Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

Pharmacophore
an International Journal
ISSN 2229-5402

AN INVESTIGATION INTO THE ASSOCIATION BETWEEN ARTERIAL CALCIFICATION IN MAMMOGRAPHY AND CAROTID INTIMA-MEDIA THICKNESS

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ARTICLE INFO

Received:
16th Dec 2016
Received in revised form:
28th May 2017
Accepted:
27th Aug 2017
Available online:
04th Sep 2017

Keywords: *breast, carotid intima-media thickness, mammography, vascular calcification*

ABSTRACT

Calcification in the arteries including coronary, carotid, and aorta can be an indication for cardiovascular diseases. This study was carried out in order to investigate the relationship between arterial calcification in mammography and carotid intima-media thickness and to examine the relationship between cardiovascular risk factors and arterial calcification in mammography. Seventy women with arterial calcification in mammography and 119 women without it with similar ages were examined and compared in terms of their BMI, increase in blood pressure, diabetes, smoking, the risk of carotid atherosclerosis, and background of coronary artery disease. The results of the study indicated that compared to the control group, the group with arterial calcification had more background of coronary artery disease, increase in blood pressure, and hypercholesterolemia (p values were respectively p-value=0.02, p<0.001, p<0.001, and p-value=0.013). This difference was however not significant in regard to diabetes (p-value=0.27). Moreover, it was observed that while the mean carotid intima-media thickness in the group with calcification was remarkably more than that of the group without calcification (respectively 0.78±0.13 and 0.61±0.1). In the group with calcification there was no correlation between different grades of calcification and carotid intima-media thickness although the level of calcification increased in the group (from 2 to 3 and 4) but the level of carotid intima-media thickness did not increase (respectively 0.78±0.12, 0.79±0.14, and 0.78±0.13).Arterial calcification in mammography developed more in individuals with blood pressure, diabetes, and hypercholesterolemia and those with the history of heart diseases. In addition, it was observed that with an increase in arterial calcification, carotid intima-media thickness increased however the grade of this calcification had no relationship with carotid intima-media thickness.

To Cite This Article: Mohammad ghasem Hanafi, Saman Sarikhani, Aliakbar Sahraeizadeh*, (2017), "An investigation into the association between arterial calcification in mammography and carotid intima-media thickness", ***Pharmacophore, 8(5),*** *47-53.*

Introduction

Presence of calcium deposits on the walls of arteries is considered as a common problem in the atherogenic process and research has shown 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 , 5]. In breast arteries, this state appears as two parallel lines similar to tram track and emerges as a small circle in cross-section [3 ,6]. This calcification shows the development of atherosclerosis. Atherosclerosis process in different parts of the body involves different parts of arteries. For instance, it involves media

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layers in the breast and media and intima layers in carotid arteries. In coronary arteries, this phenomenon only causes changes in intima layer [3 , 7].

As a cheap and easily-accessible screening test, mammography plays a vital role in early diagnosis of breast cancer and increases the possibility of timely treatment of these patients [3, 4 , 8]. This test is regarded as one of the most successful screening methods and its administration is common among women over 40. Commonly (about 9 to 17% of women before menopause and over 50% after the age of 65) arterial calcification is observed in mammography, particularly among elderly individuals and after the age of menopause, which 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 [9 , 12].

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 and is accompanied with the risk of increase in mortality particularly among elderly individuals [3 , 7] and [9 , 11]. In other words, presence of arterial calcification in mammography associates with coronary artery diseases; however this association is not much observed before menopause such that the results of a study showed that only 7% of women who had arterial calcification in mammography had developed cardiovascular diseases [14]. 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 controllable [4]. 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 [15]. 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 methods [16]. 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, and it is indicated that presence of atherosclerosis and plaques in these arteries is related with coronary artery diseases, stroke, and high risk of cardiovascular events [3 , 4] and [14]. By taking into account pathophysiology of atherosclerosis, 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, and given this important point, different studies have evaluated the relationship between arterial calcification in mammography and other cardiovascular diseases, and it is necessary to mention that cerebral artery diseases are also considered as cardiovascular diseases.

Ferreira et al [4] studied 37 over-40-year-old women with amenorrhea and evaluated the relationship between cardiovascular diseases and breast arterial calcification and reported that after menopause, women with arterial calcification in breast arteries have higher chance to develop cardiovascular diseases. Ahn et al [1] studied 168 patients aging 40 to 78 who had undergone both brain MRI and mammography. They determined the relationship between arterial calcification in mammography and cerebrovascular diseases. They reported that the presence of arterial calcification in mammography is an indication for high risk of brain stroke, and this section should not be eliminated from mammography reports and more attention should be devoted to it. In their study Sedighi et al [15] reported 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 al [9] measured the level of vascular calcification in mammography and the intensity of coronary artery disease in CT angiography and compared the two. They found out that positive predictive value of arterial calcification in mammography for coronary artery disease was 0.83 and the negative predictive value was 0.78. In other words, presence of arterial calcification in mammography associates with coronary artery disease. Newallo et al [19] examined 204 women with average age of 52.5 years and stated that arterial calcification in mammography is associated with an increase in the development risk of coronary calcification, atherosclerosis, and finally coronary artery disease. Among other studies focusing in this issue are those carried out by Yildiz et al [3 , 13], Sarrafzadegann [14], and Jiang [6]. Since regular screening mammography is recommended to diagnose breast cancer early among all women form the age of 40 onward [14, 17], 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 that can indicate changes in carotid artery atherosclerosis, at the same time, it is cheap and easily accessible.

2. Method

The present study included 454 individuals who fulfilled the inclusion criteria and had undergone mammography; 70 individuals had arterial calcification in mammography and 384 individuals 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: Not having the history of surgery or breast trauma, not having the background of breast cancer, not having the history of stroke or cerebral events, and lack of kidney failure. It should be noted that this study was carried out in 2016, and informed consent was obtained from the participants.

2.1. Study variables

Table 1. The characteristics of the study variables

Variable characteristics	Independent	Dependent	Quantitative		Qualitative		Practical definition	2Scale
			Continuous	Discrete	Nominal	Ordinal		
Age	*			*			Observing the profile	Relative
Menopause status	*		*		*		The individuals has reached menopause age or not	Nominal
intima-media thickness		*					The thickness of the two internal layers of common carotid artery	Relative
BAC grade		*				*	Grades 1, 2, 3, and 4	Ordinal
Carotid artery calcified plaque		*			*		Plaque exists or not.	Nominal

2.2. Instruments

This study had the three phases of questionnaire, mammography, and sonography.

Questionnaire phase: In this phase, the participants answered questions on age, weight, and height (to measure MBI), risk factors like increase in blood pressure, diabetes, smoking, hypercholesterolemia, background of cardiovascular diseases, and menopause conditions and parity status, and if they had the inclusion criteria, the entered the second phase.

Mammography phase: In this phase, mammography was carried out in to perspectives of CC and ML for both breasts. All images were examined by a radiologist experienced in the field of reading mammography and who was blind to the patient's demographic information. Afterwards, the patients were divided into two groups; with and without arterial calcification, and the grade of their calcification was calculated as follow.

The following method was used to calculate the grade of calcification [18].

Grade 1: No 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

Sonography phase: In the last phase, the individuals underwent common carotid artery and the internal sonography of both sides of the neck by a radiologist experienced in cervical artery sonography, and artery intima-media thickness and presence of calcification plaques were examined.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 bulb [4]. The average intima-media thickness of both sides was recorded as the final figure. Calcification plaques in common and internal carotid artery are defined as thicknesses of over 1.2 mm that do not involve all circumference of the vessel.

2.3. Data Analysis Method

The data collected in those three phases (questionnaire, mammography, and sonography) were delivered to a statistician so that he could analyze them through SPSS 16.0 using statistical methods applicable in these variables (as multivariate and univariate). Methods included mean, standard deviation, Odds Ratio, Kolmogorov-Smirnov Test, and Pearson Correlation.

3. Findings

This study shows that there was no significant difference between the two groups with and without calcification in terms of BMI (p-value=0.39). Moreover, the number of pregnancy (parity) in the group with calcification was more than the group without it, which was not statistically significant (p-value=0.07). Another notable point is that according to the results of the study, calcification was observed more among postmenopausal women. However, 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 significant difference between 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 (respectively 0.78±0.13 and 0.61±0.1) which is a remarkable difference (p-value<0.05). Furthermore, carotid plaque in 32 participants out of 70 individuals 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 2 shows 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, and more calcification cases were observed among menopausal women, and a larger percent of participants with calcification were menopausal. The individuals with calcification had more cases of coronary artery diseases, increased blood pressure, and hypercholesterolemia than the control group (p values were respectively p-value=0.02, p<0.001, p<0.001, and p-value=0.013). This difference however, was not significant with regard to diabetes (p-value=0.27). With regard to smoking, the ratio was opposite to other cases, such that a higher percentage of individuals without calcification smoked (respectively 3 and 13% in the groups with and without calcification, p-value=0.03). When the participants were compared in terms of carotid artery sonography, a remarkable relationship between high risk of carotid atherosclerosis and presence of calcification in mammography (Odds Ratio=30.55; CI 8.4-110.5).

Table 2. The relationship between demographic characteristics, cardiovascular risk factors, and carotid atherosclerosis risk in individuals with and without calcification based on univariate analysis

Risk factor	BAC+=70	BAC- =119	Odd 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		
Medium-Risk	28(40%)	52(44%)	8.43	2.40-29.57	<0.001
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		
Postmenopausal	66(94%)	79(66%)	8.35	2.84-24.56	<0.001
Parity					
Nulliparous	3(4.3%)	15(12%)	1.00		
Multiparous	67(95.7%)	104(87%)	3.22	0.9-11.55	0.07

Multivariate analysis

According to Table 3 and based in the multivariate analysis, a significant independent relationship was observed between menopause, an increase in blood pressure, and carotid atherosclerosis risk. Development of calcification had a remarkable increase after menopause. Moreover, changes in carotid atherosclerosis was independently associated with presence of calcification in mammography, and there was an increase in the risk of carotid atherosclerosis.

Table 3. 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			
Low-risk	1.00		<0.001
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 Postmenopausal	 1.00 2.53	 1.22-5.23	 0.01
Multiparity	3.22	0.9-11.55	0.07

According to Figure 1, it is observed that although the mean of intima-media thickness in the group with calcification was remarkably more that the group without calcification (0.78±0.13 and 0.61±0.1, respectively), the results show that in the group with calcification there is no relationship between different grades of calcification and intima-media thickness. To put it more simply, the higher the calcification grade in the group with calcification (from grade 2 to 3 and 4), intima-media thickness did not increase (respectively 0.78±0.12, 0.79±0.14, and 0.78±0.13) (See Table 4).

Table 4. The relationship between arterial calcificationgrade in mammography and carotid intima-media thickness

BAC Grading	N=70	IMT(mm)mean (SD)
II	43	0.78±0.12
III	22	0.79±0.14
IV	5	0.78±0.13

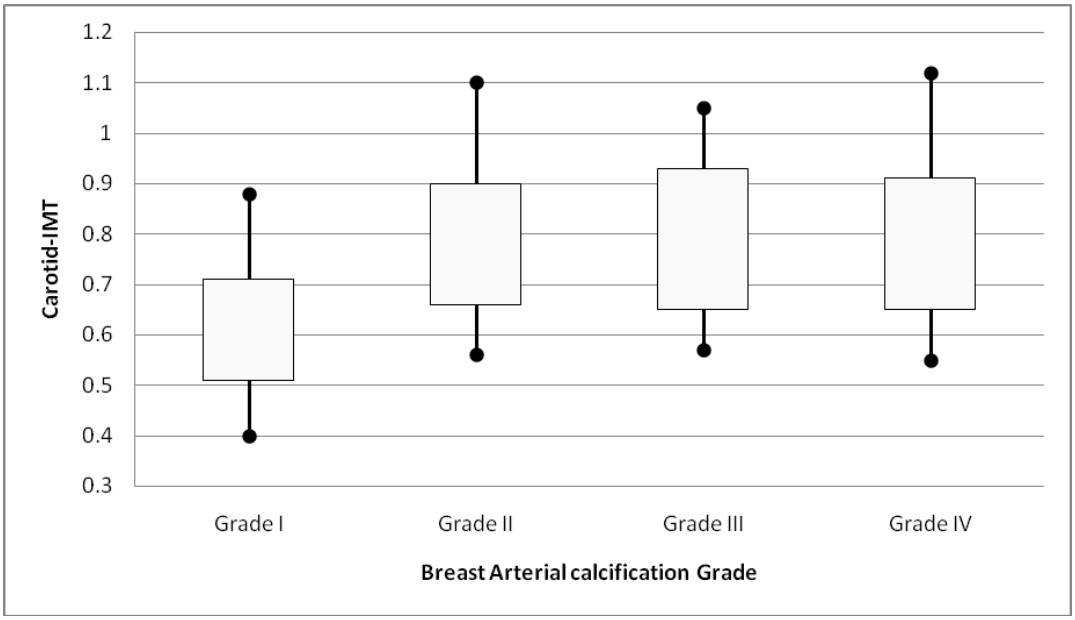

Fig. 1. The relationship between arterial calcification grade in mammography and carotid intima-media thickness

4. Discussion and conclusion

This study shows that there is a close relationship 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 had 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 & 5].In breast arteries, this state appears as two parallel lines similar to tram track and emerges as a small circle in cross-section [3 & 6]. This calcification shows the development of atherosclerosis. The process of atherosclerosis 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 & 7]. This study shows that incidence of 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 a significant relationship between parity

and calcification. In addition to these findings, it was observed that individuals with diabetes and hypercholesterolemia had higher percentage of arterial calcification, and that smoking has a reverse relationship with this phenomenon. Finally, examining 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, and with an increase in this grade, intima-media thickness did not increase. Different studies have been carried out in order to examine and determine the relationship between arterial calcification in mammography and cardiovascular diseases and carotid and cerebral arteries. These studies have reported of similar results which is different from this study therefore further studies with larger samples should be carried out in order to clarify this relationships. In this regard, Yildiz et al (2008) 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 and reported 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 were similar to that of this study although they did not examine the grade of calcification. Sarrafzadegann et al (2009) 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 found that while 40.5% of the women had disorders in coronary angiography, only 7.1% were diagnosed with arterial calcification in mammography which shows that there is no relationship between this ages before menopause. This study did not find a relationship between the period before menopause and arterial calcification (OR=1). The sample size of our study however was not sufficiently enough to judge individuals before menopause correctly. Moreover, in their meta-analysis of 10 cross-sectional studies, Jiang et al (2015) examined the relationship between arterial calcification in mammography and the risk of coronary artery disease and heart stroke. In addition to highlighting the necessity of conducting prospective studies they concluded that arterial calcification in mammography is significantly correlated with coronary diseases and stroke, and this idea that presence of arterial calcification in mammography is a benign phenomenon was questioned. In a cross-sectional study, Ferreiraet al (2009) 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 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. By studying 168 patients aged 40 to 78 who had undergone both brain MRI and mammography, Ahn et al (2011) determined the relationship between arterial calcification in mammography and cerebrovascular disease, they reported that presence of arterial calcification in mammography was an indication for high risk of brain stroke and this should not be omitted from mammography reports at all and closer attention should paid on the individuals

In final conclusion, it can be stated that arterial calcification in mammography occurs more individuals with increased blood pressure, diabetes, and hypercholesterolemia, and those with background of heart diseases. It was also observed that with an increase in arterial calcification, there was an increase in carotid intima-media thickness; however, calcification grade had no relationship with carotid intima-media thickness.

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