Ovarian morphology and prevalence of polycystic ovary syndrome in Japanese women with type 1 diabetes mellitus

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ABSTRACT

Aims/Introduction: Polycystic ovary syndrome (PCOS) is a heterogeneous disorder including polycystic ovary morphology (PCOM), ovulatory dysfunction and hyperandrogenism. PCOS is frequently associated with type 2 diabetes mellitus; however, it is unknown whether PCOM and PCOS are prevalent in Japanese patients with type 1 diabetes mellitus. The purpose of our study was to determine the frequency of PCOM and PCOS in women with type 1 diabetes mellitus.

Materials and Methods: We evaluated clinical, hormonal and ovarian ultrasound data from 21 type 1 diabetes mellitus patients whose average glycated hemoglobin levels were 7.9 ± 1.5%.

Results: Ultrasound identified PCOM in 11 patients (52.4%) and these patients also had higher levels of the androgen dehydroepiandrosterone sulfate (DHEA-S) than those without PCOM ($P < 0.05$). Of the patients with PCOM, five presented menstrual irregularities (45.5%) and three met the Japanese criteria for PCOS (27.2%); whereas all patients without PCOM had a normal menstrual cycle ($P < 0.05$).

Conclusions: Japanese premenopausal women with type 1 diabetes mellitus had a high frequency of PCOM as well as PCOS. This is the first research of this area carried out in an Asian population. (J Diabetes Invest doi: 10.1111/jdi.12040, 2013)

KEY WORDS: Irregular menstrual cycles, Polycystic ovary syndrome, Type 1 diabetes mellitus

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in premenopausal women, with 6–7% prevalence in the general population[1]. PCOS is a heterogeneous disorder recognized by irregular menstrual cycles, chronic ovulatory dysfunction and hyperandrogenism. Adult women with PCOS have polycystic ovary morphology (PCOM)[2]. PCOM is one of the morphological abnormalities that occurs in ovaries, and is characterized by ovaries becoming enlarged and polycystic. The relationship between PCOS and type 2 diabetes mellitus is well established[1], and attributed in part to elevated insulin levels caused by obesity or insulin resistance. Insulin acts synergistically with luteinizing hormone to enhance androgen production by theca cells and excess androgen plays a central role in PCOS patients[3]. With regards to type 1 diabetes mellitus and ovarian dysfunction, it was recently reported that in Western countries premenopausal women with type 1 diabetes mellitus had increased prevalence of both hyperandrogenism (~50%) and PCOM (54.8%)[4,5]. However, a prevalence of hyperandrogenism, PCOM and PCOS has not been reported in the Asian type 1 diabetes mellitus population. We carried out a prospective observational study to evaluate the frequency of PCOS and PCOM in Japanese premenopausal women with type 1 diabetes mellitus. We also studied the relationships between these abnormalities and clinical or metabolic parameters.

MATERIALS AND METHODS

All premenopausal women with type 1 diabetes mellitus that were 20 years-of-age or older and attending the Department of Medicine II, Hokkaido University Hospital, Sapporo, Japan, were invited to participate in the present study. We excluded from the study patients who were taking oral contraceptives, undergoing treatment for infertility, or suffering from severe hepatic, renal or cardiac diseases. Written informed consent from each patient was obtained before enrolment in the study, which was carried out according to the Good Clinical Practice and Helsinki Declaration principles. The ethics committees of each hospital and Hokkaido University approved the studies. PCOS was defined according to the diagnostic criteria of the Japanese Society of Obstetrics and Gynecology in 2007[2]. These criteria include the presence of PCOM, which was identified by transvaginal ultrasound and required the presence of at least 10

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Received 9 July 2012; revised 13 November 2012; accepted 14 November 2012

follicles measuring 2–9 mm in diameter in at least one ovary. When women have a menstruation disorder and 'hyper luteinizing hormone (LH) or hyper androgenism' with PCOM, they are diagnosed as PCOS in this criteria. All ultrasound examinations were carried out and analyzed by a single obstetrician (Masamitsu Takeda). Clinical and biochemical characteristics of the participants (age, age at the onset of diabetes, duration from the onset, body mass index [BMI]), daily insulin doses and presence of diabetes complications were obtained from their medical records. Next, we examined LH, follicle-stimulating hormone (FSH), LH/FSH ratio, prolactin (PRL), estradiol, total testosterone, dehydroepiandrosterone-sulfate (DHEA-S), glycated hemoglobin (HbA_{1c}), total cholesterol (T-Chol), high-density lipoprotein cholesterol (HDL-C), low-density-lipoprotein cholesterol (LDL-C) and triglycerides (TG). In addition, patients were asked to report age at menarche, days of menstrual cycle and existence of any menstrual abnormalities (amenorrhea or oligomenorrhea).

According to the diagnostic criteria, we examined the frequency of PCOS and PCOM. Additionally, we examined the frequency of PCOM in 29 patients without diabetes mellitus who consulted an obstetrician in our hospital. Clinical and laboratory data are shown as mean ± standard deviation. HbA_{1c} was collected as Japan Diabetes Society values and converted into National Glycohemoglobin Standardization Program (NGSP) values[6]. We used NGSP values as HbA_{1c} in this article. Differences between diabetic complications and menstrual abnormalities were assessed by χ^2-test, and differences in other parameters were assessed by Mann–Whitney's *U*-test using SPSS (SPSS, Chicago, IL, USA). Statistical analysis was carried out using SPSS and $P < 0.05$ was considered statistically significant.

RESULTS

A total of 21 patients consented to participating in the present prospective observational study and their clinical characteristics are shown in Table 1. On average, the patient group was aged 34.2 ± 5.9 years, they were diagnosed with type 1 diabetes mellitus at 19.5 ± 9.1 years and had been living with type 1 diabetes mellitus for the past 14.6 ± 10.5 years. Diabetic retinopathy and nephropathy were seen in 38.1% and 19.0% of patients, respectively. There were no obese patients in the present study, and the average BMI was 21.5 ± 2.6. PCOM was observed in 11 patients (52.4%).

Next, patients with type 1 diabetes mellitus were assigned to one of two groups based on the presence (PCOM) or absence (Non-PCOM) of PCOM, and differences between groups were evaluated. There was no significant difference in the average BMI between the two groups (22.6 ± 2.9 kg/m^2 and 20.3 ± 1.6 kg/m^2, respectively, in PCOS and Non-PCOS group). Daily insulin dose tended ($P = 0.08$) to be higher in patients with PCOM; however, there were no significant differences in clinical and anthropometric characteristics regarding diabetic state between the two groups (Table 2). Although the concentrations of LH and testosterone are often elevated in obese women with PCOM because of the associated hyperinsulinemia, we did not observe a significant increase in LH or testosterone in the type 1 diabetes mellitus PCOM group. Interestingly, blood DHEA-S concentrations were significantly higher in the patients with PCOM than in the Non-PCOM group (176.0 ± 73.8 *vs* 121.8 ± 46.0, $P < 0.05$; Table 3). Menstrual dysfunction was also more prevalent in the PCOM group ($P = 0.01$; Table 3). The age of patients who were diagnosed with PCOM was 32.5 ± 5.4 years. All patients were first diagnosed as PCOM in the present study.

In 29 patients without diabetes mellitus (21.4 ± 2.2 kg/m^2 and 33.0 ± 5.3 years), PCOM was observed in seven patients (24.1%).

DISCUSSION

In the present study, we are the first to report the frequency of ovarian morphological abnormalities and ovulatory dysfunction

Table 1 | Clinical and anthropometric characteristics in the women with type 1 diabetes mellitus

	n = 21
Age (years)	34.2 ± 5.9
Age at the onset of type 1 diabetes (years)	19.5 ± 9.1
Time from onset of type 1 diabetes (years)	14.6 ± 10.5
BMI (kg/m^2)	21.5 ± 2.6
HbA_{1c} (%)	7.9 ± 1.5
Insulin dose (IU/day)	43.2 ± 12.8
Diabetes retinopathy	8 (38.1%)
Diabetes nephropathy	4 (19.0%)

Values presented as mean ± standard deviation. BMI, body mass index; HbA_{1c}, glycated hemoglobin.

Table 2 | Clinical and anthropometric characteristics, and proportion of basal insulin of the women with type 1 diabetes mellitus with and without polycystic ovary morphology

	PCOM (*n* = 11)	Non-PCOM (*n* = 10)	*P*-value
Age (years)	32.5 ± 5.4	36.0 ± 6.3	0.22
Age at the onset of type 1 diabetes (years)	17.0 ± 7.8	22.3 ± 10.0	0.23
Time from onset of type 1 diabetes (years)	15.5 ± 10.5	13.6 ± 11.0	0.53
BMI (kg/m^2)	22.6 ± 2.9	20.3 ± 1.6	0.11
HbA_{1c} (%)	8.0 ± 1.0	7.8 ± 2.0	0.24
Insulin dose (IU/day)	48.3 ± 13.2	37.6 ± 10.3	0.08
Insulin dose (IU/kg/day)	0.86 ± 0.16	0.72 ± 0.21	0.14
Diabetes retinopathy	4 (36.4%)	4 (40.0%)	0.86
Diabetes nephropathy	1 (9.1%)	3 (30.0%)	0.22

Values presented as mean ± standard deviation. BMI, body mass index; HbA_{1c}, glycated hemoglobin; PCOM, polycystic ovary morphology; Non-PCOM, non-polycystic ovary morphology.

Table 3 | Clinical and biochemical characteristics, and proportion of basal insulin of the women with type 1 diabetes mellitus with and without polycystic ovary morphology

	PCOM (n = 11)	Non-PCOM (n = 10)	P-value
T-chol (mmol/L)	5.1 ± 0.8	5.1 ± 0.5	1.00
LH (IU/L)	7.8 ± 5.4	11.3 ± 14.6	0.67
FSH (IU/L)	6.1 ± 2.1	7.8 ± 4.1	0.32
LH/FSH ratio	1.2 ± 0.6	1.2 ± 0.9	0.32
Estradiol (pmol/L)	326.7 ± 239.1	497.5 ± 376.1	0.26
Total testosterone (nmol/L)	1.9 ± 0.6	1.6 ± 0.7	0.18
DHEA-S (μmol/L)	4.8 ± 2.0	3.3 ± 1.2	0.03
Gynecological age (years)	12.7 ± 1.7	13.0 ± 2.4	0.80
Menstrual cycle (days)	33.7 ± 6.1	28.8 ± 2.3	0.08
Existence of menstrual dysfunction	5 (45.5%)	0 (0.0%)	0.01
Glargine	6 (54.5%)	3 (30.0%)	0.26
Detemir	3 (27.3%)	1 (10.0%)	0.31
Human insulin	2 (18.2%)	5 (50.0%)	0.12

Values presented as mean ± standard deviation. DHEA-S, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PCOM, polycystic ovary morphology; Non-PCOM, non-polycystic ovary morphology; T-chol, total cholesterol.

in Asian women with type 1 diabetes mellitus. Overall, we identified a higher prevalence of PCOM (52.4%) as well as PCOS (14.3%) in lean premenopausal Japanese women with type 1 diabetes mellitus than in premenopausal normal women (24.1%). The prevalence of PCOM/PCOS in type 1 diabetes mellitus was similar compared with previous reports[5]. There was a previous study where Chinese women with gestational diabetes mellitus were examined in regard to the prevalence of PCOM and compared with normal women[7]. In that study, the prevalence of PCOM in premenopausal Chinese normal women was 23%. It is similar to the prevalence of PCOM in premenopausal Japanese normal women in the present study (24.1%).

PCOM is one of the morphological abnormalities that occurs in ovaries and is characterized by ovaries becoming enlarged and polycystic. PCOS is a heterogeneous disorder including ovulatory dysfunction and hyperandrogenism in addition to PCOM. In the present study, menstrual dysfunction was more prevalent in patients categorized as PCOM as compared with the Non-PCOM group. In patients with type 2 diabetes mellitus, it is well-known that hyperinsulinemia caused by insulin resistance promotes androgen secretion from the liver and ovaries[3], and in turn hyperandrogenism causes menstrual disorders, ovulatory disorders and polycystic changes of ovaries. Meanwhile, in patients with type 1 diabetes mellitus, it is reported that hyperinsulinemia caused by subcutaneously injected insulin results in hyperandrogenism in the same way[8–10]. In addition, when patients with type 1 diabetes mellitus have insulin resistance[11], excess insulin administered by injection might exacerbate androgen secretion from ovaries. Therefore, we were interested to determine whether lean Japanese women with type 1 diabetes mellitus had an increased prevalence of PCOM or PCOS, and what characteristics were associated with this difference. In the present study, there were no significant differences in daily insulin doses, BMI or total testosterone levels between the PCOM and Non-PCOM groups. Furthermore, these variables were not different between the PCOS and Non-PCOS sub-groups. This initial study was carried out with a small group of patients and an additional large prospective study will be required to verify the reported relationships among exogenous insulin doses, hyperandrogenism and PCOM/PCOS in Japanese patients with type 1 diabetes mellitus.

Serum levels of DHEA-S, which is mainly derived from the adrenal cortex, were significantly higher in the PCOM than the Non-PCOM group. It is reported that DHEA-S levels tend to be higher in patients with PCOM and PCOS, but the causes have not been clear[12–14]. The finding of increased DHEA-S levels in the women with PCOM is of particular interest, because the majority of evidence now indicates that the ovary is the primary source of androgen production in PCOS[15].

In general, the initial recommended treatments for ovulatory disorder in PCOS are beneficial lifestyle modifications, such as diet modification and exercise[16]. When these treatments are ineffective, pharmacological therapies are recommended. Although clomiphene is typically prescribed for ovarian dysfunction, it has been reported that metformin is also beneficial for restoring ovarian function in PCOM/PCOS patients with type 2 diabetes mellitus, because metformin improves insulin sensitivity and decreases hyperandrogenism[17]. There are no studies regarding medical treatment of ovarian function in PCOM/PCOS patients with type 1 diabetes mellitus; however, metformin is reported to be helpful for reducing daily insulin doses and body weight[18–20], leading to improved insulin resistance and hyperinsulinemia. Therefore, metformin might be a beneficial agent for PCOS patients with type 1 diabetes mellitus and should be investigated in future studies.

It has been reported that the insulin-like growth factor-1 (IGF-1) receptor and its downstream signals might be implicated in the pathophysiology of PCOS[3]. Physiologically, human insulin could bind to the IGF-1 receptor with a low-affinity; however, insulin analogs, such as glargine, might stimulate ovarian IGF-1 receptors with higher-affinity[21]. In the current study, glargine use was similar between the PCOM (54.5%) and Non-PCOM (30.0%) groups (Table 3). Because of the small sample size of the current study, we are unable to determine if a relationship exists between the use of different types of insulin and the prevalence of PCOM/PCOS in patients with type 1 diabetes mellitus.

In the present study, there were a low number of participants and controls, so it was a small descriptive study. Although this initial study had limitations, we have shown that the prevalence of PCOM and PCOS is increased in premenopausal Japanese women with type 1 diabetes mellitus. Those patients with

PCOM tended to have a higher daily dose of insulin and elevated serum concentrations of DHEA-S. In the future, a multicenter, longitudinal study with a larger number of participants will be required to verify and extend our initial findings.

ACKNOWLEDGEMENTS

This work was supported by grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology Foundation #22590990 and Suzuken Memorial Foundation (HM). The authors declare that they have no conflict of interest.

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