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Association between breast arterial calcifications found on mammography and coronary artery calcifications in asymptomatic Saudi women

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BACKGROUND: Currently, there are no data on the prevalence of breast arterial calcification (BAC) in Saudi women. Furthermore, there are no data on the relationship between BAC and coronary artery calcium score (CACS) as a coronary artery disease (CAD) risk factor in Saudi women who undergo mammography.

OBJECTIVE: Examine the role of BAC as a potential female-specific risk factor for CAD in Saudi women in order to investigate the relationship between BAC and CACS in women who undergo a screening mammography, and study the relationship between BAC and CAD risk factors, including age, diabetes mellitus, hypertension, chronic kidney disease (CKD), dyslipidemia, and family history of CAD.

DESIGN: Retrospective, medical records review.

SETTING: Single tertiary care center.

PATIENTS AND METHODS: The study cohort included women who had mammograms and a CACS scan, and for whom data on CAD risk stratification and CAD risk factors had been collected within one year of each other from 2014 to 2017. Women with CAD were excluded from the study.

MAIN OUTCOME MEASURES: Breast arterial calcification as a marker for coronary artery disease.

SAMPLE SIZE: 307 Saudi women.

RESULTS: BAC was found in 142 (46%) patients in the study population. BAC+ women were significantly older than the BAC- women (P=.001), and a strong association was found between BAC and CACS (P=.0001), diabetes (P=.0001), hypertension (P=.021), and CKD (P=.0031). However, no association was found between BAC and tobacco smoking, dyslipidemia, and family history of CAD. In addition, a strong correlation was found between CACS and the components of the BAC score (P<.001). Multivariate linear regression analysis revealed that age, CAC, and CKD are the only strong predictors of BAC.

CONCLUSIONS: The proportion of BAC in Saudi women is 46%, and there may be a strong association between BAC and CAC, age, hypertension, and CKD. A large-scale prospective research study is necessary to validate the role of BAC on screening mammography as a CAD risk stratification tool and before routine reporting of BAC on a mammography report.

LIMITATIONS: Because this was a retrospective study, patient selection bias cannot be excluded.

CONFLICT OF INTEREST: None.

Breast arterial calcification (BAC) is a potential new risk stratification tool for coronary artery disease (CAD) and cardiovascular (CV) mortality. Several studies have reported increased hazards for CV disease among BAC positive (BAC+) women after adjusting for age and conventional CAD risk factors.[1,2] BAC is a type of medial calcification that is seen incidentally on mammography, and it may correlate with arterial calcification. On mammography, it appears as parallel lines or has a tram-track appearance. BAC increases with advancing age, diabetes, hypertension, hyperlipidemia, chronic kidney disease (CKD), previous history of atherosclerosis, and with a history of lactation and parity.[3-6] Coronary artery calcifications (CAC) screening, with a CAC score (CACS) obtained by computed tomography (CT), is among the strongest available clinical predictors of major adverse cardiovascular events (MACE) among patients with no known CAD.[7,8] The absence of CAC in asymptotic individuals confers a very low risk of CV events in the intermediate term, and a high CACS identifies subjects who have increased risk for CAD, who are then candidates for aggressive preventive strategies and more frequent follow-up. It is well-established that CAC improves the ability to predict the risk of CAD.[9] Several studies with small cohorts have examined the relationship between BAC and CAC in different ethnic groups. Mass et al. examined 499 postmenopausal Dutch women ranging in age from 49 to 70 years who underwent breast cancer screening and CACS; in that study, the presence of BAC had a strong correlation with CAC >0 (odds ratio: 3.2) with a positive predictive value of 76%.[10] Another study reported a correlation between the presence of BAC and the severity of quantified CACS.[11] It has also been demonstrated that the presence of BAC did not have a statically significant correlation with high-risk CACS defined as a score >400.[12] In contrast, no significant correlation was found between the severity of BAC and CAC severity in Iranian women.[13]

The prevalence of BAC varies based on race/ethnicity. A study of over 1900 women found that the prevalence of BAC is 25% in Caucasian women and 24% in African American women; the highest prevalence of BAC (34%) was reported in Hispanic women and the lowest prevalence (7%) was reported in Asian women.[14] Currently, there are no data on the prevalence of BAC in Saudi women. Furthermore, there are no data on the relationship between BAC and CAD risk factors in Saudi women who are undergoing screening or diagnostic mammography. Therefore, this study aimed to examine the role of BAC as a potential female-specific risk factor for CAD in Saudi women. We investigated the relationship between BAC and CACS in women who underwent screening mammography within one year of undergoing CACS for CAD screening and risk stratification. In addition, we investigated the relationship between BAC and CAD risk factors, including age, diabetes mellitus, hypertension, CKD, dyslipidemia, and family history of CAD.

PATIENTS AND METHODS

A search of the Radiology Department database was conducted to identify all women who had undergone mammograms and a CACS scan, and for whom information on CAD risk stratification and CAD risk had been collected within one year of each other from 2014 to 2017. Women with CAD, such as those with previous myocardial infarction, previous percutaneous coronary intervention, prior coronary artery bypass surgery, and previous abnormal stress myocardial perfusion study, were excluded. The study was approved by the Institutional Review Board.

Digital mammography

Mammograms were performed using a full-field digital mammography system on either the Hologic Dimension unit (Bedford, MA, USA) or the GE Senographe Essential system (GE, Paris, France) with the acquisition of standard views. BAC scoring was reported as previously described.[15,16] Briefly, the total BAC score (ranging from 0 to 13) was generated based on three components seen on mammography: the number of calcified vessels (score ranging from 0 to 6), the severity of the calcification of the involved vessels (score ranging from 0 to 3), and the length of the calcified vessels (score ranging from 0 to 3). The total score was further categorized as follows: the zero group (no BAC identified on mammography), mild BAC (score ranging from 1 to 4), moderate BAC (score ranging from 5 to 8), and severe BAC (score ranging from 9 to 13).

Coronary artery calcium score scanning

Prospective electrocardiographic (ECG) gating was utilized on 64-slice computed tomography (CT) scanners. Images were reconstructed with a slice thickness of 3 mm and an increment of 1.5 mm using a medium convolution Kernel (B35f).The CACS was expressed in Agatston units and was calculated semi-automatically for all of the main coronary arteries.[17]

Statistical analysis

Data were analyzed using the IBM SPSS version 20 (IBM, Armonk, NY). Continuous scales measurements were summarized as means and standard deviations.

Categorical variables were summarized as percentages. The association between categorical variables was tested using Pearson's chi-squared test. The two-independent samples *t* test was used to compare the group means for age at mammography. Multiple logistic regression was used to identify the relationship between the presence or absence of BAC (dependent variable) and potential risk factors. The multiple logistic regression model was used when the dependent variable was dichotomous. The Type I error rate was set at 5%.

RESULTS

In 307 subjects, BAC was found in 142 (46%) patients. The BAC-positive women were significantly older than the BAC-negative women (55 [7] versus 59 [8] years; [*P*=.001]), and a strong correlation was found between BAC and total CAC (*P*=.001), diabetes (*P*=.001), hypertension (*P*=.021), and CKD (*P*=.0001). However, no correlation was found between BAC and tobacco smoking, dyslipidemia, and family history of CAD (**Table 1**).

Relationship between CAC and BAC

The subjects were divided into four BAC groups as follows: negative BAC or zero BAC score, mild BAC (total BAC score=1–4), moderate BAC (total BAC score=5–8), and severe BAC (total BAC score >8). A strong correlation was found between CAC and all of the BAC groups (*P*<.0001) (**Table 2**). In addition, a strong correlation was found between CAC and the components of the BAC score (number of calcified vessels, density of the calcification, and length of the calcified vessels) (*P*<.0001).

Predicting the BAC Score using multivariate analysis

A multiple logistic model to evaluate the relationship between BAC score 0 or >0) (dependent variable) and other parameters, including CAC revealed that only age and CAC predict the presence of BAC (*P*<.0001 and .002, respectively) (**Table 3**), A final multivariate linear regression analysis revealed that age, CAC, and CKD are the only statistically significant predictors of BAC (**Table 4**).

DISCUSSION

Our study results show that BAC on mammography correlates with CACS, as well as other conventional CAD risk factors, such as age, diabetes, hypertension, and CDK. Many studies have shown a correlation between BAC and CAD. Iribarren et al reported that BAC detected on screening mammography was an independent risk factor for multiple CV outcomes among women.[2] Furthermore, BAC on mammography has been associated with the prevalence of CAD after adjusting for age; however, with lower sensitivity, BAC provides additional information for identifying the risk of CV among healthy women.[18] Maas et al reported that BACs are predictive for subsequent development of CAC. That study consisted of 499 women, ranging in age from 49 to 70, who participated in a breast cancer screening program. The women were followed-up for 9 years. In contrast to our study, CV risk factors were associated with CAC but not with BACs, and only parity was significantly associated with BAC but not with CAC.[10] Another prospective study that enrolled 1000 women who underwent screening mammography reported that, across age

Table 1. Patient characteristics by presence or absence of breast arterial calcification based on CAD risk factors (n=307).

	Absence of BAC	Presence of BAC	*P* value
Number of patients (n)	165 (54)	142 (46)	<.0001
Age at mammography (years) (mean, SD)	54 (7.5)	59 (8)	<.0001
Presence of CAC	116	60	<.0001
Diabetes mellitus	64	95	.75
Hypertension	89	95	.021
Smoking	2	2	.887
Hyperlipidaemia	82	86	.752
Chronic kidney disease	11	20	.031
Family history	0	2	.126

Values are number (percentage) unless indicated otherwise. BAC: breast arterial calcification, CAC: coronary artery calcification, CAD: coronary artery disease.

Table 2. Chi-square test of independence between CAC and BAC sub-groups (N=307).

	-BAC (zero BAC)	Mild BAC (0-4)	Moderate BAC (5-8)	Severe BAC (>8)	Total	*P* value
No CAC	116	26	24	10	176	
CAC	49	22	32	28	131	.0001
Total	**165**	**48**	**56**	**38**	**307**	

Chi-square= 24.5, df=1. BAC=breast arterial calcification, CAC=coronary artery calcification

Table 3. Multiple logistic model to evaluate the relationship between BAC (dependent variable) and other parameters.

Parameter	Odds ratio	*P* value
Age	1.06	.0001
Diabetes	.983	.949
CAC	2.214	.002
CKD	.483	.089
Hypertension	.875	.825

BAC=breast arterial calcification, CAC=coronary artery calcification, CKD=chronic kidney disease.

Table 4. Final multiple linear regression model with dependent variable total BAC score.

Parameter	Regression coefficient	*P* value
CAC	1.526	.001
Age	0.127	.0001
CKD	-2.240	.001

R square=0.183, F statistic=22.55, df=3, and $P<.0001$. BAC=breast arterial calcification, CAC: coronary artery calcification, CKD: chronic kidney disease. R square=0.183 and F statistic of the ANOVA of the multiple regression model=22.55 with *P* value less than .0001, indicating that although the model has low predictive ability the relationship between the response variable and the predictors is highly significant.

groups, the odds of having CAC were approximately 6.2-times greater in women with BACs than in women without BACs, which indicates that mammography may be a useful screening tool for CAD.[19] Kemmeren et al reported that the hazard ratio for overall mortality was 1.29 for women with BAC in comparison to women without BAC after correcting for CAD risk factors; moreover, excess all-cause mortality was found in diabetic women with BAC (hazard ratio=1.74, 95% confidence interval (1.19–2.56).[20] They concluded that BAC is associated with an increased risk of subsequent death in women over the age of 50, and in diabetic women in particular. A major systematic literature review and meta-analysis conducted by Hendriks et al found that BAC appeared to be associated with an increased risk of CV events, but it was only associated with some of the known CV risk factors.[3]

Our data shows that BAC score is correlated with diabetes, hypertension, and CKD. This result is in line with the findings reported in a previous study by Chadashvili et al.[21] That study found that BAC predicts a CACS >11 and is correlated with diabetes and CKD;[21] however, as in our study, no correlation was found between BAC and hypertension. One possible explanation for this discordance is that hypertension is more prevalent in our population, which may be due to differences in the ethnicity and race of the population being studied. However, a prior study reported a strong quantitative association between BAC and age, and BAC is better tool for diagnosing the risk of CAD than standard risk factors.[16]

Only a few studies have investigated the relationship between BAC and myocardial ischemia detected on myocardial perfusion imaging (MPI), such as single-photon emission computed tomography (SPECT) or positron emission computed tomography (PET). Only one study investigated the relationship between BAC on mammography and SPECT MPI (15). That study found that while BAC on mammography does not predict myocardial ischemia on a stress test using SPECT, there was a positive correlation between age, hypertension, and CKD.[15] The relationship between BAC and angiographically-detected CAD is debatable. Zgheib et al found no correlation between BAC and coronary angiography-detected CAD, even when CAD severity was considered.[22] However, a meta-analysis of studies that included 927 patients showed a 1.59-increase in the odds of angiographically-defined CAD in patients with BAC on mammography.[23]

Over the last several years, the possible correlation between BAC and CAD has been debated. The previously mentioned studies have reported a correlation between BAC and CAC (including our study) and, subsequently, CAD. However, other studies have disputed this finding due to the confounding variables associated with BAC and CAD risk factors, especially age.[22,24] It is well known that increasing age is a risk factor for CAD, and BAC is more common in elderly women. It is also important to note that the location of BAC and CAC is different. CAC occurs in the intima of the vessels and it is closely correlated with atherosclerotic plaque burden, so the presence of CAC is virtually diagnostic for CAD.[7] However, BAC is the manifestation of Mönckeberg medial calcific sclerosis and is known by its alternative name: calcific medial sclerosis.[25] Thus, it is thought that mammary arteries are not susceptible to conventional atherosclerosis. Studies have also shown that there is a consistent relationship between CAD and age, diabetes, hypertension, smoking, dyslipidemia, and CKD, but there is no consistent relationship between BAC and conventional CAD risk factors, except for age and CKD, and there is a variable relationship between BAC other risk factors, such as hypertension, diabetes, smoking, and dyslipidemia. Our result suggests that there is a correlation between BAC and CACS and many CAD risk factors, such as age, diabetes, hypertension, and CKD.

Our study is the first to investigate the prevalence and relationship between BAC and CACs in women in Saudi Arabia. In our study, the prevalence of BAC was seen on mammography in 46% of the patients. Data reported in previous studies were derived from other races and ethnicities; thus, those findings may not be applicable to our patients. Moreover, there is significant variability in the prevalence of BAC among different races and regions.[14] To date, BAC has been shown to be correlated with CACS, and it may have value as a CAD risk stratification tool in asymptomatic women. However, a large-scale prospective research study with long-term outcomes is needed before recommending BAC to referring physicians for CAD risk stratification and prevention.

Our study has some limitations. It was a retrospective study of women in Saudi Arabia who had undergone mammography and CACs within a specific time period. Moreover, CACS was ordered to determine CAD risk stratification. Thus, patient selection bias cannot be excluded, so caution must be exercised when applying these results to a general population. Furthermore, the total BAC scores were generated visually, based on the number of calcified vessels, the density of the calcification, and the length of the calcified vessels. This method utilizes a subjective visual estimation. Quantitative and semi-quantitative techniques, which are not currently available, would be more accurate and more reproducible. Another limitation of the study is that there was no long-term follow-up of the patients to determine the role of BAC as a long-term predictor for CAD and MACE. Therefore, a prospective long-term study is highly recommended.

In summary, based on our current study, BAC was found in 46% of Saudi women on screening or diagnostic mammography, and there is a strong correlation between BAC and CAC, age, and CKD. A large-scale prospective research study is necessary to validate the role of BAC on screening mammography as a CAD risk stratification tool and before routine reporting of BAC on a mammography report.

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