Age at menarche in Japanese patients with type 1 diabetes mellitus: a look at changes since 1960s

Naoko Nishikawa-Nakamura¹, Tomoyuki Kawamura¹, Tatsuya Nakamichi¹, Yoshihiko Yuyama¹, Yuko Hotta¹, Kayako Hashimura², Tomomi Hashimoto³, Masakazu Hirose⁴, Takashi Higashide³ and Takashi Hamazaki¹

¹ Department of Pediatrics, Osaka City University Graduate School of Medicine, Osaka 545-8585, Japan
² Hashimura Clinic, Osaka 556-0014, Japan
³ HUGHUG Kids Clinic, Osaka 560-0004, Japan
⁴ D Medical Clinic Osaka, Osaka 530-0001, Japan

Abstract. Menarche is delayed in patients with type 1 diabetic mellitus (T1DM) compared to non-diabetics. The purpose of this survey study was to define the age of onset of menarche in Japanese patients with T1DM, as well the secular trends in menarcheal age across the period of 1976–2020 and determine the effects of T1DM and disease management on that age. The study subjects (n = 155) were recruited from among Japanese T1DM patients who visited the outpatient clinic of the Department of Pediatrics, Osaka City University Hospital. The study subjects experienced menarche during 1976–2020. They were divided into the menarche-post-T1DM group (n = 117) and the menarche-pre-T1DM group (n = 38), in whom menarche occurred after or before the diagnosis of T1DM, respectively. The time of birth was also stratified into five decade/time bins extending from 1960s to 2000s. The subjects filled a questionnaire on menarche. Other clinical information was obtained from the medical records. The median age at menarche was 12.5 years (11.3–13.4) (25th–75th percentile) for the menarche-post-T1DM group and 11.8 years (10.9–13.0) for the menarche-pre-T1DM group (p = 0.024). Menarche occurred at a significantly younger age in recent years in the menarche-post-T1DM group (r = –0.209, p = 0.023), but no such trend was found in the control group. Analysis of data of subjects born after 1990 still showed significant delay associated with T1DM [post-T1DM group: 12.3 years (11.3–13.2), pre-T1DM group: 11.8 years (11.0–12.2), p = 0.045]. The results suggest that recent advances in insulin therapy seem to improve metabolism under T1DM but might have not enough impact on menarche in Japanese girls.

Key words: Menarche, Type 1 diabetes mellitus, Delayed puberty, Japan

PUBERTY is delayed in women with type 1 diabetic mellitus (T1DM), compared to non-diabetics. In the USA, the estimated delay was 2 years in the 1940s [1], but the difference has become smaller in recent years, down to about 2 to 9 months, probably in association with the earlier age of onset of menarche (onset of menstruation) in both diabetic and non-diabetic girls [1-3]. In Japan, Ishiba et al. [4] reported in 1987 that age at menarche in patients with T1DM was 13 years and 2.8 months; significantly higher than that of the healthy females (12 years and 7.6 months). To our knowledge, this issue has not been investigated in Japan in the last 20 years.

Insulin therapy of T1DM has markedly evolved during the last two decades. Especially, several types of insulin analogues have become available since 2000s, including rapid- and long-acting insulins. Furthermore, basal-bolus insulin therapy is currently widely used based on its effect of improvement of glycemic control in T1DM patients. These therapeutic modalities may have minimized the effect of T1DM on the age of menarche.

The purpose of this survey study was to define the age of onset of menarche in patients with T1DM, as well the secular trends in menarcheal age across the period of 1976–2020 and determine the effects of T1DM and disease management on that age.

Patients and Methods

The survey was conducted on females with T1DM who were regularly followed-up at the Department of Pediatrics, Osaka City University Hospital between April
2019 and October 2020 for the management of T1DM. All participants or their guardians provided signed consent forms after receiving detailed explanation of the purpose and protocol of the study. We excluded patients with chronic disease at puberty, those on prolonged use of steroids, and infants diagnosed with T1DM at less than 1 year of age. The study subjects were 155 patients who answered the questionnaire on menarche. They were divided into two groups based on the timing of menarche and diagnosis of T1DM; the menarche-post-T1DM group, comprising 117 patients in whom menarche occurred after the diagnosis of T1DM, and the menarche-pre-T1DM group, comprising 38 patients in whom menarche occurred before the diagnosis of T1DM. The patients or their guardians completed the questionnaire, which also included information on age, school grade, and season of menstruation. The date of menarche found in the electronic medical records, if mentioned, was adopted after comparison to that on the questionnaire. The age at diagnosis of T1DM, HbA1c levels and body mass index (BMI) at diagnosis and menarche, disease duration, adult height, presence of thyroid disease, anti-glutamic acid decarboxylase (GAD) antibody, treatment details, total daily insulin dose (TDD) at menarche, the frequency of episodes of diabetic ketoacidosis (DKA) and severe hypoglycemia, and HbA1c levels at the age of 10, 11, and 12 years, and within 3 months and 1 year of menarche were obtained or extracted from the electronic medical records when available. In all patients, the etiology of T1DM was assumed to be autoimmune-related mechanism unless specified by the attending physician. Insulin was the treatment used by all patients irrespective of presence or absence of diabetes-associated autoantibodies.

Patients were seen at the outpatient clinic every 1–3 months for clinical evaluation and measurement of HbA1c. HbA1c levels measured in accordance with the International Diabetes Federation (IDF) classification were standardized to the NGSP. National Glycohemoglobin Standardization Program (NGSP) using the following equation: HbA1c-NGSP (%) = 1.02 × JDS (%) + 0.25 [5]. At our hospital, HbA1c levels were not standardized before 1994. They were standardized by JDS from the spring 1994 to Spring 2012 and by NGSP thereafter. Accordingly, the pre-1994 original data were used as JDS values and converted to NGSP.

DKA was defined as blood glucose level >11 mmol/L (200 mg/dL), pH of venous blood <7.3 and ketonemia or ketonuria. Severe hypoglycemia was defined as an event associated with cognitive impairment requiring assistance by another person. BMI was calculated as the weight in kilograms divided by the height in square meters. The standardized BMI, or BMI standard deviation score (BMI-SDS), was calculated using the existing Japanese population data matched for age and sex, in accordance with the guidelines of the Japanese Society for Pediatric Endocrinology [6]. GAD antibody of ≥1.5 U/mL by radioimmunoassay or 5 U/mL by enzyme-linked immune sorbent assay was considered positive. Adult height was defined as the height at 18 years of age, or the height at which the growth rate became flat for 1 year on the growth curve.

The research protocol was approved by the Ethics Review Committee for Medical Research at Osaka City University (#2020-285).

**Statistical analysis**

All data were reported as median (25th–75th quartile). The values of each parameter and age at menarche were compared between the two groups using the Mann-Whitney U test. Secular trend of age at menarche according to year of birth was tested using Kruskal-Wallis test. The relationship between age at menarche and each variable was tested using Spearman’s rank correlation coefficient. P values were two-tailed and considered significant at <0.05. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 26.0. (Armonk, NY: IBM Corp.).

**Results**

Menarche was recorded in our cohort between 1976 and 2020. Analysis of the questionnaires of the entire group (n = 155) showed that menarche occurred at 12.2 years (11.2–13.3), and at significantly older age in the menarche-post-T1DM group (12.5 years (11.3–13.4]), compared with the menarche-pre-T1DM group (11.8 years (10.9–13.0), p = 0.024). Table 1 shows the characteristics of the study subjects. By definition, age at the time of diagnosis of T1DM of the menarche-post-T1DM group was younger than that of the menarche-pre-T1DM group [6.5 years (4.8–9.8), 15.2 years (13.4–17.5), p = 0.000]. T1DM disease duration was longer in the menarche-post-T1DM group than that of the menarche-pre-T1DM group [17.0 years (10.8–22.0), 14.4 years (5.2–21.3), p = 0.039]. The prevalence rates of thyroid disease; chronic thyroiditis or Graves’ disease were higher in the menarche-pre-T1DM group than the menarche-post-T1DM group (26.5%, 4.3%, p = 0.000). None of the patients had thyroid disease before menarche. There was no difference in adult height between the two groups. In the menarche-post-T1DM group, age at menarche correlated with T1DM disease duration (r = 0.235, p = 0.011), but not with age at diagnosis of T1DM.

Next, we examined the trend in menarche age across 5 decades (1960s–2000s). For this purpose, we divided the...
subjects into different bins according to the year of birth (1960s, 1970s, 1980s, 1990s, and 2000s). The number of study subjects born in 1960s was 2 (menarche-post-T1DM group: 2, menarche-pre-T1DM group: 0), 1970s was 12 (n = 4, 8, respectively), 1980s was 27 (n = 14, 13, respectively), 1990s was 57 (n = 52, 5, respectively), and 2000s was 57 patients (n = 45, 12, respectively). Fig. 1 shows the changes in age at menarche according to the year of birth. Interestingly, age at menarche decreased with time in the menarche-post-T1DM group (r = −0.209, p = 0.023), but not in the menarche-pre-T1DM group. However, there was no significant difference in age at menarche between the two groups at the same birth year.

Next, we examined the change in age at menarche in recent years. For this purpose, we narrowed down the analysis to subjects born after 1990. For this group, age at menarche occurred significantly later in the menarche-post-T1DM group than the menarche-pre-T1DM group [12.3 years (11.3–13.2), n = 97, 11.8 years (11.0–12.2), n = 17, p = 0.045, Fig. 2].

The BMI-SDS at diagnosis measured in 41 patients of the menarche-post-T1DM group was −0.75 (−1.79–0.61) and this parameter correlated negatively with menarche age. The results also showed that the lower BMI-SDS at T1DM diagnosis was, the more delayed the age at menarche was (r = −0.392, p = 0.011). For 91 patients of the menarche-post-T1DM group whose BMI data were available, BMI-SDS at menarche was 0.46 (−0.01–0.80). In this group, the lower the BMI-SDS at menarche age was, the more delayed the menarche age was (r = −0.356, p = 0.001, Fig. 3).

Table 1 shows mean HbA1c levels at 10, 11, 12 years of age and within 3 months and 1 year prior to menarche for subjects of the menarche-post-T1DM group. There was no correlation between age at menarche and HbA1c levels at 10, 11, and 12 years of age, and within 3 months and 1 year prior to menarche.

In the menarche-post-T1DM group, age at menarche neither correlated with GAD antibody positivity, presence of DKA at diagnosis, HbA1c levels at T1DM diagnosis, frequency of DKA episodes (within 3 years of T1DM diagnosis)
Fig. 1 Changes in age at menarche according to year of birth.
Differences in age at menarche between the groups according to year of birth were analyzed by the Kruskal-Wallis test. Age at menarche decreased with time in the menarche-post-T1DM group ($r = -0.209$, $p = 0.023$), but not in the menarche-pre-T1DM group ($r = -0.101$, $p = 0.546$). There was no significant difference in age at menarche between the two groups at the same birth year. Data of 1990–1999 are not shown due to the small number of subjects in the menarche-pre-T1DM group. Box plot shows age at menarche for the two T1DM groups according to year of birth, from 1960s to 2000s. Numbers under years of birth represent numbers of subjects. In these box-and-whisker plots, lines within the boxes represent median values; the upper and lower lines of the boxes represent the 25th and 75th percentiles, respectively; and the upper and lower bars outside the boxes represent the 10th and 90th percentiles, respectively, and points above and below these bars represent data outside the 10th and 90th percentiles. × outliers.

Fig. 2 Comparison of age at menarche between the menarche-post-T1DM group and the menarche-pre-T1DM group in a subgroup of patients born after 1990.
The difference in age at menarche between the two group was analyzed by the Mann-Whitney $U$ test. Age at menarche occurred significantly later in the menarche-post-T1DM group than the menarche-pre-T1DM group [12.3 years (11.3–13.2), $n = 97$, 11.8 years (11.0–12.2), $n = 17$, $p = 0.045$]. See Fig. 1 for explanation of the box plots. ○ outliers.
menarche age) nor with frequency of severe hypoglycemic episodes (within 3 years of menarche age).

**Discussion**

The main purpose of this study was to analyze secular trends in menarcheal age in patients with T1DM. We adopted the menarche-pre-T1DM group as the control group because it is difficult to include healthy girls as the control in a retrospective study. It was assumed that age at menarche in the menarche-pre-T1DM group is similar to that of the general healthy population, because one does not expect any effect for the onset of diabetes or abnormalities of glucose metabolism in this population. In fact, several previous studies that investigated age at menarche in patients with T1DM applied the same approach in patients/subject selection [3, 7, 8]. The study of Lombardo et al. [8] reported that age at menarche of patients who developed T1DM after the first menstrual cycle matched those of their respective mothers as well as those of healthy control girls.

In our study, menarcheal age was 12.2 years (11.2–13.3) for the entire group, with delayed menarche at 12.5 years (11.3–13.4) for the patients of the menarche-post-T1DM group, compared with that of 11.8 years (10.9–13.0) for those of the menarche-pre-T1DM group. In comparison, the reported age at menarche of healthy Japanese women is 12.2 ± 0.9 years [9]. Our results showed that age at menarche of patients with T1DM is almost the same as that of the Japanese general population.

Evidence suggests that menarche starts at later age in those diagnosed with T1DM. Schweiger et al. [3] investigated whether age at menarche had changed between 1970s and 2000s in patients with T1DM. They found that menarcheal age decreased significantly over 40 years, although the delay in menarche among girls diagnosed with T1DM before menarche, relative to those affected after menarche, remained significant throughout the 40 years. Our results also showed that age at menarche started to decrease during the period between 1960s and 2000s in girls of the menarche-post-T1DM group (Fig. 1). What is the reason for the observed trend? While our study did not investigate this directly, such decrease of menarche age in the menarche-post-T1DM group is probably related to the improvement in glycemic condition during the study period. Patients born after 1990 received advanced treatment, including basal bolus insulin therapy using multiple daily injections, as well as pump therapy using various insulin analogues. Apart from comparison of the two groups, we also limited the comparison to the subgroups of patients born after 1990 to determine the trend in recent years only. The results showed that menarche was still significantly delayed in the menarche-post-T1DM group than the menarche-pre-T1DM group (Fig. 2). However, the first menstrual cycle occurred when the girls of the menarche-pre-T1DM group born after 1990 were 11.8 years of age, i.e., they were younger than those of the general population surveyed after 2000: 12 years 2.3 months [10]. Therefore, it is possible that our patient selection was somewhat biased and may have influenced the results. For patients born after 2000, delay of menarche was observed in the

![Fig. 3](image-url)  
Fig. 3 Association of age at menarche with BMI-SDS at menarche for T1DM patients of the menarche-post-T1DM group. Note the negative correlation of age at menarche with BMI-SDS at menarche based on data of 91 patients, analyzed by Spearman’s rank correlation coefficient ($r = -0.356, p = 0.001$). The line was predicted by linear regression.
menarche-post-T1DM group compared to the menarche-pre-T1DM group [12.3 years (11.3–13.1) vs. 11.8 years (11.2–12.3), \( p = 0.378 \)] though the difference was not statistically significant. The lack of significance could be due to the small number of subjects in the two groups. Therefore, further studies of larger samples of Japanese girls are needed to determine the true effect of T1DM on age at menarche in this population.

What are the factors that affect age at menarche in diabetics? Previous studies reported that low BMI, poor glycemic control, long disease duration, and age at diagnosis are associated with delayed menarche in girls with T1DM [1, 11]. With regard to HbA1c and management of diabetes, it is known that blood glucose and luteinizing hormone (LH) levels have a negative correlation [12] and glycemic control correlates with menstrual and reproductive disorders [13]. Previous studies described the association of age at menarche with HbA1c levels within 3 years prior to menarche [14], at menarche, within 1 year before menarche, and within 2 years prior to menarche [8]. However, our results showed no correlation between HbA1c levels at 10, 11, 12 years of age and within 3 months and 1 year prior to menarche. For our patients diagnosed with T1DM after 2000s, HbA1c levels at 10, 11, and 12 years of age were \( \leq 8.0\% \). Furthermore, the number of subjects who used continuous subcutaneous insulin infusion (CSII) increased significantly at the age of 10, 11, and 12, in recent years. A previous Japanese study [15] also reported that HbA1c levels in patients aged 11 and 12 were above 8.5% in 1995–1999 but below 8% in 2008–2013. Such improvement in glycemic control may affect the onset of menarche.

Is there a relationship between BMI and menarche? Several studies reported a negative correlation between age at menarche and BMI in girls with T1DM [14, 16], and between the BMI z-score for 3 years and for 3 months prior to menarche [7, 14]. Our study showed a negative correlation between BMI-SDS at menarche and age at menarche. Studies from Japan and Scandinavia demonstrated a steady increase in BMI of women with T1DM in recent years [17, 18]. Furthermore, increased BMI in T1DM correlate with a dramatic increase in intensive insulin therapy [19]. Increased BMI in T1DM reflects improvement of glycemic control and may contribute to the onset of menarche.

Our study showed that the factors that affected menarche; glycemic control and physique, improved in recent time.

Our study has certain limitations. First, the study included only a relatively small number of subjects recruited from a single institution. Second, we could not use the healthy control, because the study was retrospective in design. Third, the study is mainly based on a questionnaire that was completed by the patient or guardian, which carries inherent recall bias. Although a previous study showed a high correlation between recall and original age at menarche even after 30 years [20], we cannot rule out recall bias as a limitation. Fourth, HbA1c levels were not standardized before 1994. Fifth, we did not conduct an objective stage evaluation of Tanner classification or hormonal profiling. Finally, some questions required descriptive rather than precise answers, such as the season of menarche, which may carry errors of several months.

In conclusion, our results demonstrated a small but significant delay of menarche in Japanese T1DM patients, although such delay showed a trend of becoming shorter in recent years. The latter could be related to better management of T1DM. Advances in T1DM therapy, including new insulin compounds and the use of clever medical devices for careful monitoring of the effect of insulin therapy, could eliminate this delay in the near future.

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Disclosure
All authors declare no conflict of interest.

Authors’ Contribution
All authors identified the need for this review article, helped in developing the search terms used, and screened the search results. All authors reviewed the initial and last drafts of the manuscript, approved the final version of the manuscript and agreed on the need for submission/publication. N.N., T.N. and T.K. designed the research study, N.N., Y.Y. and Y.H. conducted the research work, K.H., Tomomi Hashimoto, M.H. and Takashi Higashide contributed to sample preparation, N.N., T.K. and Takashi Hamazaki took the lead in writing manuscript, and T.K. reviewed the manuscript for accuracy on behalf of N.N.
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