Endocrinological and symptomatic characteristics of patients with late-onset hypogonadism classified by functional categories based on testosterone and luteinizing hormone levels

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Abstract

Objectives: To divide patients with late-onset hypogonadism (LOH) into subgroups by endocrinological findings, check their testosterone (T), luteinizing hormone (LH) and other endocrinologic hormone ratios, and clarify each subgroup's characteristics.

Methods: We assessed age, BMI, laboratory/endocrinologic profiles, and symptom-specific questionnaire scores of 967 men with LOH symptoms. The patients comprised four groups by T and LH concentrations: normal group (NG), compensated hypogonadism group (CHG), primary hypogonadism group (PHG), and secondary hypogonadism group (SHG). We compared characteristics between NG and CHG in men with normal T concentration and PHG and SHG in hypogonadal men after age adjustment.

Results: NG, CHG, PHG, and SHG respectively accounted for 83.6%, 3.4%, 0.8%, and 12.2% of patients. Despite age adjustment, serum DHEA-S and IGF-1 concentrations were significantly lower in CHG than NG. Only Aging Males Symptoms scale (AMS) mental subscore was significantly different. Serum T and DHEA-S concentrations were significantly lower in PHG than SHG. Only AMS sexual subscore was significantly different.

Conclusion: Most patients with LOH symptoms were in the NG, with SH much more

frequent than PH. Endocrinological differences may induce future symptomatic characteristics, although current symptomatic differences were minor. Classifying patients by T and LH levels may provide useful information for follow-up.

Key words: compensated hypogonadal men, late-onset hypogonadism, luteinizing hormone, testosterone

Abbreviations & Acronyms

AMS = Aging Males Symptoms rating scale

BMI = body mass index

CHG = compensated hypogonadism group

DHEA-S = dehydroepiandrosterone sulfate

EHS = Erection Hardness Score

FSH = follicle-stimulating hormone

IGF-1 = insulin-like growth factor 1

IPSS = International Prostate Symptom Score

LH = luteinizing hormone

LOH = late-onset hypogonadism

LUTS = lower urinary tract symptoms

NG = normal group

PHG = primary hypogonadism group

SHG = secondary hypogonadism group

SHIM= Sexual Health Inventory for Men

T = testosterone

Introduction

While aging and depopulation have been advancing, healthy longevity has gained increased attention in many developed countries including Japan. The concept of late-onset hypogonadism (LOH) is one of the symptomatic diseases attracting the most attention because androgen, which decreases with aging, has many physiological roles in various organs. LOH was basically defined by the European Association of Urology and the International Society of Andrology in 2005 as a biochemical syndrome associated with advancing age that is characterized by a serum androgen deficiency with or without decreased genomic sensitivity to androgen.[1] Symptoms of LOH include diminished sexual desire and erectile quality, particularly nocturnal erections (sexual symptoms); changes in mood with concomitant decreases in intellectual activity, depression, and anger (mental symptoms); and fatigue, decrease in lean body mass with associated decreases in muscle volume and strength, decrease in body hair and skin alterations, decreased bone mineral density resulting in osteoporosis, increased body fat, and diabetes (physical symptoms).[2–7] Although there is no doubt that these symptoms are associated with low serum testosterone (T) concentration in some patients, several clinical studies including ours have shown no significant difference in the severity of LOH symptoms between patients with and without hypogonadism.[8–10] In fact, some

patients complain of severe LOH symptoms such as depression, fatigue, and erectile dysfunction even though their serum T concentration is within normal limits. In contrast, a cross-sectional study also showed that serum T concentration is very low in some men without LOH symptoms.[2] Thus, the basic question has arisen of how to rate patients with a serum T concentration within normal limits who complain of LOH symptoms. Furthermore, even if the serum T concentration is low in patients, it is unclear whether hypogonadism is caused by testicular dysfunction (primary hypogonadism) or decreased secretion of gonadotropin from the pituitary gland (secondary hypogonadism) and whether symptomatic differences exist between them. It was reported that the normal group (NG), compensated hypogonadism group (CHG), primary hypogonadism group (PHG), and secondary hypogonadism group (SHG) respectively accounted for 76.7%, 9.5%, 2.0%, and 11.8% of patients in only one study of several European countries with 3119 elderly men who were asked to participate by letter of invitation.[11]

In the present study, we aimed to identify specific characteristics of patients with at least one symptom of LOH by endocrinological findings, especially differences between the CHG and NG and between the PHG and SHG, after adjustment for age.

Methods

This study included 967 men aged ≥40 years old with various symptoms of LOH who visited our hospital or affiliated clinic from March 2012 to May 2017. 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.

Blood samples were collected between 09:00 and 11:00. Physical and laboratory data included age, body mass index (BMI; body weight [kg] / height^2 [m^2]), serum concentrations of total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, triglyceride, fasting blood sugar, and hemoglobin A1c. Endocrinologic data, including levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), total T, estradiol, prolactin, dehydroepiandrosterone sulfate (DHEA-S), insulin-like growth factor 1 (IGF-1), and cortisol were also evaluated. LH, FSH, and T were measured by radioimmunoassay. We assessed symptom scores with several specific questionnaires including the Aging Males Symptoms rating scale (AMS) for LOH and the International Prostate Symptom Score (IPSS) for voiding symptoms, the Sexual Health Inventory for Men (SHIM) and Erection Hardness Score (EHS) for

sexual function, and the Beck Depression Inventory for depression. No patient was undergoing T replacement therapy when they visited our hospital or affiliated clinic, and thus, this did not affect the present study.

We used two thresholds, total T level of 3.0 ng/mL (almost equivalent to 10.5 nmol/L) and LH level of 9.4 mIU/mL according to a previous study,[11] and classified the patients into four groups as follows: NG (T $\geq$3.0 ng/mL and LH $\leq$9.4 mIU/mL), CHG (T $\geq$3.0 ng/mL and LH >9.4 mIU/mL), PHG (T <3.0 ng/mL and LH >9.4 mIU/mL), and SHG (T <3.0 ng/mL and LH $\leq$9.4 mIU/mL). First, we checked the ratio of patients with symptoms of LOH in each group. Second, we compared physical characteristics, laboratory and endocrinological data, and scores of several symptom questionnaires between the NG and CHG in men with a serum T concentration within normal limits. Third, we compared these same factors between the PHG and SHG in hypogonadal men Finally, both comparisons were reconfirmed after adjustment for age.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and written informed consent was obtained from all patients. The procedures were approved by the Regional Ethics Committee of Juntendo Urayasu Hospital, Urayasu, Japan (approval no. 2018-029) and D Clinic Tokyo for men.

Statistical analysis

The Mann-Whitney U test was used to compare several factors between the CHG and NG and between the PHG and SHG, and the Van Elteren test was used for comparison after adjustment for age. Statistical significance was set at $P < 0.05$. Statistical analyses were performed with SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics are shown in Table 1. Mean patient age and BMI were 52.6 years and 23.8 kg/m^2, respectively. The mean concentrations of all laboratory values were within normal limits, although the values in some patients exceeded the upper limit. The mean concentrations of the endocrinologic values were also within normal limits, although they varied widely. In particular, the mean concentration of total T was 5.1 ng/mL, but it ranged quite widely from 0.1 to 29.1 ng/mL. The questionnaires indicated the severity of several of the symptoms. Lower urinary tract symptoms were categorized as moderate by the mean IPSS score of 8.5. Depression was categorized as mild mood disturbance by the mean Beck Depression Inventory score of 13.3. Erectile function was categorized as moderate by the mean SHIM score of 11.1, and the penis was diagnosed as not hard enough for penetration based on a mean EHS of 2.4. The mean AMS score

of 42.6 indicated the presence of moderate symptoms consistent with a low T level.

The ratio of patients in the four groups based on the relationship between total T and LH is shown in Fig. 1. Interestingly, 808 of the 967 patients (83.6%) were classified into the NG, whereas only 33 patients (3.4%) were classified into the CHG. Furthermore, 118 of the 967 patients (12.2%) were classified into the SHG, whereas only 8 (0.8%) were classified into the PHG.

Data from the NG and CHG can be compared in Table 2. Patient age in the CHG (64.7 ± 9.0 years) was significantly higher than that in the NG (51.9 ± 8.4 years; P <0.001). Conversely, BMI in the NG (23.7 ± 3.1 kg/m^2) was higher than that in the CHG (22.7 ± 3.0 kg/m^2; P = 0.045). Although no significant differences were found in the biochemical profiles, several characteristics were identified in the endocrinological profiles by this comparison. FSH and LH were higher in the CHG than those in the NG (25.3 ± 14.3 vs 6.2 ± 3.8 mIU/mL; P <0.001 and 13.9 ± 6.0 vs 3.7 ± 1.7 mIU/mL; P <0.001, respectively). Interestingly, DHEA-S and IGF-1 levels in the CHG were much lower than those in the NG (120.8 ± 61.8 vs 211.6 ± 96.7 μg/dL; P <0.001 and 106 ± 28 vs 135.1 ± 36.7 ng/mL; P <0.001, respectively). In addition, a significant difference was found in estradiol and prolactin levels between the CHG and NG (28.9 ± 9.6 vs 25.0 ± 9.3 pg/mL; P = 0.015 and 10.4 ± 4.9 vs 10.2 ± 30.5 ng/mL; P = 0.005, respectively). In

terms of symptoms, the IPSS in the CHG (11.6 ± 8.4) was worse than that in NG (8.4 ± 6.6; P = 0.034). The EHS in CHG was lower than that in the NG (2.0 ± 1.3 vs 2.5 ± 1.0; P = 0.038), although no significant difference was found in the SHIM score. Furthermore, the mental and physical subscores of the AMS were lower in the CHG than those in the NG (8.9 ± 4.4 vs 11.3 ± 4.5; P <0.001 and 15.5 ±5.1 vs 17.4 ± 5.5; P = 0.042, respectively), whereas the sexual subscore of the AMS was higher in the CHG (14.9 ± 3.1) than that in the NG (13.5 ± 3.7; P = 0.032).

We performed an additional analysis to determine an independent factor for the difference between the NG and CHG after adjusting for age with the Van Elteren test because comparative findings seemed to be caused by the aging process. The comparative results between the NG and CHG after adjustment for age are shown in Table 3. Significant differences were still found for estradiol, prolactin, DHEA-S, and IGF-1 levels. In addition, cortisol in the CHG was also found to be lower than that in the NG. However, in terms of the questionnaires, a significant difference was found only in the mental subscore of the AMS.

Data from the PHG and SHG can be compared in Table 4. Patients in the PHG were older (64.4 ± 12.8 years) than those in the SHG (52.8 ± 7.8 years; P = 0.009). No significant differences were found in the biochemical profiles. In the endocrinological

profile, however, T in the PHG (1.4 ± 1.0 ng/mL) was lower than that in the SHG (2.3 ± 0.6 ng/mL; P = 0.011), and DHEA-S in the PHG (130.5 ± 50.8 μg/dL) was also lower than that in the SHG (219.7 ± 99.9 μg/dL; P = 0.007). In terms of symptoms, only the mental subscore of the AMS showed a statistically significant difference (12.8 ± 5.1 vs 9.0 ± 3.4, P = 0.038). The comparative results between the PHG and SHG after adjusting for age are shown in Table 5. Interestingly, a significant difference was still found in T and DHEA-S levels after this adjustment. In the AMS, although no significant difference was found for the mental subscore, a significant difference was found for the sexual subscore.

Discussion

We wanted to determine biochemical, endocrinological, and symptomatic differences between the groups with low and normal T concentration. The serum concentration of T has been reported to decrease in about 40% of men over 45 years old,[2,12] indicating that many older men must have hypogonadism, regardless of whether they complain of symptoms. Moreover, when focusing on patients with symptoms of LOH, most will be expected to have hypogonadism. However, we clearly showed that the serum T concentration in the majority of patients with symptoms of LOH (87%) was within

normal limits (83.6% of patients in the NG and 3.4% in the CHG). Although this tendency was consistent with the previous European study,[11] the rates in the NG and CHG were high and low, respectively, compared with those in the European study. These differences of distribution in the patient groups might be caused by the older age of the patients in the European study (59.7 years) than in our study (52.6 years). Furthermore, not all subjects in the European study complained of symptoms of LOH, whereas our subjects all complained of at least one symptom of LOH. This difference in patient background was also associated with the difference in the distribution of the patient groups. We also clearly showed that the rate of SHG (12.2%) was much higher than that of PHG (0.8%) among the patients with hypogonadism. This tendency was also consistent with the European study. These findings indicate that LOH is mainly caused by the decreased secretion of gonadotropin and not testicular dysfunction.

Although the European study showed several characteristics of each group, their findings were emphasized to be closely affected by the aging factor. Thus, we managed to analyze the characteristics after adjustment for age. After this adjustment, it is not surprising that both the FSH and LH levels were higher in the CHG than those in the NG with respect to the feedback mechanism of the pituitary gland and testis. Low serum T concentration causes a negative feedback mechanism, and GnRH secretion from the

hypothalamus is promoted. Increased GnRH then promotes the secretion of both LH and FSH from the pituitary gland.

Interestingly, it was apparent that serum concentrations of DHEA-S and IGF-1 were significantly lower in the CHG than those in the NG. DHEA-S is a representative indicator of adrenal androgen secretion. It peaks in the 20s and decreases to 20% in the 70s compared to the peak and decreases even more to 5% in the 85-90s.[2] Recently, adrenopause, which is caused by the decreased concentration of adrenal androgens such as DHEA-S, has gained increased attention as has LOH.[13] An epidemiological study reported that DHEA-S is relatively high in long-lived groups[14] because it has many physiological roles and is deeply involved in reproductive and sexual functions, depression, cognitive function, obesity, and arteriosclerosis associated with metabolism and reducing bone density.[12–18] IGF-1, which is produced primarily in the liver under the direct influence of growth hormone, is important not only in somatic growth but also in metabolism. It peaks at puberty and then decreases with age.[14] The decrease in IGF-1 contributes to decreases in bone density and muscle mass, and the accumulation of visceral fat, which can lead to diabetes and hyperlipidemia. These symptomatic changes have been termed somatopause, which has also been focused on from the viewpoints of sarcopenia and frailty.[19] It is speculated that lower concentrations of DHEA-S and IGF-

1 in the CHG might cause adrenopause and somatopause after some time, even though no severe symptomatic changes were observed in the CHG at middle age. Furthermore, the serum concentration of cortisol was lower and those of estradiol and prolactin were higher in the CHG than those in the NG. The secretion of cortisol is promoted by stress and is related to the mental subscore of the AMS being higher in the NG than CHG.[20] Depressed patients are known to have a high cortisol level, and the NG might have felt more stress in the present study.[21] It is possible that patients in the NG were in a very weak mental state because they complained of symptoms of LOH despite having a normal T level. Further, gonadotropin was elevated in the CHG to compensate for T. Gonadotropin may cause a decrease in cortisol due to feedback through the hypothalamus.[22] These endocrinological characteristics of the CHG may also induce symptomatic changes in the future, even though T secretion is compensated by high stimulation from LH.

Comparison between the PHG and SHG clearly showed that the declines of adrenal androgen (**i.e.,** DHEA-S) and testicular androgen (**i.e.,** T) were more severe in the PHG than those in the SHG after adjustment for age, although only 8 patients (0.8%) were classified into the PHG. PH is caused by damage to the quality and quantity of Leydig cells, which may be the end stage of the physiological spectrum of the hypothalamic-

pituitary-testicular axis function encountered in aging.[11,12,23] In terms of symptoms, the sexual subscore of the AMS was higher in the PHG than that in the SHG, although no significant difference was found in the SHIM score and EHS. It is well known that erectile function declines when the serum concentration of T is low.[24,25] Recently, a large-scale retrospective study showed that the severity of erectile dysfunction, loss of early morning erection, and a decrease in sexual desire were associated with a decreased level of serum T.[26] Another cross-sectional study showed that the first symptom experienced as the T level decreased was a decrease in sexual desire and vitality.[27] SHIM is a specific questionnaire for sexual intercourse, whereas EHS is specific only for erection. However, AMS contains questions about feeling (whether the responder has passed his peak) and sexual desire/libido. These differences may be associated with our findings. DHEA-S is speculated to be associated with sexual function.[28] Thus, we surmised that the physical and mental subscores of the AMS and the SHIM and EHS will worsen in patients with PH in the future, although presently, a significant difference was found only in the sexual subscore of the AMS.

There are some limitations of the present study. First, we performed blood testing for the biochemical and endocrinological profiles only once. Blood testing should be repeated, especially the endocrinological profile, because recent studies have shown that

T is secreted seasonally and diurnally.[1,29] Second, we did not take medications and smoking into account. Lower urinary tract symptoms (LUTS) might be one indication of LOH, and smoking is one important factor affecting hypogonadal status. Unfortunately, we could not check medications for LUTS and smoking because this is a retrospective study. Although it is possible that medications for LUTS and smoking could affect our results, we believe that our findings show the situation in a real-world clinical setting. Third, the PHG seemed to be too small (0.8%) for valid comparison. However, the statistical methodology remained reliable when the Van Elteren test was used for the comparison after adjustment for age.

In conclusion, this is the first study, to our knowledge, to compare the CHG with NG and the PHG with SHG among patients with symptoms of LOH. We clearly showed that most patients complaining of such symptoms were categorized into the NG. We also showed that the ratio of patients in the SHG was much higher than that in the PHG. Comparing between the CHG and NG, serum concentrations of DHEA-S and IGF-1 were significantly lower than those in the NG, even though the serum T level was compensated for. Androgens such as T and DHEA-S were significantly lower in the PHG versus SHG. Although a significant difference was found only in the sexual subscore of the AMS, we speculated that a lower androgen level may induce several

symptoms of LOH in the future. Tracking patients in each category may reveal useful information regarding the treatment for LOH.

Conflict of interest

None declared.

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Figure legend

Fig. 1 Distribution of subgroups of the 967 patients with symptoms of late-onset hypogonadism based on serum concentration of testosterone and luteinizing hormone (LH). The normal group (NG), compensated hypogonadism group (CHG), primary hypogonadism group (PHG), and secondary hypogonadism group (SHG) respectively accounted for 83.6%, 3.4%, 0.8%, and 12.2% of patients. Thresholds for the classification were 3.0 ng/mL for total testosterone and 9.4 mIU/mL for LH.

Table 1 Characteristics of the 967 patients

Number of cases	967	
Age (y)	52.6 ± 8.8	(40-86)
BMI (kg/m^2)	23.8 ± 3.2	(15.7-37.0)
Total cholesterol (mg/dL)	207.0 ± 35.3	(89-546)
HDL cholesterol (mg/dl)	60.5 ± 15.7	(23-144)
LDL cholesterol (mg/dL)	123.9 ± 30.8	(15-245)
Triglyceride (mg/dL)	134.7 ± 169.3	(22-3556)
FBS (mg/dL)	96.8 ± 23.3	(62-386)
HbA1c (%)	5.6 ± 0.7	(4.5-10.7)
LH (mIU/mL)	4.1 ± 3.0	(0.1-34.8)
FSH (mIU/mL)	7.1 ± 6.4	(0.1-56.5)
Testosterone (ng/mL)	5.1 ± 2.1	(0.1-29.1)
Estradiol (pg/mL)	24.2 ± 9.4	(10-76)
Prolactin (ng/mL)	11.2 ± 41.6	(0.2-950.8)
DHEA-S (μg/dL)	208.7 ± 97.5	(15-741)
IGF-1 (ng/mL)	134.6 ± 37.6	(41-393)
Cortisol (μg/dL)	9.6 ± 3.7	(0.8-27.7)
IPSS	8.5 ± 6.6	(0-33)
BDI	13.3 ± 7.9	(0-42)
SHIM	11.1 ± 6.4	(1-25)
EHS	2.4 ± 1.1	(0-4)
AMS		
Total	42.6 ± 11.4	(18-80)
Mental subscore	11.4 ± 4.6	(5-25)
Physical subscore	17.6 ± 5.5	(6-35)
Sexual subscore	13.7 ± 3.8	(5-25)

AMS, Aging Males Symptoms; BDI, Beck Depression Inventory; BMI, body mass index; DHEA-S, dehydroepiandrosterone sulfate; EHS, Erection Hardness Score; FBS, fasting blood sugar; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; IPSS, International Prostate Symptom Score; LDL, low-density lipoprotein; LH, luteinizing hormone; SHIM, Sexual Health Inventory for Men.

Table 2 Comparison of compensated normal group and normal group

	Compensated normal group (N = 33; 3.4%)	Normal group (N = 808; 83.6%)	P
Age (y)	64.7 ± 9.0	51.9 ± 8.4	<0.001
BMI (kg/m^2)	22.7 ± 3.0	23.7 ± 3.1	0.045
Total cholesterol (mg/dL)	196.1 ± 41.1	206.4 ± 31.7	0.298
HDL cholesterol (mg/dl)	59.5 ± 16.7	61.0 ± 15.7	0.614
LDL cholesterol (mg/dL)	113.9 ± 35.6	124.4 ± 2.2	0.193
Triglyceride (mg/dL)	120.2 ± 67.3	123.9 ± 105.3	0.713
FBS (mg/dL)	108.1 ± 49.5	96.0 ± 22.1	0.073
HbA1c (%)	5.7 ± 1.1	5.6 ± 0.7	0.456
LH (mIU/mL)	13.9 ± 6.0	3.7 ± 1.7	<0.001
FSH (mIU/mL)	25.3 ± 14.3	6.2 ± 3.8	<0.001
Testosterone (ng/mL)	5.9 ± 2.3	5.4 ± 1.9	0.385
Estradiol (pg/mL)	28.9 ± 9.6	25.0 ± 9.3	0.015
Prolactin (ng/mL)	10.4 ± 4.9	10.2 ± 30.5	0.005
DHEA-S (μg/dL)	120.8 ± 61.8	211.6 ± 96.7	<0.001
IGF-1 (ng/mL)	106.0 ± 28.0	135.1 ± 36.7	<0.001
Cortisol (μg/dL)	8.7 ± 3.1	9.6 ± 3.6	0.168
IPSS	11.6 ± 8.4	8.4 ± 6.6	0.034
BDI	10.6 ± 6.0	13.0 ± 7.7	0.113
SHIM	9.9 ± 6.8	11.4 ± 6.3	0.144
EHS	2.0 ± 1.3	2.5 ± 1.0	0.038
AMS			
Total	39.2 ± 9.6	42.2 ± 11.2	0.13
Mental subscore	8.9 ± 4.4	11.3 ± 4.5	<0.001
Physical subscore	15.5 ± 5.1	17.4 ± 5.5	0.042
Sexual subscore	14.9 ± 3.1	13.5 ± 3.7	0.032

AMS, Aging Males Symptoms; BDI, Beck Depression Inventory; BMI, body mass index; DHEA-S, dehydroepiandrosterone sulfate; EHS, Erection Hardness Score; FBS, fasting blood sugar; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; IPSS, International Prostate Symptom Score; LDL, low-density lipoprotein; LH, luteinizing hormone; SHIM, Sexual Health Inventory for Men.

Table 3 Comparison of compensated normal group and normal group adjusted for age

	Compensated normal group N = 33				Normal group N = 808				
Age category (y)	45-49	50-59	60-69	70-79	45-49	50-59	60-69	70-79	Van Elteren test
N	2 (6.0%)	8 (24.2%)	12 (36.4%)	11 (33.3%)	195 (24.1%)	286 (35.4%)	122 (15.1%)	28 (3.5%)	P
BMI (kg/m^2)	23.5 ± 4.9	22.3 ± 3.1	23.3 ± 3.7	22.4 ± 2.1	23.8 ± 3.2	23.9 ± 3.2	23.6 ± 2.9	23.0 ± 3.0	0.074
Total cholesterol (mg/dL)	164.5 ± 10.6	186.1 ± 49.7	200.5 ± 36.8	204.2 ± 42.4	207.9 ± 31.6	207.9 ± 31.8	202.4 ± 31.7	203.6 ± 34.0	0.336
HDL cholesterol (mg/dl)	56.5 ± 13.4	65.0 ± 18.1	63.3 ± 17.0	51.9 ± 15.0	59.9 ± 15.4	62.6 ± 15.9	61.9 ± 15.6	65.4 ± 19.2	0.485
LDL cholesterol (mg/dL)	84.0 ± 9.9	100.9 ± 43.1	117.3 ± 32.6	125.3 ± 33.3	126.9 ± 28.7	124.9 ± 29.5	120.0 ± 29.7	116.9 ± 31.5	0.497
Triglyceride (mg/dL)	176.0 ± 152.7	93.9 ± 55.4	97.2 ± 56.8	154.5 ± 58.0	130.7 ± 114.9	122.3 ± 113.2	112.6 ± 85.2	86.6 ± 39.1	0.403
FBS (mg/dL)	89.5 ± 14.8	90.5 ± 16.1	131.8 ± 75.8	98.4 ± 15.0	94.2 ± 27.8	95.2 ± 16.1	103.7 ± 26.6	109.8 ± 23.6	0.658
HbA1c (%)	5.2 ± 0.1	5.5 ± 0.5	6.3 ± 1.7	5.4 ± 0.3	5.5 ± 0.6	5.6 ± 0.6	5.8 ± 0.9	6.0 ± 1.1	0.259
LH (mIU/mL)	10.0 ± 0.2	14.8 ± 8.3	12.9 ± 4.9	15.1 ± 6.0	3.3 ± 1.5	3.7 ± 1.6	4.6 ± 1.9	5.0 ± 1.8	<0.001
FSH (mIU/mL)	15.0 ± 1.2	21.8 ± 13.2	26.2 ± 16.0	8.4 ± 2.8	9.1 ± 3.5	6.5 ± 3.5	8.6 ± 4.9	9.3 ± 3.6	<0.001
Testosterone (ng/mL)	8.7 ± 0.9	6.0 ± 3.4	5.8 ± 2.1	5.5 ± 1.8	5.5 ± 2.3	5.4 ± 1.9	5.5 ± 1.9	5.7 ± 1.7	0.576
Estradiol (pg/mL)	40.5 ± 12.0	23.4 ± 9.8	30.9 ± 8.6	28.7 ± 8.7	25.3 ± 8.6	24.4 ± 9.8	25.4 ± 9.2	26.3 ± 9.3	0.046
Prolactin (ng/mL)	5.4 ± 2.6	12.1 ± 6.4	10.3 ± 3.8	10.0 ± 4.8	10.1 ± 10.5	8.0 ± 6.4	9.9 ± 11.9	8.7 ± 4.2	0.015
DHEA-S (µg/dL)	83.0 ± 39.6	105.8 ± 49.5	167.5 ± 67.1	87.5 ± 33.3	238.4 ± 99.9	199.5 ± 85.3	162.9 ± 84.1	138.9 ± 54.8	0.001
IGF-1 (ng/mL)	99.5 ± 4.9	110.1 ± 33.5	109.3 ± 30.7	100.6 ± 24.9	138.5 ± 29.9	134.3 ± 35.2	120.9 ± 41.6	111.3 ± 39.0	0.029
Cortisol (µg/dL)	6.7 ± 2.4	8.7 ± 3.8	9.3 ± 3.0	8.4 ± 2.8	9.1 ± 3.5	9.6 ± 3.3	10.3 ± 3.9	10.8 ± 2.7	0.017
IPSS	4.0 ± 2.8	13.0 ± 6.8	9.1 ± 5.4	14.7 ± 11.3	7.5 ± 6.5	8.8 ± 6.4	11.0 ±7.1	11.6 ± 8.3	0.494
BDI	13.5 ±4.9	12.8 ± 5.5	9.5 ± 6.4	9.7 ± 6.2	14.0 ± 7.9	13.0 ± 7.3	10.3 ± 7.6	8.6 ± 6.6	0.838
SHIM	14.5 ± 9.2	9.3 ± 5.1	10.3 ± 7.5	9.0 ± 7.3	11.8 ± 6.5	11.6 ± 6.0	9.8 ± 5.9	8.1 ± 5.5	0.778
EHS	3.5 ± 0.7	2.0 ± 0.8	2.2 ± 1.3	1.5 ± 1.5	2.5 ± 0.9	2.5 ± 1.0	2.1 ± 1.1	1.8 ± 1.3	0.59
AMS									
Total	42.0 ± 14.1	42.8 ± 11.0	34.9 ± 6.7	40.9 ± 10.3	42.6 ± 11.7	42.5 ± 11.0	40.0 ± 11.3	36.8 ± 9.5	0.832
Mental subscore	6.5 ± 2.1	11.8 ± 5.7	7.8 ± 3.1	8.4 ± 4.2	11.8 ± 4.5	11.4 ± 4.4	10.1 ± 4.4	8.6 ± 3.4	0.049
Physical subscore	18.5 ± 9.2	16.8 ± 4.9	12.8 ± 3.4	16.9 ± 5.5	17.6 ± 5.7	17.9 ± 5.4	15.7 ± 4.9	14.4 ± 5.2	0.4
Sexual subscore	17.0 ± 2.8	14.3 ± 1.8	14.3 ± 2.6	15.6 ± 4.3	13.3 ± 3.7	13.3 ± 3.6	14.1 ± 3.8	13.8 ± 3.7	0.112

AMS, Aging Males Symptoms; BDI, Beck Depression Inventory; BMI, body mass index; DHEA-S, dehydroepiandrosterone sulfate; EHS, Erection Hardness Score; FBS, fasting blood sugar; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; IPSS, International Prostate Symptom Score; LDL, low-density lipoprotein; LH, luteinizing hormone; SHIM, Sexual Health Inventory for Men.

Table 4 Comparison of primary hypogonadism and secondary hypogonadism

	Primary hypogonadism (N = 8; 0.8%)	Secondary hypogonadism (N = 118; 12.2%)	P
Age (y)	64.4 ± 12.8	52.8 ± 7.8	0.009
BMI (kg/m^2)	24.9 ± 3.8	25.1 ± 3.7	0.84
Total cholesterol (mg/dL)	198.8 ± 44.2	215.2 ± 52.8	0.357
HDL cholesterol (mg/dl)	54.4 ± 10.8	56.9 ± 14.9	0.773
LDL cholesterol (mg/dL)	126.0 ± 38.0	123.4 ± 36.9	0.87
Triglyceride (mg/dL)	117.8 ± 41.9	221.2 ± 402.7	0.354
FBS (mg/dL)	105.4 ± 18.2	98.3 ± 19.3	0.165
HbA1c (%)	6.0 ± 0.8	5.7 ± 0.6	0.283
LH (mIU/mL)	16.8 ± 5.5	2.5 ± 1.4	<0.001
FSH (mIU/mL)	35.8 ± 10.2	5.9 ± 3.7	<0.001
Testosterone (ng/mL)	1.4 ± 1.0	2.3 ± 0.6	0.011
Estradiol (pg/mL)	13.1 ± 4.2	17.5 ± 7.0	0.066
Prolactin (ng/mL)	7.4 ± 3.2	19.9 ± 91.3	0.671
DHEA-S (μg/dL)	130.5 ± 50.8	219.7 ± 99.9	0.007
IGF-1 (ng/mL)	123.0 ± 37.4	140.0 ± 43.0	0.22
Cortisol (μg/dL)	9.3 ± 2.8	9.7 ± 4.1	0.935
IPSS	8.6 ± 5.6	8.5 ± 5.9	0.94
BDI	11.4 ± 5.8	16.1 ± 9.7	0.267
SHIM	6.9 ± 5.4	9.9 ± 6.6	0.223
EHS	1.9 ± 1.1	2.3 ± 1.1	0.287
AMS			
Total	42.9 ± 7.3	46.9 ± 12.8	0.409
Mental subscore	9.0 ± 3.4	12.8 ± 5.1	0.038
Physical subscore	17.8 ± 3.1	19.3 ± 5.6	0.313
Sexual subscore	16.1 ± 4.6	14.9 ± 4.3	0.504

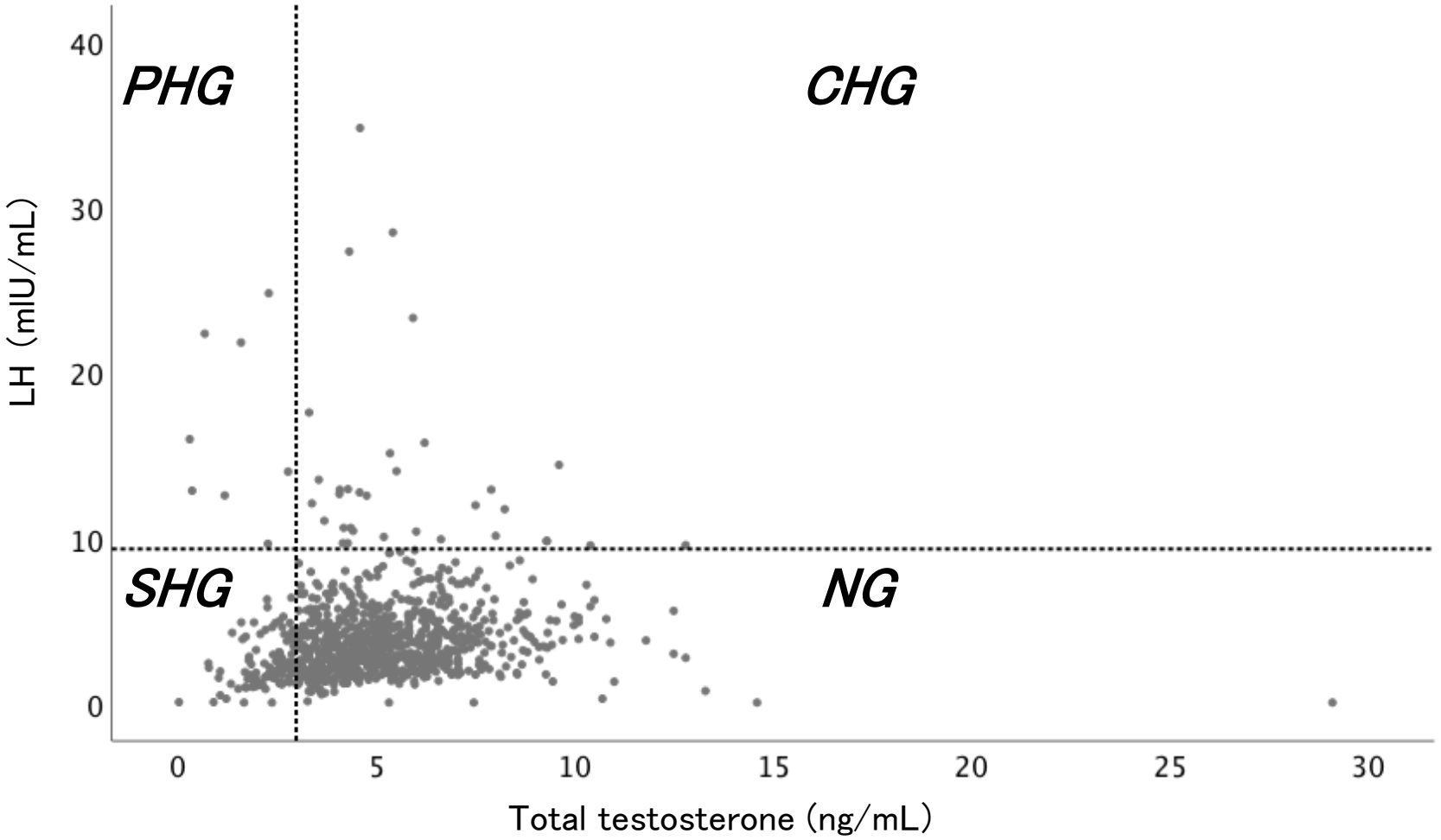
AMS, Aging Males Symptoms; BDI, Beck Depression Inventory; BMI, body mass index; DHEA-S, dehydroepiandrosterone sulfate; EHS, Erection Hardness Score; FBS, fasting blood sugar; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; IPSS, International Prostate Symptom Score; LDL, low-density lipoprotein; LH, luteinizing hormone; SHIM, Sexual Health Inventory for Men.

Table 5 Comparison of primary hypogonadism and secondary hypogonadism adjusted for age

	Primary hypogonadism N = 8				Secondary hypogonadism N = 118				
Age category (y)	45-49	60-64	65-69	70-74	45-49	60-64	65-69	70-74	Van Elteren test
N	2 (25%)	1 (12.5%)	3 (37.5%)	1 (12.5%)	27 (22.9%)	15 (12.7%)	7 (5.9%)	4 (3.4%)	P
BMI (kg/m^2)	26.0 ± 2.6	19.8	27.1 ± 4.6	23.6	25.2 ± 4.3	25.2 ± 4.0	26.6 ± 4.7	22.4 ± 3.4	0.847
Total cholesterol (mg/dL)	219.0 ± 3.9	168	197.7 ± 73.2	192	207.6 ± 42.7	234.3 ± 59.0	208.6 ± 30.7	194.3 ± 39.7	0.753
HDL cholesterol (mg/dl)	61.5 ± 4.9	49	55.3 ± 15.9	42	60 ± 15.2	54.5 ± 17.7	59.6 ± 18.7	56.3 ± 12.0	0.725
LDL cholesterol (mg/dL)	151 ± 33.9	104	127.3 ± 56.8	99	126.7 ± 41.9	121.8 ± 36.8	128.9 ± 40.7	118.3 ± 31.3	0.957
Triglyceride (mg/dL)	101.0 ± 18.4	69	114.7 ± 41.3	190	138.7 ± 87.6	348.3 ± 579.2	116.7 ± 47.9	94.3 ± 15.5	0.88
FBS (mg/dL)	94.5 ± 2.1	85	113.3 ± 13.8	136	93.3 ± 10.2	101.5 ± 13.4	108.3 ± 25.0	99.7 ± 3.2	0.453
HbA1c (%)	5.4 ± 0.5	5.7	6.5 ± 0.8	6.5	5.5 ± 0.4	6.0 ± 0.6	6.0 ± 0.8	5.7 ± 0.1	0.284
LH (mIU/mL)	18.9 ± 4.1	12.9	14.9 ± 6.6	24.8	2.5 ± 1.6	2.4 ± 1.4	3.1 ± 1.7	2.4 ± 0.8	<0.001
FSH (mIU/mL)	46.4 ± 12.7	30.3	28.3 ± 4.9	45.3	6.1 ± 4.5	5.1 ± 2.8	7.8 ± 2.7	7.8 ± 1.5	<0.001
Testosterone (ng/mL)	0.9 ± 0.9	0.4	1.4 ± 0.8	2.3	2.2 ± 0.6	2.2 ± 0.6	2.3 ± 0.5	2.5 ± 0.3	0.003
Estradiol (pg/mL)	11.5 ± 2.1	10	14 ± 4.6	20	16.2 ± 6.2	17.8 ± 7.8	16.9 ± 8.0	17.7 ± 3.5	0.214
Prolactin (ng/mL)	11.9 ± 3.0	6	5.9 ± 2.1	5.5	45.9 ± 184.7	8.5 ± 4.7	11.1 ± 9.1	11.5 ± 10.8	0.766
DHEA-S (µg/dL)	158.5 ± 84.1	93	106.3 ± 46.4	173	238.0 ± 90.1	190.6 ± 77.3	185.4 ± 69.1	209.7 ± 112.3	0.014
IGF-1 (ng/mL)	154.0 ± 24.0	119	133.3 ± 37.8	86	127.6 ± 38.8	137 ± 32.3	117.6 ± 28.8	129 ± 5.2	0.871
Cortisol (µg/dL)	7.8 ± 5.0	6.8	10.3 ± 1.6	8.4	10.4 ± 4.7	10.2 ± 3.3	10.7 ± 6.6	11.3 ± 1.2	0.151
IPSS	7.0 ± 0	-	11.0 ± 8.5	4	8.7 ± 5.5	6.9 ± 5.6	8.3 ± 4.8	14.8 ± 8.2	0.548
BDI	8.5 ± 0.7	10	16.5 ± 0.7	18	16.7 ± 10.0	13.2 ± 6.9	13.1 ± 12.0	13.3 ± 8.8	0.987
SHIM	5.5 ± 0.7	11	2.3 ± 2.3	9	12.3 ± 7.1	8.7 ± 5.2	7.9 ± 4.0	2.3 ± 2.5	0.26
EHS	2.5 ± 0.7	3	1.3 ± 1.5	1	2.8 ± 1.0	2.1 ± 1.2	1.4 ± 0.8	0.8 ± 1.0	0.912
AMS									
Total	43.5 ± 4.9	34	45.7 ± 5.7	52	48.2 ± 12.7	41.3 ± 10.8	44.7 ± 9.4	45.3 ± 12.6	0.778
Mental subscore	7.0 ± 2.8	6	11.0 ± 1.0	14	13.6 ± 4.3	10.6 ± 4.0	10.4 ± 4.9	13.5 ± 5.4	0.299
Physical subscore	19.5 ± 6.4	19	16.7 ± 2.5	18	20.4 ± 5.2	18.1 ± 6.4	18.1 ± 3.6	17.3 ± 5.3	0.797
Sexual subscore	17.0 ± 4.2	9	18.0 ± 4.4	20	14.1 ± 5.3	14.3 ± 2.7	15.3 ± 2.3	14.5 ± 7.1	0.003

AMS, Aging Males Symptoms; BDI, Beck Depression Inventory; BMI, body mass index; DHEA-S, dehydroepiandrosterone sulfate; EHS, Erection Hardness Score; FBS, fasting blood sugar; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; IPSS, International Prostate Symptom Score; LDL, low-density lipoprotein; LH, luteinizing hormone; SHIM, Sexual Health Inventory for Men.

Fig. 1


PHG
CHG
SHG
NG
LH (mIU/mL)
40
30
20
10
0
0
5
10
15
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25
30
Total testosterone (ng/mL)