Association of breast artery calcification with coronary artery disease and carotid intima-media thickness in premenopausal women

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الترابط بين تكلس الشريان الثديي مع مرض الشريان التاجي وثخانة الطبقتين البطانية والمتوسطة للشريان السباتي لدى النساء قبل سن اليأس

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الخلاصة: تبحث هذه الدراسة في ما إذا كان هناك ترابط بين تكلس الشريان الثديي ومرض الشريان التاجي لدى الشابات قبل سن اليأس، ولتقييم الترابط بين تكلس الشريان الثديي وثخانة الطبقتين البطانية والمتوسطة للشريان السباتي وعوامل الاختطار المعيارية لمرض الشريان التاجي. وقد شملت الدراسة 84 امرأة قبل سن اليأس بأعمار تقل عن 55 عاماً ممن تم إحالتهن لإجراء تصوير الشريان التاجي، ووجد لدى 34 (40.5٪) منهن موجودات غير سوية بتصوير الشريان التاجي و6 (7.1٪) منهن تكلس الشريان الثديي في تصوير الثدي الشعاعي. وقد كان منسب كتلة الجسم لدى المصابات بتكلس الشريان الثديي أعلى بوضوح ممن ليس لديهن.

ABSTRACT This study investigated whether breast arterial calcification (BAC) has an association with coronary artery diseases (CAD) in young premenopausal women and evaluated the association of BAC with carotid intima-media thickness and standard CAD risk factors. Among 84 premenopausal women aged < 55 years who were referred for coronary angiography, 34 (40.5%) had abnormal angiographic findings and 6 (7.1%) showed BAC in their mammograms. The body mass index of patients with BAC was significantly higher than those without BAC. BAC had no significant association with angiography-confirmed CAD.

Association de la calcification des artères mammaires à la coronaropathie et à l'épaisseur intima-média carotidienne chez la femme préménopausée

RÉSUMÉ Cette étude a cherché à déterminer si la calcification des artères mammaires (CAM) avait un lien avec les coronaropathies chez la femme préménopausée et à évaluer son association à l'épaisseur intima-média carotidienne et aux facteurs de risque de coronaropathie courants. Parmi 84 femmes préménopausées âgées de moins de 55 ans adressées pour une angiographie coronarienne, 34 d'entre elles (40,5 %) avaient des résultats angiographiques anormaux et 6 autres (7,1 %) présentaient une CAM à la mammographie. L'indice de masse corporelle des patientes souffrant d'une CAM était significativement supérieur à celui des autres patientes. Il n'existait pas d'association significative entre la CAM et la coronaropathie confirmée par l'angiographie.

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Introduction

The prevalence of premature coronary artery disease (CAD) and its risk factors has been increasing among Iranian men and women in recent years [*1,2*], and finding a noninvasive test to predict CAD has become more important. Carotid intima-media thickness (IMT) determined by doppler ultrasonography is a good predictor of the presence and severity of CAD [*3,4*]. With the increase in the number of women undergoing mammography for breast cancer screening [*5*], interest is growing too in the use of breast artery calcification (BAC) detected by mammography as a nonivasive indicator for CAD in women. Mammography for early detection of breast cancer is recommended annually for all women aged > 40 years [*6*], when the risk of cardiovascular disease also becomes significant. Some studies have evaluated the association between BAC and atherosclerosis in postmenopausal women and suggested that BAC is associated with advancing age, hypertension, diabetes and microvascular chronic complications [*7*]. However, few studies have evaluated the association between BAC and CAD in young premenopausal women [*8*].

The aim of this study was to determine whether BAC detected by mammography, already used as a screening test, has any association with the presence of CAD assessed by angiography in young, premenopausal Iranian women. Another objective was to evaluate the association of BAC with the carotid IMT and with conventional as well as novel risk factors of atherosclerosis in the same population.

Methods

Study design

Women undergoing coronary angiography to assess for the presence of CAD were screened for medical history and menopause status. Women meeting the eligibility criteria and confirmed as premenopausal were given Doppler ultrasonography to measure carotid IMT, and mammography to detect BAC. Risk factors for atherosclerosis were assessed from questionnaire data, clinical examination and laboratory tests.

Study setting and sample

All women aged < 55 years who were referred for diagnostic coronary angiography for CAD in the years 2000–03 were evaluated. Patients had been referred with a history of chest pain suspicious for CAD from history and physical examination. This evaluation was done on 250 women in Chamran Hospital, the biggest referral cardiac centre in Isfahan province in the Islamic Republic of Iran.

All enrolled women were asked to fill out a personal history questionnaire including questions on age, parity, menopausal status, use of oral contraceptives or hormone replacement therapy and the presence of cardiovascular disease, parathyroid, breast, renal and other chronic diseases. Questions on history of smoking, diabetes, hypertension and hyperlipidaemia, family history of cardiovascular disease and use of medications were included.

Blood samples were obtained from all 250 women. Women were excluded if they had serum follicle stimulating hormone (FSH) > 40 IU/dL (i.e. postmenopausal), serum creatinine level > 1.5 mg/dL, corrected calcium level with albumin > 10.6 mg/dL or a reported history of parathyroid, renal or breast abnormalities, amenorrhoea or bilateral oophorectomy.

The remaining 84 premenopausal women were enrolled in the study and filled out the consent forms for further investigation. Age range was 33–54 years.

Data collection

Clinical data

For each woman, weight, height, waist circumference and blood pressure were measured using the World Health Organization (WHO) standardized protocol [*9*]. Body mass index (BMI) was computed as weight (kg) divided by height squared (m^2). Hypertension was defined as systolic blood pressure (BP) ≥ 140 and diastolic BP ≥ 90 mmHg or the use of antihypertensive therapy. Diabetes mellitus was defined as self-reported, physician diagnosed or the use of antidiabetic agents.

All examinations were done in the women's unit at Isfahan Cardiovascular Research Centre, a WHO Collaborating Centre.

Laboratory data

Blood samples were taken from all participants after a 12-hour fast. Serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol and fasting blood sugar (FBS) were analysed using an enzymatic method. Serum lipoprotein A (Lp(a)) was measured by enzyme-linked immunosorbent assay (ELISA) method, plasma fibrinogen was analysed by the von Clauss method and quantitative C-reactive protein (CRP) by ELISA methods. Plasma malondialdehyde (MDA), an antioxidant, was measured by high-pressure liquid chromatography. All analyses were done in the central laboratory of Isfahan Cardiovascular Research Centre which is standardized against the reference laboratory of the University Hospital of Leuven in Belgium. Low-density lipoprotein (LDL) cholesterol was calculated from the Friedewald equation [*10*].

Metabolic syndrome was defined by Adult Treatment Panel III criteria as ≥ 3 of: FBS ≥ 110 mg/dL, TG ≥ 150 mg/dL, HDL cholesterol < 50 mg/dL (women), BP ≥130/≥ 85 mmHg, waist circumference > 88 cm [*11*]

Cardiac data

Echocardiography: Women were referred to an expert cardiologist who performed transthoracic echocardiography and measured left ventricular mass by the following formula [*12*]: left ventricular mass = 1.04 × [(interventricular thickness + left ventricle diameter + posterior wall thickness) – (left ventricle diameter)] – 13.6

Angiography: Coronary angiography was performed using Judkins techniques in standard projections. Subsequently, 3 cardiologists reviewed the patients' coronary angiograms independently to determine whether they were normal or not. If there was significant controversy in their interpretation, a 4th cardiologist would review again. Stenotic lesions more than 50% in the left main coronary artery and more than 75% in other main epicardial arteries in angiographies were considered abnormal and indicative of CAD.

Doppler ultrasound: Carotid IMT measurements were done by B-mode ultrasound using a 7.5 MHz probe by Vingmed echocardiography machine. An experienced neurologist measured 6 well-defined arterial wall segments in both right and left carotid systems: the near wall and far wall of the proximal 1 cm of the internal carotid artery, the near wall and far wall of the carotid bifurcation, beginning at the tip of the flow divider, and extending 1 cm below this point and the near and far wall of the arterial segment, extending 1 cm below the tip of the flow divider into common carotid artery. All measurements were recorded 3 times and the mean was used as the measure of carotid IMT [*3,4*].

Mammography: All mammograms were obtained using a Toshiba low X-ray mammography unit and Kodak industrial films

[*13*]. Craniocaudal and lateral views of each breast were performed. Then all views were interpreted by a single reading by an experienced radiologist who was blinded to the coronary artery angiography and carotid ultrasonography results. Mammograms were interpreted as BAC-positive if BAC was found on 1 of the 2 standard views in the right or left breast or both of them. BAC was defined as continuous and intermittent parallel tracks or linear tubular calcification clearly associated with blood vessels [*14*].

Statistical analysis

Data were presented as mean and standard deviation (SD). The statistical analysis was performed using *SPSS*, version 13. The prevalence of BAC was determined and 95% confidence intervals (CI) were calculated. The clinical parameters in patients with and without BAC were compared by the nonparametric Mann–Whitney test for continuous variables and the chi-squared test for categorical variables. Taking CAD as the dependent variable and BAC as the independent variable in logistic regression analysis, the association with CAD was evaluated. In another logistic regression analysis BAC was taken as the dependent variable and all other CAD risk factors as independent variables and odds ratios (OR) for prediction of BAC were calculated. For all analysis, a P-value < 0.05 was considered significant.

Results

Abnormal coronary angiographic findings were observed among 34 (40.5%) of the 84 women. BAC was observed in 6 (7.1%) of the studied population. The most prominent risk factors in the total group were: history of hypertension (59.9%), history of hyperlipidaemia (48.8%), positive family history of CAD (51.8%), obesity (53.9%), diabetes mellitus (39.3%) and cigarette smoking (6.0%).

When the data were analysed by BAC status, there were no significant differences between women with and without BAC (missing values were omitted) regarding age, smoking, history of hypertension and hyperlipidaemia, family history of CAD and the CAD risk factors serum Lp(a), plasma malondialdehyde, serum CRP and left ventricular mass. Plasma fibrinogen level was significantly higher in patients without BAC ($P < 0.02$) (Table 1). Metabolic syndrome was present in all of the patients with BAC compared with 74.2% of patients without BAC, although this difference was not statistically significant. BMI was significantly higher among women with BAC than women without BAC [mean 36.5 (SD 4.1) kg/m^2 versus 30.7 (SD 5.4) kg/m^2] ($P < 0.05$). Women with BAC had higher mean common carotid and internal carotid IMT values than women without BAC, although the differences were not significant (Table 1).

Taking CAD as the dependent variable on logistic regression, there was no significant relationship between angiography-defined CAD and BAC (OR = 1.20, 95% CI: 0.14–4.74, $P = 0.80$). From all traditional and novel CAD risk factors only BMI had a significant relationship with BAC (OR = 0.80, 95% CI: 0.64–0.99, $P = 0.04$) (Table 2).

Discussion

The evaluation of CAD in young women is important. Although the prevalence of CAD in premenopausal women is low, the case fatality rates for CAD have been shown to be higher for younger women [*15*]. Despite increasing interest in gender-specific CAD, its risk factors and predictors, there is an apparent paucity of information regarding

Table 1 **Baseline characteristics and risk factors for coronary artery disease in the study women according to breast artery calcification (BAC) status**

Parameter	With BAC (*n* = 6) Mean (SD)	Without BAC (*n* = 78) Mean (SD)	*P*-value
Age (years)	46.6 (1.8)	43.2 (4.7)	0.09
BMI (kg/m²)	36.5 (4.1)	30.7 (5.4)	0.02
Cardiac data			
Common carotid IMT (mm)	1.43 (1.72)	0.60 (0.10)	0.13
Internal carotid IMT (mm)	1.20 (1.40)	0.50 (0.16)	0.33
Left ventricular mass (g/m²)	138.5 (44.8)	124.5 (46.7)	0.38
Laboratory data			
Total serum cholesterol (mg/dL)	259.2 (66.3)	233.4 (78.0)	0.27
Serum HDL cholesterol (mg/dL)	33.0 (7.6)	36.5 (9.7)	0.60
Serum LDL cholesterol (mg/dL)	173.2 (58)	152 (68.8)	0.27
Serum TG (mg/dL)	264.7 (134.9)	224.0 (126.4)	0.49
Serum CRP (mg/dL)	3.1 (2.0)	3.0 (1.4)	0.76
Serum Lp(a) (mg/dL)	72.6 (90.0)	42.6 (35.8)	0.98
Plasma malondialdehyde	59.7 (4.7)	58.2 (13.9)	0.83
Plasma fibrinogen (mg/dL)	236.7 (6.0)	329.4 (82.2)	0.02
Clinical history	%	%	
Metabolic syndrome	100.0	74.4	0.30
Diabetes mellitus[a]	83.3	42.3	0.09
Hypertension[b]	66.7	43.5	0.40
Hyperlipidaemia[c]	66.7	47.4	0.66
Family history of CAD	50.0	39.7	0.68
Cigarette smoker	0.0	3.8	0.84
Oral contraceptive use	0.0	19.2	0.56

[a]History of diabetes or using antidiabetic medication; [b]history of hypertension or using antihypertensive medication; [c]history of hypercholesterolaemia, or using hypocholesterol medication.
SD = standard deviation; BMI = body mass index; TG = triglycerides; HDL = high-density lipoprotein; LDL = low-density cholesterol; Lp(a) = lipoprotein A; CRP = C-reactive protein; IMT = intima-media thickness; CAD = coronary artery disease.

younger premenopausal women, because most studies have underrepresented women in general and young or premenopausal women in particular.

There is growing interest in the evaluation of CAD using noninvasive tests. These include carotid IMT, which is a simple, noninvasive and reproducible tool to evaluate atherosclerosis and thus predict CAD [*16*]. However, IMT is not yet considered a screening test. Mammography, a relatively inexpensive test which is increasingly used as a screening test for breast cancer, may also be a useful predictive tool for early detection of atherosclerosis among postmenopausal women [*8,17*]. Calcified deposits are a common feature in atherosclerosis. Several studies have shown that coronary and aortic calcifications are independently associated with an increased risk of cardiovascular disease [*18*]. However, fewer studies have reported the relationship between calcium deposits in other vessels, such as breast arteries, and atherosclerosis [*19–22*].

Table 2 **Predictors of breast arterial calcification by logistic regression analysis**

Variable	OR	95% CI	*P*-value
Age	0.77	0.56–1.06	1.00
BMI	0.80	0.64–0.99	0.04
CAD (angiography defined)	1.20	0.14–4.74	0.80
Common carotid IMT	0.05	0.00–0.33	0.51
Internal carotid IMT	0.14	0.00–13.5	0.40
Left ventricular mass	0.99	0.98–1.01	0.50
Serum CRP	0.96	0.54–1.72	0.89
Serum Lp(a)	0.99	0.97–1.01	0.26
Plasma malondialdehyde	0.99	0.88–1.11	0.87
Plasma fibrinogen	1.05	0.98–1.12	0.16
Metabolic syndrome	0.00	–	0.80
Diabetes mellitus	6.91	0.01–1.39	0.09
Hypertension	2.43	0.06–2.59	0.34
Hyperlipidaemia	2.13	0.07–2.94	0.42
Oral contraceptive use	0.00	–	0.85

OR = odds ratio; CI = confidence interval; BMI = body mass index; CAD = coronary artery disease; IMT = intima-media thickness; CRP = C-reactive protein; Lp(a) = lipoprotein A.

Our study was undertaken to evaluate the relationship of BAC with carotid IMT and angiography-confirmed CAD as well as the classic and novel CAD risk factors in young premenopausal Iranian women. To our knowledge, this relationship has not been reported in the literature before.

The focus of our study was the associations of BAC and CAD among young women. BAC on mammography may be a sign of coexisting diabetes mellitus [*21*], hypertension [*21*] or CAD [*6,19–21*], which have a higher prevalence in older women [*19,20*]. The increased prevalence of BAC in older patients with diabetes mellitus, hypertension and CAD may be related to the long duration of the disease, as arterial wall changes seen in elderly patients may be aggravated by the disease process. This mechanism led us to select young women for the present study. Since definitions of "young" have varied from less than 65 years old in the Framingham study [*23*] to 21–30 years old in another study [*24*], and in order to adjust for the effect of menopausal status, we decided to recruit only premenopausal women.

A significant correlation has been reported between BAC and CAD in women aged less than 59 years, particularly among diabetics [*8*]. This disagrees with our main finding that BAC had no association with angiography-confirmed CAD in young premenopausal women. However, we investigated only women confirmed as premenopausal by their FSH level and the women were younger on average than women in the previous report. Furthermore, we found no significant relationship between age and the presence of BAC in premenopausal women. Some previous studies also found no significant positive relationships between BAC and CAD [*22*] or between BAC and CAD risk factors [*25*]. Some studies have reported on the relationship between the presence of BAC by mammography with the amount of coronary calcium detected by multislice computed tomography as a predictor for CAD rather than angiography-confirmed CAD [*26*]. Our study used angiography confirmation of CAD, which is the gold standard test for diagnosing CAD worldwide, and carotid IMT which indicates arterial stiffness as a well-recognized predictor of CAD.

Previous studies reported that novel CAD risk factors such as Lp(a) [*27*], CRP [*28*], fibrinogen and low levels of antioxidants are associated with CAD and some with coronary calcification [*29,30*] but not with BAC, particularly in young women. The current study specifically assessed the relationship of these risk factors with BAC in young

premenopausal women and also found no significant relationships. Aside from plasma fibrinogen, the only factor that was significantly associated with BAC was BMI. We noted that all the patients with BAC suffered from metabolic syndrome. The finding is an interesting one in this young population. Another study found no association between BAC and BMI [*31*], but previous studies have not addressed the association of BAC and metabolic syndrome.

An unexpected result in our study was the 40.5% prevalence of angiography-confirmed CAD in young premenopausal patients referred for investigation, which may be explained by the rising prevalence of CAD risk factors in Islamic Republic of Iran [*1,2*].

There were some limitations in this study, including the small sample size, the composition of the study population and the lack of other radiological data such as the size, number and location of BAC. However, there were also some important strengths. These include the careful baseline measurements and the laboratory-based selection criteria for the whole study population. Also these correlations have been studied in young premenopausal women, while previous studies were mainly done on postmenopausal, and to a lesser degree on young, women but not on laboratory-confirmed premenopausal women.

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