

An Investigation into the Relationship between Arterial Calcification in Mammography and Carotid Intima-Media Thickness

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ABSTRACT

Background: Calcification in the arteries including coronary, carotid, and aorta can be an indication for cardiovascular diseases.

Aim: To investigate the relationship between mammography detected arterial calcification and carotid intima-media thickness in addition to evaluating the related cardiovascular risk factors.

Methods: Seventy women with arterial calcification in their mammography and 119 women without this finding were selected for assessing intima-media thickness (IMT) of carotid arteries and presence of plaque in ultrasound examination. Risk factors for atherosclerosis were attained from medical records for independent effects.

Results: Compared to the control group, the group with arterial calcification had more background of coronary artery disease, increase in blood pressure, and hypercholesterolemia ($p=0.02$, $p<0.001$, and $p=0.013$ respectively). It was also observed that while the mean carotid intima-media thickness in the group with calcification was remarkably more than that of the control group (0.78 ± 0.13 and 0.61 ± 0.1 respectively), there was no correlation between different grades of calcification and carotid IMT.

Conclusions: Arterial calcification in mammography developed more in individuals with higher blood pressure, diabetes, and hypercholesterolemia and those with the history of heart diseases. In addition, it was observed that with an increase in breast arterial calcification, carotid intima-media thickness would increase; however, the grade of this calcification had no relationship with carotid intima-media thickness.

Keywords: Mammography, Carotid Intima-Media Thickness, Vascular Calcification

INTRODUCTION

Presence of calcium deposits on the walls of arteries is considered as a common problem in the atherogenic process and researches show that calcification in the arteries including coronary, carotid, and aorta can be an indication for cardiovascular diseases^{1,2}. Arterial calcification is referred to as calcified sclerosis in the arterial medial layers and usually involves small and medium-sized arteries^{3,4}. In breast arteries, this state appears as two parallel lines similar to tram track and emerges as a small circle in cross-section^{3,5}. As a cheap and easily-accessible screening test, mammography has a vital role in early diagnosis of breast cancer and increases the possibility of timely treatment of these patients^{3,6,7}. Arterial calcification is observed in mammography of about 9-17% of women before menopause and over 50% after the age of 65. It is one of the most typical findings of mammography and has no correlation with breast malignant diseases; therefore, it is not normally referred to in reports^{8,9}.

Different studies have indicated that arterial calcification in mammography can indicate atherosclerosis of other important arteries of the body and different types of diseases of coronary arteries, blood pressure, diabetes, and even osteoporosis. It is also accompanied with the increase risk of mortality particularly among elderly individuals^{3,8,10,11}. In other words, presence of arterial calcification in mammography associates with coronary artery diseases; however, this association is not much observed before menopause. Results of a study showed that only 7% of women who had arterial calcification in mammography had developed cardiovascular diseases¹².

Cerebrovascular diseases can also happen as a result of atherosclerosis. As a consequence of cerebrovascular insufficiency, stroke is one of the main causes of morbidity and disability in communities, and carotid artery atherosclerosis which is one of the most important causes of stroke is controllable⁶. Studies have indicated that an increase in thickness

of intima-media carotid artery can better predict the risk of heart stroke than of the methods of measuring cardiovascular problems including Framingham risk score¹³. Moreover, the results of another study showed that by adding this criterion to the methods of measuring the risk of cardiovascular diseases can enhance the diagnostic capacity of these methods¹⁴.

One of the methods of evaluating atherosclerosis in carotid arteries is to use sonography in which intima-media thickness and arterial plaques can be distinguished easily and without any invasive measures. It has been indicated that presence of atherosclerosis and plaques in these arteries is related with coronary artery diseases, stroke, and high risk of cardiovascular events^{3,6,12}. Taking pathophysiology of atherosclerosis into account, it can be claimed that the calcification process of breast arteries is the same as that of other arteries of the body including heart and brain arteries. Accordingly, different studies have evaluated the relationship between arterial calcification in mammography and other cardiovascular diseases. It is necessary to mention that cerebral artery diseases are also considered as cardiovascular diseases.

In their study, Sedighi et al¹³ stated that diagnosis of arterial calcification in mammography is independently related with changes in atherosclerosis in the carotid arteries, and patients who have arterial calcification in mammography have thicker intima media in carotid arteries. Mostafavi et al⁸ measured the grade of vascular calcification in mammography and the intensity of coronary artery disease in CT angiography. They found out that the presence of arterial calcification in mammography associates with coronary artery disease.

Since regular screening mammography is recommended to early breast cancer diagnose among all women from the age of 40 onward^{12,15}, the present study was carried out in order to examine the relationship between the grade of arterial calcification in mammography and carotid intima-media thickness. Moreover, figuring out a factor which could be able to indicate changes in

carotid artery atherosclerosis and, at the same time, be cheap and easily accessible.

MATERIALS AND METHODS

Patient selection: In the present study, among 454 participants who were undergone mammography in Imam Khomeini hospital of Ahwaz (from Dec 2015 to Dec 2016); 70 individuals had arterial calcification in mammography and 384 did not, among whom 119 individuals were in harmony with those 70 patients with calcification in terms of their age; therefore, they were chosen as the control group to undergo cervical artery sonography.

Inclusion criteria of the study comprise negative history of surgery or breast trauma, negative background of breast cancer, negative history of stroke or cerebral events, and lack of kidney failure. The exclusion criteria were any of mentioned disease that diagnosed during study.

Data collection

Data gathering in this study was conducted through three phases of questionnaire, mammography, and sonography. The participants answered questions on age, weight, height, risk factors such as increase in blood pressure, diabetes, smoking, hypercholesterolemia, background of cardiovascular diseases, menopause condition, and parity status. Those who had the inclusion criteria entered the second phase. In this phase, mammography was carried out in perspectives of CC and ML for both breasts. All images were examined by a radiologist experienced in the field of reading mammography who was blind to the patient's demographic information. Afterwards, the patients were divided into two groups: with and without arterial calcification. The following method was used to calculate the grade of calcification¹⁶:

Grade 1: without vascular calcification

Grade 2: Few punctuate vascular calcification

Grade 3: Coarse or tram track calcifications affecting < 3 vessels

Grade 4: Coarse or tram track calcifications affecting ≥ 3 vessels

In the last phase, the participants underwent common carotid and internal carotid artery sonography of both sides of the neck using an Accuson 2000 ultrasound unit (Siemens, USA) equipped with a 5–12 MHz linear transducer by a radiologist experienced in cervical artery sonography. Intima-media thickness and the presence of calcification plaques were also examined in the supine position with the subject's neck extended and the head turned 45° to the left or right. Intima-media thickness was calculated as the interval of the vessel lumen and intima to media and adventitia vessels at the thickest point at 1.5 to 2 cm from carotid bulb⁶. The average intima-media thickness of both sides was recorded as the final figure. Calcification plaques in common and internal carotid artery were defined as thicknesses over 1.2 mm that do not involve all circumference of the vessel.

Data analysis : Data analyses were done using SPSS 16.0 software. Variables were obtainable as means and standard deviations and the distribution of them was analyzed by the Kolmogorov–Smirnov test. The association between carotid IMT and age was calculated by the Pearson correlation test. Univariate and multivariate analysis were done. A P-value of less than 0.05 was considered statistically significant.

Ethics: Regarding the ethical considerations, all of the participants were enrolled to the investigation after completing the written informed consent. Moreover, the study protocol was approved by Ethics Committee for Research in Ahwaz

Jundishapur University of Medical Sciences (ID: IR.AJUMS.REC.1395.391)

RESULTS

In this study of 454 appropriate participants; 70 individuals with mean age of 59.9 ± 7.2 years, had arterial calcification in mammography and 384 did not, 119 age-matched participants (mean age 58.8 ± 7.4 years) were chosen as the control group to undergo cervical artery sonography.

The results of the study indicated that there was no significant difference between the two groups in terms of body mass index (p-value=0.39). Moreover, the number of pregnancy (parity) in the group with calcification was more than that of the group without it; however, it was not statistically significant too (p-value=0.07).

Calcification was observed more among postmenopausal women. However, this point should be mentioned that 94% of the individuals (n=66) with calcification were menopausal despite of their compatibility with the control group in terms of their age. On the contrary, in the control group, only 66% of the participants (n=79) were menopausal, and there was a considerable difference among the two groups with regard to menopause conditions (p-value<0.001).

Regarding carotid intima-media thickness that was reported in the form of mean and standard deviation, the group with calcification had a higher thickness than the control group (0.78 ± 0.13 and 0.61 ± 0.1 respectively) which is a significant difference (p-value<0.05). Furthermore, carotid plaque in 32 out of 70 participants of the group had calcification (46%) compared to the 15 participants out of 119 individuals without calcification (12.6%), which was a completely significant difference (p-value<0.001).

Univariate analysis: Table 1 indicates the relationship between demographic characteristics, cardiovascular risk factors, and carotid atherosclerosis risk in individuals with and without calcification. As indicated in this table, BMI of below and over 30 had no effect on development of calcification. The percentage of multiparous women in the group with calcification was higher. In addition, more calcification cases were observed among menopausal women and a larger percent of participants with calcification were menopausal.

The group with calcification had more cases of coronary artery diseases, increased blood pressure, and hypercholesterolemia compared the control group (p=0.02, p<0.001, p<0.001, and p-value=0.013 respectively). This difference, however, was not significant with regard to diabetes (p-value=0.27). Considering smoking, the ratio was opposite to other cases, such that a higher percentage of individuals without calcification smoked (p-value=0.03). When the participants were compared in terms of the results of carotid artery sonography, a considerable association between high risk of carotid atherosclerosis and presence of calcification in mammography was seen (Odds Ratio=30.55; CI 8.4-110.5).

Multivariate analysis: According to Table 2 and based on multivariate analysis, a significant independent relationship was observed between menopause, an increase in blood pressure, and carotid atherosclerosis risk. There was a significant difference between the breast arterial calcification of pre and post-menopausal women. Moreover, changes in carotid atherosclerosis were independently associated with presence of calcification in

mammography and there was an increase in the risk of carotid atherosclerosis.

It was also observed that although the mean of intima-media thickness in the group with calcification was more than the

group without calcification (0.78 ± 0.13 and 0.61 ± 0.1 respectively), the results demonstrated that in the group with calcification there is no relationship between different grades of calcification and intima-media thickness (Figure 1).

Table 1: The relationship between demographic characteristics and carotid atherosclerosis risk in individuals with and without calcification

Risk factor	BAC+=70	BAC- =119	Odds Ratio	95%CI	P-value
BMI					
≤30	58(84%)	104(87.4%)	1.00		0.39
>30	12(16%)	15(12.6%)	1.43	(0.63-3.52)	
Hypertension	31/70(56%)	19/119(16%)	4.18	(2.11-8.26)	<0.001
Diabetes Mellitus	15/70(21%)	18/119(15%)	1.53	(0.71-3.27)	0.27
Smoking	2/70(3%)	15/119(13%)	0.2	(0.04-0.92)	0.03
Carotid Atherosclerosis risk					
Low-risk	3(4%)	47(39%)	1.00		<0.001
Medium-Risk	28(40%)	52(44%)	8.43	2.40-29.57	
High-Risk	39(56%)	20(17%)	30.55	8.4-110.5	
Presence of plaque	32/70(46%)	15/119(12.6%)	5.83	2.85-11.95	<0.001
Hypercholesterolemia	28/70(40%)	33/119(28%)	2.2	1.19-4.35	0.013
History of CAD	13/70(14%)	9/119(8%)	2.78	1.12-6.91	0.02
Menopausal status					
Premenopausal	4(6%)	40(33.6%)	1.00		<0.001
Postmenopausal	66(94%)	79(66%)	8.35	2.84-24.56	
Parity					
Nulliparous	3(4.3%)	15(12%)	1.00		0.07
Multiparous	67(95.7%)	104(87%)	3.22	0.9-11.55	

Fig. 1: The relationship between arterial calcification grade in mammography and carotid intima-media thickness

IMT: intima-media thickness
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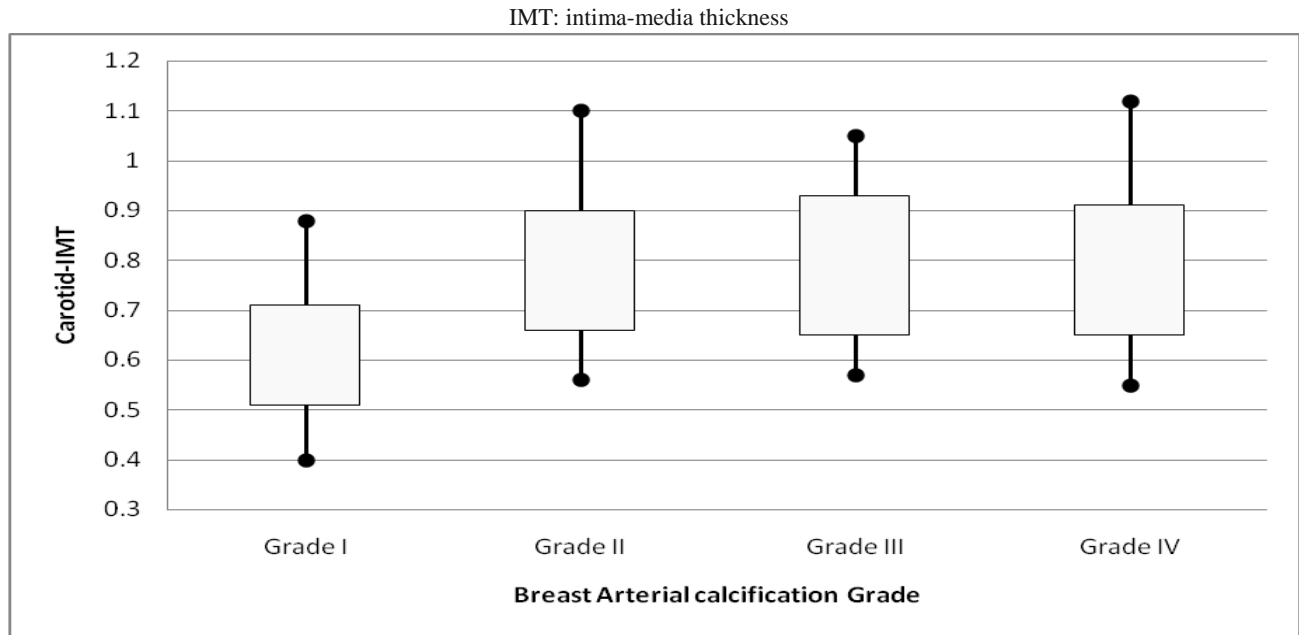


Table 2: Multivariate analysis of the relationship between carotid atherosclerosis risk and other risk factors with presence of calcification in mammography

Risk factor	Odd Ratio	95%CI	P-value
Hypertension	4.01	(1.63-8.26)	0.005
Diabetes Mellitus	1.56	(0.69-3.52)	0.59
Smoking	0.70	(0.21-2.38)	0.6
Carotid Atherosclerosis risk			<0.001
Low-risk	1.00		
Medium-Risk	5.28	1.73-16.1	
High-Risk	23.03	7.3-76.95	
Hypercholesterolemia	2.1	1.1-4.1	0.01

History of CAD	2.27	0.89-5.81	0.08
Menopausal status			
Premenopausal	1.00		
Postmenopausal	2.53	1.22-5.23	0.01
Multiparity	3.22	0.9-11.55	0.07

CAD: coronary artery diseases

DISCUSSION

The present study indicated that there is a close association between arterial calcification in mammography and intima-media thickness (regardless of the calcification grade) and carotid atherosclerosis risk. The results showed that the risk of carotid atherosclerosis development rises with an increase in arterial calcification in mammography and individuals with arterial calcification have a higher mean intima-media thickness in their carotid arteries.

There are two types of arterial calcification: the first type only involves intima and occurs in medium-sized and big arteries; the second type is referred to as calcified sclerosis in media layer of the arteries and usually involves small and medium-sized arteries^{3,4}. In breast arteries, this state appears as two parallel lines similar to tram track and emerges as a small circle in cross-section^{3,5}. This calcification shows the development of atherosclerosis. Atherosclerosis process in different parts of the body involves different parts of arteries. For instance, it involves medial layers in the breast and medial and intima layers in carotid arteries. In coronary arteries, this phenomenon only cause changes in intima layer^{3,10}.

This investigation revealed that breast arterial calcification in individuals with increased blood pressure is higher. Moreover, according to the results of the univariate and multivariate analyses, this is more common among menopausal women. There was also a significant relationship between parity and calcification. In addition to these findings, it was observed that individuals with diabetes and hypercholesterolemia have a higher percentage of arterial calcification. Adversely, smoking was seen to have a reverse relationship with this phenomenon.

Finally, examination of the relationship between calcification grade and intima-media thickness showed that although the individuals with calcification had a higher intima-media thickness than the control group, there was no relationship between the grade of this calcification and carotid artery thickness. In fact, with the rise of grade, intima-media thickness did not increase.

Different similar studies have been carried out in order to examine and determine the relationship between arterial calcification in mammography and cardiovascular, carotid, and cerebral artery diseases.

In this regard, Yildiz et al.¹⁶ studied the relationship between breast arterial calcification and carotid intima-media thickness. They examined 25 postmenopausal women with arterial calcification in mammography and measured carotid intima-media thickness through sonography. It has been shown that those women who had arterial calcification in their mammography image had more childbirths, longer menopausal period, more diabetes, higher blood pressure, and higher carotid intima-media thickness. They reported that more attention should be devoted to arterial calcification in mammography and hoped that this measure could help prevent the complications of atherosclerosis. These findings are in line with present study although they did not examine the grade of calcification.

Sarrafzadegann et al¹⁷ studied the relationship between arterial calcification in mammography and coronary artery disease and carotid intima-media thickness in 84 women before their menopausal age. They only indicated that while 40.5% of the women had disorders in coronary angiography, only 7.1% were diagnosed with arterial calcification in mammography; the finding which shows that there is no relationship between these two at ages before menopause. The present study did not find a relationship between the period before menopause and arterial calcification, either (OR=1). However, as a limitation of our study, sample size may not be sufficient enough to judge correctly about individuals before menopause. Moreover, in their meta-analysis including 10 cross-sectional studies, Jiang et al⁵ examined the relationship between arterial calcification in mammography and the risk of coronary artery disease and heart stroke. They concluded that arterial calcification in mammography is significantly correlated with coronary diseases and stroke. In addition, this idea that presence of arterial calcification in mammography is a benign phenomenon was questioned.

In a cross-sectional study, Ferreira et al.⁶ focused on the relationship between cardiovascular diseases and arterial calcification in mammography and also the prevalence of these among menopausal women. By examining 307 over-40-year-old women with amenorrhea, they evaluated the relationship in between cardiovascular diseases and breast arterial calcification. They found out that after menopause, women with arterial calcification in breast arteries had a higher chance to develop cardiovascular problems. Studying 168 patients aging 40-78 years who had undergone both brain MRI and mammography, Ahn et al¹ determined the relationship between arterial calcification in mammography and cerebrovascular disease. They reported that presence of arterial calcification in mammography is an indicator of higher risk of brain stroke. Accordingly, this section should not be omitted from mammography reports at all and these individuals should be paid more attention.

CONCLUSION

It can be concluded that arterial calcification in mammography occurs more in individuals with increased blood pressure, diabetes, and hypercholesterolemia, and in those with background of heart diseases. It should also be mentioned that with an increase in arterial calcification, there would be an increase in carotid intima-media thickness; however, calcification grade had no relationship with carotid intima-media thickness. Further studies with larger sample size should be carried out in order to fully clarify these associations.

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Conflict of interest: The authors declare that don't have any conflict of interest

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