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THE ASSOCIATION OF INTRAMAMMARIAN ARTERIAL CALCIFICATIONS DETECTED ON MAMMOGRAPHY WITH CORONARY ARTERY DISEASE AND ITS RISK FACTORS

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Aim of the study: **To evaluate the association of intramammarian arterial calcifications seen on mammography with coronary artery disease and its risk factors and to discuss intramammarian arterial calcifications value as a predictor of coronary artery disease.**
Material and methods: **Mammography was performed on 55 women over 40 years of age who have undergone coronary angiography and have not had a mammography in the past year. Coronary angiography results, coronary artery disease risk factors and intramammarian arterial calcifications are evaluated.**
Results: **The prevalance of intramammarian arterial calcifications was 41.8%. A significant relationship between intramammarian arterial calcifications and coronary artery disease was indicated (OR 10,8, 95% CI 3,02-38,59). The positive predictive value and negative predictive value of intramammarian arterial calcifications for coronary artery disease was 78.3% and 75% respectively. Also advancing age was found relevant with these calcifications (OR 1,15, 95% CI 1,05-1,25).**
Conclusion: **The results support the present literature and suggest that mammography, already widely in use as a screening tool among women over 40, may be used simultaneously in coronary artery disease risk assessment. These results should be confirmed by further larger group controlled studies.**

Key-words: Breast radiography – Breast neoplasms, calcification – Coronary vessels, diseases.

Coronary artery disease (CAD) and cancer are the leading causes of female mortality and morbidity, especially in western countries (1, 2). Breast cancer is among the most common deaths caused by cancer. It is known that with early detection it is possible to lower the mortality rate (3). Currently, mammography is used as a screening tool for breast cancer and it is recommended yearly for women over the age 40 (4). Intramammarian arterial calcifications (IMAC) are defined as medial arterial sclerosis or Mönckeberg's medial sclerosis and its prevalence varies from less than 1% to more than 50% on mammograms (5-7). These calcifications are unrelated to cancer and therefore, usually not mentioned in the final reports (5). There is a growing body of literature investigating the relationship of IMAC with cardiovascular diseases, diabetes and hypertension. It is suggested that IMAC can be used as a predictor of cardiovascular diseases (6, 8-11).

CAD is the result of systemic arterial disease (12). Early detection of CAD is important because first cardiovascular events are often fatal in women (13). Currently there are no widespread inexpensive suitable screening tests available for CAD (2). Detection of coronary artery calcifications with Electron Beam Tomography and ultrasound measurement of carotid intima-media thickness techniques could be used for risk assessment whereas there are large group studies showing these methods do not provide additional information to the traditional Framingham risk assessment in predicting future coronary events in high-risk individuals (14). Other drawbacks of these tests are not being always readily available for a large group of population, higher costs and possible difficulties in being accepted as a screening tool by patients. However mammography is a widely accepted, low cost screening tool for breast cancer and if IMAC is proved to be relevant to CAD, mammography could be simultaneously used to predict CAD risk without any additional health care costs.

The purpose of the study was to evaluate the association of IMAC with CAD and its risk factors and to discuss intramammarian arterial calcifications value as a predictor of CAD.

Material and methods

During a one-year period (November 2008 and October 2009) mammography was performed on 55 women over the age 40 who had undergone coronary angiography and have not had a mammography in the past year [age range 40-79 (mean age 63)]. All coronary angiographies were planned due to angina pectoris or exertional dyspnea. At least 50% lumen narrowing at least in one coronary artery is regarded as positive for CAD. This criteria was used in previous studies and relies on the fact that significant decrease of blood flow occurs with ≥ 50% stenosis (9, 15, 16). Patients hospital records were examined to evaluate CAD risk factors; hypertension, diabetes mellitus (DM), dyslipidemia and obesity. Hypertension is defined as systolic blood pressures 140 mmHg and higher, diastolic blood pressures 90 mmHg and higher or prescribed antihypertensive agents (17). Diabetes is regarded as positive when the patient is on antidiabetic treatment or fasting blood glucose levels are 126 mg/dl and higher or a random glucose level of 200 mg/dl. Dyslipidemia is regarded as positive if total cholesterol levels are 200 mg/dl and higher, LDL cholesterol levels are 130 mg/dl and higher, HDL cholesterol levels are 35 mg/dl and lower or if anti lipidemic agents are being used (18). The standard BRFSS (Behavioral Risk Factor Surveillance System) definition for obesity (body

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mass index [BMI] ≥ 30.0 kg/m^2, calculated by using self-reported height and weight) was used.

All patients underwent mammography 7-14 days after coronary angiography. For all patients standard views (craniocaudal and mediolateral-oblique) were obtained by Fischer HF-X Plus (Denver, CO) conventional mammography unit. Further views such as spot compression, and magnification were obtained when necessary. Two radiologists who have more than 6 years of experience in breast imaging, who were blind to coronary angiography results, clinical data and patients' hospital records analysed the mammograms according to BIRADS (breast imaging and reporting data system) classification, also presence of IMAC was noted in the final reports. Parallel, linear calcifications and amorphic calcifications in between along the course of a vessel in one or both breasts, at least on one mammographic view was defined as positive for IMAC (19). IMAC severity was not graded by any scoring system.

Statistical analysis

Data analysis was performed by using Statistical Package for Social Sciences (SPSS) version 11.5 software (SPSS Inc., Chicago, IL, United States). Whether the metric discrete variables were shown as mean ± standard deviation, otherwise, percentages were used for categorical variables. The mean differences between groups were evaluated by Student's t test. Categorical date was analyzed by Pearson Chi-square or Fisher's exact test, where appropriate. Multiple Logistic Regression Analyses (Backward method) were used to control for potential confounding effects. Any variable whose univariable test had a p value less than 0.25 was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Odds ratio (OR) and 95% confidence intervals (CI) for all independent variables were also calculated. A p value less than 0.05 was considered statistically significant.

Results

Coronary angiography results of 55 patients were evaluated; 26 of them (47.3%) had significant CAD, whereas 29 of them (52.7%) had no significant coronary artery stenosis (Table I). The prevalence for IMAC was calculated as 41.8%.

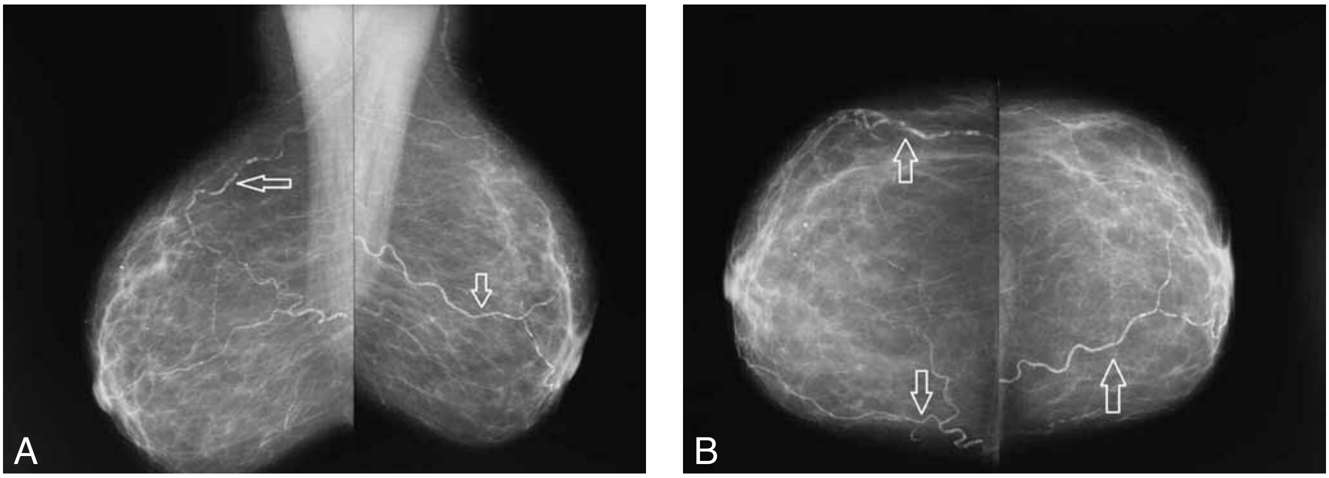

Fig. 1. — 72-year-old patient. A. Bilateral MLO and B. Bilateral CC mammogram views showing IMAC. Significant stenosis of coronary arteries detected on coronary angiography. The patient also had hypertension and dyslipidemia.

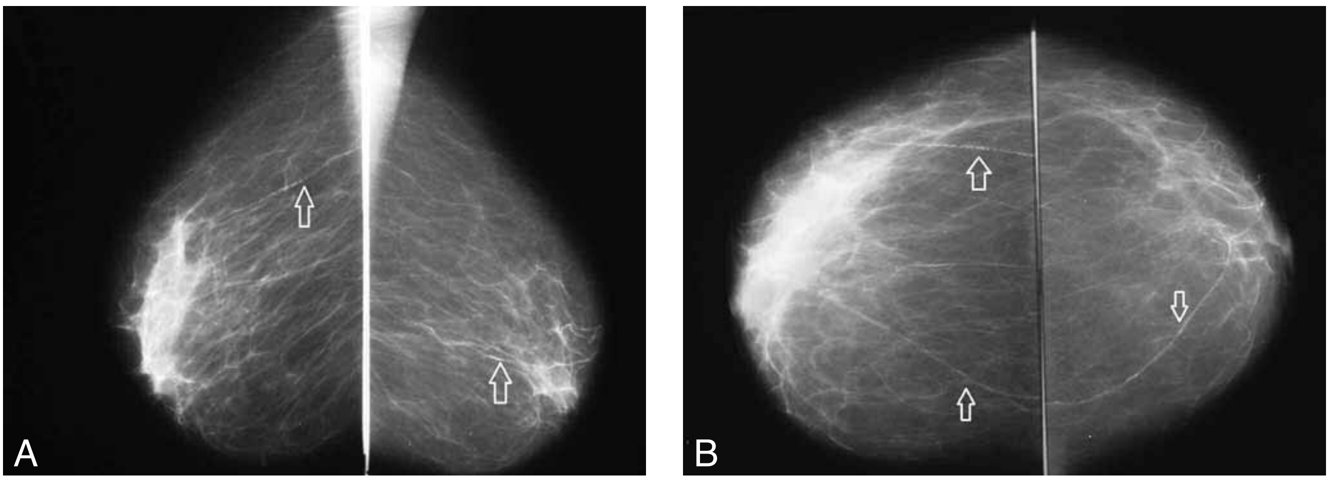

Fig. 2. — A. Bilateral MLO and B. bilateral CC mammogram views showing IMAC. Significant stenosis of coronary arteries detected on coronary angiography. The patient did not have hypertension, dyslipidemia or obesity.

The mean age of CAD positive patients (67.3 ± 7.5) was higher than CAD negative group (59.1 ± 8.5) ($p < 0.001$). It is shown that advancing age was associated with significant increased risk of CAD ($p < 0.001$, OR 1.1). Among patients with positive findings for CAD, 18 (69.2%) patients also had IMAC on their mammograms (Fig. 1,2). Only 5 (17.2%) of the patients with negative CAD findings had IMAC on their mammograms It is calculated that recognition of IMAC on mammography increased the detection of the significant coronary artery stenosis ($p < 0.001$, OR 10.8). Hypertension was found to be a risk factor which increased the development of CAD ($p < 0.05$, OR 5.4). In the CAD positive group 92.3% of the patients were hypertensive compared with 69% hypertensive patients in the CAD negative group.

The patients were also evaluated in terms of DM, dyslipidemia and obesity. DM and dyslipidemia prevalence was found higher in CAD positive group whereas the difference between CAD positive and negative groups was not statistically significant.

All results regarding these issues are summarized in Table II.

When multivariate logistic regression analyses were performed for risk factors, strong correlation was found between CAD and IMAC (OR: 5.4, $p < 0.05$). This correlation was even stronger after adjustment for risk factors (OO: 6.3, $p < 0.05$). Hypertension was not a significant factor for CAD on multivariate analyses (Table III).

The correlation between IMAC and CAD and its risk factors is shown at table IV. Advancing age (OR 1.1), hypertension (OR 10) and positive CAD on angiography (OR 10.8) was found significantly associated with IMAC. DM and dyslipidemia prevalence was also higher in IMAC positive group but the difference between two groups did not a reach statistically significant level.

Table I. — Patients distribution of CAD and IMAC.

	IMAC (-) (n)	IMAC (+) (n)	Total (n)
CAD (-)	24	5	29
CAD (+)	8	18	26
Total	32	23	55

The sensitivity, specificity, and positive and negative predictive value of IMAC detected on mammograms for predicting prevalent CAD were 69.2%, 82.8%, 78.3% and 75%, respectively.

Discussion

IMAC is the result of calcium deposition in the media layer of arteries and it has a characteristic appearance on mammograms. These calcifications are rare under the age 50 and seen as railroad track pattern or ring-like on 'en face' images. Their mechanism is not clearly known (20). Calcium deposits were considered as a natural part of aging and were thought to have no clinical significance but recent studies show correlation between IMAC and CAD and cardiovascular mortality (6, 8, 9). The prevalence of IMAC varies from less than 1% to more than 50% in previous studies (7). The possible reasons for this wide range are the differences in baseline risks of study groups, increase in detection of calcification with advancing imaging technology and IMAC not being mentioned in the final reports because it is not relevant to malignity.

Iribarren et al performed a large group cohort study among 12 761 women over the age 40 who attended multiphasic health check ups that included mammography (8). IMAC prevalence was low (3%) compared with other studies (2, 6, 10, 21). This could be explained by low prevalence of CAD and its risk factors among the study population which consisted of generally healthy check up patients. Besides, the radiologists also might have overlooked IMAC as the tests were run for screening purposes. Iribarren et al. found significant positive correlation between IMAC and DM, increasing age and parity. After adjustment for other variants (age, education level, race, cigarette smoking, alcohol use, BMI, serum total cholesterol, hypertension, DM, parental history of myocardial infarction (MI), parity, and hormone replacement therapy), IMAC was associated with a 1.32-fold increased risk of CAD (8). Another study by Von Noord et al. reported a 9.1% IMAC prevalence among a 12.239-patient group which consisted of women over the age 50 who participated in a population-based breast cancer screening project. IMAC was found significantly related with hypertension, stroke and MI (6). In the present study, similar to Irribaren and Von Noord's large group studies, significant relation was found between IMAC and CAD. On the other hand IMAC prevalence was 41.8 % which is a high value compared with mentioned other two studies. This is could be due to

Table II. — Comparison of IMAC and CAD risk factors prevalence between positive and negative CAD patients.

Variants	CAD negative (n = 29) (%)	CAD positive (n = 26) (%)	p	OR* (%95 CI**)
Age	59,1 ± 8,5	67,3 ± 7,5	< 0,001	1,136 (1,049-1,231)
IMAC	5 (17,2%)	18 (69,2%)	< 0,001	10,800 (3,022-38,594)
Hypertension	20 (69,0%)	24 (92,3%)	0,031	5,400 (1,044-27,924)
DM	10 (34,5%)	13 (50,0%)	0,244	1,900 (0,642-5,623)
Dyslipidemia	18 (62,1%)	17 (65,4%)	0,799	1,154 (0,383-3,476)
Obesity	9 (31,0%)	3 (11,5%)	0,081	0,290 (0,069-1,220)

* Odds Ratio
** Confidence Interval.

Table III. — Correlation of positive CAD with IMAC after adjustment for risk factors.

Variants	Odds Ratio	Wald	p	%95 Confident Interval
Model I				
Age	1,095	3,781	0,052	0,999-1,201
Hypertension	1,979	0,529	0,467	0,315-12,451
DM	2,870	2,064	0,151	0,681-12,093
Obesity	0,574	0,369	0,543	0,096-3,435
IMAC	5,415	5,083	0,024	1,247-23,512
Model 2*				
Age	1,098	4,070	0,044	1,003-1,203
Hypertension	2,077	0,616	0,432	0,335-12,877
DM	2,757	1,955	0,162	0,665-11,428
IMAC	5,796	5,602	0,018	1,353-24,838
Model 3**				
Age	1,102	4,425	0,035	1,007-1,207
DM	2,784	2,026	0,155	0,680-11,402
IMAC	6,652	6,971	0,008	1,629-27,156
Model 4***				
Age	1,091	3,906	0,048	1,001-1,190
IMAC	6,315	6,976	0,008	1,609-24,789

* adjustment for obesity
** adjustment for obesity and hypertension
*** adjustment for obesity, hypertension and DM.

Table IV. — Correlation between IMAC and CAD and its risk factors.

Variants	IMAC Negative (n = 32)	IMAC positive (n = 23)	p	OR*(%95 CI**)
Age	59,4 ± 8,9	68,0 ± 6,5	< 0,001	1,152 (1,056-1,256)
CAD (+) Angiography	8 (25,0%)	18 (78,3%)	< 0,001	10,800 (3,022-38,594)
Hypertension	22 (68,8%)	22 (95,7%)	0,017	10,000 (1,178-84,900)
DM	13 (40,6%)	10 (43,5%)	0,832	1,124 (0,380-3,327)
Dyslipidemia	19 (59,4%)	16 (69,6%)	0,438	1,564 (0,503-4,862)
Obesity	10 (31,3%)	2 (8,7%)	0,046	0,210 (0,041-1,071)

* Odds Ratio
** Confidence Interval.

increased CAD risk in the present study population, also attention was paid to mention the presence of IMAC on mammography reports as a part of study design.

Henkin et al. reported IMAC prevalence as 41% among 319 patients (187 patients with severe CAD and 132 patients with negative CAD on coronary angiography) (21). The study population was parallel with the present study and consisted of patients who had undergone coronary angiography with suspicion of CAD. Although the IMAC prevalence of the two studies show noteworthy similarity, Henkin et al. did not find significant relation between IMAC and CAD. The authors reported that regarding only severe stenosis as CAD positive might have a role in this result. They found significant relation between IMAC and increasing age, hypertension and DM. In our study IMAC and hypertension was found correlated on univariate analyses whereas on multivariate analyses the correlation was not found significant. This result might have been due to our limited study population.

IMAC detected on mammography might point to CAD and increasing age seems an important risk factor for CAD and IMAC. Dale et al. found significant relation between IMAC and CAD, between IMAC and increasing age (2). The present study also supports their result showing significant relation between IMAC and CAD, and also between IMAC and increasing age. Another study by Moshyedi et al. evaluated the relation between IMAC and CAD in a 182-patient study and they divided the patients into two age-groups; aged below 59 and aged above 59. All patients had undergone coronary angiography and mammography, similar to the present study. In the age-below-59 group IMAC's positive predictive value and negative predictive value for CAD was found 88% and 65% respectively which is a statistically significant result. On the other hand they did not find a strong correlation in the aged above 59 group and stated that the correlation decreased with increasing age (9). In the present study, the patients were not classified according to age and IMAC's positive predictive value and negative predictive value for CAD is 78.3% and 75% respectively.

Oliveira et al. evaluated CAD and its risk factors relation in their study and on multivariate analyses, they found hypertension, family history and IMAC associated with CAD (22). In the present study, in addition to increasing age and IMAC, hypertension was also found to be associated with CAD on univariate analyses. Hypertension is a well known risk factor for CAD, whereas on multivariate analyses it was not found to be significant for CAD. This could be due to small population of the present study as previously mentioned.

There are several studies showing significant association between DM and IMAC and suggesting IMAC as an additional risk factor for diabetic women (7, 23, 24). On the contrary, there are other authors claiming IMAC and DM are not related (25, 26). Sickles and Galvin's study showed IMAC to be related to increasing age rather than DM (25). Similarly in the present study, IMAC and increasing age showed correlation ($p < 0,001$) although IMAC and DM did not have a significant relation ($p > 0.05$).

Although the present study supports significant association between IMAC and CAD, a limitation of the study is that the number of cases is too limited for broad generalizations. Before IMAC could be considered a clue for CAD, confirmation by further large group controlled studies is necessary.

Conclusion

CAD is a leading cause of death and it may present as a fatal cardiovascular event. Early detection is highly important whereas there are no current widespread suitable screening tests for CAD and the patients are evaluated for risk factors.

Mammography is a widely used, well accepted screening tool for another leading cause of death among women, breast cancer. If IMAC is proved to be an independent risk factor for CAD, mammograms could be simultaneously used to predict CAD risk.

The results of the present study support the present literature, indicating a significant relationship between IMAC and CAD. After adjustment for well known risk factors, increasing age and IMAC are found to be independently and significantly important to predict CAD.

This study suggests that mammography, already widely in use as a screening tool among women over 40, may be used simultaneously in coronary artery disease risk assessment without any additional health costs. Indicating IMAC in the final mammography reports is important as it could alert the clinician to evaluate the previously unsuspected patient for CAD with further tests. However it has to be emphasized that the results of the study are based on a relatively low number of patients and they should be supported with larger group controlled studies before IMAC could be considered an indicator of CAD, grading of IMAC and CAD could also be useful.

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