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Late Age At Menarche Increased Common Carotid Artery Intima-Media Thickness In Overweight And Obese Women

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Abstract

Objective: To determine whether age at menarche is an independent predictor of common carotid artery intima-media thickness in overweight and obese adult women.

Methods: 403 overweight and obese women, aged 18–72 years, were evaluated. We examined the associations among common carotid artery intima-media thickness (CCA-IMT), age at menarche, body mass index, central fat accumulation (indirectly measured by waist circumference), and other well-known cardiovascular risk factors (blood pressure; fasting serum insulin, glucose and lipids concentrations; insulin resistance [estimated by homeostasis model assessment for insulin resistance]).

Results: CCA-IMT was significantly and positively correlated with age (r=0.632, p<0.001), age of menarche (r=0.156, p<0.01), waist circumference (r=0.110, p<0.05), systolic (r=0.292, p<0.001) and diastolic (r=0.183, p<0.001) blood pressure, fasting blood glucose (r=0.265, p<0.001), triglycerides (r=0.204, p<0.001) and total cholesterol (r=0.396, p<0.001) levels. Conversely, CCA-IMT was negatively associated with high-density lipoprotein cholesterol (r=-0.111, p<0.05).

Age at menarche was associated with CCA-IMT (r=0.156, p<0.01), age (r=0.110, p<0.05) and waist circumference (r=0.121, p<0.05). Multiple linear analysis showed that only age and age at menarche maintained an independent positive relationship with the CCA-IMT.

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Running Title: Menarche and carotid thickness in obese

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Introduction

Age at menarche is a key maturity indicator of female development. It reflects population health[1]. Several studies showed a reduction in the mean age at menarche[1-6], influenced by variables such as genetic factors, race, body mass index, nutrition, geography, socioeconomic status, maternal menarche age, maternal age at birth and sleep time[6-11]. Girls with earlier age at menarche demonstrate worse cardiovascular risk factor in adulthood than those with later age at menarche[12-19]. By contrast, the JACC study showed that women with age at menarche > 17 years had higher risk of mortality due to stroke events as compared to women with age at menarche < 13 years, even though late menarche was not associated with risk of mortality from coronary heart disease[20].

Atherosclerosis is accelerated in obese, and above all central obese subjects as shown by higher common carotid artery intima media thickness [21-26]. Common carotid artery intima media thickness is a well-established early marker of asymptomatic atherosclerosis and precedes the development of plaque and stenosis in the arterial wall[27,28]. Central obesity is associated with early carotid intima-media thickening independently of other risk factors[21,23,25,26]; even leptin, a protein quite exclusively produced by adipose tissue, is independently associated with the common carotid artery intima-media thickness[21].

To the best of our knowledge, no study has previously examined in a population of overweight and/or obese subjects whether the common carotid artery intima-media thickness in adulthood is influenced by earlier or later age at menarche, independently of common cardiovascular risk factors. Study aim is to find the relationship between carotid vasculature alterations and age at menarche in an obese/overweight female population.

Methods

Subject Population

We consecutively recruited 403 euthyroid apparently healthy overweight and obese women at the Outpatient Clinic Nutrition Unit, Policlinico di Bari, Bari, Italy. They were referred to the Outpatient Clinic due to their increased weight and/or to be educated to have correct food and lifestyle habits.

Exclusion criteria were: smokers, subjects taking any kind of drugs, patients known to be affected by thyroid dysfunction, endocrinological diseases, diabetes mellitus, stable and drug-treated hypertension, stroke, transient ischemic attack, angina pectoris, myocardial infarction, claudicatio intermittens, congenital heart disease or electrocardiographic abnormalities. Furthermore, overweight/obese patients were only included in our study.

Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure > 90 mmHg, or antihypertensive drugs use[29]; hypercholesterolemia was defined according to NCEP ATP III criteria[30] (total-cholesterol > 220 mg/dl or the use of lipid-lowering drug(s)); diabetes as fasting blood sugar > 126 mg/dl in at least two determinations, or blood sugar during 75 gr oral glucose tolerance test > 200 mg/dl, or the use of antidiabetic drug(s)[31].

According to the above exclusion criteria, 403 women, aged 18–72 years (mean age 38.5 ± 12.5 years old), were enrolled. All subjects gave their written informed consent before enrolment, which was performed in agreement with Helsinki Declaration. The study was approved by the Institutional Review Board of Bari University General Hospital.

All patients showed normal fasting blood glucose levels (see table 1).

All study subjects were judged to be in good health on the basis of physical examination, medical history,

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Table 1. General, anthropometric, and metabolic parameters in women under study.

	N=403
Age (years)	38.5 ± 12.5
Age of menarche (years)	11.9 ± 1.6
Body mass index (kg/m^2)	34.8 ± 6.7
Waist circumference (cm)	107.1 ± 14.8
Systolic blood pressure (mmHg)	121.1 ± 12.4
Diastolic blood pressure (mmHg)	78.0 ± 8.3
Fasting insulin (μ UI/ml)	24.4 ± 14.6
Fasting blood glucose (mg/dl)	91 ± 11
$HOMA_{IR}$	5.61 ± 3.81
Triglycerides (mg/dl)	90.7 ± 47.0
Total cholesterol (mg/ml)	189.6 ± 37.1
HDL cholesterol (mg/dl)	49.6 ± 11.0

The data are expressed as mean values ± standard deviation. HDL: high-density lipoprotein; $HOMA_{IR}$: homeostasis model assessment for insulin resistance.

routine blood examinations, urinalysis and electrocardiogram.

Free thyroid hormones and thyroid-stimulating hormone (< 4.0 mUI/ml) were in the normal range in all subjects. None of patients were receiving any kind of medication (including oral contraceptives for pre-menopausal women and hormone replacement therapy for post-menopausal women) when they entered the study. Moreover, none of them had been involved into intensive or competitive physical activity prior to the enrollment. During the testing period, all subjects were asked to keep their normal mixed diet and not to perform any sporting activity.

Questionnaire-based Interview

A questionnaire-based interview was adopted in order to collect information on the participants' occupations, physical activity, smoking habit, cardiovascular diseases history, women's periods and reproductive history, including age at menarche.

Measurements of the Common Carotid Artery Intima-media Thickness

Determinations of common carotid artery intima-media thickness were performed as previously described[21,26,32]. Briefly, measurements were obtained from the far wall of the distal common carotid arteries (immediately proximal to the carotid bulb). This location was chosen a priori because of its demonstrated reproducibility, compared with measurements of common carotid artery intima-media thickness at other sites[32]. The mean value for the bilateral measurement had been reported.

All studies were performed on a single ultrasound machine (Hewlett Packard Sonos 1500B) using a linear-array 8.0 MHz scan head with standardized image settings, including resolution mode, depth of field, gain, and transmit focus. Ultrasound study was performed in a standard fashion by an examiner who was specifically trained to perform the prescribed study examination. All sonograms were obtained with the patient in the supine position and the head turned slightly to the contralateral side. Each ultrasound examination was performed as an

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independent study, without any knowledge of the patients' cardiovascular risk factors. The near-field (intimal-luminal surface) and far-field (medial-adventitial) arterial wall borders were manually traced for measurement of minimal and maximal common carotid artery intima-media thickness.

Anthropometric Measurements and General Data

Weight was measured to the nearest kg. Height was determined to the nearest cm. Body mass index was calculated as the weight (kg) divided by the square of height (m) in order to identify obese and/or overweight subjects (overweight: 25 $\leq$ body mass index < 30 kg/m^2; obesity: body mass index $\geq$ 30 kg/m^2). Waist circumference was measured at the narrowest part of the abdomen, *i.e.*, at the natural indentation between the 10th rib and the iliac crest (minimum waist). It is related to the presence of abdominal obesity (waist circumference > 88cm for women and > 102 cm for men)[33].

Blood pressure was recorded on at least three different occasions, using a mercury manometer with an appropriate cuff size.

Hormonal and Metabolic Parameters

Blood samples were drawn between 08:00h and 09:00 h after an overnight fast. Serum insulin concentrations were measured by radioimmunoassay (Behring, Scoppitto, Italy) and intra- and interassay coefficients of variation were 3.7% and 7.5% respectively.

Plasma glucose levels were determined by the glucose-oxidase method (Sclavo, Siena, Italy). Plasma lipids (triglycerides, total cholesterol and high-density lipoprotein (HDL)-cholesterol) were determined by an automatic colorimetric method (Hitachi; Boehringer Mannheim, Mannheim, Germany). Insulin resistance was assessed by using the homeostasis model assessment ($HOMA_{IR}$)[34].

Statistics:

Results are presented as mean and standard deviation for all parameters. Significant relationships between study parameters were evaluated by Pearson's correlation coefficient. A multiple linear regression analysis was also performed to test the joint effect of different variables on common carotid artery intima-media thickness. All statistical analyses were performed using the STATISTICA 6.0 for Windows, StatSoft Inc. (Tulsa, OK, USA).

Results:

Table 1 shows general, anthropometric, and metabolic parameters of enrolled women.

Table 2 shows the associations between age at menarche and all the parameters investigated. Apart from the relationship with common carotid artery intima-media thickness (r=0.156, p<0.01), age of menarche was significantly correlated with age (r=0.110, p<0.05) and waist circumference (r=0.121, p<0.05).

Table 3 shows the relationship between common carotid artery intima-media thickness and all the parameters investigated. Common carotid artery intima-media thickness was significantly and positively correlated with age (r=0.632, p<0.001), age at menarche (r=0.156, p<0.01), waist circumference (r=0.110, p<0.05), systolic (r=0.292, p<0.001) and diastolic (r=0.183, p<0.001) blood pressure, fasting blood glucose (r=0.265, p<0.001), triglycerides (r=0.204, p<0.001) and total cholesterol (r=0.396, p<0.001) levels. Conversely, common carotid artery intima-media thickness was negatively associated with HDL cholesterol (r=-0.111, p<0.05).

Table 4 shows the results of the multiple linear analysis of different variables in relation to common carotid artery intima-media thickness, considered as the dependent variable (R^2=0.406, p<0.001). All parameters showing a significant linear association with common carotid artery intima-media thickness were entered as independent variables in the multiple regression

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Table 2. Pearson correlation coefficients of age of menarche with all other parameters in all women under study (n=403)

	r
CCA-IMT (mm)	0.156**
Age (years)	0.110*
Body mass index (kg/m^2)	0.091
Waist circumference (cm)	0.121*
Systolic blood pressure (mmHg)	0.039
Diastolic blood pressure (mmHg)	-0.017
Fasting blood glucose (mg/dl)	0.001
Fasting insulin (μ UI/ml)	0.051
HOMA$_{IR}$	0.038
Triglycerides (mg/ml)	0.060
Total cholesterol (mg/ml)	-0.015
HDL cholesterol (mg/ml)	0.046

CCA-IMT: common carotid intima-media thickness; HDL: high-density lipoprotein; HOMA$_{IR}$: homeostasis model assessment for insulin resistance.

* p < 0.05, ** p < 0.01, *** p < 0.001

Table 3. Pearson correlation coefficients of common carotid intima-media thickness with all other parameters in all women under study (n=403)

	r
Age of menarche (years)	0.156**
Age (years)	0.632***
Body mass index (kg/m^2)	0.041
Waist circumference (cm)	0.110*
Systolic blood pressure (mmHg)	0.292***
Diastolic blood pressure (mmHg)	0.183***
Fasting blood glucose (mg/dl)	0.265***
Fasting insulin (μ UI/ml)	0.008
HOMA$_{IR}$	0.061
Triglycerides (mg/ml)	0.204***
Total cholesterol (mg/ml)	0.396***
HDL cholesterol (mg/ml)	-0.111*

HDL: high-density lipoprotein; HOMAIR: homeostasis model assessment for insulin resistance.

* p < 0.05, ** p < 0.01, *** p < 0.001

analysis. Only age and age at menarche maintained an

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Table 4. Determinants of common carotid intima-media thickness in multiple regression analysis.

Variable	β	T (393)	P-value
Age of menarche (years)	0.089	2.264	<0.05
Age (years)	0.560	11.364	<0.001
Waist (cm)	0.047	1.114	Ns
Systolic blood pressure (mmHg)	0.048	0.903	Ns
Diastolic blood pressure (mmHg)	0.014	-0.281	ns
Fasting blood glucose (mg/dl)	0.019	0.449	ns
Triglycerides (mg/dl)	-0.004	-0.888	ns
Total cholesterol (mg/ml)	-0.027	1.627	ns
HDL cholesterol (µ g/24 h)	-0.078	-0.593	Ns

HDL: high-density lipoprotein.

independent positive relationship with the common carotid artery intima-media thickness.

Discussion:

The present study, performed in a population of healthy euthyroid overweight and obese women, shows a high positive relationship between age at menarche and the common carotid artery intima-media thickness, independently of common cardiovascular risk factors such as glucose, lipids, blood pressure, body mass index, body fat distribution and insulin resistance. This is an important result, since the thickening of the intima and tunica media is considered an early marker of asymptomatic atherosclerosis and precedes the development of plaque and stenosis in the arterial wall[27,28]. Nevertheless, the relationship between common carotid intima-media thickness and age at menarche is an almost controversial subject. Literature data offer examples of the opposite results obtained and the different theories produced to explain them.

Our findings are apparently in line with the JACC study[20]. This international research showed that women with age at menarche $\geq$ 17 years tended to have increased risk of mortality from stroke compared to women with age at menarche $\leq$ 13 years[20]. Later menarche would correspond to a shorter period of exposure to estrogens in women, and the positive relationship between age at menarche and the common carotid artery intima-media thickness in adulthood could be explained by an early protective effect of endogenous estrogen on the development of atherosclerosis. Nevertheless, our data are apparently in contrast with previous studies showing that girls with earlier age at menarche tend to have worse cardiovascular risk factor levels in adulthood than those who underwent menarche at a later age[12–19].

Chang et al.[35] pointed out that the risk of coronary heart disease mortality was lower in 17-18 years old at menarche women than that in younger than 17 years at menarche in a population of 3,257 post-menopausal women. Lakshman et al.[36] found that early age at menarche (before age 12 years old) induced an increased risk of cardiovascular disease events/mortality and overall mortality in 15,807 women aged 40-79 years old. This relationship was only partly in relation to an increased adiposity[37].

However, our study is not comparable to previous studies, since our patients are overweight and obese women, in contrast with the general population enrolled in previous studies.

The most consistent evidence relates to higher adult body mass index in women who had earlier menarche on average[13,15-18]; moreover, an inverse association of menarcheal age has been reported with blood pressure[15], glucose intolerance[15], insulin resistance[38] and risk of ischemic heart disease and stroke[14,20,39]. However, none of these studies has demonstrated that earlier menarche is an independent predictor of adverse adult outcomes. The recent Cardiovascular Risk in Young Finns study showed that early menarche is only a risk marker and greater childhood BMI seemed to contribute to earlier age at menarche [40]. Moreover, all the available studies do not exclude that either earlier or later menarche have an unfavorable effect on the arterial intima-media thickness and the cardiovascular risk.

Limitations of this study concern the sample characteristics. In particular, the present study was performed in women with a wide range of age, and only in overweight and obese women, enrolled at an Outpatient Clinic Nutrition Unit. Therefore, we cannot exclude that results might be different in the general population not selected according to our exclusion criteria. Furthermore, we did not consider a lean group as control. Furthermore, the research did not reach the same sample size of previous researches. Nevertheless, other literature data consider for example general population, with at least many confounding factors able to influence the overall cardiovascular risk profile of each patient enrolled. On the contrary, our study considered only selected patients who showed an increased BMI, different according to age. These reduced the biases and improved the selection of the population in order to try to understand the real weight of age at menarche in the development of cardiovascular risk. For this reason further evaluations and researches will be developed in order to improve our results.

Conclusion:

In conclusion, the present study shows that later menarche is a predictive factor of arterial thickening in the adult age, independently of common cardiovascular risk factors, in overweight and obese adult women. Further studies are needed in order to confirm or not these results.

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