

Age at Menarche and Brachial-ankle Pulse Wave Velocity in Women with Metabolic Syndrome

Yoon-Kyung Jo¹ and Jee-Aee Im^{2,†}

¹Department of Clinical Laboratory Science, Dongnam Health College, Suwon, 440-714, Korea.

²Sport and Medicine Research Center, INTOTO Inc., Seoul, 152-740, Korea

Early age at menarche, which is indicator of early biological maturity, has been shown to be associated with increased adult body mass index. Early menarche has also been associated with many cardiovascular disease risk factors and metabolic syndrome. To evaluate the impact of menarche to cardiovascular risk factor, we assessed by age at menarche, brachial-ankle pulse wave velocity (baPWV), which represents arterial stiffness, in women with or without metabolic syndrome. The subjects recruited for this study were three hundred one women. Relatively early menarche and relatively late menarche were classified according to less than 50th percentile for relatively early menarche, and great than the 50th percentile for relatively late menarche. Subject were divided four group, 1) women who had not adulthood metabolic syndrome and relatively early menarche, 2) women who had not adulthood metabolic syndrome and relatively late menarche, 3) women who had adulthood metabolic syndrome and relatively early menarche, 4) women who had adulthood metabolic syndrome and relatively late menarche. Women who had a relatively early menarche with adulthood metabolic syndrome had significantly high levels of blood pressure, triglyceride, fasting insulin and homeostatic model assessment of insulin resistance (HOMA-IR) levels than women with late menarche with adulthood metabolic syndrome, and had significantly lower HDL-cholesterol levels. And also, women who underwent a relatively early menarche with metabolic syndrome had highest level of baPWV in adult. In this study we found effect of age at menarche on adulthood metabolic risk factors for cardiovascular disease (e.g., baPWV, insulin resistance, hyperlipidemia) in Korean women.

Key Words: Menarche, Pulse wave velocity, CVD

INTRODUCTION

The metabolic syndrome is a clustering of metabolic risk factors, including abdominal obesity, high blood pressure (BP), high triglyceride levels, low levels of HDL-cholesterol, and high levels of fasting glucose. The metabolic syndrome is associated with subsequent increases in the incidence of type 2 diabetes mellitus, cardiovascular disease (CVD) morbidity and even mortality (Isomaa et al., 2001; Laaksonen et al., 2002; Onat et al., 2002).

Early age at menarche, which is indicator of early

biological maturity, has been shown to be associated with increased adult body mass index (BMI) (Parsons et al., 1999). Early menarche has also been associated with many cardiovascular disease risk factors and metabolic syndrome (Ibanez et al., 1998; Cooper et al., 1999; Frontini et al., 2003; Remsberg et al., 2005). Between 1972 and 2003, several longitudinal studies found a negative relation between age at menarche and adult weight-for-height (Garn et al., 1986; St George et al., 1994; Van Lenthe et al., 1996; Biro et al., 2001; Okasha et al., 2001), least one longitudinal study showed no relation between age at menarche and adult BMI (Wellens et al., 1992). Girls who experience a relatively early sexual maturation, typically assessed by age at menarche, tend to be more obese as adults (Helm et al., 1995; van Lenthe et al., 1996; Power et al., 1997). Although there is at least one negative report (Frisancho et al., 1988), the lack of association between menarcheal age and adult

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†Corresponding author: Jee-Aee Im, Sport and Medicine Research Center, INTOTO Inc., Seoul, 152-740, Korea.
Tel: 02-6340-5533, Fax: 02-6340-5905
e-mail: jeaeim@hanmail.net

obesity may be due to the difficulty in recalling an event that occurred several decades in the past (Must et al., 2002). Early age at menarche is associated with both proximal and longer-term hyperinsulinemia and insulin resistance (Ibanez et al., 1998). Furthermore, body composition during adolescence is significantly associated with adult levels of fasting insulin, insulin utilization, BP, HDL-cholesterol, LDL-cholesterol, and total cholesterol (Labarthe et al., 1991; Katzmarzyk et al., 2001; Steinberger et al., 2001). Whether early age at menarche is causally associated with increased adult CVD risk is unclear because many factors are related to both age at menarche and adult obesity and CVD risk factors.

Increasing arterial stiffness is one of the pathological symptoms of vascular damage and is closely associated with atherosclerotic cardiovascular diseases (Cohn, 2001). One of these new factors is the brachial-ankle pulse wave velocity (baPWV), which represents arterial stiffness.

In this study, we investigated unfavorable effects age at menarche on adulthood CVD risk such as arterial stiffness, measured as baPWV in women with or without metabolic syndrome.

MATERIALS AND METHODS

1. Subjects

The subjects recruited for this study were three hundred one women. The participants visited the hospital for a periodic health checkup in a health promotion center in Seoul, Korea. In the interview, each female subject was asked age at the time of menarche. Relatively early menarche and relatively late menarche were classified according to less than 50th percentile for relatively early menarche, and great than the 50th percentile for relatively late menarche.

The metabolic syndrome was defined as three or more of the following abnormalities according to the modified NCEP ATP III definition (Grundy et al., 2005) and the Korean Society for the Study of Obesity criteria (Lee et al., 2007): abdominal obesity (waist circumference ≥ 90 cm in men or ≥ 85 cm in women); hypertriglyceridemia (triglyceride levels ≥ 150 mg/dL or receiving drug treatment for elevated triglycerides); low HDL-cholesterol (< 40 mg/dL

in men, < 50 mg/dL in women or receiving drug treatment for reduced HDL-cholesterol); hypertension (systolic BP ≥ 130 mmHg, diastolic BP ≥ 85 mmHg or receiving anti-hypertensive drug treatment with a history of hypertension); and high fasting glucose (≥ 100 mg/dL or receiving drug treatment for elevated glucose).

In this study, subjects were divided into four groups, 1) women who had relatively early menarche without adulthood metabolic syndrome, 2) women who had relatively late menarche without adulthood metabolic syndrome, 3) women who had relatively early menarche with adulthood metabolic syndrome, 4) women who had relatively late menarche with adulthood metabolic syndrome and relatively late menarche.

2. Anthropometric measurements

Height to the nearest 0.1 cm and weight to the nearest 0.1 kg were measured by an automatic height-weight scale. BMI was calculated as the participants' weight divided by their height squared. Waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest.

3. Measurement of baPWV

baPWV was measured using a volume-plethysmographic apparatus (PWV/ABI, Colin Co., Komaki, Japan) as previously described (Kubo et al., 2002; Yamashina et al., 2002). A previous study reported that in healthy subjects, the coefficient of variation for interobserver reproducibility (N=15) was 2.4%, while intraobserver reproducibility (N=17) was 5.8% (Yamashina et al., 2002).

4. Laboratory measurement of CVD risk factors

High sensitivity C-reactive protein (hs-CRP), fasting glucose, total cholesterol, triglyceride, and HDL-cholesterol were measured using an ADVIA 1650 Chemistry system (Siemens, Tarrytown, NY, USA), and LDL-cholesterol was calculated from the Friedewald equation (Friedewald et al., 1972). Fasting insulin was measured by an electrochemiluminescence immunoassay (Roche, Indianapolis, IN, USA). Insulin resistance was estimated by the homeostatic model assessment of insulin resistance (HOMA-IR); the calculations were as follows: $HOMA-IR = (\text{Insulin } (\mu\text{IU/mL}) \times$

Fasting blood glucose (mg/dL)/18) / 22.5.

5. Statistical analysis

Data are expressed as means \pm S.D. Clinical and metabolic characteristics of subjects with or without metabolic syndrome were compared using the t-test for continuous variables. Clinical characteristics were compared among the four groups using one-way analysis of variance (ANOVA). Significance was defined at the 0.01 level of confidence.

Table 1. Characteristics of subjects with or without metabolic syndrome

Variables	Without MS (N=245)	With MS (N=56)	P
Age (years)	54.8 \pm 5.0	57.8 \pm 5.4	<0.01
Height (cm)	155.4 \pm 5.0	155.6 \pm 5.2	0.76
Weight (kg)	53.6 \pm 5.7	58.3 \pm 8.1	<0.01
BMI ^a (kg/m ²)	22.2 \pm 2.2	24.1 \pm 3.0	<0.01
Waist circumference (cm)	74.4 \pm 7.1	80.4 \pm 8.5	<0.01
SBP ^b (mmHg)	113.4 \pm 9.1	126.8 \pm 15.5	<0.01
DBP ^c (mmHg)	69.0 \pm 7.5	76.8 \pm 11.9	<0.01
Cholesterol (mg/dL)	204.9 \pm 32.3	209.9 \pm 34.4	0.28
Triglyceride (mg/dL)	76.0 \pm 27.3	100.6 \pm 52.0	<0.01
HDL-cholesterol (mg/dL)	64.1 \pm 11.2	54.5 \pm 12.3	<0.01
LDL-cholesterol (mg/dL)	125.7 \pm 29.3	135.3 \pm 31.3	0.02
Glucose (mg/dL)	86.2 \pm 5.9	95.3 \pm 15.1	<0.01
Insulin (μ IU/mL)	3.2 \pm 2.4	4.1 \pm 2.3	0.01
HOMA-IR ^d	0.7 \pm 0.5	1.0 \pm 0.6	<0.01
Hs-CRP ^e (mg/mL)	0.3 \pm 1.2	0.1 \pm 0.3	0.09
baPWV ^f (cm/sec)	1356.7 \pm 168.3	1503.7 \pm 294.5	0.01

Data are shown as means \pm the standard deviation.

^aBody mass index; ^bsystolic blood pressure; ^cdiastolic blood pressure; ^dHomeostasis model assessment insulin resistance; ^eHigh sensitivity C-reactive protein; ^fbrachial-ankle pulse wave velocity.

All calculations were performed using the Statistical Package for Social Sciences software, version 15.0 (SPSS, Chicago, IL, USA).

RESULTS

The clinical and metabolic characteristics of subjects with or without metabolic syndrome are shown in Table 1. BMI, waist circumference, systolic BP, diastolic BP, WBC counts, and hs-CRP levels were significantly higher in subjects with metabolic syndrome as compared with those without metabolic syndrome. In addition, the subjects with metabolic syndrome had significantly higher levels of fasting glucose, fasting insulin, HOMA-IR, and triglyceride, and lower levels of HDL-cholesterol than subjects without metabolic syndrome ($P<0.01$).

Table 2 showed anthropometric parameter according to age of menarche in subjects with or without metabolic syndrome. Weight, BMI, and waist circumference were significantly higher in women who had a relatively late menarche with adulthood metabolic syndrome.

Women who had a relatively early menarche with adulthood metabolic syndrome had significantly high levels of SBP, DBP, triglyceride, fasting insulin and HOMA-IR levels than women with late menarche with adulthood metabolic syndrome, and had significantly lower HDL-cholesterol levels. Interestingly, relatively early menarche with adulthood metabolic syndrome had lower BMI, but increased CVD risk than relatively late menarche with adulthood metabolic syndrome. And also, women who underwent relatively early menarche with metabolic syndrome had highest level of mean baPWV in adult (Table 3).

Table 2. Anthropometric parameter according to age of menarche in subjects with or without metabolic syndrome

Variables	Without MS ^a		With MS		P
	REM ^b (N=126)	RLM ^c (N=119)	REM (N=24)	RLM (N=32)	
Age of menarche (years)	14.3 \pm 1.1	17.0 \pm 1.4	14.1 \pm 1.0	16.4 \pm 1.2	<0.001
Height (cm)	155.3 \pm 5.5	155.9 \pm 4.6	156.0 \pm 4.8	155.1 \pm 5.3	0.77
Weight (kg)	55.3 \pm 6.3	58.8 \pm 8.1	59.3 \pm 8.4	66.6 \pm 9.4	<0.001
BMI ^d (kg/m ²)	22.9 \pm 2.3	24.2 \pm 3.1	24.3 \pm 3.1	27.6 \pm 3.3	<0.001
Waist circumference(cm)	77.5 \pm 8.7	79.5 \pm 8.1	80.7 \pm 9.7	89.9 \pm 6.8	<0.001

Data are shown as means \pm the standard deviation.

P-values (<0.01) were calculated by the ANOVA model.

^aMetabolic syndrome; ^brelatively early menarche; ^crelatively late menarche; ^dBody mass index.

Table 3. Cardiovascular risk factor according to age of menarche in subjects with or without metabolic syndrome

Variables	Without MS ^a		With MS		P
	REM ^b (N=126)	RLM ^c (N=119)	REM (N=24)	RLM (N=32)	
Age of menarche(years)	14.3±1.1	17.0±1.4	14.1±1.0	16.4±1.2	<0.001
SBP ^d (mmHg)	120.9±16	124.2±14.3	140.2±17.9	130.0±15.0	<0.001
DBP ^e (mmHg)	73.6±12.2	75.0±10.3	84.6±11.4	78.0±7.9	<0.001
Glucose (mg/dL)	91.2±14.7	92.6±11.2	101.8±19.1	119.1±37.4	<0.001
Insulin (μIU/mL)	3.7±2.5	4.0±2.3	7.8±6.3	5.8±3.3	<0.001
HOMA-IR ^f	0.8±0.6	0.9±0.6	2.1±1.8	1.7±1.0	<0.001
Cholesterol (mg/dL)	211.1±34.0	204.7±32.4	206.8±38.9	214.1±43.6	0.39
Triglyceride (mg/dL)	92.5±40.1	94.1±54.1	193.9±122.6	151.3±81.4	<0.001
HDL-cholesterol (mg/dL)	58.0±13.1	57.1±12.6	44.1±7.3	45.9±7.7	<0.001
LDL-cholesterol (mg/dL)	134.7±30.4	128.8±30.8	123.9±35.8	138.0±40.4	0.23
baPWV ^g (cm/sec)	1417.9±266	1491.8±270	1591.5±282	1541.1±278	0.01
hs-CRP ^h (mg/ml)	0.2±0.9	0.1±0.3	0.4±1.6	0.3±0.6	0.274

Data are shown as means ± the standard deviation.

P-values (<0.01) were calculated by the ANOVA model.

^aMetabolic syndrome; ^brelatively early menarche; ^crelatively late menarche; ^dsystolic blood pressure; ^ediastolic blood pressure; ^fHomeostasis model assessment insulin resistance; ^gHigh sensitivity C-reactive protein; ^hbrachial-ankle pulse wave velocity.

DISCUSSION

The current study shows that women who had a relatively early menarche with adulthood metabolic syndrome had a significant higher baPWV levels. This is the first time that menarcheal age affects on adult baPWV. And also interesting to note in this study, women who had relatively early menarche with adulthood metabolic syndrome had lower BMI, but increased serum levels of BP, triglyceride, insulin and HOMA-IR than relatively late menarche with adulthood metabolic syndrome. It suggests that women who had a relatively early menarche with adulthood metabolic syndrome are at a greater risk of developing CVD. Our results confirm the findings of other studies, there were an inverse association of age at menarche with CVD in later life (Remsberg et al., 2005). Although the biological mechanisms underlying the inverse association between menarcheal age and adult CVD risk are uncertain, it has been suggested that early maturing girls may have a longer period of positive energy balance (Garn et al., 1986), or that various endocrine factors influence both the rate of sexual maturation and the accumulation of body fat (van Lenthe et al., 1996). It is also possible that the apparent influence of menarcheal age on adult obesity reflects the underlying importance of

childhood obesity, with relatively fat children at increased risk for both early menarche and adult obesity (Serdula et al., 1993; Jaruratanasirikul et al., 1997; Power et al., 1997; Koprowski et al., 1999; Biro et al., 2001; Freedman et al., 2002). A recent cohort study of children born in the 1950s suggests that age at menarche is a predictor of adult BMI independent of childhood BMI (Pierce and Leon, 2005). However, childhood BMI, adult BMI, and age at menarche could all be related to hormonal variations that relate to hereditary metabolic predispositions that interact with population-wide changes in nutrition. The onset of puberty is mediated by certain known neuroendocrinological mechanisms (Dunger et al., 2006), the causative model is not yet fully elucidated. Although it is not yet clear that a trend of younger menarche indicates a pathology of public health concern, recent epidemiologic evidence suggests women who experience earlier menarche also experience earlier mortality compared to their peers (Jacobsen et al., 2007). Variables such as prepubertal BMI, adulthood BMI, and age at menarche could share a common relationship to metabolic disposition that exhibits a lifelong influence. One possible mechanism by which metabolic predisposition could influence both BMI and age at menarche is through insulin metabolism. Both hyperinsulinemia (increased insulin secretion) and insulin resistance (loss of sensitivity to

insulin) promote increases in BMI (Lustig et al., 2006). A connection between age at menarche and insulin metabolism is suggested by the recent observations that treatment with insulin-sensitizing medication delays the onset of puberty and menarche (Ibanez et al., 2006). The exact mechanism by which insulin metabolism impacts age at menarche is largely unknown, although previous studies show insulin receptors in the ovary, and suggest an interaction with the changes of adrenarche and other hormonal precursors to puberty, including sex hormone metabolism (Dunger et al., 2006).

In this study, we found that women who had a relatively early menarche with adulthood metabolic syndrome had significantly high levels of systolic BP, diastolic BP, triglyceride, fasting insulin and HOMA-IR levels and lower levels of HDL-cholesterol. Early menarche was significantly associated with some vascular-unfavorable lipid profile (increased serum total cholesterol and decreased HDL-cholesterol) in adult women independent of the normal ageing process (Moisan et al., 1990). The impact of age at menarche on lipoprotein and lipid concentrations is less clear. In a cross-sectional comparison in the Bogalusa Heart Study, the correlations between sexual maturation and lipid and lipoprotein concentrations were very low or negative for total cholesterol, triglyceride, and LDL-cholesterol positive for HDL-cholesterol (Freedman et al., 1987). Therefore, early menarche may not be itself a determinant of an unfavourable cardiovascular profile, but may simply reflect a negative metabolic imprinting during the pre-puberal life. It has been shown that ischemic heart disease risks decreased with increasing age at menarche in elderly women (Cooper et al., 1999) and girls with early menarche have more deleterious changes in insulin, glucose, BP and lipid through childhood, adolescence and young adulthood (Frontini et al., 2003; Remsberg et al., 2005). Age at menarche remained an independent predictor of changes in insulin, abdominal circumference, SBP, and DBP. The effect of early menarche on CVD risk factors is only partially explained by the lean and adipose tissue components of body mass. Menarcheal age and CVD risk factors demonstrated that girls with early menarche had higher fasting insulin concentrations, comparable fasting glucose concentrations girls with average

and late menarche (Remsberg et al., 2005). Although insulin resistance is a recognized feature of the onset of the pubertal transition (Cook et al., 1993; Travers et al., 1995), girls with early menarche tended to retain hyperinsulinemia and/or insulin resistance throughout puberty (Remsberg et al., 2005). Excessive caloric intake and reduced physical activity in the early life may be also a cause of early menarche. However, the potential risk of early menarche on some chronic diseases which are associated with obesity and dyslipidemia, such as cardiovascular diseases, requires further investigation.

Our study has a few limitations. First, this is a cross-sectional study, therefore the effect of childhood BMI on association between age at menarche and adult body composition and CVD cannot be studied. Secondly, ages at menarche was self-reported and subject to recall bias.

In this study we found effect of age at menarche on adulthood metabolic risk factors for CVD (e.g., ba-PWV, insulin resistance, hyperlipidemia) in Korean women. Earlier menarche could be an additional indicator to use in clinical assessment of risk for the spectrum of disorders linked to CVD.

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