Breast arterial calcifications and carotid intima-media thickness and haemodynamics: Is there any association?

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Abstract

Objective: In this study, we aimed to research the relation between breast arterial calcifications (BACs) detected on mammography and two well-known markers of cardiovascular diseases-carotid artery intima-media thickness (C-IMT) and haemodynamics parameters like carotid peak-systolic velocity (PSV), end-diastolic velocity (EDV) and resistive index (RI).

Methods: The study group consisted of 50 consecutive BAC (+) women and the control group consisted of 55 BAC (-) women. In all participants, BAC was diagnosed using mammography and C-IMT was measured using B-mode and Doppler ultrasonography. BAC was defined as two linear calcification depositions in a conical periphery or as calcific rings at the mammographic evaluation. Doppler spectrum samples were obtained from 2 cm proximal to the main carotid artery bifurcation.

Results: Postmenopausal female patients ranging in age from 40 to 86 included in this study. When the groups were adjusted for age, a statistically significant difference was found between mean C-IMT of BAC (+) and BAC (-) groups (0.81±0.2 vs. 0.69±0.2 mm; $p<0.001$). No significant differences were observed between BAC (+) and BAC (-) groups in terms of PSV, EDV, RI.

Conclusion: The findings of the present study suggest that BAC, diagnosed by mammography, is independently associated with C-IMT. C-IMT measurement is suggested as a useful tool to detect early atherosclerotic changes. However, haemodynamic variables (PSV, EDV, RI) were not statistically different between the BAC (+) and BAC (-) groups. Prospective larger cohort studies are needed to further elucidate whether BAC is an independent risk factor for cardiovascular disease. *(Anadolu Kardiyol Derg 2014; 14: 378-82)*

Key words: atherosclerosis, breast calcification, intima-media thickness, Doppler ultrasonography

Introduction

Breast arterial calcifications (BACs) are infrequent in patients less than 50 years old, and the prevalence ranges from 9% to 17% in the female population. The prevalence increases with age and exceeds 50% among women aged 65 years and above (1). Radiologically observed calcifications in the coronary arteries, thoracic aorta, and abdominal aorta are used to correlate with the increased prevalence of coronary artery disease. Epidemiological studies also showed that BACs are correlated with hypertension, diabetes, cardiovascular diseases, and cardiovascular mortality (1-11).

In this study, we aimed to investigate the relation between BAC detected by mammography and two well-known markers of cardiovascular diseases-carotid artery intima-media thickness (C-IMT) and haemodynamics.

Methods

Study design and patient selection

This study was conducted in two-center and mammography of the total 1450 postmenopausal women was assessed in terms of BAC. Data were obtained by a questionnaire, physical examination of the cardiovascular system, sampling of blood, recording of a resting electrocardiogram, measurement of C-IMT, and performing mammographies. After assessing the data, 105 women who did not have any exclusion criteria listed below were selected as the final study cohort. The study protocol was approved by the ethics committee of our university, and every subject signed a consent form. The patients were divided into two groups according to the presence/absence of BACs: BAC (+) group (n=50) and BAC (-) group (n=55). The BAC (-) group served as the control group.

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Exclusion criteria

To avoid confounding by other known risk factors for atherosclerosis, we used the following exclusion criteria for all the study participants: (i) hypertension, as defined by blood pressure >140/90 mm Hg or use of antihypertensive medication; (ii) hyperlipidaemia, as defined by a level of low-density lipoprotein (LDL) cholesterol >160 mg/dL, triglycerides >200 mg/dL, or use of lipid-lowering medication; (iii) diabetes mellitus, as diagnosed according to the World Health Organization criteria or use of anti-diabetic medication; (iv) body mass index >27; and (v) history of ischaemic heart disease or cerebrovascular events.

Mammographic evaluation

Overall, 105 mammographic examinations involving the mediolateral oblique and craniocaudal views of both breasts was conducted with a Mammomat 3000® (SIEMENS, Germany). If calcifications were present on the right, left, or both projections of the breast, the mammogram was categorised as BAC (+). Mammographies were studied with respect to BACs, and the main C- IMT, peak-systolic velocity (PSV), end-diastolic velocity (EDV) and resistive index (RI) were measured with Doppler ultrasonography by another radiologist. 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). Mammographically detected BACs were graded as follows:

Grade 1 was mild, in which the artery or arteries were mildly surrounded by calcium.

Grade 2 was moderate, in which the artery or arteries were markedly surrounded by calcium.

Grade 3 was severe, in which the artery or arteries were markedly surrounded by calcium in the form of a thick column (3).

Table 1. Comparison of clinical and Doppler variables of the study groups

Characteristics	BAC (-) Mean±SE (n=55)	BAC (+) Mean±SE (n=50)	*P**
Age, years	55.2±8.2	61.8±8.4	<0.0001
C-IMT, mm	0.69±0.2	0.81±0.2	<0.0001
PSV, cm/sec	58.8±2.3	56.8±2.4	0.575
EDV, cm/sec	18.0±0.83	17.3±0.87	0.601
RI	0.68±0.12	0.68±0.13	0.748
Parity	2.73±0.29	4.37±0.31	<0.0001
Postmenopausal period	10.2±1.01	13.38±1.06	0.06

BAC - breast arterial calcification; C-IMT - carotid artery intima-media thickness; EDV - end-diastolic velocity; PSV - peak-systolic velocity; RI - resistive index
*Analysis of covariance (ANCOVA)

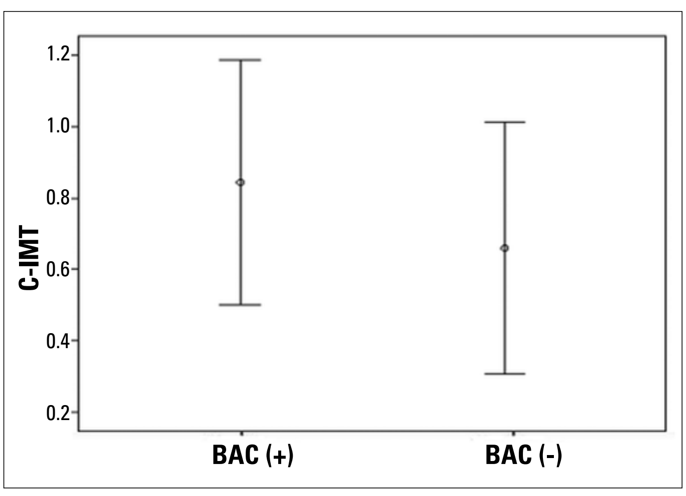

Figure 1. Box plots of carotid artery intima-media thickness (mm) in patients with breast arterial calcification (+) and without breast arterial calcification (-) (p <0.001). The horizontal bars indicate extreme values. The circles mark the median value of the respective group

Carotid artery evaluation by B-mode ultrasonography and Doppler ultrasonography

Carotid artery examination was conducted by B-mode ultrasonography, and duplex Doppler examination was performed using a 7.5-13.5-MHz multi-frequency linear array probe (EUB 6500; Hitachi, Tokyo, Japan and Aplio 500; Toshiba, Tokyo, Japan). All ultrasonography examinations were conducted by the two radiologist. For this examination, the participant's neck muscles were relaxed by extending the neck 20° forward after 15 minutes of rest in the supine position. Only the posterior (distal) wall of the carotid artery was evaluated and intima-media thicknes measurements were carried out. Both right and left intima-media thickness were measured using grey-scale examination and the thicker one of the two was recorded.

On the longitudinal plane, sampling interval was placed parallel to the middle section of arterial lumen, and current spectrums were obtained with the Doppler angle being 45–60°. Doppler spectrum samples were obtained from 2 cm proximal to the main carotid artery bifurcation. PSV, EDV, and RI values were obtained by using manual measurements over the spectral trace.

Statistical analyses

Covariance analysis was used for differences between BAC (+) and BAC (-) groups of clinical characteristics and Doppler variables after adjusted according to age effect. Spearman rank correlation analysis was used for relation between BAC grade and CCA haemodynamics parameters and C- IMT. Statistical analyses were carried out using PASW Statistics 18.0 (SPSS Inc., Chicago, Illinois, USA) and a p value <0.05 was considered significant.

Results

The comparison of patient demographics and clinical variables is presented in Table 1. The BAC (+) patients were significantly older (p<0.001).

Statistically significant difference was found between BAC groups about a mean C-IMT after adjusted for age (0.81±0.2 mm vs. 0.69±0.2 mm; p<0.001). The relation between BAC and IMT is presented in Figure 1. Haemodynamic variables were not statistically different between the study groups.

Table 2. Comparison of clinical and Doppler changes with BAC grade

Characteristics	BAC grade	
	r	P*
Age, years	0.988	0.002
C-IMT, mm	0.135	0.359
PSV, cm/sec	-0.048	0.763
EDV, cm/sec	0.179	0.213
RI	-0.154	0.285
Parity	-0.199	0.166
Postmenopausal period	-0.41	0.779

BAC - breast arterial calcification; C-IMT - carotid artery intima-media thickness; EDV - end-diastolic velocity; PSV - peak-systolic velocity; RI - resistive index
*Spearman rank correlation

BAC grade was not significantly associated with the other variables in BAC (+) group (Table 2).

Furthermore, the mean postmenopausal period in the BAC (+) group and BAC (-) group was 13.38±1.06 and 10.2±1.01 years, respectively. However, the difference between the two groups was not significant when the effect of age was statistically eliminated (p=0.06). The mean number of births (parity) in the BAC (+) group was higher than BAC (-) group after adjusted for age (p<0.001).

Discussion

Cardiovascular disease is associated with systemic arterial disease. Arterial calcifications are marker of atherosclerotic disease and therefore an indicator to predict cardiovascular future (4). Although there are many studies examining various aspects of the relationship between cardiovascular disease and BAC in the literature, there is limited number of studies available investigating the association between C-IMT and BAC (7, 8). Carotid artery hemodynamic parameters have not been studied in these studies. In this study, relationship between mammographically detected BAC and the main C-IMT with carotid artery hemodynamic parameters were investigated as the good markers of cardiovascular disease.

Arterial calcification is divided into 2 groups according to the involvement of the intima and media layer. Arterial intimal calcifications are characterized by large, irregular and discontinuous calcium deposits. Medial calcifications are smooth, granular and circumferential deposits. Also intimal calcifications occur in the elastic arteries and large muscular arteries, medial calcifications (Mönckeberg's medial calcific sclerosis) occur in smaller diameter muscular arteries (2). Medial type usually seen in the extremities. It is also observed in the breast and owing to typical appearance it is easily identifiable. These linear and parallel appearing deposits are defined as railway configuration (12). Mönckeberg's medial calcific sclerosis has also been described in patients with diabetes and end-stage renal failure (13, 14). Although intimal arterial calcification is a component of atherosclerotic disease, medial calcification results from a process that belongs to aging, which does not have much clinical significance (2, 7, 14).

Different methods were used in the evaluation of BAC. Binnary classification has been used in some studies (2, 4). Some researchers were scored BAC visually as in our study (3, 11). In recent years, BAC can be detected more quantitatively using specialized computer software in parallel with technological advances. However, these methods are relatively new and limited studies are available. In this study, some measurement problems depending on the differences of breast density and limitations such as false positive results due to differences in defining of calcification have been reported (15).

A prospective study conducted on young adults reported that increased C-IMT is closely related with coronary artery calcifications and cardiovascular diseases that would develop in future. Therefore, C-IMT measurement is suggested as a useful tool to detect early atherosclerotic changes (5, 6, 16, 17). Intimal changes reflect coronary artery disease (7). Although numerous previous studies have analyzed the correlation between BAC and cardiovascular risk, the correlation between BAC and intima-media thickness has been rarely investigated (7, 8). Concordant with our findings, C-IMT was significantly higher in patients with BAC than in patients without (8). However, we have further analyzed the carotid haemodynamic parameters and compared intimal thickness according to BAC grade. Our results did not reveal any significant difference regarding these measurements.

A significant relation has been shown between coronary calcium score and BAC. However, coronary artery disease risk factors (such as previous cardiovascular disease, smoking, and hypercholesterolaemia) had no correlation with BAC (9). This is possibly due to the differences between the pathophysiological mechanisms underlying coronary arterial calcifications and BAC. Coronary artery calcification is well known to be localised only in the intima of the arterial wall whereas BAC affects the medial layer of the artery, without causing inflammation. In their study, BAC was inversely related to smoking, a finding that has been previously shown as another indication of BAC lacking an inflammatory effect (9). Similarly, Zgheib (18) and Sarrafzadegann (19) did not find a statistically significant relation between angiographically detected coronary heart disease and BAC.

Schnatz et al. (20) suggest that presence of breast arterial calcifications on mammograms indicates a significantly increased risk of developing CVH or a stroke. These results suggest that breast arterial calcifications should be routinely reported on mammograms and viewed as a marker for the development of CVH. Reddy et al. (21) suggest that osteoporosis and breast arterial calcification are strongly and independently correlated. Duhn et al. (14) hypothesized that breast arterial calcification is a specific marker of generalized medial calcification and that mammography can be used to determine the prevalence and risk factors for medial calcification in chronic kidney disease. Wada et al. (22) BAC in a MG study showed a significant association between vertebral fractures and hypertension. In addition, hypertension was linked to the presence of prevalent vertebral fractures. These findings might show that the pathogenesis of vertebral fracture, BAC and hypertension share common metabolic abnormalities.

In our study, mean carotid IMT was 0.81 in BAC (+) patients and was 0.69 with BAC (-) patients. The difference between the two groups calculated by excluding the age, an independent factor for increased IMT, was statistically significant ($p<0.001$). However, there was no correlation between grade of BAC and IMT excluding age again in BAC (+) patients. PSH, DSH and RI of common carotid artery in the BAC (+) and BAC (-) groups was not found significantly different statistically. We think that only detected significant relationship between MAK and IMT was due to measurement of both intima and media layer of the artery in the IMT measurement. Most of the BAC is known to be due to calcification of media layer and result of a process of aging. We believe that same pathologic processes occur in the common carotid arteries of BAC (+) patients who have medial sclerosis of the breast vessels due frequently to aging and consequently IMT increases.

RI is an indication of vascular resistance. RI increase occurs in advanced age, vascular diseases, and clinically proven cardiovascular disease. C-IMT may be normal despite RI deteriorating during the early stages of atherosclerosis (10). Even though we showed a statistical relation between BAC (+) and BAC (-) groups, we did not find a significant difference between the RIs. This reflects the fact that IMT increase in the BAC (+) group is a result of calcific sclerosis of the medial layer.

In our study, the average postmenopausal period was found to be 13.38±1.06 and 10.2±1.01 years in the BAC (+) and BAC (-) groups, respectively. Since in our study a relation was found significant between age and BAC. This result was concordant with previous literature findings. The differences between BAC (+) and (-) groups with regard to postmenopausal period was found significant after excluding the effect of age. However, a significant correlation was not found between postmenopausal period and presence of BAC. This led us to infer that the real cause of BAC in patients with longer postmenopausal period was not the length of the postmenopausal period but the advancing age of the patient. Oestrogen increases the blood levels of high-density lipoproteins, which have cardiovascular protective effects, while lowering the levels of low-density lipoprotein and total cholesterol, which increase the risk of cardiovascular disease. The production of oestrogen reduces during the premenopausal period and its level further decreases after menopause. This, in turn, increases the atherosclerosis risk in postmenopausal women (23, 24). Our finding that postmenopausal BAC was associated with age but not with the time after menopause suggests that BAC was related to the aging process rather than atherosclerosis.

Study limitations

This study has a few limitations. The sample size of the study was small. In addition, variables such as total cholesterol, high-density lipoprotein cholesterol, glucose, serum creatine, and body mass indices of the patients were not evaluated. Visual scoring was applied in breast arterial calcification assessment, the calcification mass scoring which have been used at the digital mammography was not performed.

Conclusion

In conclusion, BAC was found to be significantly and independently associated with C-IMT, while the haemodynamic variables were not statistically different between the BAC (+) and BAC (-) groups. However, the most important result of our study is the lack of significant difference between RI of the BAC positive patients with increased IMT and BAC negative patients. According to the knowledge of a normal RI indicates undamaged vascular structure, increased IMT in BAC positive group may be questionable whether atherosclerotic or belonging to a process of aging. Therefore, we suggest that, whether there is a relationship between increased carotid IMT and AS should be clarified with larger series of histopathological studies in BAC positive patients.

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