Original article:

Clinical relevance of low androgen to gastroesophageal reflux symptoms

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Running title: Testosterone level and FSSG score

Key words*:* Free testosterone, Frequency scale for the symptoms of gastroesophageal reflux disease (FSSG), Gastroesophageal reflux disease (GERD), and Late onset hypogonadism (LOH).

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Abstract

The aim of this study was to determine the relationships between free testosterone (FT) level and parameters including laboratory data and data from questionnaires and to determine symptoms leading to the detection of late onset hypogonadism (LOH). We retrospectively reviewed medical records of patients in whom serum FT was measured in our hospital. Aging Male Symptoms (AMS) score, self-rating depression scale (SDS) and frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) score were used for questionnaires. A total of 205 patients were included in the analysis (55.2 ± 15.6 years of age, mean ± SD). Among them, 119 patients (58.0%) had an FT level of less than 8.5 pg/mL, which fulfills the diagnostic criterion of LOH syndrome according to the clinical practice manual for LOH in Japan. It was revealed that FSSG score was inversely correlated to serum FT levels (R=-0.3395, p<0.001), although SDS and AMS scales did not show significant correlations to FT levels. Our study revealed a high prevalence of LOH syndrome among patients in whom the majority complained of general symptoms. Although GERD symptoms are generally not considered to be typical symptoms of LOH, our study indicates that those symptoms might be clues for the detection of LOH.

Introduction

Late onset hypogonadism (LOH) is a clinical and biochemical state with advancing age that is characterized by particular symptoms and a low level of serum testosterone [1, 2]. LOH syndrome is a condition that can affect the functions of multiple organ systems, and widely recognized clinical signs of LOH syndrome are erectile dysfunction, decrease in muscle strength, obesity, osteoporosis, anemia, depression and deterioration of insulin resistance [3-5]. In Japan, a clinical practice manual for LOH was published by the Japanese Urological Association and the Japanese Society for the Study of Aging Males [6].

In the European guidelines, the algorithm for diagnosis of LOH syndrome is based on total testosterone (TT) level [1]. However, several studies showed that there was no age-dependent decrease of TT level in Japanese men, and it was found in other studies that free testosterone (FT) level shows a linear decrease with aging in the Japanese population. [7, 8]. Therefore, the clinical practice manual for LOH recommends the use of FT levels for the diagnosis of LOH in Japan [6].

Although measurement of FT is important for early detection and diagnosis of LOH syndrome, studies on the relationships between FT level and other parameters

including laboratory data and questionnaires associated with LOH syndrome have been limited. Moreover, clinicians should know what symptoms will lead to the detection of low FT level and the diagnosis of LOH syndrome. The aim of the present study was to determine those relationships by investigating the symptoms and other parameters in patients in whom serum FT level was measured.

Patients and Methods

Study subjects

We retrospectively reviewed medical records of 273 patients in whom serum FT level was measured between January 2014 and December 2017 in Okayama University Hospital. The following patients were excluded from this study: female patients, patients younger than 20 years, patients with primary or secondary hypopituitarism, and those who were receiving androgen replacement therapy (ART). Patient selection is shown in **Fig. 1**. During the study period, serum FT was measured in 273 patients; 205 patients were found to be eligible and were included in the analysis. Serum FT was measured once in 154 patients and multiple times in 51 patients during the study period. When FT was measured multiple times in one patient in the study

period, the first measurement during the study period was used for analysis. This study was approved by the Ethical Committee of Okayama University Hospital and adhered to the Declaration of Helsinki (No. 1703-026).

Study protocol

Crucial symptoms that were triggers for measurement of serum FT concentrations were reviewed and evaluated, and the major one to three symptoms from each patient were used for analysis. The symptoms were categorized into six groups: general symptoms, psychological symptoms, urological symptoms, musculoskeletal symptoms, gastrointestinal symptoms and others. We also compared FT values in each group. In addition, according to the FT values, patients were categorized into three groups based on cut-off values of 8.5 and 11.8 pg/mL. These cut-off values were determined in a previous study in which the mean value of FT in Japanese young adults in their 20s was calculated and in which it was shown that the standard value for diagnosis of LOH is FT of less than 8.5 pg/mL, and that for diagnosis of LOH borderline is FT of less than 11.8 pg/mL [7]. In our study, the FT<8.5 pg/mL group, 8.5≤FT<11.8 pg/mL group, and 11.8≤FT pg/mL group were defined as the LOH group, Borderline group, and Non-LOH group, respectively.

107

108 ***Analysis of biochemical and radiological markers***

109 Data were obtained from hospital medical records. Body mass index (BMI),
110 blood biochemical data including HbA1c, low-density lipoprotein cholesterol (LDL-C),
111 high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), c-reactive protein
112 (CRP), total testosterone (TT), and dehydroepiandrosterone sulfate (DHEA-S), and
113 radiological data including dual energy X-ray absorptiometry % young adult mean
114 (DEXA %YAM) in the femoral bone and lumbar spine were evaluated. Biochemical
115 data obtained within 2 weeks from the day when FT was measured were used.

116 Aging Male Symptoms (AMS) score was evaluated when LOH syndrome was
117 suspected. In addition, patients who visited the outpatient department of general
118 internal medicine (GIM) in our hospital were routinely asked to complete some
119 questionnaires including questionnaires on self-rating depression scale (SDS) and
120 frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) score, and
121 those data were also evaluated. FSSG score is commonly used to assess symptoms of
122 GERD [9]. The FSSG questionnaire is a questionnaire comprising 12 questions
123 including 7 questions for assessing acid reflux symptoms and 5 questions for assessing
124 dysmotility-related symptoms, and an FSSG score ≥8 is considered to indicate probable

GERD [9, 10]. FT values were measured by a radioimmunoassay using a commercially available kit (Beckman Coulter, Brea, CA, USA).

Statistical analysis

The data were subjected to ANOVA and linear regression analysis to determine differences. If differences were detected by ANOVA, Tukey-Kramer's post-hoc test was used to determine which means differed. p-values<0.05 were considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, ver. 3.1.1) [11].

Results

Patients' characteristics and serum free testosterone (FT) levels

The primary departments and patients' ages are summarized in **Table 1**. The mean ages of patients were 55.2 ± 15.6 (range: 20-89) years in all cases and 59.2 ± 15.7 (range: 22-89) years in LOH cases. FT was most frequently measured in the GIM department (61.5% of all cases, 61.3% of LOH cases), followed by the urology

143 department (23.4% of all cases, 24.4% of LOH cases). **Table 2** shows the main
144 symptoms of patients when FT was measured in all cases and in LOH cases. Among
145 all patients, frequent symptoms when FT was measured were general fatigue (22.0%),
146 dizziness (9.4%), erectile dysfunction (8.4%), weight loss (7.3%), hot flashes (6.3%)
147 and headache (6.3%). In LOH patients, frequent symptoms were general fatigue
148 (22.1%), weight loss (9.8%), dizziness (9.8%), erectile dysfunction (9.2%), hot flashes
149 (6.7%) and depression (6.1%).

150 When FT was categorized into three groups based on cut-off values of 8.5 and
151 11.8 pg/mL, the LOH group (FT<8.5 pg/mL) had 119 patients (58.0%), the Borderline
152 group (8.5≤FT<11.8 pg/mL) had 53 patients (25.9%), and the Non-LOH group
153 (11.8≤FT pg/mL) had 33 patients (16.1%; **Fig. 2A**). The numbers of patients less than
154 50 years of age were 37 (31.0%) in the LOH group, 22 (41.5%) in the Borderline group,
155 and 24 patients (72.7%) in the Non-LOH group. Correlation between FT and age is
156 shown in **Fig. 2B**. Linear regression analysis showed that FT decreased with advance
157 of age (R=-0.4191, p<0.001). **Fig. 3** shows a comparison of the main symptoms of
158 patients who visited the GIM department and other departments. Among the patients
159 who visited GIM, frequent symptoms were general symptoms (52%), psychological
160 symptoms (28%), and gastrointestinal symptoms (8%). Frequent symptoms of patients

161 who visited other departments were general symptoms (34%), urological symptoms
162 (32%), and psychological symptoms (17%).
163
164 ***Correlations between serum FT levels and other clinical factors***
165 **Fig. 4** shows the correlations between FT and each categorized group in all
166 cases and in LOH cases. The differences in FT between categorized groups were not
167 statistically significant. The correlation coefficients between FT and parameters are
168 shown in **Table 3**. Total testosterone levels were significantly correlated with FT
169 levels (R=0.5588, p<0.001). The correlations of FT with SDS, AMS scale and FSSG
170 score and the correlation of TT with FSSG score are shown in **Fig. 5**. Although SDS
171 and AMS scale did not show significant correlations with FT levels (SDS: R=0.0717,
172 p=0.4527; AMS scale: R=0.1966, p=0.4061), FSSG score was inversely correlated with
173 FT levels (R=-0.3395, p<0.001). In addition, FSSG score tended to be high in patients
174 with low TT levels; however, it was not statistically significant (R=-0.4312, p=0.0653).
175 FSSG scores were higher in patients with low FT levels, and the average FSSG scores
176 in the LOH group, Borderline group and Non-LOH group were 10.69±8.32, 6.00±5.62
177 and 4.79±4.84, respectively (**Fig. 5E**). The LOH group had a statistically higher FSSG
178 score than those in the Borderline group (p=0.03) and Non-LOH group (p<0.01).

Discussion

In our study, among the patients who were suspected of having LOH syndrome and in whom FT level was measured, 119 patients (58.0%) had an FT level of less than 8.5 pg/mL, which fulfills the diagnostic criterion of LOH syndrome according to the clinical practice manual for LOH in Japan [6]. Among those patients, 37 patients (31.0%) were less than 50 years of age. Considering that the common symptoms of our patients were systemic symptoms such as fatigue and weight loss, these findings suggest a high prevalence of LOH syndrome in middle-age males who visit hospital with general complaints. We analyzed the associations between FT levels and categories of symptoms but did not find any significant association. This finding may imply that a deficiency of testosterone can widely affect the functions of multiple organs including psychological and physical systems [1].

SDS and AMS scale are frequently used to assess the severity of depression and LOH syndrome, respectively [7, 12, 13]. Since typical symptoms of LOH include depression, they are believed to be helpful for LOH screening [5, 6, 14]. However, in our study, no significant association between FT and SDS or AMS scale was found.

Since our results together with results of previous studies suggest that SDS or AMS scale has a poor degree of specificity, these scales alone are not ideal tools for screening latent conditions of testosterone deficiency [15-17].

In the present study, it was of note that FSSG score showed a linear decrease with FT level. To the best of our knowledge, the present study is the first study showing a negative correlation between androgen level and GERD symptoms. Although the direct effect of androgen on GERD is still unknown, several studies have been performed to determine the relationships between sex hormone and gastroesophageal diseases. Men develop esophageal adenocarcinoma more frequently than do women [18]. Barretts esophagus is a known precursor to the development of esophageal adenocarcinoma, and a positive association between FT level and Barrett's esophagus has been shown [19, 20]. In women, hormone replacement therapy and pregnancy are associated with GERD symptoms, suggesting that estrogen plays a role in precipitating GERD; however, a direct relationship between female sex hormone levels and GERD has not been shown [21].

Although the etiology of the negative association between FT level and GERD symptoms is unclear, there are several possible explanations. First, psychological stress might be related to both LOH and exacerbation of GERD symptoms.

Psychosocial stress and work-related stress are thought to decrease testosterone levels in males [22, 23]. In addition, some studies have suggested that psychosocial stress has a significant relationship with GERD, exacerbating heartburn symptoms by enhancing perceptual response to acid exposure in the esophagus [24, 25]. Furthermore, GERD itself is also associated with depression and anxiety due to poor sleep quality, which in turn may lead to a decrease of androgen levels [26].

Secondly, obesity is related to both conditions of LOH syndrome and GERD. An association between LOH and obesity was previously reported [27, 28]. Obesity is also a risk factor for GERD because surrounding adipose tissue compresses the stomach, leading to an increase in intragastric pressure and subsequent relaxation of the lower esophageal sphincter [29]. Although no significant association between FT and BMI was found in our study, this may explain a direct interrelationship between FT level and FSSG scores. Finally, the potential mechanism of our hypothesis is related to inflammation. Testosterone is thought to play an anti-inflammatory role [30]. Given that the pathogenesis of GERD may be cytokine-mediated inflammation rather than the result of chemical injury [31], these findings suggest that lowered endogenous testosterone in LOH syndrome might be associated with delayed wound healing of the esophagus due to the lack of an anti-inflammatory effect, inducing GERD symptoms.

There were some limitations of the present study. Firstly, the sample size was relatively small. Secondly, the reason for measuring FT level in each patient could not be fully revealed. Thirdly, not all FT levels were measured early in the morning. The situation and exact time when blood samples were drawn were not completely determined. Finally, this was a retrospective study, being conducted in a single, tertiary care center; thus, the results obtained in this study may not be directly interpreted for general hospitals or primary care clinics.

In conclusion, our study revealed a prevalence of LOH syndrome among patients in whom the majority complained of general symptoms. We also found that a high FSSG score was associated with low FT level. Although GERD symptoms are generally not considered to be typical symptoms of LOH, our study indicates that those symptoms might be clues for the detection of LOH syndrome. Further study is needed to reveal the relationship between LOH syndrome and GERD.

Acknowledgements

We are sincerely grateful to all of the clinical staff in the Department of General Medicine who contributed to the present work.

Disclosure

The authors declare no conflicts of interest in association with the present study.

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Figure Legends:

Fig. 1. Patients' characteristics. Among 273 patients in whom serum free testosterone (FT) was measured, 205 were found to be eligible and were included in the analysis. FT was measured once in 154 patients and multiple times in 51 patients.

Fig. 2. Population of patients with LOH. The late onset hypogonadism (LOH) group (FT<8.5 pg/mL) had 119 patients (58.0%), the Borderline group (8.5≤FT<11.8

359 pg/mL) had 53 patients (25.9%), and the Non-LOH group (11.8≤FT pg/mL) had 33
360 patients (16.1%; **A**). Linear regression analysis showed that FT decreased with
361 advance of age (R=-0.4191, p<0.001; **B**).
362
363 **Fig. 3. Frequency of symptoms related to LOH.** The main symptoms when FT was
364 measured are shown. Among the patients who visited the GIM department (**A**),
365 general symptoms and psychological symptoms were frequent, while the frequencies of
366 general symptoms and urological symptoms were almost the same in patients who
367 visited other departments (**B**).
368
369 **Fig. 4. Distribution of serum FT levels and disease background.** The relationships
370 between FT levels and categorized main symptoms are shown in all cases (n=205
371 patients, 287 symptoms; **A**) and LOH cases (n=119 patients, 163 symptoms; **B**). The
372 differences in FT between categorized groups were not statistically significant by
373 ANOVA. Explanation of the box plot: upper horizontal line of the box, 75th percentile;
374 lower horizontal line of the box, 25th percentile; horizontal bar within the box, median;
375 upper horizontal bar outside the box, 90th percentile; and lower horizontal bar outside
376 the box, 10th percentile.

Fig. 5. Correlations between serum testosterone levels and scorings of SDS, AMS and FSSG. The correlations between serum FT levels and scores for SDS (**A**), AMS (**B**) and FSSG (**C**) and correlation of TT levels with FSSG score (**D**) are shown. FSSG scores showed a significant inverse correlation with FT levels (R=-0.3395, p<0.001; **C**). The averages of FSSG scores in the LOH group, Borderline group and Non-LOH group are shown (**E**). The LOH group had statistically higher FSSG scores than those in the Borderline and Non-LOH groups by ANOVA. Explanation of the box plot is the same as that in the legend of **Fig. 4**. **p<0.01 and *p<0.05 between the indicated groups.