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*Original Article*

# Clinical Characteristics of Low Androgen Status in Males with Type 2 Diabetes Mellitus

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**To determine the clinical characteristics of low androgen status in adult males with diabetes, we retrospectively analyzed the medical records of patients with type 2 diabetes mellitus in whom serum free testosterone (FT) levels were examined for 1 year. Among the 46 patients (56 ± 1.5 years old), decreases in serum FT levels to < 8.5 pg/ml (indicating the occurrence of late-onset hypogonadism [LOH]) were detected in 18 (39%). The percentages of patients with low FT levels were high in the ≥ 50 years age group (83%), the HbA1c < 7% group (67%), and the 25 ≤ BMI < 30 kg/m$^2$ group (56%). The serum FT levels tended to decrease age-dependently. The level of HbA1c was significantly correlated with the Heinemann Aging Male Symptoms (AMS) score ($R = 0.47$). The low-FT group had decreased levels of hemoglobin. Of note, the serum FSH level ($R = -0.32$) was negatively correlated with the serum FT level, whereas the serum TSH level ($R = 0.36$) was positively correlated with the serum FT level. Collectively, these results revealed that many diabetic males may have low FT levels and that the AMS score is related to the HbA1c level. A slightly anemic condition, thyroid dysfunction, and obesity (class 1) might be involved in LOH in middle-aged diabetic males.**

**Key words:** androgen, diabetes mellitus, late-onset hypogonadism, testosterone, thyroid function

Population-based surveys have shown that male testosterone levels decline progressively with age [1]. Testosterone levels generally decrease by 0.4-2% per year in middle-aged and older males, and the underlying mechanisms of this phenomenon remain to be elucidated. Late-onset hypogonadism (LOH) indicates a clinical as well as biochemical condition with advancing age. The condition of LOH is characterized by symptoms such as general fatigue and obesity in addition to lowered levels of serum testosterone [2, 3]. LOH is a disorder that affects various functions of multiple organs, and characteristic clinical signs for LOH are erectile dysfunction (ED), loss of muscle strength, obesity, osteoporosis, anemia, depression, and deterioration of insulin resistance [4-6].

An increased occurrence of type 2 diabetes mellitus (T2DM) has been shown to be, in part, associated with obesity and aging in males [7]. Of interest, testosterone deficiency appears to be quite frequent in males with T2DM, with a prevalence of about one-third of a male cohort [7]. However, the pathogenic mechanisms underlying obesity and diabetes-related hypogonadism remain unclear.

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In the European guidelines, the process for the diagnosis of LOH is based on total testosterone levels [2]. However, in a study in Japanese males, there was no age-dependent decrease in total testosterone levels, while another study in the Japanese general population found that the serum free testosterone (FT) level decreased linearly with aging [8,9]. Therefore, in Japan, the examination of serum FT levels rather than the total testosterone levels has been recommended for the diagnosis of LOH in clinical settings [10]. Although the measurement of patients' serum FT concentrations is important for the early detection and diagnosis of LOH status, there have been few investigations of the relationships between serum FT levels and conditions of diabetes mellitus.

We conducted the present study to clarify the clinical and laboratory characteristics of low androgen status in men with diabetes. We retrospectively investigated the relevance of serum FT levels and the typical clinical features of T2DM patients who visited Okayama City Hospital with various symptoms. It is of interest that we observed significant correlations between these subjects' serum FT levels and laboratory and endocrine markers. Our findings may expand the utility of serum FT measurement in men with diabetes.

## Patients and Methods

***Patients.*** We retrospectively analyzed the epidemiologic records of 46 male patients with T2DM in whom serum FT levels were measured during the period from June 1, 2017 to May 31, 2018 at Okayama City Hospital. Laboratory data obtained from the 46 patients were analyzed. We also analyzed the data of the 28 of the 46 patients who had sufficient records of questionnaires regarding Self-Rating Depression Scale (SDS) scores, a frequency scale for symptoms of gastroesophageal reflux disease (FSSG) scores, and the Heinemann Aging Male Symptoms (AMS) scores to evaluate the relationships between the laboratory findings and the results of these questionnaires.

The SDS questionnaire has 20 items that include 10 positively worded and 10 negatively worded questions [11]. The SDS has been recognized as a representative scale for clarifying the respondent's status of depression, with a score of $\geq 60$ indicating a depressive condition [12,13]. The FSSG score is commonly used to assess symptoms of gastroesophageal reflux disease (GERD) [14,15]. The FSSG questionnaire has 12 questions, with 7 assessing acid reflux symptoms and 5 assessing dysmotility-related symptoms; an FSSG score $\geq 8$ is considered to indicate probable GERD [13-16]. The AMS score is designed as a self-administered scale to assess LOH [17]. In the scoring of the AMS, there are 17 items containing 3 domains for a psychological score, somatic score, and sexual score, and an AMS score $\geq 27$ indicates probable LOH [18].

***Study protocol.*** Decisions for examining the patients' serum FT concentrations were made by the individual physicians for clinical purposes when patients complained of various uncertain symptoms such as fatigue, malaise, and depressive mood suggesting LOH. Data for other biochemical parameters were obtained at the same time as the measurement of FT levels. Blood tests were performed in cases with adequate insurance coverage. The information about enrollment in this retrospective study was disclosed on our hospital's website and by poster notice at our hospital with an opportunity for a denial of participation, and we provided a contact point for participants' opt-out. The protocol of this study was approved by the Ethical Committees of Okayama University Hospital (KEN-2002-021) and Okayama City Hospital (No.1-247) and adhered to the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects.

***Analysis of clinical and laboratory parameters.*** We evaluated the recorded information of the patients' characteristics including age, body mass index (BMI), SDS, FSSG, and AMS results. The blood biochemical data included the following parameters: hemoglobin (Hb) for blood cell counts; aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), creatinine (CRE), and blood urea nitrogen (BUN) for liver and renal functions, and hemoglobin A1c (HbA1c), total cholesterol (TC), uric acid (UA), and postprandial plasma glucose (PPG). The levels of the above-mentioned factors were determined using an auto-analyzer system at the Central Laboratory of Okayama City Hospital.

For endocrine data, the levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyrotropin (TSH), and free thyroxine (FT4) were measured by a chemiluminescent enzyme immunoassay (CLIA), and FT values were determined by a radioimmunoassay

(RIA) at LSI Medience Corp. (Tokyo).

***Statistical analyses.*** The data were analyzed by the Mann-Whitney *U*-test and Fisher's exact test to determine significant differences between pairs of groups. For the evaluation of inter-relationships between the parameters, we performed a linear regression analysis and obtained Spearman's rank correlation coefficients. *P*-values $<0.05$ were considered 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. 3.5.2) [19].

## Results

***Patients' characteristics and the populations with lowered FT.*** Table 1 summarizes the clinical backgrounds of the 46 patients divided into a group with serum FT levels $<8.5$ (n=18; low-FT group) and a group with serum FT levels $\geq 8.5$ (n=28; normal-FT group). There were no significant differences between the low- and normal-FT groups in patient characteristics including age, duration of diabetes, body weight, BMI, the number of diabetic complications (including neuropathy, nephropathy, and retinopathy), the number of medications used (including insulin, glucagon-

**Table 1** Comparison of clinical backgrounds in the low and normal groups of serum free testosterone (FT)

| FT groups | Low FT (FT<8.5) (n=18) | Normal FT (FT≥8.5) (n=28) | *p* value |
|---|---|---|---|
| Patient's profile | | | |
| Age [years] | 58.5 (2.5) | 53.6 (1.8) | 0.219 |
| Duration [years] | 8.1 (2.0) | 7.8 (1.3) | 0.883 |
| Body weight [kg] | 81.3 (4.1) | 77.3 (2.5) | 0.693 |
| BMI [kg/m$^2$] | 28.6 (1.5) | 27.2 (0.9) | 0.761 |
| Diabetic complications | | | |
| Nephropathy % (n) | 56.3 (9/16) | 41.7 (10/24) | 0.52 |
| Neuropathy % (n) | 72.2 (13/18) | 42.9 (12/28) | 0.0716 |
| Retinopathy % (n) | 16.7 (3/18) | 21.4 (6/28) | 1 |
| Medication | | | |
| Injection therapy | | | |
| Insulin % (n) | 27.8 (5/18) | 17.9 (5/28) | 0.48 |
| GLP1RA % (n) | 5.6 (1/18) | 3.6 (1/28) | 1 |
| Oral therapy | | | |
| Number of OAD | 2.6 (0.2) | 2.8 (0.3) | 0.746 |
| BG % (n) | 61.1 (11/18) | 57.1 (16/28) | 1 |
| TZD % (n) | 22.2 (4/18) | 21.4 (6/28) | 1 |
| SU % (n) | 22.2 (4/18) | 46.4 (13/28) | 0.125 |
| Glinide % (n) | 5.6 (1/18) | 7.1 (2/28) | 1 |
| DPP4i % (n) | 66.7 (12/18) | 60.7 (17/28) | 0.761 |
| α GI % (n) | 38.9 (7/18) | 50.0 (14/28) | 0.551 |
| SGLT2i % (n) | 38.9 (7/18) | 35.7 (10/28) | 1 |
| Questionnaire | | | |
| SDS score | 42.3 (2.0) | 47.4 (1.5) | 0.108 |
| FSSG score | 3.9 (1.0) | 3.9 (1.0) | 0.731 |
| AMS score | 31.9 (3.4) | 38.5 (4.3) | 0.496 |

Values are shown as mean (SEM) or % (n) and were statistically analyzed by the Mann-Whitney *U*-test and the Fisher's exact test. Significant level was set at $^*p<0.05$.

BMI, body mass index; GLP1RA, glucagon-like peptide-1 receptor agonist; OAD, oral antidiabetic agent; BG, biguanide; TZD, thiazolidine; SU, sulfonylurea; DPP4i, dipeptidyl-peptidase IV inhibitor; αGI, α-glucosidase inhibitor; SGLT2i, sodium/glucose cotransporter 2 inhibitor; SDS, self-rating depression scale; AMS, Heinemann aging male symptoms; FSSG, frequency scale for the symptoms of GERD, and GERD, gastroesophageal reflux disease.

like peptide-1 receptor agonist, sulfonylurea, glinide, α-glucosidase inhibitor, biguanide, thiazolidine, dipeptidyl-peptide IV inhibitor, and sodium/glucose cotransporter 2 inhibitor), or the results of questionnaires including the SDS, FSSG and AMS.

The mean ± SEM age of the 46 male patients with T2DM was 56 ± 1.5 years. Decreases of serum FT levels to < 8.5 pg/ml, fulfilling the definition of LOH [10], were detected in 18 (39%) of the 46 patients. As shown in Figure 1A, the percentage of patients with normal FT was large in the 40s-to-60s age group (38/46: 83%), whereas the percentage of patients with low FT was large in the ≥ 50-years age group (15/34: 44%). The mean ± SEM HbA1c level in all patients was 7.6 ± 0.21% (Fig. 1B). There was a large percentage of patients with HbA1c levels < 8% (33/46: 72%), and there was a large percentage of patients with low FT among the patients with HbA1c < 7%: (12/18: 67%). The mean ± SEM BMI of the patients was 28 ± 0.78 kg/m$^2$ (Fig. 1C). There was a large percentage of patients with BMI levels ranging from 25 to 30 (24/46: 42%), and there was a large percentage of patients with low FT among the patients with 25 ≤ BMI < 30 (10/18: 56%).

***Relationships between parameters of diabetes and LOH.*** Age-dependent changes in the levels of serum FT, HbA1c, and BMI were evaluated as shown in Fig. 2. The patients' serum FT levels tended to decrease gradually in an age-dependent manner, though the difference was not significant ($R = -0.22$, $p = 0.14$; Fig. 2A). Of note, the level of HbA1c ($R = -0.31$, $p < 0.05$; Fig. 2B) and the BMI ($R = -0.41$, $p < 0.01$; Fig. 2C) both decreased significantly in an age-dependent manner.

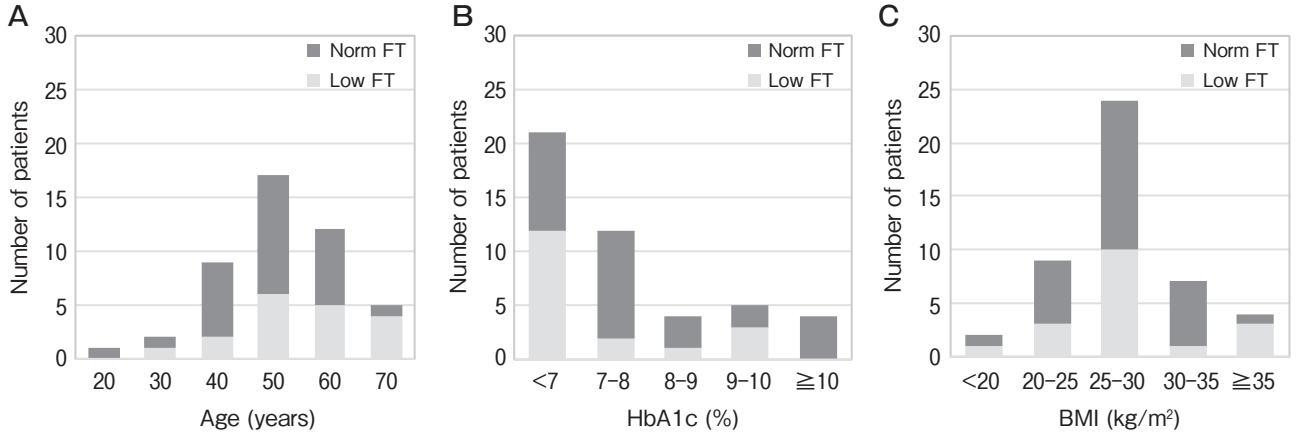


**Fig. 1** Patients' characteristics. Patients' age (**A**), HbA1c levels (**B**), and body mass index (BMI) (**C**) are shown. Bars in each panel divide the two groups based on the patients' serum free testosterone (FT) levels: low FT < 8.5 pg/ml and normal FT ≥ 8.5 pg/ml.

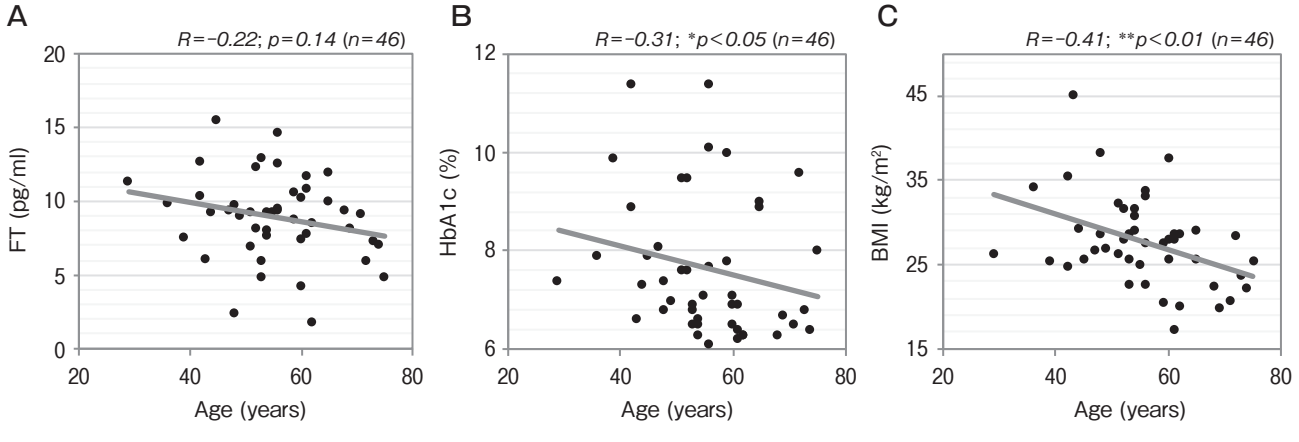


**Fig. 2** Relationships of age with serum free testosterone (FT), HbA1c, and BMI. The correlations of age with (**A**) serum FT, (**B**) HbA1c, and (**C**) BMI were determined. $^{**}p < 0.01$ and $^{*}p < 0.05$ between the indicated factors.

The relationships of HbA1c with the patients' scores on the FSSG, SDS, and AMS were evaluated (Fig. 3). The level of HbA1c was significantly correlated with the AMS score ($R = 0.47$, $p < 0.05$; Fig. 3C) but not with the FSSG score ($R = -0.0085$, $p = 0.97$; Fig. 3A) or SDS score ($R = 0.12$, $p = 0.54$; Fig. 3B).

***Comparison of laboratory data in the low-FT and normal-FT groups.*** We examined and compared the laboratory data of the low-FT group (FT < 8.5 pg/ml) and normal-FT group (FT ≥ 8.5 pg/ml) (Fig. 4). The two groups' levels of hemoglobin (Hb) and liver and muscle enzymes (AST, ALT, LDH, and CPK), renal functions (BUN, CRE, and UA), glucose and lipid levels (PPG, HbA1c, and TC), and endocrine data (TSH, FT4, FSH, and LH) were compared. The Hb concentration was significantly lower in the low-FT group compared to the normal-FT group (14.6 ± 0.29 g/dl vs. 15.3 ± 0.23 g/dl as mean ± SEM), but the other biochemical data were not significantly different between the 2 groups.

***Relationships between levels of endocrine parameters and FT.*** We evaluated the relationships between endocrine markers and FT to determine the possible mechanisms underlying the onset of LOH in men with diabetes. As shown in Fig. 5, our analyses revealed that serum gonadotropin levels including serum levels of FSH ($R = -0.32$, $p < 0.05$) were negatively correlated with serum FT levels compared to the serum levels of LH ($R = -0.057$; $p = 0.71$), and the serum FSH levels were significantly related to changes in FT levels, indicating that the onset of LOH is closely linked to gonadal dysfunction and a secondary increase in FSH secretion as a feedback mechanism.

Moreover, the patients' serum TSH levels ($R = 0.36$, $p < 0.05$) showed a significant positive correlation with their serum FT levels (Fig. 5C), suggesting that a low level of androgen may be related to the suppression of TSH secretion, *i.e.*, occult hyperthyroidism, in men with diabetes.

## Discussion

We observed that 39% of the 46 men with diabetes who visited a city hospital had low levels of FT. The percentages of diabetic patients with low FT levels were large in the ≥ 50-years age group (83%), the HbA1c < 7% group (67%), and the 25 ≤ BMI < 30 group (56%). The level of HbA1c was significantly correlated with the AMS score, suggesting that the AMS score can be one of the indicators for diabetic control. The low-FT group had a moderate decrease of Hb concentrations, but other biochemical data including liver and renal functions were not different from those in the normal-FT group. Given the finding that androgen is involved in erythropoietic activity in males [20], it is reasonable that decreased Hb was related to lowered serum FT levels in the present patient series.

Of interest, our patients' serum FSH levels were negatively correlated with their FT levels ($R = -0.32$), whereas the TSH levels were positively correlated with FT levels ($R = 0.36$). Thus, based on the present results, we speculate that a slightly anemic status, thyroid dysfunction, and moderate obesity might be indicators of LOH syndrome in middle-aged diabetic males.

In our previous study [21] of patients who were sus-

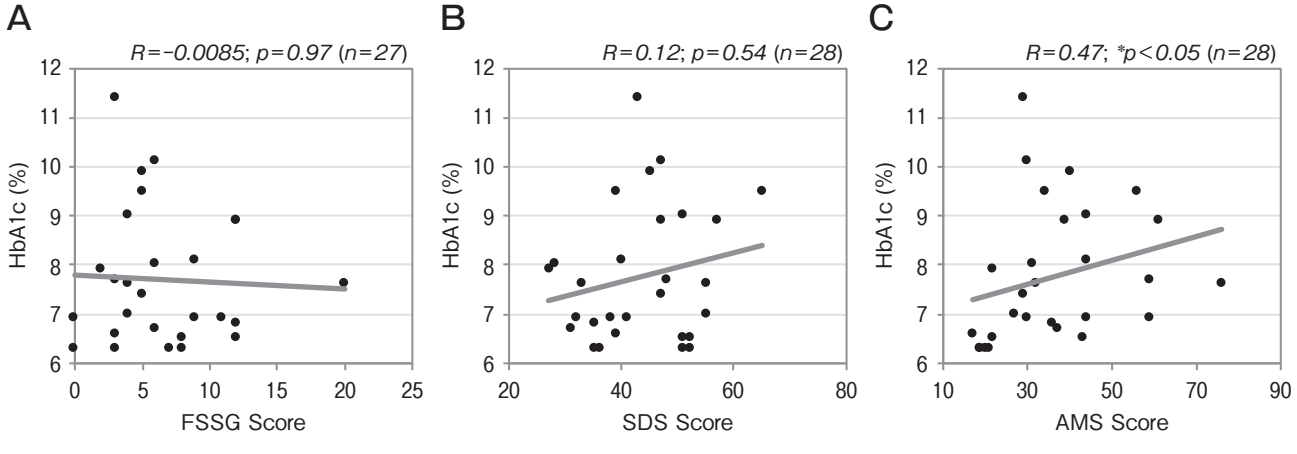


Fig. 3 Relationships of HbA1c with the patients' FSSG, SDS and AMS scores. The correlations of HbA1c with the (A) FSSG score, (B) SDS score, and (C) AMS score were determined. *$p < 0.05$ between the indicated factors.

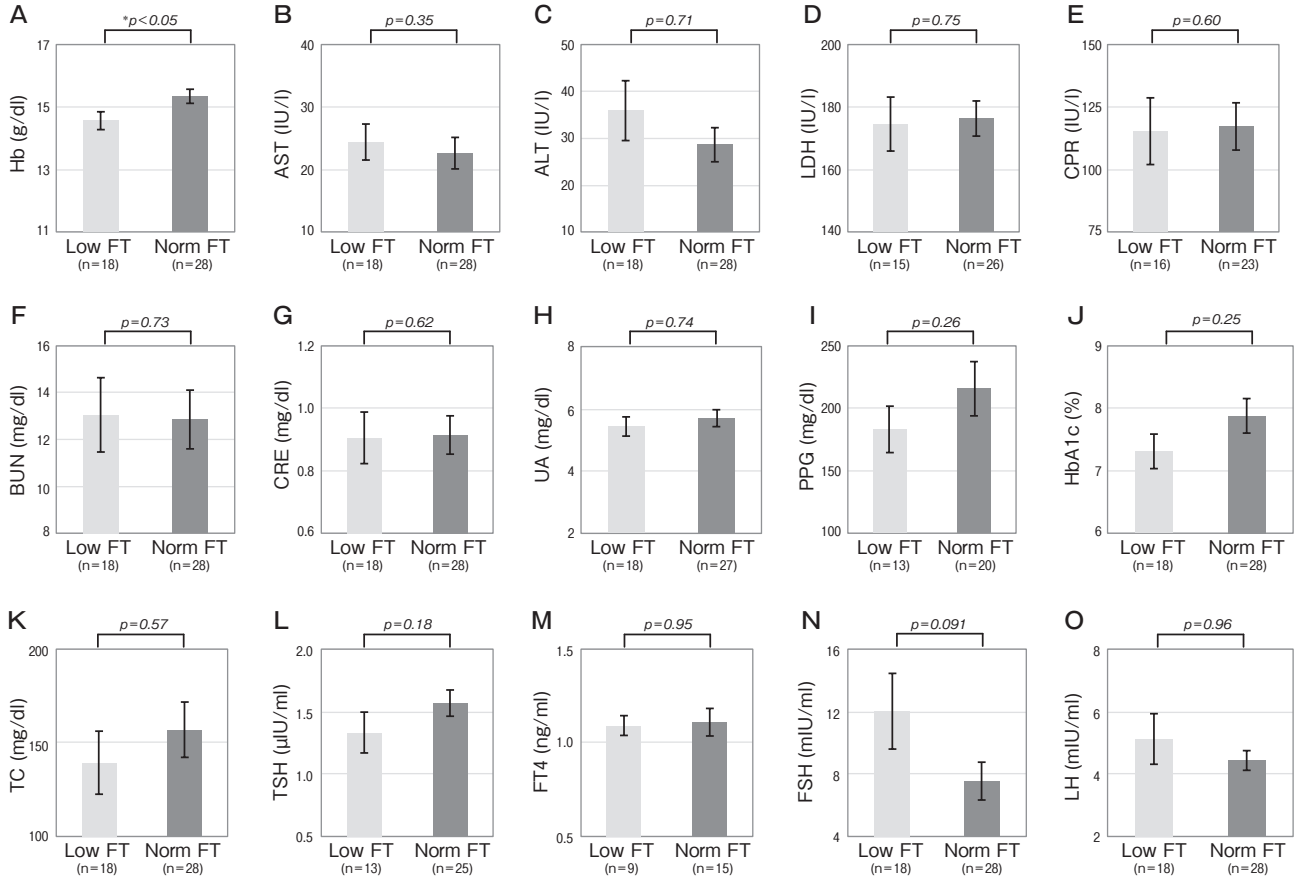


**Fig. 4** Comparison of laboratory data in the low and normal serum free testosterone (FT) groups. The patients were divided into 2 groups based on their serum FT levels: low FT <8.5 pg/ml and normal FT ≥8.5 pg/ml. Laboratory data for (**A**) Hb and the serum concentrations of (**B**) AST, (**C**) ALT, (**D**) LDH (**E**) CPK, (**F**) BUN, (**G**) CRE, (**H**) UA, (**I**) PPG, (**J**) HbA1c, (**K**) TC, (**L**) TSH, (**M**) FT4, (**N**) FSH, and (**O**) LH were analyzed by the unpaired *t*-test. *$p<0.05$ between the indicated factors.

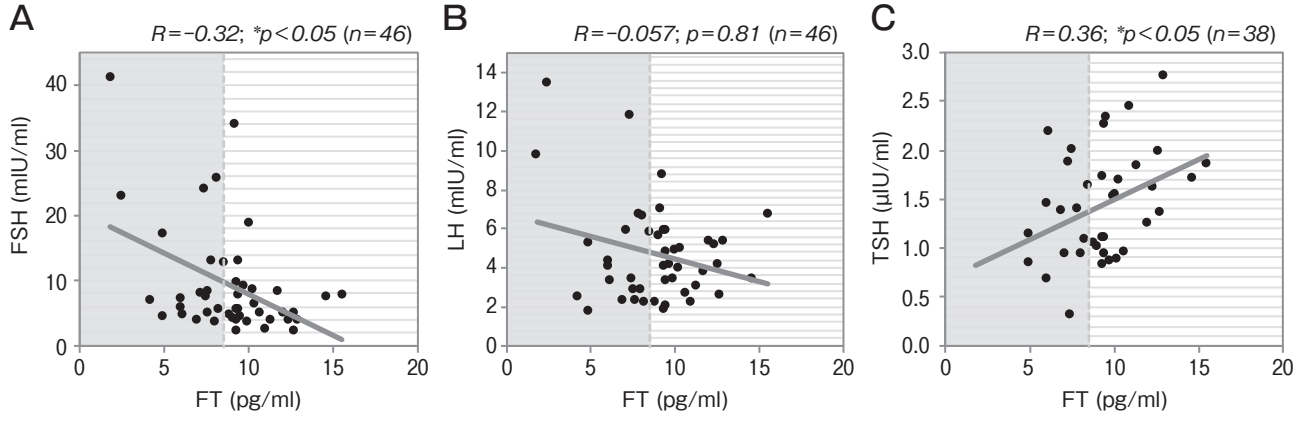


**Fig. 5** Relationships of the serum FT level with endocrine factors. The correlations of serum FT levels with (**A**) FSH, (**B**) LH, and (**C**) TSH are shown. *$p<0.05$ between the indicated factors. *Dotted lines* indicate the levels of FT: 8.5 pg/ml in each panel.

pected of having LOH and in whom serum FT levels were measured, 58% of the patients treated at a general medicine department met the criteria for the diagnosis of LOH syndrome. Deficiency of testosterone affects the functions of not only physical but also psychological systems [2]. Our present findings indicate the usefulness of the AMS score (compared to the SDS and FSSG scores, which are closely linked to psychological conditions [13, 15]) for the estimation of diabetic control in males with diabetes. Underlying endocrine impairment related to a depressive status might also be involved in the deterioration of the diabetic condition.

The relevance of depressive symptoms to the prevalence of ED has also been reported in Japanese males with T2DM [22], in whom overweight status seemed to be involved in both ED and declining testosterone levels. In regard to the relation between LOH and obesity, previous studies reported that LOH was diagnosed in only 0.4% of men with normal weight but in 1.6% of men with a BMI of 25-30 kg/m$^2$ and in 5.2% of men with a BMI > 30 kg/m$^2$, suggesting that LOH is associated with a high BMI in males [23, 24]. In the present study, the incidence of low FT was high in the group with BMIs at 25-30 kg/m$^2$, suggesting that attention should be paid to obesity (class 1) in males with diabetes regarding the possibility of a latent LOH condition.

Male hypogonadism is characterized by impairment of gonadal function with lowered circulating testosterone levels [25]. Hypogonadism is classified into primary and central disorders caused by hypothalamus-pituitary dysfunction. The endocrine status of LOH cannot be simply classified into either of the specific categories of hypogonadism [26]; that is, an LOH state is associated with gonadal dysfunction, due mainly to impaired steroidogenesis and a loss of Leydig cell sensitivity to gonadotropins, which results in a decreased secretion of testosterone [26]. However, the detailed relationships between FT and gonadotropins are not yet clear. We observed a negative correlation between the serum levels of FT and FSH (rather than LH) in our present series of male diabetic patients, suggesting that an LOH condition is primarily involved in the gonadal impairment with a secondary increase of the serum FSH level.

Regarding the relationship between serum FT levels and thyroid function [27], several studies have shown an interesting role of thyroid hormones in human sexual dysfunction [28] in addition to the mutual comorbidity of diabetes and thyroid diseases [29]. An increased prevalence of both hyperthyroidism and hypothyroidism has been reported in men with ED related to LOH status. In hyperthyroid males, it is known that serum total testosterone concentrations are often elevated as a result of increased serum levels of sex hormone-binding globulin (SHBG), while their serum FT concentrations usually remain within the normal range [30]. It has also been shown that gonadotropin responses to gonadotropin-releasing hormone are enhanced in hyperthyroid males [30].

In this regard, Zahringer *et al*. [31] investigated the function of the hypothalamic-pituitary-gonadal axis and showed that both LH secretion and FSH secretion were increased in hyperthyroid patients. In that study, gonadotropin secretion was greater in the patients with hyperthyroidism than in healthy subjects, suggesting that hyperthyroid males are relatively resistant to gonadotropins, indicating the existence of primary gonadal insufficiency. This phenomenon was also indicated by our present finding that the cases of patients with low TSH, indicating occult hyperthyroidism, were related to an LOH status that may be due to an impaired response to gonadotropins.

Collectively, our present results suggest that unexpectedly, many patients with diabetes have low FT levels and that the AMS score tends to be related to HbA1c levels. There are some study limitations to consider, however. The sample size of this study was relatively small (n = 46), and effects of some of the patients' medications for diabetes and lifestyle-related diseases could have been involved in the changes of serum FT, although no significant difference in the number of medications was detected. In addition, this was a retrospective analysis conducted at a single city hospital. The results obtained herein thus cannot be interpreted directly. However, our findings indicate that a slightly anemic condition, thyroid dysfunction, and obesity (class 1) are clues to a latent LOH status in middle-aged diabetic males.

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