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SHORT COMMUNICATION

Survey for late-onset hypogonadism among old and middle-aged males in Shanghai communities

Kai Sun[1], Guo-Qing Liang[2], Xiang-Feng Chen[1], Ping Ping[1], Wen-Liang Yao[1], Shi-Jun Zhang[1], Bo Wang[3], Ying-Hao Sun[4] and Zheng Li[1]

This study sought to investigate late-onset hypogonadism (LOH) in old and middle-aged males in Shanghai communities, using symptom score evaluation systems and measurements of sex hormone levels. One thousand cases of males aged 40–70 years were investigated. The aging male symptoms (AMS) scale and androgen deficiency in aging males (ADAM) questionnaire were used at the beginning of the investigation, followed by measurement of the sex hormone-related factors (total testosterone (TT), free testosterone (fT), sex hormone-binding globulin (SHBG) and bioavailability of testosterone (Bio-T)). There were 977 valid questionnaires. The LOH-positive rates shown by AMS and ADAM were 59.88% and 84.65%, respectively; values increased with the age of the patients. There were 946 results related to sex hormone measurements, which showed the following results: TT was not related to aging ($P>0.05$); levels of SHBG increased with age; and fT and Bio-T decreased with age. There was a significant difference in fT between LOH-positive and LOH-negative patients, as shown by the ADAM. In summary, TT levels were not related to aging, even though SHBG did increase while fT and Bio-T decreased with aging. Clinically, the diagnosis of LOH cannot be based on serum TT level.
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Keywords: ADAM; AMS; late-onset of hypogonadism; male aging; old and middle-aged males; survey

INTRODUCTION

Testosterone deficiency in elderly males has become a rather interesting and controversial topic. Late-onset hypogonadism (LOH) is a common condition for old and middle-aged males around the world, and it is an acquired state of reduced function in gonads during later life stages.[1–3] The condition is affected by many factors. It can severely impact the life quality of old and middle-aged males, while it also has a negative effect on the functions of many organs and systems.[4]

The general consensus is that the partial deficiency in levels of testosterone from gonads leads to the onset of LOH, but the exact pathogenesis and mechanism remain unclear. The diagnosis of LOH is primarily performed through the combination of symptom evaluation and the measurement of serum testosterone. Currently, the aging male symptoms (AMS) scale and the androgen deficiency in aging males (ADAM) questionnaire, because of the high sensitivity, ease of operation and time-saving characteristics, have become well recognized and widely used. The Chinese versions of the two charts have been in use for several years, but there are still no research data on the LOH-positive rates for both charts. Furthermore, epidemiological data on LOH from large community populations are even rarer. In order to understand the prevalence of LOH in old and middle-aged males in Shanghai communities, we initiated a large-sample survey on a community population aged 40–70 years in Shanghai between November 2009 and June 2010. By using AMS, ADAM questionnaire and the measurement of serum testosterone level, it was possible to extrapolate the actual prevalence rate of LOH in old and middle-aged males from Shanghai communities.

MATERIALS AND METHODS

Enrolled males

For local residents in nine communities in the Weifang area of Pudong District, Shanghai, China, according to the demographic data from the local statistics bureau, using the stratified cluster sampling method at the ratio of 10 : 1, 1000 cases of old and middle-aged males aged 40–70 years were randomly selected. The mean age was 59.41 ± 7.42 years, the weight ranged from 45 to 111 kg and the body mass index was 24.92 ± 3.33 kg m^{-2}. Patients diagnosed with prostate cancer or in a psychotic state were excluded from the study.

Questionnaires

AMS[5] and ADAM questionnaires[6] were used. The clinical investigator, after strict training, instructed the enrollee on how to complete the questionnaires. After investigators checked the answers for completeness, all the questionnaires were archived by the researcher for subsequent analysis.

Serum measurements of sex hormones

In this study, 946 samples of venous blood were collected after 12 h of fasting as subjects had finished the questionnaires, at which point the concentration of serum sex hormones was tested. Test items included: total testosterone (TT), sex hormone-binding globulin (SHBG), free

[1]Department of Urology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200127, China; [2]Department of Urology, Shanghai Hospital of TCM, Shanghai 200071, China; [3]Family Planning Research Institute of Shanghai City, Shanghai 200032, China and [4]Department of Urology, Shanghai Hospital, Second Medicinal Military University of PLA, China, Shanghai 200433, China
Correspondence: Dr Z Li (doc.zheng.li@gmail.com); Dr YH Sun (profsunyinghao@hotmail.com)
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Table 1 LOH-positive rates in different age groups by AMS and ADAM questionnaires

Age group (years)	*AMS,* n *(%)*			*ADAM,* n *(%)*		
	Positive	*Negative*	P[a]	*Positive*	*Negative*	P[a]
~40	47 (51.65)	44 (48.35)	<0.01	65 (71.43)	26 (28.57)	<0.01
~50	219 (55.58)	175 (44.42)		311 (78.93)	83 (21.07)	
60–70	319 (64.84)	173 (35.16)		451 (91.67)	41 (8.33)	

Abbreviations: ADAM, androgen deficiency in aging males; AMS, aging male symptoms; LOH, late-onset hypogonadism.
[a] The ANOVA results for the LOH-positive rate for the age groups of ~40, ~50 and 60–70 years with statistical significance ($P<0.01$).

Table 2 Comparison of TT, FT, SHBG and Bio-T in different age groups ($\bar{x}\pm s$)

Age group (years)	*TT (nmol l^{-1})*	*fT (nmol l^{-1})*	*SHBG (nmol l^{-1})*	*Bio-T*
~40	15.047±4.153	0.506±0.120[a]	30.316±12.758[a]	7.682±2.295[b]
~50	15.418±4.708	0.476±0.135	42.021±23.611	6.310±2.106
60–70	15.387±4.919	0.447±0.128	49.863±24.137	5.539±2.059

Abbreviations: Bio-T, bioavailability of testosterone; fT, free testosterone; SHBG, sex hormone-binding globulin; TT, total testosterone.
[a] $P<0.05$, [b] $P<0.01$, the ANOVA results for three age groups.

testosterone (fT) and bioavailable testosterone (Bio-T). Each index was measured using a chemical or luminescent method (instruments and test agents were manufactured by the Beckmann Co., Bremen, German). The Bio-T[7] was calculated from known values of TT, SHBG and serum albumin.

Statistical analysis

All data were recorded twice via EpiData 3.0 software by two individuals. The SPSS software (version 11.0; Chicago, IL, USA) was used for statistical analysis. $P<0.05$ was considered statistically significant.

RESULTS

There were 977 valid questionnaires, and the effective response rate was 97.7%. According to AMS and ADAM questionnaires, the LOH-positive rates were 59.88% and 84.65%, respectively. When divided into three age groups (~40, ~50 and 60–70 years old), the result showed a significant elevation in LOH-positive rate with aging ($P<0.01$) (**Table 1**). There were 946 sets of sex hormone level test results, which revealed the existence of statistical differences in TT levels among the different age groups. With aging, fT and Bio-T levels continued to decrease, while the level of SHBG increased gradually (**Table 2**). The serum levels of TT/fT/SHBG in both populations (LOH-positive and -negative) were compared (**Table 3**). The results showed no significant differences in TT and SHBG between LOH-positive and LOH-negative populations through the use of AMS and ADAM questionnaires ($P>0.05$). There was a significant difference in the level of fT between the two populations when using ADAM ($P<0.05$), although AMS revealed no difference ($P>0.05$).

DISCUSSION

Some males aged 40–50 years showed reduced memory, decreased ability to focus, easily agitated, depression, sudden heat, sweating and reduced sexual function, which were similar to the menopause period in females. In 1939, Werner[8] termed this the male climacteric syndrome. In 2002, the International Society of the Study of the Aging Male renamed the condition LOH.[9] Currently, there is no standard for the diagnosis of LOH, and the doctor can only depend on relevant clinical symptom evaluations, lab analysis of serum testosterone levels, and sometimes, diagnostic treatment.

Clinical symptom evaluation is the first step in diagnosing LOH, and it is achieved by a survey or questionnaire. Currently, AMS and ADAM questionnaires are used most commonly in practice. AMS was proposed by Heinemann *et al.*[5] of Germany in 1999. It is widely accepted with high authority around the world and has been translated into at least 17 languages. Kratzik *et al.*[10] from Austria studied 664 middle-aged males (40–60 years in age). In that study, the sensitivity and specificity of AMS were 75% and 71%, respectively. Other authors reported that the AMS score was related to age, while the score or the symptom was unrelated to the level of serum testosterone.[11] These results were similar to those published previously. The LOH-positive rate determined by AMS was 59.88% and increased with aging. There was no statistical significance in the levels of TT, fT or Bio-T between the positive and the negative populations when using the AMS chart.

Morley *et al.*[12] recommended the use of the ADAM questionnaire for screening LOH in 2000. The advantage of the ADAM questionnaire is its simple design and its reliance on items that are easy to understand and handle. However, it lacks a scoring system and cannot differentiate the severity of a symptom. Morley *et al.*[11] reported that the sensitivity and the specificity of the ADAM questionnaire were, respectively, 97% and 30%. The questionnaire was not designed to screen LOH by itself and should be used along with measurements of serum hormone levels. During this research effort, the result obtained using the ADAM questionnaire was fairly similar to those published previously. The LOH-positive rate was 84.65%; this increased with aging. There was no significant difference in TT or SHBG between the positive and the negative populations, while fT differed significantly between the groups.

The study suggested that the level of physiologically active testosterone in males aged 40–70 years decreased annually by 1.2%.[13] Testosterone primarily exists in three forms in the blood circulation:

Table 3 Comparison of TT, fT, and SHBG in relation to AMS and ADAM ($\bar{x}\pm s$)

Item	*Population mean*	*AMS*		*ADAM*	
		Positive	*Negative*	*Positive*	*Negative*
TT(nmol l^{-1})	15.380±4.767	15.248±4.837	15.529±4.628	15.307±3.671	15.785±5.003
fT (nmoll^{-1})	0.465±0.132	0.456±0.130	0.476±0.133	0.459±0.128	0.497±0.148[a]
SHBG(nmol l^{-1})	44.906±23.853	46.526±25.484	42.642±21.211	45.663±24.389	40.821±20.168

Abbreviations: ADAM, androgen deficiency in aging males; AMS, aging male symptoms; fT, free testosterone; LOH, late-onset hypogonadism; SHBG, sex hormone-binding globulin; TT, total testosterone.
[a] *t*-test $P<0.05$ for the difference in fT levels between LOH-positive and LOH-negative groups when using the ADAM questionnaire.

(i) fT (2%–3%); (ii) albumin-binding testosterone (20%–40%); and (iii) SHBG testosterone (60%–80%). FT and albumin-binding testosterone can be used by tissues and are therefore denoted as bioavailable testosterone. With aging, interstitial cells (Leydig cells) in the gonads decrease not only in number but also in their response to gonadotropin. The relevant enzyme for testosterone synthesis also decreases in activity, which induces a reduction in synthesis and the secretion of testosterone by Leydig cells.[14] Travison *et al.*[15] performed a prospective study on 1667 male patients aged 40–70 years and proved that serum TT and fT dropped significantly with age. Andersson *et al.*[16] concluded from 5350 cases (males, aged 30–70 years) that SHBG increased with aging. When adjusted by body mass index, the reduction in TT was not significant; SHBG and fT did vary significantly with age. In this study, we discovered that with aging, TT did not drop significantly, which could imply that serum TT will not help to diagnose LOH. However, the levels of fT and SHBG showed a gradient change with aging, where SHBG showed a positive correlation, while fT showed a negative relationship. The result was fairly similar to other reports.[17] In addition, the study was the first to calculate serum Bio-T levels in 946 cases, based on measured levels of TT, SHBG and albumin. The statistical results showed that with aging, serum levels of Bio-T were significantly reduced. Compared with former research, the measured levels serum fT and the calculated Bio-T were slightly higher in this study, which could be contributed to the measuring method and test agents used in the lab.

In summary, scholars in China are currently focusing more on LOH study, and yet, the sensitivity and specificity of AMS and ADAM questionnaires have not yet been verified. In the future, it will be necessary to perfect and verify each screening scale or questionnaire for use in the Chinese population to find the optimal screening system for LOH. It is only when a doctor combines the results from scales or questionnaires and the measurement of testosterone that he or she can make a more accurate diagnosis.

AUTHOR CONTRIBUTIONS

ZL and YHS designed the experiments. XFC, KS, PP, GQL, WLY, SJZ, BW carried out the survey and lab testing work. XFC and KS participated in drafting, interpreting the data and critically revising the paper for key intellectual content. All authors read and approved the final manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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