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Original Article

Incidence of menstrual cycle abnormalities and polycystic ovary syndrome in female Japanese patients with type 1 diabetes mellitus. The role of androgens

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Highlights

- This is the first large-case analysis of oligomenorrhea in Japanese with T1DM.
- Patients with T1DM are at higher risk of oligomenorrhea than the general population.
- Female patients with T1DM are more likely to have high serum testosterone levels.

Abstract. Type 1 diabetes mellitus (T1DM) adversely affects gonadal function. This study aimed to define the characteristics and factors associated with menstrual cycle abnormalities and polycystic ovary syndrome (PCOS) in Japanese patients with T1DM. Our study enrolled 157 patients, including 55 with oligomenorrhea (prolonged menstrual cycle) and 102 without oligomenorrhea. LH/FSH ratio ($p = 0.04$) and total testosterone levels ($p = 0.03$) were significantly higher in the oligomenorrhea group than in the non-oligomenorrhea group. No significant differences were found between the two groups regarding age at menarche, age at T1DM diagnosis, treatment, glycated hemoglobin, or total daily insulin dose. Of the 55 patients in the oligomenorrhea group, 27 were diagnosed with PCOS based on the Rotterdam criteria. We concluded that female patients with T1DM, as well as abnormal menstrual cycles and hyperandrogenism, may suffer from undiagnosed PCOS and should be referred to a gynecologist for full assessment, diagnosis, and treatment.

Key words: type 1 diabetes mellitus, menstrual cycle, testosterone

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Introduction

Type 1 diabetes mellitus (T1DM) can occur at various ages, with a predilection for childhood and adolescence (1). T1DM is associated with a number of complications (2), including ovarian function in women and delayed menarche (3, 4). The mechanisms of gonadal dysfunction in female patients with T1DM remain unclear. Nestler *et al.* (5) reported that insulin increases testosterone production in the ovarian capsular cells. Elevated testosterone levels have been shown to delay menarche and increase the risk of menstrual cycle abnormalities in female patients with T1DM (6, 7). Menarche is delayed in females with T1DM compared with the general population (3). However, we previously reported improvement in menarche age in Japanese women with T1DM in recent years (8). Another related complication of T1DM is the negative impact of poor glycemic control on fertility, whereas good glycemic control is reported to reduce the risk of infertility (9, 10).

The incidence of T1DM in Japan (approximately 1.5–2.5 per 100,000 person-years) is lower than that in Europe and the US (11). Unlike in Western countries, only a few studies have examined the effects of T1DM on gonadal function in Japanese women with T1DM. Polycystic ovary syndrome (PCOS) is a frequent and important cause of gonadal dysfunction in reproductive-age women, and since its pathogenesis differs by race (12), it needs to be investigated in Japanese patients. In the study of 21 Japanese women with T1DM by Miyoshi *et al.* (13), they found a high frequency of polycystic ovary morphology and PCOS. To our knowledge, apart from the above studies, the menstrual cycle patterns have not been examined in a large number of Japanese women with T1DM. Thus, we aimed to investigate the effects of T1DM on the menstrual cycle and assess the current status of PCOS in a relatively large number of Japanese patients with T1DM.

Patients and Methods

This retrospective study analyzed the medical records of patients who had been admitted to Osaka City University Graduate School of Medicine, including female patients diagnosed with T1DM who visited the Department of Pediatrics, Osaka City University Hospital, between April 2020 and March 2022. The exclusion criteria were as follows: *1)* Patients aged > 40 yr who might have reduced ovarian function due to aging, based on the definition of premature ovarian failure (i.e., menopausal women aged < 40 yr) (14); *2)* Patients with menarche for <2 yr, because their menstrual cycle might not yet be fully established (15, 16); *3)* Patients within 6 mo of the onset of diabetes, because they might not have recovered from acute metabolic failure at onset; *4)* Patients with amenorrhea associated with chemotherapy and radiotherapy; *5)* Patients who were seen within the observation period but became pregnant. No other patients seen during the period were amenorrheic.

Using the above criteria, the present study included 157 patients. The study Participants were divided into two groups based on their menstrual cycle patterns; patients with a regular cycle of ≤ 38 d were included in the "non-oligomenorrhea group," and those with oligomenorrhea (menstrual cycle of ≥ 39 d) in the "oligomenorrhea group". Next, we estimated the prevalence of PCOS based on meeting two of the three Rotterdam criteria: ovulatory dysfunction, hyperandrogenemia, and polycystic ovaries. Rotterdam criteria were used in this study for two reasons. First, these criteria are widely used globally (17). Second, only a few cases had undergone imaging studies; they had participated in a retrospective study. Accordingly, we did not adopt the Japanese diagnostic criteria for the diagnosis of PCOS, which include imaging findings (18).

Each participant completed a questionnaire on menstruation. Information on two or more menstrual cycles was obtained from the patients, and the calculated average value was used as the menstrual cycle. Patients were also assessed regarding masculinizing signs. Other clinical information, such as age at menarche, childbearing, smoking status, age at onset of T1DM, total daily dose of insulin (TDD), and treatment modality (multiple daily injections [MDI] or continuous subcutaneous insulin infusion [CSII]/sensor-augmented pump [SAP]), was obtained from the medical records.

Standing height (measured using a stadiometer) and body weight were recorded at the study entry. Non-fasting blood samples were obtained regardless of the phase of the menstrual cycle. Endocrine assays, including LH, FSH, PRL, total testosterone, E2, and C-peptide immunoreactivity (CPR), were conducted using the LSI Medience measurement system (CLIA method).

The study research protocol was approved by the Ethics Review Committee for Medical Research at Osaka City University (#2020-285). All patients or their guardians were informed of the significance and protocol of the present study and provided informed consent.

Statistical analysis

Data on age, body mass index (BMI), age at T1DM diagnosis, TDD/kg, LH/FSH, PRL, total testosterone, E2, and CPR were presented as median values (25th–75th quartiles). Data from the non-oligomenorrhea and oligomenorrhea groups were compared using the Mann-Whitney U test. BMI was compared between the non-PCOS and PCOS groups using the Mann-Whitney U test. We used Fisher's test to investigate the correlation between menstrual cycle abnormalities and the following two factors related to diabetes mellitus: whether differences in treatment (MDI or CSII/SAP) affected the menstrual cycle and if the menstrual cycle differed between the groups with T1DM before and after menarche. The relationship between testosterone and each variable was examined using Spearman's rank correlation coefficient. Two-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were

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performed using R version 4.0.3 (programmed by Y. Kanda) for Windows.

Results

Table 1 summarizes the basic characteristics of the 157 study participants. The non-oligomenorrhea group comprised 102 (65%) participants, while the oligomenorrhea group included 55 (35%) patients. The age of the entire group ranged from 14.0 to 39.9 yr, with a median age of 24.3 yr. Current age, age at diagnosis of T1DM, age at menarche, time since T1DM onset, insulin dose, glycated hemoglobin (HbA1c), CPR, BMI, PRL, and E2 were not significantly different between the non-oligomenorrhea and oligomenorrhea groups. Treatment (MDI or CSII/SAP) and appearance of menarche before or after the onset of T1DM did not correlate with abnormal menstrual cycle (**Table 2**). Contrastingly, endocrine assays showed a significantly higher total testosterone level in the oligomenorrhea group than in the non-oligomenorrhea group (**Table 1**, p = 0.03). Furthermore, the LH/FSH ratio was significantly higher in the oligomenorrhea group than in the non-oligomenorrhea group (p = 0.04). These results suggest the potential role of high total testosterone and LH/FSH ratio in oligomenorrhea in female patients with T1DM. As reported previously, total testosterone levels are higher in patients with T1DM than in the general population (19). In this study, our analysis also showed that total testosterone levels in 24.4% of patients were above the +2SD of previous reports (20).

Further analysis of T1DM-associated factors affecting total testosterone levels demonstrated a negative correlation between total testosterone and HbA1c (**Fig. 1a**, correlation coefficient r = –0.247, p = 0.005). Notably, the above correlation disappeared when patients with poor glycemic control (HbA1c ≥ 10%) were excluded from the analysis (**Fig. 1b**). Furthermore, testosterone levels were lower in patients with HbA1c ≥ 10% than in those with HbA1c < 10% (0.31 ng/mL [0.24–0.33] vs. 0.44 ng/mL [0.25–0.58], p < 0.01). Interestingly, total testosterone levels did not correlate with BMI, HbA1c, or TDD/kg. These findings indicate that no simple factors related to high testosterone are among those analyzed in this study.

We also investigated the prevalence of PCOS. Of 157 patients, 27 (17.2%) were diagnosed with PCOS based on the Rotterdam criteria (**Table 3**). Further analysis showed that 27 (49.1%) of the 55 patients in the oligomenorrhea group met the PCOS diagnostic criteria. The frequency of signs of masculinization did not correlate with PCOS. Furthermore, BMI did not differ

Table 1. Participant characteristics

	All	n	Non-Oligomenorrhea group	n	Oligomenorrhea group	n	p value
Age (yr)	24.3 (18.6–30.5)	157	24.05 (18.53–31.18)	102	25.5 (19.15–29.95)	55	0.835
Age at T1DM diagnosis (yr)	9.5 (5.5–11.9)	157	9.5 (5.03–12.05)	102	9.2 (6.35–10.9)	55	0.89
Duration of T1DM (yr)	16.0 (10.0–21.3)	157	16.15 (9.85–21.97)	102	16.00 (11.25–19.85)	55	0.802
Age at Menarche (yr)	12.2 (11.2–13.2)	156	12.2 (11.2–13.0)	102	12.45 (11.43–13.53)	54	0.16
Insulin dose (U/kg/d)	0.76 (0.62–0.93)	157	0.75 (0.61–0.94)	102	0.76 (0.63–0.90)	55	0.873
HbA1c (%)	7.5 (6.9–8.4)	157	7.5 (6.9–8.56)	102	7.7 (7.0–8.1)	55	0.854
BMI (kg/m^2)	22.84 (21.3–24.62)	157	22.76 (21.14–24.50)	102	22.97 (21.42–25.18)	55	0.344
PRL (ng/mL)	12.56 (8.87–17.17)	129	12.90 (9.10–17.02)	79	11.25 (8.75–18.37)	50	0.547
CPR (ng/mL)	< 0.1 (< 0.1–0.055)	155	< 0.1 (< 0.1–0.04)	101	< 0.1 (< 0.1–0.09)	54	0.65
Estradiol (pg/mL)	69.5 (39–152)	128	87 (39.5–154)	79	57 (39–95)	49	0.099
Total Testosterone (ng/mL)	0.42 (0.32–0.57)	127	0.38 (0.31–0.50)	80	0.47 (0.33–0.73)	47	**0.033***
LH/FSH {(mIU/mL)/(mIU/mL)}	1.35 (0.79–2.36)	129	1.33 (0.77–1.97)	79	1.69 (0.86–3.06)	50	**0.042***

Data are shown as the median (25th–75th percentiles) or number of participants analyzed. * p < 0.05, between the non-oligomenorrhea and oligomenorrhea groups. BMI, body mass index; CPR, C-peptide immunoreactivity. P-values were assessed by the two-tailed Mann-Whitney U test.

Table 2. Method of insulin administration and the relationship between the timing of menarche and the onset of type 1 diabetes

		Non-Oligomenorrhea group	Oligomenorrhea group	p value
Treatment	MDI	40	21	1
	CSII+SAP	62	34	
Menarche	Menarche before T1DM	29	11	0.337
	Menarche after T1DM	73	44	

MDI, multiple daily insulin injections; CSII, continuous subcutaneous insulin infusion; T1DM, type 1 diabetes mellitus. P-values were assessed using the Fisher's exact test.

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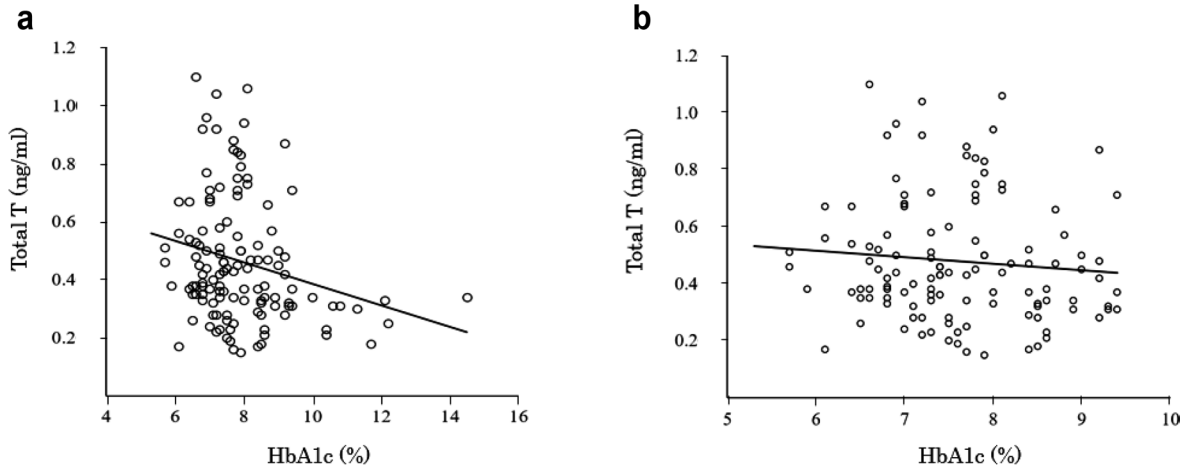

Fig 1. Relationship between testosterone and glycated hemoglobin (HbA1c). 1a shows a negative correlation between total testosterone and HbA1c based on the data of 128 patients, as analyzed by Spearman's rank correlation coefficient (r = –0.247, p = 0.005). When Spearman's analysis was performed following the exclusion of patients with HbA1c ≥ 10%, in 1b, the correlation between testosterone and HbA1c disappeared (r = –0.119, p = 0.2).

Table 3. Comparison of masculinizing signs and BMI in PCOS vs non-PCOS

	Non-PCOS (n = 125)	PCOS (n = 27)	p value
Masculinization	34 (27.2%)	10 (37.0%)	0.351
BMI (kg/m^2)	22.8 (21.2–24.6)	23.2 (21.47–24.7)	0.441

PCOS, polycystic ovarian syndrome. The Rotterdam Criteria were used to diagnose PCOS. Masculinization was assessed using Fisher's exact test. When performing Fisher's exact test, unknown cases were excluded. BMI is shown as the median (25th–75th percentiles). P-values were assessed by the two-tailed Mann-Whitney U test.

significantly between the non-PCOS and PCOS groups (p = 0.44). These results suggest a very high incidence of PCOS in patients with T1DM and oligomenorrhea; however, these patients lacked the characteristic features of PCOS, such as masculinization and obesity.

Discussion

In the present study, we investigated the frequency of oligomenorrhea and PCOS and their clinical and endocrinological characteristics in female Japanese with T1DM. Compared to the reported frequency of abnormal menstrual cycle of 19.6% in the general female Japanese population (21), 35.0% of the female patients with T1DM in this study had oligomenorrhea, indicating a relatively high frequency of abnormal menstrual cycle in female Japanese patients with T1DM. Our analysis also showed significantly high total testosterone levels in the oligomenorrhea group. Similarly, the results demonstrated a relatively high frequency of PCOS (17.2%) in our patients with T1DM. In particular, approximately 50% of the patients with oligomenorrhea had PCOS. Prolonged anovulation due to PCOS has been reported to increase the risk of uterine cancer (22). Our study showed that clinical features of PCOS, such as obesity and masculinization, were absent in these patients. This clinical finding suggests the potential underdiagnosis of PCOS and the need for vigorous investigation of PCOS in females with T1DM.

Total testosterone levels are known to be high in T1DM (19). In this study, total testosterone was higher than +2SD of age-specific normal participants in approximately 25% of our patients with T1DM. A previous study also reported high total testosterone levels in patients with T1DM and that its origin was ovarian, not adrenal (23). Hyperinsulinemia in individuals with obesity and type 2 diabetes is considered to be associated with increased testosterone production through two mechanisms: direct action of insulin on insulin receptors in the ovaries, which produces androgens, and gonadotrophic action of insulin that stimulates androgen production and LH by theca cells in the ovaries (24). Physiologically, insulin is secreted from the pancreas, and 50–70% enters the portal circulation (25). Blood glucose levels are reduced by insulin after it traverses the portal vein. In patients with T1DM, subcutaneously administered exogenous insulin reaches the portal vein at much lower concentrations than those from physiological pancreatic secretion. To maintain blood glucose levels within the appropriate range, patients have to inject large doses of insulin that exceed the physiological doses (25, 26). Consequently, insulin concentrations in the systemic circulation are high in such patients, thus exposing the ovaries to high concentrations of

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insulin. Thus, the ovaries produce excess androgens by the two mechanisms described above. Contrary to our expectations, total testosterone levels measured in this study did not correlate with TDD/kg. Since the source of high total testosterone is hyperinsulinemia, it seems that more TDD/kg would result in higher total testosterone. Unfortunately, we could not measure insulin serum concentrations in our patients in this study. Nevertheless, we propose two reasons for the lack of correlation between total testosterone and TDD/kg. One is inaccurate TDD/kg data since some of the data was self-reported by the participating patients; another is suppression of testosterone secretion in the presence of metabolic abnormalities in those patients with poor glycemic control. In the present study, total testosterone level was lower in patients with poor glycemic control. This result is in agreement with a previous study that found poor glycemic control to be associated with hypogonadotropic hypogonadism (27).

Previous studies reported a higher prevalence of PCOS in T1DM than in the general population. The reported prevalence of PCOS in patients with T1DM was estimated at 24% (19), whereas the prevalence of PCOS among Spanish non-T1DM patients ranged from 6–15% (28). In Japan, only a few studies have examined the relationship between T1DM and PCOS (13, 29). Miyoshi *et al.* (13) examined the frequency of PCOS in a small number (n = 21) of Japanese women with T1DM. They found three (14.3%) patients who met all the Japanese PCOS diagnostic criteria, which included irregular menstruation, polycystic ovaries findings, and hyperandrogenemia or an elevated LH/FSH ratio. In the present study, 27 (17.2%) of the 157 patients were diagnosed with PCOS using the Rotterdam criteria. In Japan, the incidence of PCOS is reported to be 5–8% in the general population, which is lower than that in Western countries (18, 29, 30). Considered together, the above studies and our findings suggest a high incidence of PCOS in female Japanese with T1DM.

PCOS is reported to be associated with low rates of masculinizing signs in Japanese patients (18). Masculinization in PCOS is attributed to the elevated androgen levels. The etiology of androgen hypersecretion includes hyperinsulinemia associated with insulin resistance and high levels of LH caused by pulsed hypersecretion of gonadotropin-releasing hormone. High LH can cause abnormal menstrual cycle and polycystic ovarian folliculin, independent of testosterone levels (31). Japanese patients with PCOS are reported to have higher LH with normal testosterone levels more often than Western patients (18). This may explain the fewer signs of masculinization observed in our patients. Genetic and epigenetic factors, including lower insulin secretion capacity compared to Western countries, may explain why LH elevation is the major cause of PCOS in Japanese patients (31, 32). In this regard, it has been reported that PCOS in patients with T1DM is less likely to show signs of masculinization than in T2DM, even in the Caucasian population (19). Based on the lack of clinical manifestations of masculinization, it is often clinically challenging to diagnose hyperandrogenism in people with diabetes. Patients with T1DM do not exhibit the clinical signs of hyperandrogenism despite the presence of high total testosterone levels because, in contrast to T2DM, the levels of sex hormone-binding globulin (SHBG) are not low in such patients (19). SHBG suppresses the effects of testosterone by binding to free testosterone (33). In T2DM, a decrease in SHBG increases free testosterone, which causes the clinical or biochemical signs of hyperandrogenism (34). High insulin levels suppress the production of SHBG in the liver; therefore, increased insulin resistance in patients with T2DM leads to higher concentrations of whole-body insulin, including those in the portal vein, and lower concentrations of SHBG (35). In contrast, it is speculated that patients with T1DM do not have high insulin levels in the portal vein, and thus, SHBG concentrations remain unchanged. Thus, masculinization is not apparent in female patients with T1DM since free testosterone is not elevated in these patients. Future studies should investigate the levels and roles of SHBG in T1DM.

The present study has several limitations. Due to the retrospective nature of the study, the timing of blood sampling was not aligned with the menstrual cycle. The menstrual cycle is associated with fluctuations in LH levels but only mild changes, if any, in testosterone concentrations (20). In addition, insulin sensitivity decreases during the luteal phase (36). These limitations could influence the correlation between hyperinsulinemia and hyperandrogenemia. Another limitation is that the criteria applied in the present study for the diagnosis of PCOS were inconsistent with those of other studies. We did not use the Japanese PCOS diagnostic criteria (which require imaging studies), and, in fact, only a few of our patients underwent imaging studies. In this regard, Lizneva *et al.* (37) found that imaging studies were normal in only approximately 15% of patients with PCOS, as well as abnormal menstrual cycles and hyperandrogenism. Therefore, we believe that the use of the Rotterdam criteria in this study was not associated with PCOS overdiagnosis.

Conclusion

The results of the present study demonstrated a higher incidence of oligomenorrhea in patients with T1DM than in the general population. The results also showed the presence of higher levels of total testosterone in these patients relative to the general population. In the same patients, the LH/FSH ratio and total testosterone levels were significantly higher in those with oligomenorrhea than in those with normal menstrual cycles. Japanese females with T1DM may have hyperandrogenemia; however, the absence of visible signs makes diagnosis difficult. Abnormal menstrual cycle in Japanese females with T1DM is most likely related to high testosterone levels. We conclude that female patients with T1DM who present with a history

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of menstrual cycle abnormalities and hyperandrogenism may suffer from undiagnosed PCOS and that such patients should be referred to a gynecologist for a full assessment, diagnosis, and treatment.

Conflict of interests: All authors declare no conflicts of interest associated with this research.

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