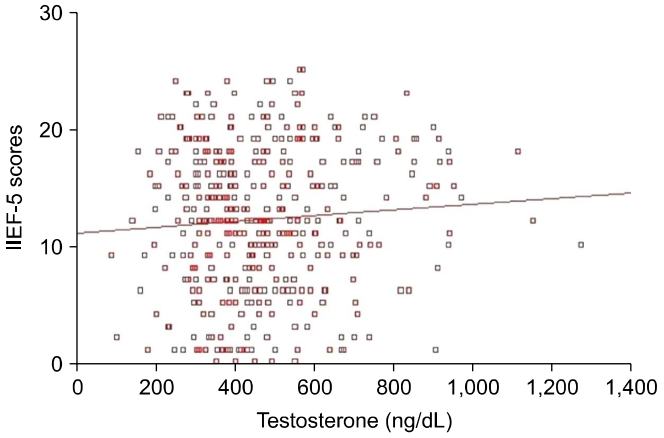

FIG. 2. International index of erectile function (IIEF-5) score according to total testosterone level. r^2=0.004, p=0.112.

5. Serum total testosterone level according to IIEF-5 score

The IIEF-5 score tended to increase with an increase in serum total testosterone, but not significantly so (r^2=0.004, p=0.112) (Fig. 2).

DISCUSSION

As QoL has improved in recent years, the life span in males has increased and the aging population in Korea has increased. Along with such changes have come drastic changes in the awareness of the health of elderly individuals. In other words, more attention has been paid to the diseases that influence QoL instead of to life-threatening diseases. LOH is one such disease that affects QoL in elderly individuals, who were not of great interest as study subjects in the past owing to their short remaining life span and the small number of available patients.

The most important clinical implication of LOH is that even though it markedly lowers QoL, the disease can be treated easily with simple methods if testosterone replacement therapy is carried out. In particular, the treatment generally includes mild medication and is thus associated with a relatively lower burden for elderly individuals. However, hormone agents should not be abused or misused in any cases, especially hormone replacement for management of nonspecific symptoms. Because severe clinical adverse effects are possible, hormones should be handled carefully. Thus, it is important to diagnose LOH as early as possible to maintain QoL.

It is commonly believed that the symptoms, clinical index, and serum total testosterone level should be thoroughly examined in the diagnosis of LOH. It is especially important to determine if the serum total testosterone level is lowered before any management of symptomatic aging males with LOH. In most cases, the symptoms of LOH in males progress slowly and the manifestations do not change drastically, which is the opposite of female climacteric symptoms. It is necessary to use biochemical diagnostic procedures, such as measurement of the serum total testosterone level, for appropriate diagnosis of LOH be-

cause the differential diagnosis of naturally derived aging phenomena is difficult. In addition, an understanding of the relationship between serum total testosterone and the symptoms of LOH is essential for the development of a theoretical rationale to carry out testosterone replacement therapy. However, although various questionnaires and diagnostic biochemical methods have been used to measure the symptoms of LOH, the criteria for an obvious diagnosis remain controversial. Two studies evaluated the symptoms of LOH, testosterone levels, and their relationship to hormonal changes in the body. Basar et al. [7] suggested that serum dehydroepiandrosterone sulfate and estradiol (E_2) were associated with the symptoms of LOH by use of the Aging Male Symptoms scale and the IIEF in 348 subjects. By contrast, Christ-Crain et al. [8] reported that serum total testosterone, serum free testosterone, and biologically active testosterone levels were not related to the symptoms of LOH. Lin et al. [9] also found that neither serum free testosterone nor biologically active testosterone levels were associated with the symptoms of LOH as determined by the ADAM questionnaire in 650 subjects; this agrees with the results of the present study. In contrast, Tancredi et al. [10] reported that a positive response rate was significantly higher in men with serum free testosterone levels of <70 ng/dL. Positive answers were associated with specific questions on the ADAM questionnaire, including the first (Did you experience a reduction in libido?), fourth (Did you experience a reduction in height?), seventh (Did you experience a reduction in erectile function?), and tenth (Did you experience a reduction in job performance?) questions. Even though several studies, including the present one, have indicated no relationship between serum testosterone and symptoms of LOH, oral, intramuscular, pellet, patch, and gel products have been developed and are widely utilized. Many studies have shown positive effects of these testosterone replacement therapies, such as increased libido and erectile function, protection against fractures owing to an increase in bone density, increased muscle mass, improved muscle strength and physical capacity, improved body shape, energy regain, and improved happiness and mood [11-13]. In previous studies [14,15], we also demonstrated significant improvements in the symptoms of LOH after percutaneous administration of a testosterone patch and oral testosterone agents. Likewise, a number of studies reported that there is insufficient evidence to conclude that the testosterone level is related to the symptoms of LOH, especially sexual function. However, multiple studies reported improvement in the symptoms of LOH by testosterone replacement therapy in patients with lower testosterone levels. This may be because despite a decrease in androgens and the development of associated symptoms, endocrinological dysfunction, which is the most distinctive phenomenon of aging, is considered to be the most vital clinical manifestation associated with LOH and may be induced by a decrease in hormone secretion, including adrenal hormones such as corticosteroid and growth hormone [16,17]. Therefore, endocrine disorders cannot be explained simply by the reduction in testosterone level in patients with LOH. From a medical treatment perspective, changes in testosterone levels are easily diagnosed. In addition, progress such as the development of various treatments to correct hypotestosteronemia, the disappearance and delay of the symptoms owing to these treatments, and confirmation of the treatment results, including QoL improvement, might have forced clinicians to focus on testosterone replacement therapy only.

In the present study, the ADAM questionnaire created by Morley et al. was used as a screening test for the symptoms of LOH [5]. However, the ADAM questionnaire possesses high sensitivity but relatively low specificity for the diagnosis of LOH, meaning that its utility may be somewhat limited [10,18]. The incidence of LOH according to the ADAM questionnaire in this study was 92.6%; thus, biochemical diagnostic tests, including measurement of the serum testosterone level, should accompany the ADAM questionnaire when used as a screening test. Moreover, another limitation is the determination of the effects of LOH treatments, because the ADAM questionnaire is difficult to quantify. Besides the ADAM questionnaire, the AMS questionnaire by Heinemann et al. [19], and the Pusan National University Hospital QoL scoring system by Park et al. [15] can be used. One study used quantitative version of androgen deficiency in aging males questionnaire, which scores and then quantifies each item on the ADAM questionnaire [10]. In the future, the reliability and validity of the screening tests and the results of testosterone replacement therapy according to the questionnaire responses should be investigated.

In the present study, we showed that the IIEF-5 score tended to be increased with elevated serum total testosterone levels, but no significant correlation was found. This result agrees with the results of Korenman et al. [20], who reported no difference in serum biologically active testosterone levels according to the absence or presence of erectile dysfunction in aging males. The MMAS [21] also agreed with our results, suggesting that the free testosterone level, biologically active testosterone level, and total testosterone level are not related to erectile dysfunction. Similar to the studies that reported recovery of sexual functions, such as libido and erectile function, after testosterone replacement therapy [22,23], most patients with LOH who visit urological clinics consider sexual function to be the most important issue, and testosterone replacement therapy is the major practical treatment of LOH. Thus, further studies are required.

There were some limitations to this study. Because we used only the ADAM questionnaire and IIEF-5 to assess the symptoms of LOH through an andropause screening program, the detailed medical and social history of the patients for a full analysis of LOH symptoms were lacking. In addition, serum total testosterone was the only biochemical parameter measured; various endocrinological changes influencing the symptoms of LOH were not included in the study. Although there is consensus that pa-

tients with serum total testosterone levels below 230 ng/dL will usually benefit from testosterone replacement therapy according to the ISSAM guideline [18], we used the cut-off value of 350 ng/dL. This was for focused evaluation of the relationship between serum total testosterone and LOH symptoms in patients with serum testosterone levels between 230 to 350 ng/dL, who constitute a large portion of those with LOH. Also, debate remains about the effect of testosterone treatment in these patients. Furthermore, this study may have had some bias, because it was a community-based study, not a cross-sectional or cohort study. However, our findings are important because this is the first large-scale study of Korean males aged >40 years.

CONCLUSIONS

Among men over 40 years of age, 25.6% met the clinical and biochemical diagnostic criteria for LOH. There was no relationship between serum testosterone levels and symptoms of LOH.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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