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Relationship between breast arterial calcification and lipid profile, plasma atherogenic index, Castelli's risk index and atherogenic coefficient in premenopausal women

Abdulmelik Yıldız [a], Özlem Seçen [b], Cennet Yıldız [c,*], Mehtap Çiçekçi [d]

[a] Nişantaşı University, Cardiology, Istanbul, Turkey
[b] Elazığ Education and Training Hospital, Cardiology, Elazığ, Turkey
[c] Tekden Hospital, Cardiology, Istanbul, Turkey
[d] Elazığ Education and Training Hospital, Radiology, Elazığ, Turkey

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ABSTRACT

Objective: The aim of this study was to investigate the relationship between the breast arterial calcification (BAC) and the plasma atherogenic index (PAI), atherogenic coefficient (AC), Castelli risk index-I (CRI-I) and Castelli risk index-II (CRI-II).

Methods: This retrospective study included 60 premenopausal women aged over 40 years with BAC on mammograms and control group of 60 women without BAC. Serum glucose, triglyceride (TG), low-density lipoproteincholesterol (LDLc), high-density lipoprotein-cholesterol (HDLc), and total cholesterol (TC), levels were measured. Lipid indices were calculated using the appropriate formula.

Results: LDLc, non-HDLc levels were significantly higher, HDLc levels were siginificantly lower in patient group compared to the control group ($p = 0.007$, $p = 0.027$, and $p = 0.014$, respectively). Patient group had significantly higher PAI, AC, CRI-I and CRI-II levels than the control group ($p = 0.003$, $p = 0.002$, $p = 0.002$ and $p = 0.003$, respectively). A significant positive correlation was found between BAC and PAI, AC, CRI-I and CRI-II ($r = 0.267$ and $p = 0.003$, $r = 0.282$ and $p = 0.002$, $r = 0.282$ and $p = 0.002$, $r = 0.271$ and $p = 0.003$, respectively). LDLc and non-HDLc were positively correlated whereas HDLc was negatively correlated with the BAC ($r = 0.188$ and $p = 0.039$, $r = 0.202$ and $p = 0.027$, $r = -0.223$ and $p = 0.014$, respectively).

Conclusion: BAC is a valuable tool for the prediction of deranged lipid profile. Dyslipidemia, PAI, AC, CRI-I and CRI-II are risk factors for the development of atherosclerosis. Our results indicate that BAC is potentially useful tool for the detection of dyslipidemia and early atherosclerosis in premenopausal women.

1. Introduction

Breast arterial calcification (BAC) on mammography is uncommon in women less than 50 years old. The prevalence of BAC ranges from 9 to 17% and increases with age [1]. Several studies have found correlations between BAC and hypertension, diabetes mellitus, cardiovascular disease and cardiovascular mortality [2–4]. Similarly, BAC has predictive value for cerebral, carotid and peripheral artery disease [5]. Current guidelines recommend annual mammography screening for all healthy women beginning at the age 40 for early detection of breast cancer. BAC detected during routine mammography may provide potential insights into metabolic disorders responsible for atherosclerosis. Many epidemiological studies have shown that high levels of low-density lipoprotein cholesterol LDLc, TG and low HDLc play an important role in the pathogenesis of atherosclerosis [6]. Although high TG levels correlate with the presence of small, dense LDLc particles and associated with increased risk of coronary artery disease, the risks appear to have neglected in NCEP ATP III target recommendations [6–8].

There are new cardiovascular risk predictors obtained by different combinations of lipid profile parameters. These are; atherogenic index of plasma (PAI); based on two important parameters TG and HDLc, both of which are independent risk factors for coronary artery disease (CAD) [9]. Castelli risk index-I (CRI-I); calculated as (TC / HDLc), Castelli risk index-II (CRI-II); as (LDLc/HDLc) is another fraction which involves independent risk factors for CAD [10,11] and atherogenic coefficient (AC) calculated as {(TC − HDLc) / HDLc} is yet another ratio relying on the significance of HDLc in predicting the risk of CAD [12].

The purpose of this study was to investigate whether BAC has a relation with PAI, AC, CRI-I and CRI-II in premenopausal women over 40 years of age.

* Corresponding author at: Konaklar mah. Org Izzettin Aksalur cad. Oyak sitesi sok. 38. Blok daire 2, Beşiktaş, Istanbul, Turkey.
E-mail address: cennet_yildiz@live.com (C. Yıldız).

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2. Methods

2597 consecutive premenopausal women over 40 years of age that were sent for screening and diagnostic mammography between January and November 2015 were recruited for this retrospective study. The study protocol was approved by the Medipol University Ethics Committee. A Mammomat 3000 Nova equipment (Siemens AG, Germany) was utilized for acquisition of craniocaudal and mediolateral oblique images. If calcifications were present on the right, left, or both projections of the breast, the mammogram was categorized as BAC (+). BAC was defined as two linear calcification depositions in a conical periphery when the arterial wall is imaged longitudinally or as calcific rings when the artery is cut transversely [2]. The women were divided into two groups: those with BAC and those without BAC. 125 women with BAC were included in the study. The women in postmenopausal state or having obesity, past history of hypertension, liver disease, renal disease, diabetes mellitus, thyroid dysfunction, coronary artery disease, valvular heart disease, cerebrovascular disease and malignancy were excluded from the study. A total of 60 women met all study criteria were entered in the study and 60 subjects without BAC accepted as the control group. All women were contacted by telephone and underwent physical examination. All subject underwent 12-lead ECG (Comen CM100B, China) in the supine position. Echocardiographic examinations were performed using Vivid 3 pro equipment (GE Vingmed Ultrasound AS, Horten, Norway) according to the guidelines of the American Society of Echocardiography [13]. All blood samples were taken from antecubital vein in the morning, after overnight fasting. All samples were evaluated on the same day. Serum TC, TG, HDLc levels were assayed on Cobas c311 clinical chemistry analyzer (Roche Diagnostics, Germany). Serum LDLc calculated using Freidwald formula [14]. Non-HDLc is calculated as total cholesterol minus HDLc. The atherogenic ratios were calculated as follows: PAI = log TG / HDLc, CRI-I = TC / HDLc, CRI-II = LDLc / HDLc, AC = (TC − HDLc) / HDLc.

3. Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percentages. To compare parametric continuous variables, Student's t-test was used; and to compare categorical variables, the Chi square-test was used. Pearson's correlation analysis was used for relation between BAC lipid parameters. All variables are showing significant values < 0.05. Two-tailed P values less than 0.05 were considered significant and the confidence interval was 95%. All statistical studies were carried out using the SPSS program (version 22.0; SPSS Inc., Chicago, Illinois, USA).

4. Results

2597 consecutive premenopausal women that were sent for screening and diagnostic mammography were evaluated and 60 women with BAC who met entry criteria were enrolled in the study. (An example of breast arterial calcification is shown in Fig. 1). 60 subjects without BAC accepted as the control group. The demographic characteristics of both groups including age, height, weight, body mass index (BMI), blood pressure were similar. Both groups had BMI > 25 kg/m^2 indicating overweight. Serum LDLc and non-HDLc levels of the patient group were significantly higher than the control group (p = 0.007 and p = 0.027, respectively), whereas serum HDLc level of the patient group was lower than the control group (p = 0.014) PAI, AC, CRI-I and CRI-II were found to be increased significantly in the patient group as compared to their values in the control group (p = 0.003, p = 0.002, p = 0.002 and p = 0.003, respectively) (Table 1). Pearson bivariate correlations analysis results showed that BAC was positively correlated with non-HDLc and LDLc levels (r = 0.202, p = 0.027 and r = 0.188, p = 0.039, respectively) and negatively correlated with HDLc levels (r = 0.223, p = 0.014). There was a significant positive correlation between BAC and PAI, AC, CRI-I and CRI-II (r = 0.267 and p = 0.003, r = 0.282, and p = 0.002, r = 0.282 and p = 0.002, r = 0.273 and p = 0.003, respectively) (Table 2).

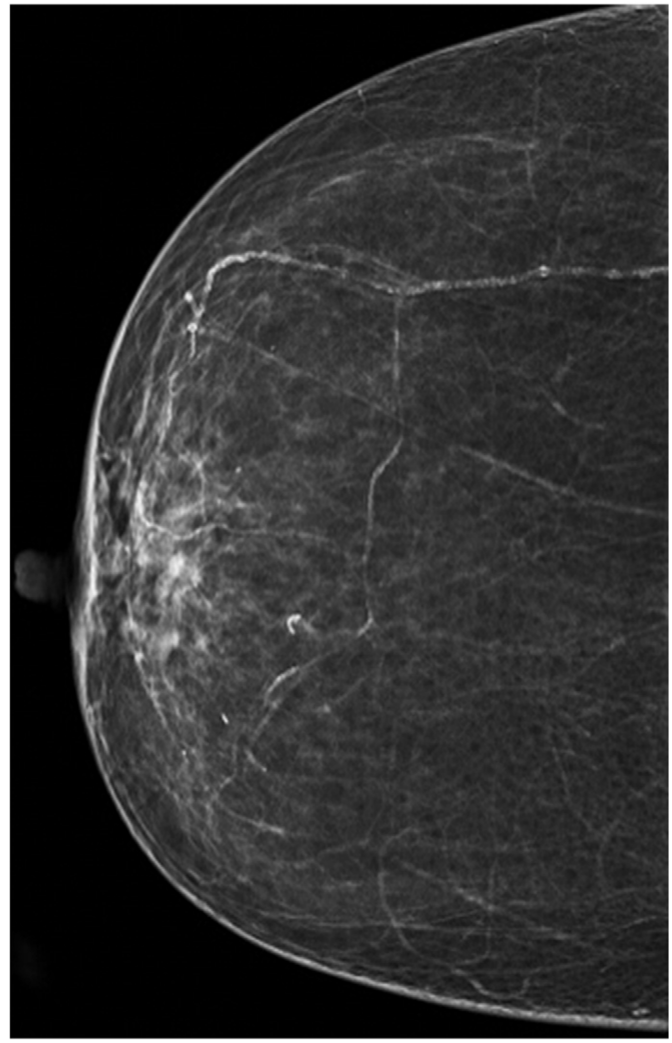

Fig. 1. Example of breast arterial calcification.

Table 1
Patient's clinical, lipid profile and ratios among study groups.

Parameters	BAC + (N:60)	BAC − (N:60)	P
Age	45.1 ± 3.1	45.6 ± 3.6	0.3
BMİ (kg/m^2)	27.4 ± 1.4	26.2 ± 1.8	0.5
Systolic tension (mm Hg)	127.1 ± 8.3	126.3 ± 9.3	0.7
Diastolic tension (mm Hg)	72.5 ± 9.8	70.1 ± 7.3	0.6
Lipid profile (mg/dl)			
TC	207.7 ± 22.9	201.8 ± 18.4	0.135
HDLc	46.5 ± 7.2	49.6 ± 5.8	0.014
LDLc	133.2 ± 23.2	122.8 ± 18.3	0.007
TG	150.8 ± 12.3	146.9 ± 12.2	0.093
Non HDLc (TC − HDLc)	161.1 ± 23.5	152.2 ± 18.8	0.027
Lipid ratios			
Atherogenic index of plasma	0.51 ± 0.07	0.47 ± 0.06	0.003
Atherogenic coefficient	3.55 ± 0.83	3.12 ± 0.60	0.002
Castelli's risk index-I	4.55 ± 0.83	4.12 ± 0.60	0.002
Castelli's risk index-II	2.89 ± 0.75	2.52 ± 0.53	0.003

P value ≤ 0.05 is considered statistically significant, BAC: breast arterial calcification, BMI: Body mass index, TC: total cholesterol, HDLc: high density lipoprotein cholesterol, LDLc: low density lipoprotein cholesterol, TG: triglyceride.

Table 2
Pearson's correlations between BAC and lipid profile and ratios.

Parameters	r	p
Plasma atherogenic index	0.267	0.003
Atherogenic coefficient	0.282	0.002
Castelli's risk index-I	0.282	0.002
Castelli's risk index-II	0.271	0.003
Non-HDLc	0.202	0.027
TC	0.137	0.135
HDLc	−0.223	0.014
LDLc	0.188	0.039

P value ≤ 0.05 is considered statistically significant, TC: total cholesterol, HDLc: high density lipoprotein cholesterol, LDLc: low density lipoprotein cholesterol, TG: triglyceride.

5. Discussion

Atherosclerosis is a systemic disease. Arterial calcifications are predictor of cardiovascular disease. New diagnostic techniques now allow noninvasive visualization of calcifications within the walls of the coronary and peripheral arteries. Several studies have evaluated the relationship between BAC and CAD. The majority of these studies demonstrated a positive association between BAC and CAD [5]. BAC has been associated with age, diabetes, hypertension, osteoporosis, hypertriglyceridemia, chronic kidney disease, albuminuria, hyperhomocysteinemia, BMI and high levels of hs-CRP [15–18]. We excluded from the study all women who had all the risk factors listed above except hyperlipidemia.

Pathologically calcification occurs at 2 anatomic sites within the vascular wall; the intima and the media. These different locations represent 2 pathophysiologically different processes [19–21]. Intimal calcification is an active, regulated process that is similar to bone formation and involves expression of growth factors, matrix proteins, and other bone relate proteins [22], and has been associated with inflammatory cells, lipid deposits, and vascular smooth muscle cells. Medial arterial (Mönckeberg type) calcification occurs in the absence of macrophages or lipid deposits [23]. Studies have confirmed that medial calcification is an independent predictor of CAD events. Although, intimal calcification is more frequently associated with coronary artery disease, the imaging techniques used cannot distinguish between intimal and medial calcification.

In this study, we investigated the relationship between BAC and lipid indices. To the best of our knowledge, no study has described the association between BAC and PAI, AC, CRI-I and CRI-II in premenopausal women.

A gradual change in ovarian function and estrogen production begins at age 40. As estrogen levels decline lipid profiles change adversely, increasing women's risk for atherosclerosis. Estrogen increases the blood levels of HDLc, which have cardiovascular protective effects, while lowering the levels of LDLc and TC, which increase the risk of cardiovascular disease [24–26]. Dyslipidemia is one of the most important risk factors for atherosclerosis. High levels of LDLc, TG and low levels of HDLc are associated with increased CAD risk [27,28]. In addition to the traditional lipid parameters, lipid indices have been used to assess the risk of atherosclerosis. It has been suggested that the different combinations of these lipid profile parameters can be used to identify such high risk individuals. PAI, CRI and AC are the three ratios predicting the risk atherosclerosis and CAD. These are the calculated fractions which can be used in the clinical setting for assessing the risk of cardiovascular disease beyond the routinely done lipid profile. Atherogenic lipoprotein phenotype is characterized by high TG, low HDLc and rise in small dense LDLc [29]. It has been suggested that PAI values of −0.3 to 0.1 are associated with low, 0.1 to 0.24 with medium and above 0.24 with high cardiovascular risk [30]. In our study PAI of the study group was 0.51 ± 0.07. High PAI values may be connected with the increased risk of cardiovascular disease.

In PROCAM study, it was observed that subjects with LDLc/HDLc > 5 had six times higher rate of coronary events [31]. Studies have shown non-HDLc being similar to Apo-B in assessing atherogenic cholesterol and lipoprotein burden [32]. The aforementioned observations suggest that lipid ratios like PAI, CRI and AC could be used for identifying individuals at higher risk of atherosclerosis and cardiovascular disease, when the absolute values of individual lipoproteins seem normal and in individuals with elevated TG concentrations.

Our study showed that premenopausal women >40 years old with BAC had altered lipid profile and PAI, AC, CRI-I and CRI-II values. A number of clinical trials have shown that alterations in these parameters are important risk factor for CAD and BAC is associated with CAD.

6. Study limitations

There are several limitations in this study. The osteoporotic status and vitamin D levels of the women were not evaluated. Inflammatory markers such as CRP, RDW were not assessed in the study population. Visual scoring of conventional mammography was applied in BAC assessment, the calcification mass scoring which have been used at the digital mammography was not performed.

7. Conclusion

BAC detected during routine mammography is an important finding, since they may indicate an increased risk for CAD. Evaluation of lipid profile and lipid indices (PAI, AC, CRI-I and CRI-II) of these patients contributes to risk assessment and identifies an important proportion of dyslipidemia. Women with BAC require careful evaluation for the presence of coronary artery disease. Improvements in cardiovascular risk factors, including BMI, lipid pattern would therefore be of great importance.

Conflict of interest

None declared.

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