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International Prostate Symptom Score and Quality of Life Index for Lower Urinary Tract Symptoms Are Associated with Aging Males Symptoms Rating Scale for Late-Onset Hypogonadism Symptoms

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Purpose: Although patients with late-onset hypogonadism (LOH) often experience lower urinary tract symptoms (LUTS), LUTS are not generally included in LOH symptoms. No study has examined the direct relation of the Aging Males Symptoms rating scale (AMS) and the International Prostate Symptom Score (IPSS) with the quality of life (QOL) index. We analyzed the relation between the IPSS and QOL index and various factors including the AMS in patients with LOH syndromes.

Materials and Methods: This study comprised 1,688 men with LOH symptoms who visited our hospital or affiliated clinic. Factors associated with the IPSS were assessed in terms of age, scores of several questionnaires including the AMS, endocrinological variables, and serum concentration of PSA. Among these same factors, those associated with the QOL index were also evaluated. Finally, the same analyses were repeated in 187 patients with low serum testosterone concentration (<3.0 ng/mL).

Results: In a multivariate analysis using the significant items from the univariate analysis, AMS, age, and Erection Hardness Score correlated significantly with the IPSS. A trend analysis using items other than the AMS as adjustment factors also confirmed the relationship between an increase in QOL index and an increase in AMS. Similar results were obtained in the analysis of patients with low serum testosterone concentration.

Conclusions: We revealed that the relation of IPSS with the QOL index for LUTS is closely associated with the AMS for LOH, regardless of testosterone level. When patients complain of LOH symptoms, a careful, detailed inquiry into LUTS is required.

Keywords: Hypogonadism; Lower urinary tract symptoms; Prostate; Quality of life; Testosterone

INTRODUCTION

In the current aging society, the concept of late-onset hypogonadism (LOH), defined as "a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels," has gained increased attention [1]. The prevalence of hypogonadism in men

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ranges from 6.0% to 12.3% between the ages of 40 and 69, and it is estimated that 2.4 million men in the United States have testosterone deficiency [2]. Because testosterone plays many physiological roles in various organs and tissues such as skin, muscle, liver, bone and bone marrow, brain, and sexual organs, LOH caused by decreased serum testosterone levels is thought to be one of the causes of a reduced quality of life (QOL) in middle-aged men [3-5]. It was also reported that not only QOL but also even mortality is associated with low serum testosterone concentration in a study of men older than 40 years [6]. Furthermore, the European Male Aging Study conducted in eight European countries with 2,599 community-dwelling men aged 40 to 79 years with LOH symptoms, especially sexual symptoms, revealed that severe LOH is associated with substantially higher risks of all-cause and cardiovascular mortality, to which both the level of serum testosterone and the presence of sexual symptoms contribute independently [7]. The prevalence LOH symptoms in a population-based, observational survey of middle-old aged men whose total testosterone concentration was <300 ng/dL was low libido (12%), erectile dysfunction (ED) (16%), and two or more of nonspecific symptoms (20%) such as depression, anger, lack of concentration, fatigue, and a decrease in lean body mass with associated decrease in muscle volume and strength [8]. The Japanese guideline for LOH clearly includes seven typical symptoms: ED in sexual dysfunction, changes in mood and depression, sleep disturbances, decrease in lean body mass, increase in visceral fat, decrease in body hair and skin alterations, and decreased bone mineral density [9]. It is surprising that lower urinary tract symptoms (LUTS) are not included in LOH symptoms in the Japanese guideline and other previous studies, although it is well known that LUTS, ED, and LOH, each of which is significantly associated with a reduced QOL, are closely associated with each other in aging men [10,11]. It is especially apparent that the prevalence of LUTS increases with age [12] and that LUTS can significantly affect QOL by causing loss of sleep, reduced productivity, impaired sexual life, social isolation, and clinical depression. Actually, we have often experienced patients who wondered about LOH because of worsening LUTS. In these cases, we usually assess symptoms by their specific questionnaires, the Aging Males Symptoms rating scale (AMS) for LOH and the International Prostate Symptom Score (IPSS) and QOL index for LUTS, respectively. However, the direct relation between the AMS and the IPSS has not been investigated in a cross-sectional study of patients with typical LOH symptoms.

Thus, in the present study, we analyzed the relation between the IPSS and QOL index and various factors including the AMS in patients with LOH symptoms to clarify which factors are actually associated with LUTS.

MATERIALS AND METHODS

This study comprised 1,688 men with various symptoms of LOH who visited our hospital or affiliated clinic between November 2016 and April 2018. They had at least one symptom of LOH as follows: lethargy, general fatigue, malaise, depression, insomnia, frustration, reduced concentration, sweating, hot flashes, coldness, tinnitus, headache, numbness, dizziness, stiff shoulder, night sweats, sexual dysfunction, and decreased libido. We assessed symptom scores with several specific questionnaires including the AMS for LOH, the IPSS and QOL index for LUTS, the Sexual Health Inventory for Men (SHIM) and Erection Hardness Score (EHS) for sexual function, and the Beck Depression Inventory (BDI) for depression. Endocrinologic data, including total testosterone (1.92–8.84 ng/mL), dehydroepiandrosterone sulfate (DHEA-S; 70–495 μg/dL), insulin-like growth factor 1 (IGF-1; 89–248 ng/mL), and cortisol levels (6.2–22.7 μg/dL) were evaluated. The serum concentration of prostate-specific antigen (PSA; 0.000–4.000 ng/mL) was also assessed because we did not evaluate prostate volume. All blood samples were collected between 09:00 and 11:00 to monitor endocrinological variables.

First, the factors associated with the IPSS were assessed in terms of age, scores of the questionnaires including SHIM, EHS, AMS, and BDI, endocrinological variables, and serum concentration of PSA. Second, we divided patients into severe/moderate level and others based on the score of the AMS and IPSS to show the sensitivity and specificity for the relation of them. Third, the factors associated with the QOL index were also evaluated in terms of these same factors. Finally, we subsequently performed the same statistical evaluation regarding the IPSS and the QOL index only in 187 men with a low serum testosterone concentration of <3.0 ng/mL.

1. Statistical analysis

Continuous variables and scores of the questionnaires are expressed as mean±standard deviation. To identify the contributors of the IPSS, the associations between the IPSS and several factors were assessed in a univariate linear regression model. The same analysis was performed by multivariate linear regression model after adjustment for the statistically significant factors identified by the univariate linear regression model. Regarding the QOL index, stepwise associations were performed using a trend analysis. Finally, a trend analysis between the QOL index and the AMS score was also performed after adjustment for statistically significant factors identified by a trend analysis that excluded the AMS. Statistical significance was set at $p<0.05$. Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

2. Ethics statement

The procedures were approved by the Regional Ethics Committee of Juntendo Urayasu Hospital, Urayasu, Japan (approval number: 2018-029) and D-Clinic TOKYO for men. Written informed consent was obtained from all of the patients. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

RESULTS

1. Patients with late-onset hypogonadism symptoms

The clinical characteristics of all patients with LOH symptoms in the present study are shown in Table 1. The mean age of the patients was 48.5±11.1 years. The severity of several symptoms was assessed by the scores of the questionnaires. ED was categorized as mild to moderate by the mean SHIM score (12.1±6.7) and the mean EHS score (2.6±1.1). LOH was categorized as moderate by the mean AMS score (40.3±12.5). Depression was categorized as mild by the mean BDI score (12.3±8.1). LUTS were categorized as moderate by the mean IPSS score (7.7±6.3) and the mean QOL index (2.7±1.6). The mean total testosterone concentration was 5.2±2.2 ng/mL, and other endocrinological profiles were within normal range, as was the mean value of PSA at 1.2±1.3 ng/mL. The comparison of these factors between patients with normal (>3.0 ng/mL) and low (<3.0 ng/mL) testosterone concentration was also shown in Table 1. No significant difference was found between them in any factor.

Factors influencing the IPSS in all patients by univariate and multivariate analyses are shown in Table 2A. We omitted the QOL index from the independent variables because it was considered to be a confounding

Table 1. Clinical characteristics of 1,688 patients with LOH symptoms

Characteristic	All patients		Patients with normal serum testosterone concentration		Patients with low serum testosterone concentration		p-value
	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	
Number of patients	1,688		1,501		187		
Age (y)	48.5±11.1	21–86	48.2±11.2	22–86	50.6±10.5	21–86	0.359
SHIM	12.1±6.7	1–25	12.3±6.6	1–25	11.4±7.1	1–25	0.089
EHS	2.6±1.1	1–4	2.6±1.1	1–4	2.5±1.1	1–4	0.111
AMS	40.3±12.5	17–80	39.9±12.3	17–75	42.8±13.2	17–80	0.560
BDI	12.3±8.1	0–47	12.1±7.9	0–47	13.9±9.0	0–42	0.128
IPSS	7.7±6.3	0–33	7.6±6.4	0–33	7.9±5.7	0–26	0.136
QOL index	2.7±1.6	0–6	2.6±1.6	0–6	2.9±1.5	0–6	0.051
Testosterone (ng/mL)	5.2±2.2	0.3–29.1	5.5±2.0	3.0–29.1	2.3±0.6	0.3–3.0	<0.001
DHEA-S (μg/dL)	228.9±107.7	15.0–751.0	228.7±107.7	16.0–751.0	232.4±107.2	24.0–585.0	0.861
IGF-1 (ng/mL)	137.9±38.1	41.0–393.0	137.4±37.2	41.0–393.0	141.7±44.6	62.0–374.0	0.066
Cortisol (μg/dL)	9.1±3.3	0.8–27.2	9.1±3.6	1.20–27.2	9.1±4.0	0.8–22.2	0.107
PSA (ng/mL)	1.2±1.3	0.01–20.90	1.2±1.3	0.10–20.90	1.1±1.2	0.01–8.10	0.515

LOH: late-onset hypogonadism, SHIM: Sexual Health Inventory for Men, EHS: Erection Hardness Score, AMS: Aging Males Symptoms rating scale, BDI: Beck Depression Inventory, IPSS: International Prostate Symptom Score, QOL: quality of life, DHEA-S: dehydroepiandrosterone sulfate, IGF-1: insulin-like growth factor 1, PSA: prostate-specific antigen.

factor to the IPSS score. Univariate analysis showed that age, the SHIM, EHS, BDI, and AMS scores, and serum concentrations of DHEA-S, IGF-1, and PSA were independent factors influencing the IPSS score. Then, a multivariate analysis with these factors as independent variables, after omitting the SHIM because of a risk of confounding factor to the EHS, showed age ($p<0.001$) and the score of EHS ($p=0.044$), and AMS ($p<0.001$) to be the independent factors influencing the IPSS score. We also found that 540 of 1,005 patients with severe/moderate level of the AMS showing severe/moderate level of the IPSS, thus the sensitivity of this relation was 53.7% (Table 3). Similarly, the specificity of that was found to be 73.1%. The relation between the QOL index and other factors by trend analysis is shown in Table 4A. As we expected, men with a higher score for QOL index were significantly older ($p_{trend}<0.001$). Regarding symptoms, a higher level of QOL index was associated with lower SHIM ($p_{trend}<0.001$), EHS ($p_{trend}<0.001$), and BDI ($p_{trend}<0.001$) scores and a higher AMS score ($p_{trend}<0.001$). Men with a higher level of QOL index also had significantly lower concentrations of serum DHEA-S ($p_{trend}<0.001$) and IGF-1 ($p_{trend}=0.006$) and a higher concentration of serum PSA ($p_{trend}=0.008$). Finally, the relation between the QOL index and the AMS score was investigated after adjustment for sta-

Table 2A. Factors influencing IPSS in 1,688 patients with LOH symptoms

Factor	Univariate analysis				Multivariate analysis			
	Regression coefficient	p-value	95% confidence interval		Regression coefficient	p-value	95% confidence interval	
			Lower	Upper			Lower	Upper
Age (y)	0.193	<0.001	0.167	0.219	0.142	<0.001	0.113	0.172
SHIM	-0.168	<0.001	-0.213	-0.123				
EHS	-1.317	<0.001	-1.592	-1.041	-0.283	0.044	-0.558	-0.172
AMS	0.184	<0.001	0.161	0.206	0.138	<0.001	0.100	0.176
BDI	0.215	<0.001	0.179	0.251	0.032	0.277	-0.026	0.090
Testosterone (ng/mL)	-0.044	0.539	-0.184	0.096				
DHEA-S (μg/dL)	-0.008	<0.001	-0.011	-0.006	-0.002	0.100	-0.005	0.000
IGF-1 (ng/mL)	-0.015	<0.001	-0.023	-0.007	-0.003	0.445	-0.010	0.005
Cortisol (μg/dL)	0.028	0.518	-0.056	0.111				
PSA (ng/mL)	0.519	<0.001	0.286	0.752	0.111	0.139	-0.053	0.380

IPSS: International Prostate Symptom Score, LOH: late-onset hypogonadism, SHIM: Sexual Health Inventory for Men, EHS: Erection Hardness Score, AMS: Aging Males Symptoms rating scale, BDI: Beck Depression Inventory, DHEA-S: dehydroepiandrosterone sulfate, IGF-1: insulin-like growth factor 1, PSA: prostate-specific antigen.

Table 2B. Factors influencing IPSS in 187 patients with LOH symptoms and low serum testosterone concentration

Factor	Univariate analysis				Multivariate analysis			
	Regression coefficient	p-value	95% confidence interval		Regression coefficient	p-value	95% confidence interval	
			Lower	Upper			Lower	Upper
Age (y)	0.121	0.003	0.043	0.199	0.080	0.043	0.002	0.158
SHIM	-0.168	0.004	-0.282	-0.054				
EHS	-0.732	0.046	-1.449	-0.014	0.211	0.565	-0.512	0.934
AMS	0.204	<0.001	0.148	0.259	0.249	<0.001	0.144	0.354
BDI	0.212	<0.001	0.126	0.299	-0.090	0.240	-0.240	0.060
Testosterone (ng/mL)	-1.111	0.112	-2.483	0.260				
DHEA-S (μg/dL)	-0.007	0.062	-0.015	0.000				
IGF-1 (ng/mL)	-0.002	0.848	-0.021	0.017				
Cortisol (μg/dL)	0.019	0.854	-0.187	0.226				
PSA (ng/mL)	0.007	0.984	-0.667	0.681				

IPSS: International Prostate Symptom Score, LOH: late-onset hypogonadism, SHIM: Sexual Health Inventory for Men, EHS: Erection Hardness Score, AMS: Aging Males Symptoms rating scale, BDI: Beck Depression Inventory, DHEA-S: dehydroepiandrosterone sulfate, IGF-1: insulin-like growth factor 1, PSA: prostate-specific antigen.

tistically significant factors by the trend analysis that excluded the AMS. Fig. 1A shows that the AMS score increased significantly as the QOL index increased (p_{trend}<0.001).

Table 3. Relation between AMS and IPSS based on the severity

IPSS	AMS	
	Severe/moderate	Slight/no symptom
Severe/moderate	540	184
Mild	465	499

Values are presented as number only.
AMS: Aging Males Symptoms rating scale, IPSS: International Prostate Symptom Score.

2. Patients with late-onset hypogonadism symptoms and low serum testosterone concentration

The clinical characteristics of the patients with LOH symptoms and low serum testosterone concentration are shown in Table 1. Factors influencing the IPSS by univariate analysis included age (p=0.003) and the scores of SHIM (p=0.004), EHS (p=0.046), BDI (p<0.001),

Table 4A. Factors influencing QOL index in 1,688 patients with LOH symptoms

Factor	QOL index							p_{trend}
	0	1	2	3	4	5	6	
Number of patients	183	278	279	406	312	167	63	
Age (y)	41.9±10.4	45.6±10.6	48.8±11.0	48.8±10.4	51.0±10.6	52.1±10.8	55.7±10.8	<0.001
SHIM	14.0±7.1	13.5±7.0	12.5±6.5	11.7±6.6	11.2±5.9	11.2±6.4	9.3±7.2	<0.001
EHS	2.9±1.0	2.8±1.0	2.7±1.0	2.5±1.0	2.4±1.0	2.4±1.2	1.9±1.3	<0.001
AMS	33.1±12.9	35.7±11.5	38.3±11.4	41.9±12.3	43.6±11.2	44.6±11.6	50.6±11.0	<0.001
BDI	8.8±8.2	10.0±6.9	10.8±7.5	13.7±8.1	13.6±7.5	15.0±8.7	16.9±9.4	<0.001
Testosterone (ng/mL)	5.3±1.9	5.1±1.7	5.3±2.4	5.0±1.9	5.1±2.5	5.3±2.7	5.1±2.1	0.914
DHEA-S (μg/dL)	250.0±111.9	240.2±115.2	225.0±98.0	230.1±109.5	217.4±99.9	223.4±113.3	197.8±101.6	<0.001
IGF-1 (ng/mL)	141.1±39.7	143.0±35.1	137.1±40.6	138.1±37.5	135.0±40.1	134.8±35.0	129.8±36.7	0.006
Cortisol (μg/dL)	8.9±3.8	9.2±3.5	8.9±3.6	9.2±3.9	9.0±3.4	9.2±3.3	9.2±3.6	0.591
PSA (ng/mL)	1.0±0.9	1.2±1.4	1.1±0.9	1.1±0.8	1.3±1.6	1.4±1.9	1.4±1.4	0.008

Values are presented as mean±standard deviation.
QOL: quality of life, LOH: late-onset hypogonadism, SHIM: Sexual Health Inventory for Men, EHS: Erection Hardness Score, AMS: Aging Males Symptoms rating scale, BDI: Beck Depression Inventory, DHEA-S: dehydroepiandrosterone sulfate, IGF-1: insulin-like growth factor 1, PSA: prostate-specific antigen.

Table 4B. Factors influencing QOL index in 187 patients with LOH symptoms and low serum testosterone concentration

Factor	QOL index							p_{trend}
	0	1	2	3	4	5	6	
Number of patients	15	24	26	45	53	18	6	
Age (y)	43.4±10.4	49.2±11.8	48.0±10.7	50.4±8.3	54.5±11.3	51.1±6.9	54.3±10.7	0.009
SHIM	14.0±8.6	11.9±8.3	14.7±7.1	11.8±6.5	9.2±5.9	10.4±6.8	7.0±8.6	0.008
EHS	2.5±1.2	2.8±1.1	2.6±1.3	2.6±1.0	2.2±1.1	2.6±1.2	1.7±1.4	0.062
AMS	35.9±19.0	34.3±10.5	36.2±10.6	44.6±12.5	46.7±10.3	51.1±13.8	51.2±6.6	<0.001
BDI	11.8±14.2	9.5±5.8	9.8±7.9	14.4±8.4	15.9±7.5	18.4±10.4	18.3±9.6	0.002
Testosterone (ng/mL)	2.2±0.6	2.5±0.4	2.3±0.5	2.2±0.6	2.3±0.6	2.2±0.8	2.7±0.4	0.528
DHEA-S (μg/dL)	267.9±124.0	218.8±81.0	251.5±116.8	239.8±112.8	213.0±96.4	251.3±124.9	171.2±84.9	0.124
IGF-1 (ng/mL)	133.9±36.1	143.2±32.8	145.7±63.9	146.7±45.0	137.5±43.1	144.3±36.4	128.3±42.0	0.754
Cortisol (μg/dL)	8.4±4.9	9.0±3.2	8.5±4.8	9.6±4.3	9.8±3.9	8.19±1.5	6.2±4.2	0.298
PSA (ng/mL)	0.7±0.4	1.6±2.2	0.8±0.6	1.1±1.3	1.3±1.1	0.7±0.5	1.6±1.6	0.517

Values are presented as mean±standard deviation.
QOL: quality of life, LOH: late-onset hypogonadism, SHIM: Sexual Health Inventory for Men, EHS: Erection Hardness Score, AMS: Aging Males Symptoms rating scale, BDI: Beck Depression Inventory, DHEA-S: dehydroepiandrosterone sulfate, IGF-1: insulin-like growth factor 1, PSA: prostate-specific antigen.

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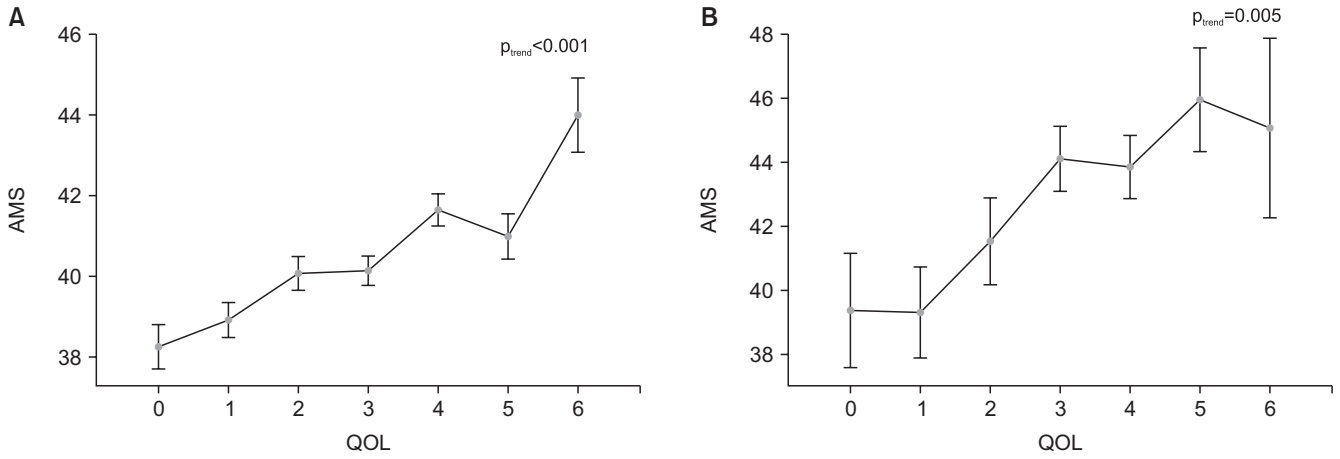

Fig. 1. The AMS score increased significantly as the QOL index increased (p_{trend}<0.001) after adjustment for statistically significant factors such as age, SHIM, EHS, and BDI scores and serum concentrations of DHEA-S, IGF-1, and PSA by trend analysis in 1,688 patients with LOH symptoms (A). The AMS score also increased significantly as the QOL index increased (p_{trend}=0.005) after adjustment for statistically significant factors such as age and SHIM and BDI scores by trend analysis in 187 patients with LOH symptoms and low serum testosterone concentration (B). AMS: Aging Males Symptoms rating scale, QOL: quality of life, SHIM: Sexual Health Inventory for Men, EHS: Erection Hardness Score, BDI: Beck Depression Inventory, DHEA-S: dehydroepiandrosterone sulfate, IGF-1: insulin-like growth factor 1, PSA: prostate-specific antigen, LOH: late-onset hypogonadism.

and AMS (p<0.001), whereas no association between the IPSS and endocrinological variables or PSA level was found (Table 2B). Multivariate analysis with symptomatic factors as independent variables after omitting the SHIM showed only age (p=0.043) and AMS score (p<0.001) to be independent factors influencing the IPSS score (Table 2B). The relation between the QOL index and other factors by the trend analysis is shown in Table 4B. Even in the analysis of patients with low serum concentration of testosterone, men with a higher QOL index were significantly older (p_{trend}=0.009). Regarding symptoms, a higher QOL index was associated with lower SHIM (p_{trend}=0.008), higher BDI (p_{trend}=0.002), and AMS (p_{trend}<0.001) scores. No other association was found with endocrinological variables or PSA level. Fig. 1B shows that the AMS score increased significantly (p_{trend}=0.005) as the QOL index increased after adjustment for the statistically significant factors of age and SHIM and BDI scores.

DISCUSSION

As LOH has gained increased attention in the general public, many characteristic symptoms are now recognized to be caused by LOH. They include physical symptoms such as general fatigue, hot flashes, sleep disturbance, and metabolic change; mental symptoms such as depression, anxiety, and lack of concentration; and sexual symptoms such as ED and loss of libido [1,13,14]. There is no doubt that prostate tissue grows and prostate volume enlarges in the presence of androgen. A double-blind study with placebo in 1993 showed that testosterone replacement treatment (TRT) of 8 months increased the mean prostate volume by 12% [15]. Thus, it would seem to be common sense that LUTS are not included in the characteristic symptoms of LOH caused by a declining testosterone concentration. Indeed, a cross-sectional study of 312 men aged 40 years and older (62.8±10.6 years) with untreated LUTS (IPSS >7) already showed that hypogonadism in patients (serum testosterone concentration <3.0 ng/mL) had no impact on LUTS (IPSS, peak flow rate, and prostate volume) [16]. Furthermore, it is obvious that one of essential adverse events of TRT is considered to be LUTS based on benign prostatic hyperplasia (BPH). However, in the clinical setting, we often experienced patients with LOH symptoms who are concurrently bothered by LUTS despite having a low testosterone concentration. As if to support this clinical situation, recent studies have shown that testosterone deficiency is linked with the development of LUTS [17]. One study showed that the number of patients with LOH (AMS >27) increased with increasing LUTS severity based on evaluation of the IPSS; LOH prevalence rates were 54.7%, 72.2%, and 81.1% in the mild (IPSS <7), moderate (IPSS of 8–19), and severe (IPSS >20) LUTS groups, respectively [18]. From the point of view of TRT, several clinical studies have shown that TRT can improve

LUTS in hypogonadal men with BPH [19-21]. In a previous study of Japanese patients with LOH, the AMS score and IPSS were significantly improved after TRT. It was also reported that storage symptom, not voiding symptom, scores of the IPSS were significantly improved by analysis of the subscore after TRT [20]. Furthermore, a systematic review and meta-analysis of 16 randomized controlled trials involving 1,030 patients showed that neither short-term nor long-term TRT increased the risk of prostate growth regardless of the administration method [22]. Another meta-analysis of 14 randomized controlled trials involving 2,029 participants showed that there was no statistically significant difference in pooled changes in IPSS from baseline to follow-up in men treated with TRT compared with those receiving placebo [23]. Thus, it does not appear to be true that TRT always causes LUTS simply by enlarging prostate volume; that is a rather classical theory. In other words, the relation of serum testosterone concentration and LOH with LUTS is still controversial. Especially, the direct association of the IPSS with the QOL index on AMS has not been clarified.

The present study showed that the AMS score, as well as age and the EHS score, was an independent factor influencing the IPSS in patients with LOH symptoms. Although it is already well known that aging and sexual dysfunction are closely associated with LUTS, our results also indicate a close relation between LOH symptoms and LUTS. Furthermore, this tendency was not attenuated even when the analysis was repeated only in patients with hypogonadism. We additionally showed the sensitivity and specificity of the relation of the AMS and the IPSS were 53.7% and 73.1%, respectively.

We also investigated the relation between the AMS score and the QOL index because this relation has not been evaluated directly in previous studies. As we expected, the AMS score clearly increased significantly as the QOL index increased after adjustment for statistically significant factors by trend analysis that excluded the AMS. As with the IPSS, this tendency was not attenuated even when the analysis was repeated only in patients with hypogonadism. Taken together with these findings, a close relation exists between LOH symptoms and LUTS in patients with LOH symptoms, regardless of their serum testosterone concentration.

Although several mechanisms for the improvement of LUTS by TRT have been speculated, the main theory is considered to be metabolic syndrome caused by low serum testosterone concentration. It is well known from recent epidemiologic and clinical studies that metabolic syndrome is involved in the pathogenesis and progression of prostatic diseases such as BPH [24]. It is also speculated that insulin resistance, visceral obesity with chronic inflammation, deregulations of the hypothalamic-pituitary adrenal axis, and atherogenic dyslipidemia with the atherosclerosis of metabolic syndrome can be involved in its pathogenesis and potential interactions [24]. From the point of view of the relation between metabolic syndrome and low testosterone concentration, several studies including ours have already reported a close association [25]. Furthermore, it was reported that the AMS was significantly positively correlated with fasting blood glucose level, fasting insulin concentration and homeostatic model assessment of insulin resistance [26]. In addition, 60 months of TRT for hypogonadal men with metabolic syndrome already resulted in significant improvements in metabolic factors such as waist circumference, body weight, insulin sensitivity, lipid profile, and systolic and diastolic blood pressure [27]. We also reported that low serum testosterone concentration was one of the major causes of atherosclerosis [28] and that atherosclerosis was independently associated with LUTS, probably due to ischemia in the bladder and prostate [29]. Thus, it is largely taken for granted that LOH caused by low serum testosterone concentration may cause LUTS *via* metabolic syndrome or atherosclerosis. In addition, an animal model of castrated rats treated with testosterone showed a significant increase in bladder capacity and decreased bladder compliance on urodynamic testing and reduced bladder fibrosis on histological examination compared to the non-treated group [30]. These previous findings accounts for our data showing a close association between LOH assessed by the AMS score and LUTS assessed by the IPSS and the QOL index. However, the present study clearly showed a close relation between LOH symptoms and LUTS in patients with LOH symptoms, regardless of their serum testosterone concentration. Therefore, we suggest that not only a direct effect of testosterone but also physical and psychogenic upset are related to LUTS in men and that LUTS must be confirmed in patients who visit a medical institution because of LOH symptoms, even though LUTS are not included as typical symptoms of LOH in the Japanese guideline for LOH.

The present study has some limitations. First, we only performed blood testing for the biochemical and endocrinological profiles once. Blood testing should be repeated, especially the endocrinological profile, because several endocrinological profiles vary seasonally and diurnally. Second, several co-morbidities such as diabetes, hypertension and atherosclerosis might be risk factors of both LUTS and LOH. In addition, several drugs are also related with these diseases. Unfortunately, we could not check co-morbidities and medications in as much as 1,688 men, because this is a record based retrospective study. Although it is possible that co-morbidities and medications could affect our results, we believe that our findings show the situation in a real-world clinical setting. Third, the present study included patients with at least one LOH symptom and investigated the relation between LOH and LUTS. Although we clearly showed a cross-relation between them, this relation is still unclear if the patients with at least one LUTS were enrolled in the study and the relation between LUTS and LOH was evaluated. In the future, we will construct a new cross-sectional study based on this clinical question.

CONCLUSIONS

In conclusion, we clearly showed for the first time, to our knowledge, a direct, close relation between the AMS and the IPSS with the QOL index in patients with LOH symptoms. The relation of testosterone and LUTS has gained increased attention. It is still controversial whether androgen deviation therapy can improve LUTS by shrinking the prostate volume or worsen LUTS *via* LOH with decreased testosterone level. Before discussing this issue, the relation between the AMS and the IPSS/QOL index hasn't been apparent. Our findings gave us the clinical benefits in consideration of the relation between LOH as well as testosterone and LUTS. When patients complain of LOH symptoms, a detailed careful inquiry into LUTS must also be conducted.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: TT, AT, SH. Data curation: TT, AT, KM, MK, AK. Formal analysis: YU, TN, MS. Investigation: TT. Methodology: TT, AT. Project administration: KK, SH. Supervision: AT, TN, MS. Validation: TT, AT, SH. Visualization: TT, AT, SH. Writing original draft: TT. Writing review & edting: AT, SH.

Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at https://doi.org/10.7910/DVN/AHCDXA.

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