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Original Article

Impact of age at menarche on glycosylated hemoglobin levels in Korean non-diabetic women: the Korean National Health and Nutrition Examination Surveys

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Abstract: Evidence indicates that age at menarche is independently associated with dysglycemia in adult life. The aim of this study was to evaluate the association between age at menarche and glycosylated hemoglobin (HbA1c) levels in non-diabetic women using the Korea National Health and Nutrition Examination Survey (KNHANES). Data from 7,800 non-diabetic women from KNHANES 2010-2013 were analyzed. Participants were divided into three categories according to the age at menarche: early (<12 years), normal (12 to 16), late (≥16 years) age at menarche. The mean HbA1c levels were 5.49%, 5.55%, and 5.73% in the early, normal, and late menarche groups, respectively (p<0.001). The age at menarche was positively correlated with HbA1c in Pearson's correlation analysis. The mean HbA1c levels were higher in women with early age at menarche (5.676%) than those with normal and late age at menarche (5.605%; p=0.010, and 5.611%; p=0.022, respectively) after adjusting for age. In a multivariate linear regression analysis, increasing age at menarche was associated with a U-shaped pattern of HbA1c after adjusting for relevant confounders, including current age and BMI (p=0.033). The HbA1c level was 0.028%, and 0.014% higher in women with early menarche than in those with normal and late menarche, respectively. The age at menarche is significantly and independently associated with HbA1c levels and has a curvilinear (U-shaped) relationship with HbA1c levels. Early and late menarche are risk factors for increased levels of HbA1c.

Keywords: Early menarche, late menarche, age at menarche, HbA1c, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by high blood glucose and its associated complications. The disease has become a significant public health problem and poses an economic burden for both developed and developing countries, including Korea [1]. A large proportion of individuals with diabetes mellitus remain undiagnosed [2]. For these individuals, disabling and life-threatening complications may have developed at the time of diagnosis. It is important to plan preventive strategies and methods for addressing the growing epidemic of T2DM. Early identification and age-specific intervention of individuals at high risk for T2DM are main strategies for preventing the burden of disease-related morbidity and mortality [3].

Menarche is an indicator of maturation at puberty and is a benchmark of the beginning of normal reproductive life for women. In addition to gaining fertility, emerging evidence is indicating that age at menarche is associated with a future risk of health problems such as higher BMI [4], cardiovascular disease [5], metabolic risk factors [6] and mortality [7]. Most studies have focused on the association between early age at menarche and the development of diabetes and have demonstrated that age at menarche is associated with T2DM [8-11].

In the present study, we aimed to evaluate whether there is an association between age at menarche and glucose metabolism using glycosylated haemoglobin levels in Korean non-diabetic women. We also investigated whether this was an independent association or whether the relationship was mediated by confounders.

Materials and methods

Subjects

Data from the Korea National Health and Nutrition Examination Survey (KNHANES) 2010-

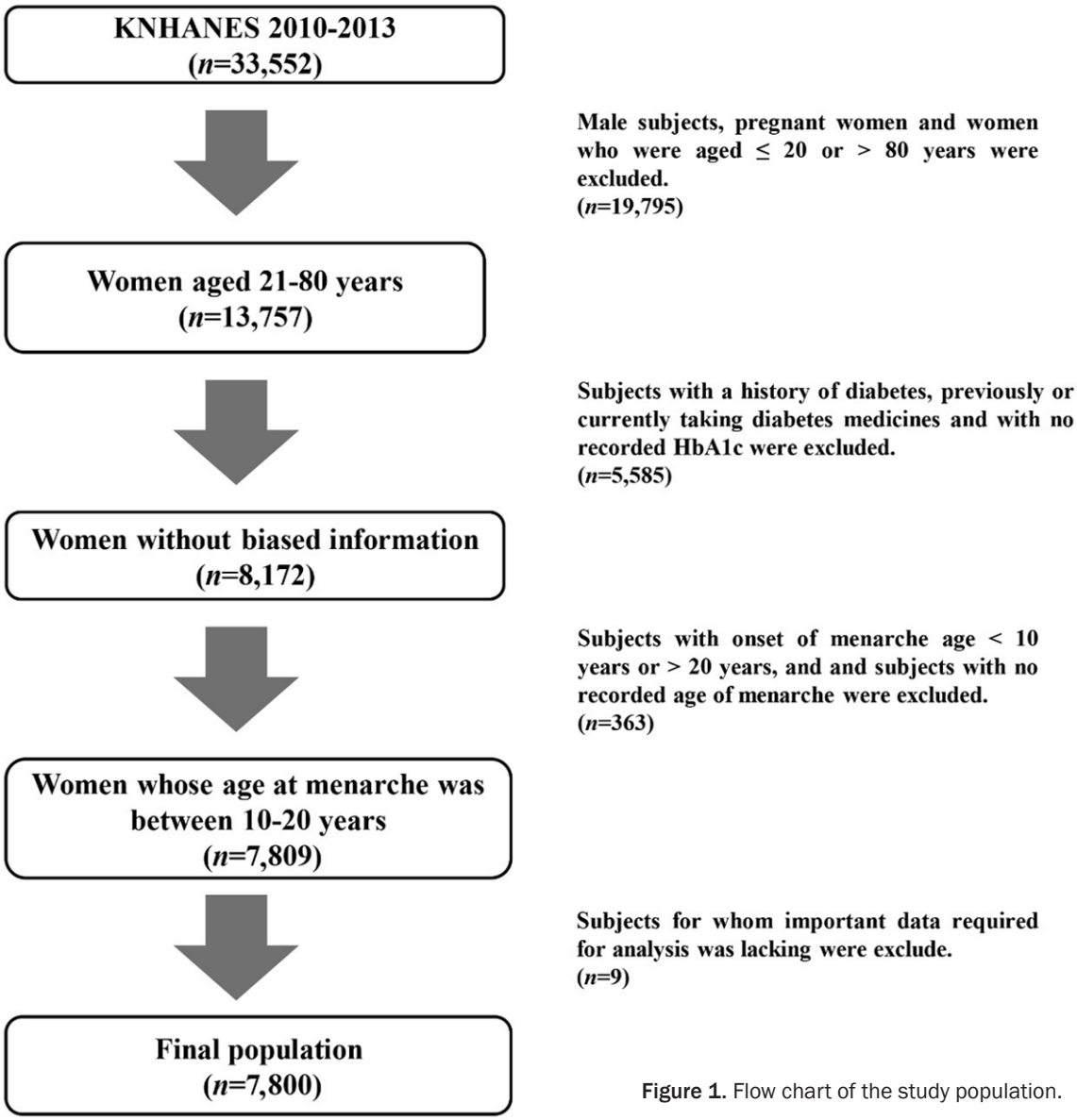

Figure 1. Flow chart of the study population.

2013 were used in this study. KNHANES is a cross-sectional, nation-wide and representative survey with a multistage and stratified sampling design that was conducted by the Division of Chronic Disease Surveillance, Korea Center for Disease Control and Prevention [12]. Details about the KNHANES have been described previously [13]. Of 33,552 participants in the KNHANES 2010-2013, 13,757 subjects were women aged 20-80 years (**Figure 1**). To avoid biasing the results, pregnant women were excluded because of the distinct hormonal changes that accompany pregnancy. Women with a previous or current diagnosis of diabetes, who were taking diabetes medicines and who did not have a recorded HbA1c were excluded (*n*=5,585). To exclude women with diabetes, diabetes was defined using a self-reported questionnaire: "Have you ever been diagnosed with diabetes by a physician?" and included type 1 and type 2 diabetes mellitus. Of the remaining 8,172 women, individuals were further excluded if they had onset of menarche age <10 or >20 years and had no records of their age at menarche (*n*=363). Subjects who were lacking important analytic data, such as fasting glucose, current blood pressure, current body mass index (BMI) and current waist circumference were also excluded (n=9). In the end, 7800 women were included in the present study. The database is available to the public at the website of KNHANES (http://knhanes.cdc.

go.kr) [13]. Informed consent was provided by all participants.

Anthropometric measurements

Anthropometric assessment was conducted by a trained expert using standard methods. In brief, height and body weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. Body mass index (BMI) was calculated as the weight (kg)/square of height (m^2). Waist circumference was assessed at the area between the lower rib margin and iliac crest to the nearest 0.1 cm. Systolic and diastolic blood pressure (BP, mmHg) were measured three times on the right upper arm using a calibrated sphygmomanometer with an appropriately sized cuff. Every measurement was taken 2 minutes apart. Then, the mean of the two last values was used for analysis.

Laboratory measurement

Blood samples were collected from the antecubital vein after fasting ≥10 hours. Serum concentrations of total cholesterol (T-C, mg/dL), high-density lipoprotein cholesterol (HDL-C, mg/dL), triglycerides (TG, mg/dL), low-density lipoprotein cholesterol (LDL-C, mg/dL), and fasting glucose (mg/dL) were measured using an automatic analyzer, Hitachi 7600 (Hitachi; Tokyo, Japan). In women with TG levels ≤400 mg/dL, LDL cholesterol was determined with the Friedewald formula: LDL-C (mg/dL) = T-C (mg/dL) - HDL-C (mg/dL) - (TG (mg/dL)/5) [14]. Glycosylated haemoglobin or the haemoglobin A1c (HbA1c, %) level was determined using high-performance liquid chromatography-723-G7 (Tosho; Tokyo, Japan).

Data collection of general characteristics

The data regarding general characteristics of the participants were obtained from the KNHANES. Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or current administration of anti-hypertensive medicine. Coronary heart disease was assessed using a self-reported questionnaire: "Have you ever been diagnosed with myocardial infarction or angina pectoris by a physician?" or use of medication for myocardial infarction or angina pectoris. Cerebrovascular disease was assessed using a questionnaire: "Have you ever been diagnosed with stroke by a physician?" or use of medication for stroke. Dyslipidaemia was also assessed by "Have you ever been diagnosed with dyslipidaemia by a physician?" or administration of medicine for the treatment of dyslipidaemia.

Assessment of gynaecological history, lifestyle, and socio-demographic characteristics were included in the general characteristics. The gynaecological characteristics included menopause, parity, and use of oral contraceptives. Menopause was categorized into two groups: yes or no. Parity was divided into two groups: labour ≥1 in a lifetime or never. Use of oral contraceptives was also categorized into two groups: administration of oral contraceptives ≥1 in a lifetime or never. The lifestyle characteristics included smoking status, regular alcohol intake, and physical activity. Smoking status was categorized into two groups: current or former vs. never. Former smoking was defined as ≥5 packs in one's lifetime. Regular alcohol intake was divided into three groups: ≤1/mo, ≥1/week, or daily. Physical activity was categorized into two groups: exercise or no exercise. Exercise was defined as intense physical activity for 20 min for ≥3 days/week, moderate physical activity for 30 min for ≥5 days/week, or walking for 30 min for ≥5 days/week. Education and household income were included in socio-demographic characteristics. Household income was reported in the currency of the Republic of Korea "won" (KRW) and was categorized into two groups: <4,000,000 KRW/mo or ≥4,000,000 KRW/mo. Education level was divided into two categories: ≤ elementary school or ≥ elementary school.

Age at menarche

Age at menarche was defined as the age of the first menstrual period. This information was obtained from an open-ended questionnaire: "At what age did your first menstrual period begin?" Participants were divided into three categories according to the age at menarche: early (<12 years), normal (12 to 16), late (≥16 years) age at menarche.

Statistical analyses

All analyses were performed using SPSS for Windows version 21 (IBM SPSS Inc., Chicago, IL, USA). Clinical characteristics of the study population were analyzed by three categories stratified according to the age at menarche (<12, 12-16, and ≥16 years). One-way analysis

Table 1. Clinical characteristics of the study population according to age at menarche (n=7,800)

	Age at menarche (years)			*P*
	Early (<12)	Normal (12-16)	Late (≥16)	
N	301	4,830	2,669	
Age (years)	32.85 ± 10.27	43.88 ± 13.30	58.61 ± 12.28	<0.001
Age at menarche (years)	10.81 ± 0.39	13.72 ± 1.03	17.08 ± 1.11	<0.001
Height (cm)	159.78 ± 5.20	15.39 ± 6.00	154.86 ± 6.32	<0.001
Weight (kg)	59.60 ± 11.53	57.46 ± 8.85	57.30 ± 8.40	<0.001
Body mass index (kg/m^2)	23.33 ± 4.29	22.92 ± 3.39	23.89 ± 3.17	<0.001
Waist circumference (cm)	76.00 ± 10.61	76.39 ± 9.18	80.37 ± 9.21	<0.001
Systolic blood pressure (mmHg)	107.82 ± 13.46	112.27 ± 15.94	122.63 ± 17.70	<0.001
Diastolic blood pressure (mmHg)	71.85 ± 9.72	72.97 ± 9.53	75.66 ± 9.77	<0.001
Fasting glucose	89.06 ± 8.51	91.46 ± 9.00	94.43 ± 9.90	<0.001
HbA1c	5.49 ± 0.34	5.55 ± 0.38	5.73 ± 0.41	<0.001
Fasting total cholesterol (mg/dL)	178.16 ± 32.41	188.46 ± 35.02	198.66 ± 36.76	<0.001
Fasting HDL-cholesterol (mg/dL)	58.19 ± 13.22	56.55 ± 12.40	53.75 ± 12.49	<0.001
Fasting triglyceride (mg/dL)	91.99 ± 68.48	104.68 ± 69.72	126.80 ± 83.00	<0.001
Fasting LDL-cholesterol (mg/dL)	101.57 ± 28.07	110.97 ± 30.82	11.55 ± 32.42	<0.001
Hypertension (%)	3.3	11.1	29.3	<0.001
Coronary heart disease (%)	0	0.8	3.1	<0.001
Cerebrovascular diseases (%)	0.3	0.6	1.8	<0.001
Dyslipidemia (%)	1.7	8	16.7	<0.001
Menopause (%)	7.6	30.3	76.5	<0.001
Labor ≥1 (%)	52.8	81.3	94.3	<0.001
Ever use of oral contraceptives (%)	9.6	12.4	19.7	<0.001
Ever smoking (%)	8.3	4.8	3.3	<0.001
Alcohol intake ≥1/week (%)	9.6	8.9	6.4	<0.001
Physical activity (%)	46.8	43.3	40.5%	0.017
Education ≤12 years (%)	4.3	12.3	50.7	<0.001
Household income <4,000,000 KRW/mo (%)	7.6	10.7	28.4	<0.001

Differences between early menarche or late menarche groups and the reference group were compared using analysis of variance (ANOVA) for continuous variables and chi-square test for categorical values. HDL, High-density lipoprotein; LDL, low-density lipoprotein.

of variance (ANOVA) with post-hoc test of Bonferroni was used for comparing the differences in the means between the groups. The mean and standard deviation (SD) are presented for normally distributed variables. For categorical variables, percentages are presented. Pearson correlation coefficients (r) among age, age at menarche, and HbA1c were determined by univariate linear regression analyses. Analysis of covariance (ANCOVA) was used to evaluate the association between HbA1c levels and age at menarche after adjustment for current age that was strongly associated with HbA1c levels. To investigate the independent association between HbA1c and age at menarche in three categories, a stepwise multivariate linear regression test was used after adjusting for confounders, such as age, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, fasting glucose, fasting lipid battery, hypertension, coronary heart disease, cerebrovascular disease, dyslipidaemia, menopause, labour, smoking, alcohol intake, physical activity, education, and household income. All significant tests were analyzed using a two-tailed method, and *p* values <0.005 were considered statistically significant.

Results

Clinical characteristics of the study population

The mean age of the participants and the mean age at menarche were 48.49 ± 14.93 years

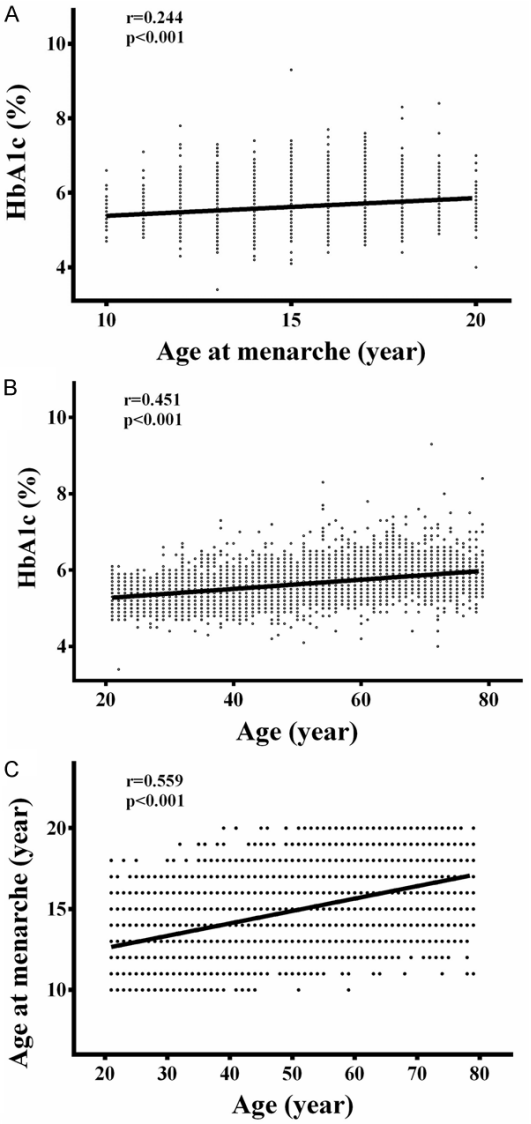

Figure 2. Correlation between HbA1c and age at menarche (A), age (B) and correlation between age at menarche and age (C).

and 14.76 ± 2.05 years, respectively. The clinical characteristics of the study population according to the age at menarche are provided in **Table 1**. Women with early menarche had a younger current age, a higher mean BMI, a greater waist circumference, a higher HDL-C, lower systolic BP and diastolic BP, a lower fasting glucose, a lower mean HbA1c, lower T-C, lower TG, lower LDL-C than women with normal menarche (p<0.05). They were less likely to have hypertension, coronary heart disease, cerebrovascular disease, dyslipidaemia, menopause, labour, and ever use of oral contraceptives and more likely to have ever smoking, a higher level of education, and a higher household income than women with normal menarche (p<0.05). Women with late menarche had an older current age, a higher mean BMI and waist circumference, systolic BP, diastolic BP, fasting glucose, fasting T-C, fasting TG, and fasting LDL-C and lower mean of HDL-C (p<0.05). They were also more likely to have hypertension, coronary heart disease, cerebrovascular disease, dyslipidaemia, menopause, labour, and ever use of oral contraceptives and less likely to be individuals with ever smoking, alcohol intake, a higher level of education, and a higher household income (p<0.05).

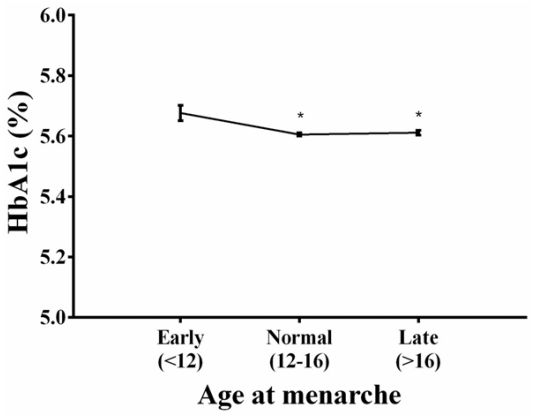

Figure 3. Relationship between HbA1c levels and age at menarche. The mean HbA1c levels according to age at menarche in the study population (n=7,800). HbA1c levels were adjusted for age using covariance analysis (ANCOVA). (*; p<0.05. compared with early age at menarche).

Correlation between HbA1c and age at menarche

Pearson correlation coefficients between HbA1c and age at menarche were determined for all 7,800 subjects. Additionally, **Figure 2** shows the correlation between age, age at menarche, and HbA1c. There were significant positive correlations between age, age at menarche, and HbA1c. Although HbA1c correlated with both age and age at menarche, correlation coefficients between age and age at menarche (r=0.559, p<0.001) were greater than those between HbA1c and age (r=0.451, p<0.001), and age at menarche (r=0.244, p<0.001). HbA1c were most strongly associated with age. We analyzed the association between HbA1c levels and age at menarche after adjusting for age (**Figure 3**). The mean HbA1c levels were

Table 2. Stepwise multivariate linear regression analysis for the association between HbA1c as the dependent variable and clinical parameter as independent variables in Korean women (*n*=7,800)

Variables	beta	SE	*P*
Age (years)	0.005	5.0×10^{-4}	<0.001
Age at menarche			0.033
Normal (12-16)	Reference	Reference	
Late (≥16)	0.014	0.007	
Early (<12)	0.028	0.007	
Body mass index (kg/m^2)	0.010	0.001	<0.001
Diastolic blood pressure (mmHg)	-0.002	4.0×10^{-4}	<0.001
Fasting glucose (mg/dL)	0.015	0.000	<0.001
Fasting triglyceride (mg/dL)	4.0×10^{-4}	5.0×10^{-5}	<0.001
Fasting LDL-cholesterol (mg/dL)	0.001	0.000	<0.001
Hypertension	0.039	0.011	0.001
Coronary heart disease	0.051	0.030	0.088
Dyslipidemia	0.077	0.013	<0.001
Menopause	0.055	0.013	<0.001
Alcohol intake	-0.031	0.010	0.002

Stepwise multivariate linear regression analysis was conducted for the association between HbA1c as the dependent variable and clinical parameters as independent variables, which included age, age at menarche, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, fasting glucose, fasting lipid battery, hypertension, coronary heart disease, cerebrovascular disease, dyslipidemia, chronic renal failure, menopause, labor, smoking, alcohol intake, education, household income. LDL, low-density lipoprotein.

higher in women with early age at menarche (5.676%) than those with normal and late age at menarche (5.605%; p=0.010, and 5.611%; p=0.022, respectively).

Multivariate linear regression analysis between HbA1c and age at menarche

We conducted a stepwise multivariate linear regression analysis of all participants of HbA1c as a dependent variable and clinical parameters as independent variables, namely current age, age at menarche in three categories, adult BMI, waist circumference, systolic blood pressure, diastolic blood pressure, fasting glucose, fasting lipid profile, hypertension, coronary heart disease, cerebrovascular disease, dyslipidaemia, menopause, labour, smoking, alcohol intake, physical activity, education, and household income. The association between HbA1c and clinical parameters are shown in **Table 2**. Increasing age at menarche was associated with a U-shaped pattern of HbA1c levels (p=0.033). Women with early menarche had 0.028%, and 0.014% higher HbA1c levels than those with normal and late menarche, respectively. HbA1c levels were also 0.014% higher in women with late age at menarche than in women with normal age at menarche. The HbA1c level was significantly associated with current age (p<0.001), current BMI (p<0.001), diastolic BP (p<0.001), fasting glucose (p<0.001), fasting TG (p<0.001), fasting LDL-C (p<0.001), hypertension (p=0.001), menopause (p<0.001), and alcohol intake (p=0.002).

Discussion

The present study demonstrated that age at menarche is positively correlated with glycosylated haemoglobin levels in Korean non-diabetic women, but this association was not significant after adjusting for relevant confounders including current age, adult BMI, gynaecologic variables and socio-economic status. Age at menarche was independently associated with HbA1c and its relationship to HbA1c was curvilinear (U-shaped). Women with early and late menarche had a 0.028% and 0.014% higher level of HbA1c, respectively, than those with normal menarche. After controlling for confounders, the HbA1c level was 0.014% higher in individuals with early age at menarche than in those with late age at menarche.

Puberty is induced by the awakening of complex neuroendocrine machinery. It begins with thelarche, which marks the beginning of breast development and is defined as Tanner stage B2 [15] and ends with the onset of menarche. Age at menarche is a milestone for female maturation and heralds the beginning of reproductive life. Menarcheal age has also been decreasing from approximately 17 years in the mid-19th century to approximately 12-13 years in the mid-20th century in many western countries including the US and Europe [16]. This trend also has developed in Asian countries [17, 18]. In the republic of Korea, there has also been a downward secular trend in the age at menarche. Cho *et al*. [19] found that the mean age

at menarche decreased from 16.90 years for women born between 1920 and 1925 to 13.79 years for those born between 1980 and 1985, indicating a downward trend of 0.68 years per decade. The downward secular trend of menarcheal age may reflect the changes in the socioeconomic and demographic environments, particularly as it pertains to nutrition and physical activity [20]. Several studies have also indicated that age at menarche is associated with chronic diseases in later life [21-24]. More studies need to be conducted to evaluate the decreasing secular trend in the age at menarche and its relationship to health problems in adulthood. There are a few studies that have evaluated the association between age at menarche and glucose metabolism, including dysglycaemia, prediabetes, diabetes, though the results have been inconsistent. The Rancho Bernardo Study found no association between age at menarche and abnormal glucose tolerance and type 2 diabetes [10]. In contrast, the KORA (German Cooperative Health Research in the Region of Augsburg) F4 study demonstrated that menarcheal age was significantly associated with prediabetes and diabetes. Furthermore, a significant association persisted after controlling for potential confounders, such as current BMI and socioeconomic status [9]. A study of 121 women with polycystic ovary syndrome from the Mediterranean region reported that earlier age at menarche was associated with glucose intolerance [24]. Consistent with previous studies of the association between age at menarche and glucose metabolism, this is the first study to report that age at menarche is independently associated with HbA1c levels in non-diabetic women.

In this study, earlier age at menarche was associated with higher HbA1c levels than normal and late age at menarche. How early menarche affects glucose metabolism is unclear. Most studies reporting an association between age at menarche and glucose metabolism have shown that early menarche is associated with increased risk of DM [24-26]. A potential hypothesis is that the link between early age at menarche and glucose metabolism involves childhood obesity or insulin resistance. Early onset of menarche and puberty have been correlated with obesity [27] and insulin resistance [28, 29]. Obesity-related hyperinsulinemia has been shown to be independently associated with an earlier onset of puberty. Increased insulin levels can lead to decreased levels of sex-hormone-binding globulin (SHBG) resulting in a higher concentration of free sex-hormone (bioavailable hormone) [30]. Decreased concentration of SHBG is associated with earlier puberty and early menarche [31]. Another possible explanation is that oestrogen, which plays an important role in the onset of menstruation, modulates the growth hormone (GH)-insulin-like growth factor-1 (IGF-1) axis in a biphasic manner [32, 33]. Relatively low levels of oestrogen increase levels of IGF-1, which is accompanied by enhanced GH secretion. By contrast, relatively high levels of oestrogen, which are usually associated with menarche, inhibit the production of IGF-1. Even in young adults, low IGF-1 levels are associated with diabetes [33]. Thus, earlier exposure to high levels of oestrogen may impair glucose metabolism leading to diabetes.

In the current study, multivariate regression analysis revealed that late age at menarche was associated with increased HbA1c levels after controlling for possible confounders, such as age and BMI. The relationship between late menarche and glucose metabolism is inconsistent. Some studies reported that late age at menarche was a protective factor for glucose metabolism. A German study demonstrated that fasting glucose concentration was inversely associated with menarcheal age. Furthermore, fasting blood glucose levels were -0.004 mmol/L (95% CI -0.008, 0.001) lower for each additional year of age at menarche after adjusting for relevant confounders such as current age and BMI [6]. In the Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk) study, women who reached menarche at 15-18 years had a reduced risk of dysglycaemia (OR=0.66, after adjustment for confounders, p for trend <0.001) [4]. A recent Bangladeshi study demonstrated that fasting glucose concentration was 5.81 mmol/L, 6.29 mmol/L, and 6.78 mmol/L in women with age at menarche <12 year, 12-13 years, and >13 years, respectively (p<0.01) [34]. A recent Korean study reported that HbA1c levels were 8.0%, 7.2% and 7.4% in Korean postmenopausal women with early, normal and late menarche, respectively, although statistical significance was marginal after adjusting for confounders (p=0.054) [35]. In a study by Stockl et al., [6] subjects with late

age at menarche had a higher mean HbA1c (5.6 ± 0.6%) than those with early and normal menarche (5.5 ± 0.5% and 5.5 ± 0.5%, p= 0.016). Moreover, a series of studies demonstrated that women with late menarche had an increased risk of adult MetS and cardiometabolic abnormalities [36]. Furthermore, menarche at age >17 years tended to be associated with an increased risk of mortality from stroke [37]. Differences in the characteristics of the study population such as ethnicity and socioeconomic status may account for these inconsistent findings.

In the field of paediatrics, gonadotropin-releasing hormone agonist (GnRHa), which effectively and selectively suppresses gonadal sex steroid secretion and inhibits premature sexual maturation, is the treatment of choice in children with precocious puberty, which is associated with early menarche [38]. Most studies suggest that treatment with GnRHa does not lead to diabetes [39] or obesity [40]. There are a few reports evaluating that GnRHa treatment can improve glucose metabolism. A Danish study demonstrated that girls with CPP had adverse metabolic profiles at the time of diagnosis compared with puberty-matched controls. In addition, one-year treatment with GnRHa failed to prevent deterioration of the metabolic profiles [41]. However, this Danish study was conducted in a small population and had short follow-up periods. Future studies with a larger sample size and longer duration of follow-up are needed to evaluate whether GnRHa treatment of precocious puberty improves glucose metabolism in women.

There are several limitations to the current study. First, because this was a cross-sectional design, causality cannot be determined. Second, age at menarche was reported based on memory recall so misclassification may have occurred. However, because menarche is important event in the lives of women, recall bias may not have presented a major issue [42]. Moreover, misclassification of age at menarche is less likely to be associated with current HbA1c levels. Third, we could not adjust the participant's BMI and insulin levels (HOMA-IR) for both the peri-menarcheal and current age. Additionally, we excluded participants diagnosed with diabetes or women who were currently taking diabetes medicines. Our results cannot be extrapolated to include diabetes because an HbA1c level equal to or less than 6.5% is not diagnostic of diabetes.

In conclusion, the present study showed that age at menarche is associated with HbA1c levels in non-diabetic Korean women. After adjustment for confounders including current age, current BMI, current fasting glucose, current fasting lipid profiles, gynaecological history and socio-economic status, HbA1c levels were higher in women with early and late menarche than those with normal menarche (U-shaped pattern of HbA1c). Women with early menarche also had higher HbA1c levels than those with late menarche. This finding suggests that age at menarche is independently associated with HbA1c levels. Taking a history that includes age at menarche, particularly before the age of 12 years and after the age of 16 years, may help to identify women at risk for developing dysglycaemia.

Disclosure of conflict of interest

None.

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