Impact of age at menarche on obesity and
glycemic control in Japanese patients with
type 2 diabetes: Fukuoka Diabetes Registry

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ABSTRACT
Aims/Introduction: A younger age at menarche is associated with obesity and type 2 diabetes in adult life. The impact of early-onset menarche on obesity and glycemic control in type 2 diabetes has not been investigated. The present study examined the relationship between age at menarche and obesity and glycemic control in type 2 diabetes.

Materials and Methods: A total of 2,133 patients with type 2 diabetes aged ≥20 years were divided into groups according to age at menarche (≤11, 12, 13, 14 and ≥15 years). A retrospective cohort study examined the association of menarcheal age with adiposity and hemoglobin A1c.

Results: Age at menarche was inversely associated with body mass index (BMI) and abdominal circumference (P < 0.001). Each 1-year decrease in age at menarche was associated with a 0.25-kg/m2 and 0.6-cm increase in BMI and abdominal circumference, respectively, using a multivariate-adjusted model. Odds ratios for obesity and abdominal obesity significantly increased in participants with age at menarche ≤11 years after multivariable adjustments when age at menarche of 13 years was used as the reference (odds ratio 1.95, 95% CI 1.33–2.88, odds ratio 1.95, 95% CI 1.32–2.87, respectively). Younger age at menarche was significantly associated with higher hemoglobin A1c (P < 0.001); however, the association was not statistically significant after adjusting for BMI.

Conclusions: Age at menarche of ≤11 years was associated with obesity after adjusting for confounding factors, and poor glycemic control associated with high BMI in type 2 diabetes. Age at menarche should be considered during clinical assessments.

INTRODUCTION
There is a trend towards a younger age at which people are reaching puberty, possibly associated with the impact of Westernization. In Japan, the mean age at menarche decreased from 13.2 years in 1961 to 12.2 years in 2011 in school-aged girls1. Earlier-onset menarche is reported to be associated with obesity2–5, type 2 diabetes mellitus6–11, cardiovascular disease4–14, breast cancer15 and increased all-cause mortality4,13,16–18. It is therefore possible that age at menarche can provide important information to help prevent non-communicable diseases.

Obesity is a global health problem. Although the prevalence of obesity is lower in Japan than Western populations generally (prevalence of body mass index [BMI] ≥30: 3.7% in Japan vs 38.2% in the USA19), there has been an increase in the level of obesity in patients with type 2 diabetes in Japan (mean BMI increased from 24.1 kg/m2 in 2002 to 25.0 kg/m2 in 201320).

It is reported that a younger age at menarche is associated with obesity in later life2–5. This raises the question as to the association between age at menarche and obesity in patients with type 2 diabetes, and whether early-onset menarche is associated with plasma glucose levels and could be used to predict the future onset of type 2 diabetes6–11. Against this background, the present retrospective cohort study examined the
relationship between age at menarche and obesity and glycemic control in Japanese patients with type 2 diabetes.

**METHODS**

**Study participants**

The Fukuoka Diabetes Registry was designed as a prospective, multicenter, observational study to investigate the effects of modern therapy on the prognosis of Japanese patients with diabetes mellitus. Briefly, the Fukuoka Diabetes Registry cohort comprised patients aged ≥20 years who regularly attended educational research hospitals approved by the Japan Diabetes Society or certified diabetes clinics in Fukuoka Prefecture (UMIN Clinical Trial Registry 000002627) between April 2008 and October 2010. Exclusion criteria were people with drug-induced diabetes mellitus or receiving corticosteroid therapy; those who had undergone renal replacement therapy; those with serious diseases other than diabetes, such as advanced malignancy or decompensated liver cirrhosis; and those who were unable to visit a diabetologist regularly. Of the 2,263 women registered, after excluding those with type 1 diabetes, 2,133 female patients with type 2 diabetes mellitus remained, and were enrolled in the study. The study was approved by the Kyushu University Institutional Review Board and was carried out in accordance with the provisions contained within the Declaration of Helsinki. All patients provided written informed consent for participation in the study.

**Clinical evaluation and laboratory measurements**

Participants completed a self-administered questionnaire that sought information on age at diagnosis of diabetes, family history of diabetes, smoking habits, alcohol intake, physical activity, maximum bodyweight before enrollment, age at menarche and the occurrence of menopause. Smoking habits and alcohol intake were classified as either current use or not. Metabolic equivalent hours per week were calculated using Ainsworth’s methods. A dietary survey was carried out using a brief-type self-administered diet history questionnaire (Gender Medical Research, Inc., Tokyo, Japan) that sought information on the frequency of consumption of 58 items to assess the participants’ dietary intakes. The dietary intake estimates for total energy and dietary fiber were calculated using an ad hoc algorithm developed for the brief-type self-administered diet history questionnaire based on the Standard Tables of Food Composition in Japan. The medical records of participants were examined for medications including oral hypoglycemic agents and insulin therapy. Bodyweight and height were measured, and BMI was calculated. Obesity was defined as BMI ≥25 kg/m² according to the Japan Society for the Study of Obesity criteria. Abdominal circumference at the umbilical level was measured in the standing position. Abdominal obesity was defined as an abdominal circumference of ≥90 cm according to the Japan Society for the Study of Obesity criteria.

Blood tests were carried out in either the fasting or postprandial state. Hemoglobin A₁c (HbA₁c) was determined by high-performance liquid chromatography (Tosoh Corp., Tokyo, Japan), and serum C-peptide was determined using chemiluminescent immunoassays (Kyowa Medex, Tokyo, Japan). High-sensitivity C-reactive protein (HS-CRP) and serum adiponectin were determined by latex immunonephelometry (Siemens Healthcare Diagnostics, Tokyo, Japan; Mitsubishi Chemical Medience, Tokyo, Japan). β-Cell function (homeostatic model assessment of β-cell [HOMA2-%β] index) and insulin resistance (homeostatic model assessment of insulin resistance [HOMA2-IR] index) were estimated based on fasting glucose and C-peptide concentrations using a HOMA calculator (version 2.2.2; http://www.dtu.ox.ac.uk, accessed June 2012) after exclusion of individuals with unacceptable levels of plasma glucose (<3.0 mmol/L or >25 mmol/L) or C-peptide (<0.2 nmol/L or >3.5 nmol/L).

**Statistical analysis**

HOMA2-%β, HOMA2-IR, serum adiponectin and HS-CRP were log-transformed for statistical analyses because of their skewed distributions. They are presented with 95% confidence intervals (95% CI) that were back-transformed. Participants were divided into five categories according to age at menarche: ≤11, 12, 13, 14 and ≥15 years, as reported in previous studies. Baseline characteristics by categories of age at menarche were explored using one-way analysis of variance and analysis of covariance to compare means of continuous variables, and using χ²-tests to compare proportions of categorical variables. Trend associations for age at menarche were assessed using multivariable regression analyses, and included age, duration of diabetes, current smoking, current drinking, leisure-time physical activity, daily energy intake, oral hypoglycemic agent use and insulin use as covariates. Associations between age at menarche and the prevalence of obesity, history of obesity and abdominal obesity were tested using multivariable logistic regression analyses. All analyses were carried out using the SAS software package (version 9.4; SAS Institute Inc., Cary, NC, USA). A P-value <0.05 was considered statistically significant.

**RESULTS**

**Participant characteristics**

Baseline characteristics of the study participants by categories of age at menarche are shown in Table 1. The mean age at menarche was 13.7 ± 1.8 years. Those with a younger age at menarche were diagnosed with diabetes at a younger age, had a shorter duration of diabetes, were more likely to be premenopausal, had lower energy and dietary fiber intake, and exercised less. These statistical differences were absent after adjusting for age.

**Associations between age at menarche and obesity**

The age at menarche was inversely associated with BMI (P for trend <0.001; Table 2). The association remained statistically significant after multivariable adjustments including age, duration of diabetes, current smoking, current drinking, leisure-time physical activity, daily energy intake, oral hypoglycemic agent use and insulin use as covariates.
Table 1 | Clinical characteristics of the study participants by categories of age at menarche

|                         | Total                  | Categories of age at menarche (years) | P for trend |
|-------------------------|------------------------|--------------------------------------|-------------|
|                         |                        | ≤11 (11.0–15.0)                      |             |
| n                       | 2,133                  | 169                                  |             |
| Age (years)             | 65.8 ± 10.4            | 53.2 ± 11.4                          |             |
| Age at diabetes diagnosis (years) | 51.0 ± 11.9           | 40.3 ± 12.9                          |             |
| Duration of diabetes (years) | 14.3 ± 9.8             | 12.4 ± 9.2                           |             |
| Family history of diabetes (%) | 61.5                  | 68.6                                 |             |
| Menopause (%)           | 92.3                   | 63.9                                 |             |
| Age at menopause (years) | 49.4 ± 5.3             | 48.9 ± 5.4                           |             |
| Reproductive years      | 35.5 ± 5.5             | 38.2 ± 5.4                           |             |
| Current smoker (%)      | 6.8                    | 10.7                                 |             |
| Current drinker (%)     | 16.5                   | 17.2                                 |             |
| Energy intake (kcal/day) | 1,509 ± 412            | 1,479 ± 384                          |             |
| Dietary fiber intake (g/1,000 kcal) | 83 ± 2.2           | 76 ± 2.1                             |             |
| LTPA (MET h/week)       | 163 ± 16.4             | 134 ± 14.0                           |             |
| Oral hypoglycemic agents (%) | 63.5                 | 63.9                                 |             |
| Insulin (%)             | 30.8                   | 36.7                                 |             |

Data are mean ± standard deviation or percentage. Numbers in parenthesis represent interquartile range. LTPA, leisure-time physical activity; NS, not significant.
Table 2 | Association of categories of age at menarche with adiposity, stratified by age in Japanese patients with type 2 diabetes

| Categories of age at menarche (years) | ≤11 | 12 | 13 | 14 | ≥15 |
|--------------------------------------|-----|----|----|----|-----|
| Age at menarche (years)              | 10.7 (10.0–11.0) | 12.0 (12.0–12.0) | 13.0 (13.0–13.0) | 13.9 (14.0–14.0) | 15.8 (15.0–16.0) |
| BMI (kg/m²)                          | 26.3 ± 6.1 | 24.7 ± 4.6 | 24.1 ± 4.5 | 23.4 ± 3.7 | 23.4 ± 3.8 |
| Maximum BMI (kg/m²)                  | 29.7 ± 6.3 | 28.2 ± 4.9 | 27.4 ± 4.7 | 26.7 ± 3.8 | 26.7 ± 3.9 |
| Abdominal circumference (cm)         | 89.0 ± 14.3 | 87.0 ± 11.7 | 86.0 ± 12.4 | 84.8 ± 10.5 | 85.3 ± 11.2 |

Data are mean ± standard deviation. Numbers in parenthesis represent interquartile range. Multivariable adjustments include age, duration of diabetes, current smoking, current drinking, leisure-time physical activity, daily energy intake, oral hypoglycemic agent use and insulin use. BMI, body mass index; NS, not significant.
were obtained in participants aged <65 years, whereas there were no associations in those aged ≥65 years.

**DISCUSSION**

In the present study, age at menarche was inversely associated with adiposity in patients with type 2 diabetes. To the best of the authors’ knowledge, this is the first study to report on the association between age at menarche in patients with type 2 diabetes. It is reported that earlier-onset menarche is associated with obesity and the development of type 2 diabetes mellitus in later life. The present results extend the association between age at menarche and obesity to patients with type 2 diabetes. Although people with obesity and type 2 diabetes are strongly urged to modify their lifestyle habits, including diet and exercise, there were twice as many patients in the ≤11 years-of-age at menarche group compared with the 13 years-of-age at menarche group. It is possible that obesity contributes to worsened glycemic control in those with age at menarche ≤11 years.

In a meta-analysis of 10 studies including 246,671 women, mostly from Western populations, early menarche (<12 vs 12 years) was associated with 0.34 kg/m² higher BMI. Of 303,000 women in the China Kadoorie Biobank, increases in BMI and abdominal circumference per 1-year earlier onset of menarche were reported to be 0.19 kg/m² and 0.38 cm, respectively. In the current study, increases in BMI and abdominal circumference per 1-year earlier onset of menarche were 0.25 kg/m² and 0.6 cm in the multivariate-adjusted model. It appears that the impact of earlier-onset menarche on obesity is greater in the current study. This difference might be explained by the populations studied. For example, the general population vs patients with type 2 diabetes, or Western populations vs Asian populations, in whom those with type 2 diabetes are not typically obese.

The association between age at menarche and BMI was observed in both the <65 years and ≥65 years age groups. One of the mechanisms that has been proposed to explain the
Table 4 | Association of categories of age at menarche with glycemic control, insulin secretion, insulin resistance, adiponectin and microinflammation in Japanese patients with type 2 diabetes

| Categories of age at menarche (years) | 
|--------------------------------------|
| ≤11 | 12 (12.0–15.0) | 13 (13.0–14.0) | 14 (14.0–15.0) | ≥15 (15.0–16.0) |
| HbA1c (%) |  
| All | 7.77 ± 1.29 | 7.63 ± 1.16 | 7.59 ± 1.09 | 7.48 ± 0.97 | 7.47 ± 1.02 |
| <65 years | 7.78 ± 1.31 | 7.72 ± 1.27 | 7.62 ± 1.12 | 7.49 ± 0.99 | 7.59 ± 1.18 |
| ≥65 years | 7.70 ± 1.16 | 7.45 ± 0.85 | 7.56 ± 1.06 | 7.47 ± 0.97 | 7.45 ± 0.99 |
| HbA1c (mmol/mol) |  
| All | 59.8 (56.8–63.8) | 58.4 (55.8–61.8) | 58.0 (55.1–61.1) | 56.8 (52.9–60.9) | 56.8 (52.4–61.2) |
| <65 years | 59.9 (57.9–63.9) | 59.2 (56.3–63.3) | 58.3 (55.4–61.4) | 56.9 (53.0–60.0) | 57.9 (53.9–61.9) |
| ≥65 years | 59.1 (55.1–63.1) | 56.6 (53.6–63.6) | 57.7 (54.8–63.7) | 56.7 (53.7–63.7) | 56.5 (52.5–63.5) |
| HOMA2-%β |  
| All | 39.6 (36.5–43.0) | 38.9 (36.8–41.1) | 39.5 (37.6–41.6) | 40.8 (38.9–42.8) | 41.1 (39.4–43.0) |
| <65 years | 42.3 (39.3–50.1) | 37.6 (34.3–41.3) | 39.6 (36.9–42.4) | 41.6 (39.4–44.1) | 41.4 (39.5–43.4) |
| ≥65 years | 39.2 (35.7–43.0) | 39.5 (36.8–42.4) | 39.5 (36.7–42.5) | 39.4 (36.2–42.8) | 39.9 (35.8–44.5) |
| HOMA2-IR |  
| All | 1.12 (1.05–1.20) | 1.02 (0.97–1.06) | 0.98 (0.94–1.02) | 0.95 (0.91–0.99) | 0.98 (0.94–1.01) |
| <65 years | 1.14 (1.06–1.23) | 1.06 (1.00–1.13) | 0.99 (0.93–1.05) | 0.96 (0.90–1.03) | 1.03 (0.95–1.13) |
| ≥65 years | 1.04 (0.88–1.24) | 0.93 (0.86–1.00) | 0.97 (0.92–1.03) | 0.94 (0.90–0.99) | 0.97 (0.93–1.00) |
| Adiponectin (μg/mL) |  
| All | 9.0 (8.2–9.8) | 10.0 (9.5–10.7) | 10.6 (10.1–11.2) | 10.7 (10.2–11.2) | 11.4 (10.9–11.9) |
| <65 years | 8.9 (8.1–9.8) | 9.3 (8.6–10.0) | 10.4 (9.6–11.2) | 10.6 (9.7–11.5) | 9.8 (8.7–10.9) |
| ≥65 years | 9.6 (7.7–12.0) | 11.9 (10.8–13.2) | 11.0 (10.2–11.7) | 10.7 (10.1–11.4) | 11.8 (11.2–11.4) |
| HS-CRP (mg/L) |  
| All | 0.64 (0.52–0.79) | 0.49 (0.42–0.56) | 0.48 (0.43–0.55) | 0.50 (0.44–0.56) | 0.50 (0.45–0.56) |
| <65 years | 0.67 (0.54–0.84) | 0.49 (0.41–0.58) | 0.42 (0.35–0.50) | 0.45 (0.37–0.55) | 0.48 (0.37–0.62) |
| ≥65 years | 0.48 (0.28–0.82) | 0.49 (0.38–0.63) | 0.56 (0.47–0.66) | 0.53 (0.45–0.61) | 0.51 (0.45–0.57) |

Data are mean ± standard deviation, percentage or odds ratios. Numbers in parenthesis represent interquartile range or 95% confidence. Multivariable adjustments include age, duration of diabetes, current smoking, current drinking, leisure-time physical activity, daily energy intake, oral hypoglycemic agent use and insulin use. BMI, body mass index; HbA1c, hemoglobin 1c; HS-CRP, high-sensitivity C-reactive protein; HOMA2-%β homeostasis model assessment of β-cell function; HOMA2-IR, homeostasis model assessment of insulin resistance; NS, not significant.
association between early age at menarche and obesity is that earlier-onset menarche might result in longer exposure to estrogen and adrenal steroids, which tend to maintain adiposity. Furthermore, an overlap between single-nucleotide polymorphisms implicated in the timing of puberty and in determining BMI in adulthood has been reported. These single-nucleotide polymorphisms include TCF7, which was shown to be a risk factor for obesity and type 2 diabetes, and LIN28B, which is associated with insulin sensitivity and oxidative stress-related β-cell apoptosis. Individuals who have these single-nucleotide polymorphisms tend to gain weight faster during infancy and early childhood, and show earlier-onset menarche.

Earlier age at menarche is associated with the future development of type 2 diabetes in Western and Asian populations, and was associated with elevated HbA1c, secondary to high BMI in the current study. These associations can be largely explained by increased adiposity. In the current study, earlier age at menarche was not associated with insulin secretion, but was associated with increased insulin resistance, reduced serum adiponectin and increased systemic inflammation (Table 4). However, adjusting for age and BMI removed these associations, being in line with HbA1c.

Analyses stratified according to age (<65 years and ≥65 years) showed that there were significant associations between age at menarche and history of obesity or abdominal obesity in participants aged <65 years, but not in those aged ≥65 years (Table 3). This might be due to the small number of participants who went through menarche at ≤11 years (n = 23) among those aged ≥65 years. In addition, there were no significant interactions between the age of the participant (<65 and ≥65 years) and their age at menarche.

The present study had some limitations. First, there is the possibility of recall bias regarding age at menarche, although previous studies report that recalling age at menarche is reliable over many years. Second, we could not clarify the influence of childhood or pubertal BMI on adulthood obesity because of a lack of information. Finally, the conclusions of the study should not be generalized to other ethnic populations, especially with high BMI, without caution.

In conclusion, age at menarche of ≤11 years was associated with obesity after adjusting for confounding factors, and poor glycemic control associated with BMI in type 2 diabetes. As obesity can accelerate the development and progression of diabetic complications, age at menarche should be a factor for consideration when determining clinical management of patients with obese type 2 diabetes.

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DISCLOSURE
The authors declare no conflict of interest.

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