Mammary vascular calcifications and correlation to cardiovascular risk in postmenopausal patients attending the Department of Human Reproduction Biology of the Juarez de Mexico Hospital

I. Hernández-Marín[1], A.C. Salazar-Romo[1], L. Valle-Molina[2], B.Y. Alvarez-Alfonso[3]

[1]Department Head of Human Reproduction Biology, Hospital Juarez de México, México City, D.F., México
[2]Department of Cardiology, Methodological Advisor, Hospital Juárez de México, México City, D.F., México
[3]Department of Radiology, Hospital Juarez de México, México City, D.F., México

ABSTRACT — OBJECTIVE: *Mammary diseases include a wide spectrum of alterations, ranging from benign tumour, trauma, pain or hypersensitivity of the breast, infections, to metastatic cancer, with distinct clinical manifestations, including breast tenderness, nipple discharge, palpable tumour, or with other tissues involvement. Belonging to the most frequent results of mammogram exam for menopausal women, together with several types of calcification, solid or cystic tumours, mammary fibroadenoma and fibrocystic breast, vascular calcifications are more important considering their general prevalence, approximately of 30%, albeit variable according to ethnicity. In some studies, these benign alterations, easily observable with mammogram exam, were associated with calcifications of coronary arteries and with a higher cardiovascular risk (CVR). For these reasons, mammary vascular calcifications (MVC) have attracted the attention of scientific community as predictive markers of potential cardiovascular events. The aim of this work is to evaluate the correlation between MVC and CVR degree, following the American Heart Association (AHA) scale, in postmenopausal patients attending the Department of Human Reproduction Biology of the Juarez De Mexico Hospital.*

PATIENTS AND METHODS: Two hundred six postmenopausal women classified as +2 degree of Stages of Reproductive Aging Workshop + 10 scale (STRAW+10) (late post menopause), attending to the Hospital Juarez de Mexico, were selected. Patients have been subjected to bilateral diagnostic mammogram and to lipid profile evaluation. Moreover, for every patient, CVR was evaluated following AHA criteria.

RESULTS: Correlation between CVR and presence of MVC was resulted statistically significative ($p<0.05$, RR 5.97, OR 19.53, IC 95% 9.31-40.9).

CONCLUSIONS: By this study, a strictly relationship between MVC and a higher CVR emerges clearly.

KEYWORDS
Mammary vascular calcifications, Mammogram, Cardiovascular risk, Late post menopause, Prevention.

INTRODUCTION

Mammary diseases include a wide spectrum of alterations, ranging from benign tumour, trauma, pain or hypersensitivity of the breast, infections, to metastatic

Corresponding Author
I. Hernández-Marín, MD; e-mail: marime64@hotmail.com

cancer, with distinct clinical manifestations, including breast tenderness, nipple discharge, palpable tumour, or with the involvement of other tissues. Belonging to the most frequent results of mammogram exam for menopausal women, together with several types of calcification, solid or cystic tumours, mammary fibroadenoma and fibrocystic breast, vascular calcifications are more important considering their general prevalence approximately of 30%, albeit variable according to ethnicity[1-3]. Considering the clinical importance of breast cancer screening program, one of the most useful of preventive medicine in the world, a mammographic study in postmenopausal women could be a good opportunity to expand its medical application. Indeed, mammogram is the only one imaging method able to reduce the mortality for breast cancer by about 30% in the screened population, allowing an early diagnosis, if performed in a rigorous and scheduled way[4]. According to the American Cancer Society recommendations, mammogram must be performed annually for an efficient screening in women over 40 years of age[5]. Thanks to this exam, detection of non-palpable lesions, calcifications, asymmetries and distortions of gland architecture, imperceptibles to physical exploration, is possible, with a sensibility of 77-95% and specificity of 94-97% for breast cancer. Once mammogram was performed, for data evaluation, physicians should use the Breast Imaging Reporting and Data System (BI-RADS), introduced in the 1992 by the American College of Radiology (ACR) and now in its fifth edition, to classify mammogram results in a standardized way, reducing physician subjectivity impact[6,7]. As previously reported, one of the most important mammogram results, considering its prevalence (about of 30%), is undoubtedly the mammary vascular calcification (MVC)[2,3]. MVC can be defined as an inappropriate and pathological deposition of calcium phosphate salts in vascular tissues, characterized by thickening and loss of elasticity of arterial wall muscular layers, due to the calcification of middle layer or intimate vascular. Although this may happen normally aging, however, this process is accelerated in certain disease states, e.g. presence of diabetes mellitus, high blood pressure or chronic kidney diseases[8]. In blood vessels, calcified deposits can be present in different histological layers and related to some underlying pathologies. Intimal calcifications occur in atherosclerotic lesions, while medial calcifications (known as Mönckeberg's medial sclerosis) are associated with vascular stiffness and age-related atherosclerosis, diabetes, and end-stage renal diseases. Interestingly, intimal calcifications onset can be independent by medial calcification and vice versa[9,10]. These two different locations present physio-pathologically different processes of calcifications development. Calcification of intimal layer is an active process, regulated in a similar way to bone formation, involving the expression of growth factors, matrix proteins and proteins related to bone tissue, and is associated with inflammatory cells, lipid deposits and vascular smooth muscle cells. Considering their pathophysiological impact, increasingly, vascular calcifications are considered predictors of coronary vascular diseases, as reported in several studies. Although intimal calcifications are more frequently associated to coronary artery diseases, imaging techniques used nowadays cannot distinguish between the two layers[11]. In the last years, the interest for alternative uses of mammogram is grown, considering its ability to reveal abnormalities related to diseases not only of mammary gland, e.g. observing arterial calcifications presence or sclerosis of Mönckeberg (located in the tunic vascular media). These typically benign changes, associated to MVC of intermediate layer, easily detectable with mammogram, have resulted related to arterial calcifications of extremities and coronary arteries, increasing cardiovascular risk (CVR)[2]. For these reasons, MVC have attracted the attention of scientific community as predictive markers of potential cardiovascular events[7,8,12]. Several studies[2,6,9,13-16] and metanalysis have confirmed the relationship between MVC, cardiovascular diseases and atherosclerotic coronary diseases. In the 2001, Schnatz et al[17] have reported, in a 5-year prospective study on 1454 women, 3.5 times higher CVR in women with MVC. This result has been confirmed also in the metanalysis of Jiang et al[18] which have reported a higher risk of coronary diseases of 3.9 times in women with MVC[2]. The relationship between MVC and presence of chronic-metabolic diseases (diabetes mellitus, hypertension and chronic kidney disease) has been evaluated in some studies which have shown a higher prevalence of MVC in these diseases, confirming its potential role as marker[7,12].

One of these is a Turkish study of 2014 that showed an association between diagnosis of metabolic syndrome and presence of MVC. Among metabolic syndrome characteristics, low levels of high-density lipoproteins (HDL) and high blood pressure have been resulted able to predict MVC in mammography, with an increasing probability according to the age. Considering all these results, patients with MVC should be evaluated for their metabolic profile, informed of their CVR factors and eventually encouraged to consider appropriate lifestyle changes[19]. A further confirmation of MVC-CVR relationship has been reported in a study of Hendricks et al[9]. In a cohort of 5196 patients, undergoing to whole-body computed tomography, authors have founded a strong association between cardiovascular morbidity/mortality and presence of MVC, while calcifications of other body regions (such as iliac or splenic arteries) have been resulted weaker markers of cardiovascular diseases, without reaching statistical significance[9]. As it is known, cardiovascular diseases represent a serious global public health problem for many countries due to the wide presence of its risk factors in world population. The main risk factors, associated with coronary diseases, are undoubtedly: age, male gender, total hypercholesterolemia, Low Density Lipoproteins (LDL)

- HDL ratio, hypertriglyceridemia, hypertension, smoking, diabetes, presence of coronary diseases, family history, obesity and sedentary lifestyle[20]. For these reasons, it is not a surprise that cardiovascular diseases are the main world cause of death. Among these pathologies, atherosclerosis represents the most important cause of death and disability in developed countries and the presence of arterial calcifications is a common feature of atherosclerosis. Considering that atherosclerosis associated diseases often show clinical symptoms only after a long period of silence, the importance of CVR assessment is obvious. Considering the impact of arterial calcifications on atherosclerosis, assuming the potential predictive power of MVC for cardiovascular diseases detection and clinical importance of breast cancer screening program, the importance to confirm and to adopt MVC as CVR marker is evident. However, published works, which evaluate MVC and CVR relationship, report discordant results. For this reason, the aim of this work is to analyse MVC/CVR relationship in late postmenopausal women by mammogram exams and lipid profiles evaluation to confirm the potential use of MVC as CVR marker.

PATIENTS AND METHODS

Two hundred six postmenopausal women, under 79 years old, classified as +2 degree of Stages of Reproductive Aging Workshop + 10 scale (STRAW+10) (late post menopause), attending to the Hospital Juarez de Mexico between March 2017 and April 2018 to perform annual scheduled mammography belonging breast cancer screening program, were selected for this prospective, observational study. All patients were subjected to mammography, CVR evaluation and lipid profile analysis. To evaluate the presence/absence of MVC, all patients underwent to bilateral mammography on radial and anti-radial planes and calcifications were evaluated according to BI-RADS classification system[21]. For CVR evaluation, age, total cholesterol and HDL cholesterol serum levels, systolic and diastolic blood pressure, antihypertensive treatment, diagnosis of diabetes, and smoking were considered. Data obtained were used to analyse the CVR by the American Heart Association (AHA) calculator (available on-line at the site http://www.cvriskcalculator.com/). To complete lipid profiles of patients, also the serum levels of LDL cholesterol, non-HDL cholesterol and triglycerides and Body Mass Index (BMI) were evaluated for a more comprehensive account. Lastly, to analyse the associations between MVC, CVR and metabolic profiles, presence/absence of MVC has been considered as an independent variable while CVR, total cholesterol, HDL cholesterol, LDL cholesterol, non-HDL cholesterol, triglycerides, diabetes mellitus type 2, hypertension, age, body mass index, smoking

Table I. Units and scales of measurement of dependent and non-dependent variables.

Variable	Unit	Scale
MVC	Present	Presence of MVC (unilateral or bilateral) by mammography. Positive results for MVC where defined by parallel radiopaque lines which suggest longitudinal projection of blood vessel.
	Absent	Absence of MVC
Cardiovascular risk	Low	0 to 4.99%
	Medium	5 to 9.99%
	High	≥10%
Total Cholesterol	mg/dl	Fasting serum measurement
HDL level	mg/dl	Fasting serum measurement
LDL level	mg/dl	Fasting serum measurement
No-HDL cholesterol	mg/dl	Fasting serum measurement
Triglycerides	mg/dl	Fasting serum measurement
Diabetes	YES	Patients with a Diabetes Mellitus diagnosis, with or without treatment, independently of whether it is controlled
	NO	Patients without a Diabetes Mellitus diagnosis
Systematic arterial Hypertension	YES	Patients with a hypertension diagnosis, with or without treatment, independently of whether it is controlled
	NO	Patients without systemic arterial hypertension diagnosis
Age	Years	Age on the date of laboratory study
BMI (according to WHO)	Normal	18.5-24.9 kg/m^2
	Overweight	25-29.9 kg/m^2
	Grade I obesity	30-34.5 kg/m^2
	Grade II obesity	35-39.9 kg/m^2
	Grade III obesity	≥ 40 kg/m^2

Table II. Distribution of mammographic evaluations according to BI-RADS classification.

BI-RADS	No. of Patients	Percentages
0	5	2.42%
1	2	0.97%
2	196	94.66%
3	3	1.45%
4	0	0%
5	0	0%
6	0	0%

have been considered dependent variables (Table I). The sample size of 206 patients was calculated considering a *p*-value of 5% and a frequency of 16%. For the statistical analysis U test of Mann-Whitney was performed using Statistical Package for Social Science (SPSS) program. All patients gave a written informed consent to the procedure and trial was approved by the Local Ethics Committee.

Exclusion criteria

Exclusion criteria used for this work have been: women classified -1,-2 or +1 degrees for STRAW+10 scale, women aged over 69 years (max age for mammographic screening), women with a total cholesterol >320 mg/dl and/or with a level of HDL >100 mg/dl or <20 mg/dl which represent the AHA calculator limits for CVR evaluation, women with a history of mastectomy, breast cancer and/or acute myocardial infarction and patients which performed mammography not at the Hospital Juárez de México.

RESULTS

From data collected in this study, 95% of patients reported a BI-RADS classification of 2 (196 cases) (Table II). All data were recorded and reported on a data collection form (Table III). Relatively to the presence of MVC, 32.04% (66 cases) of patients included in this study have reported the presence of this condition. A similar result has been obtained also for CVR evaluation with a risk higher 7.5% at AHA calculator in the 32.52% (67 cases) of patients. Of these 67 patients with high CVR, 49 cases have reported also MVC (73,1% of population with a CVR >7.5%, and 74.2% of population with MVC). In agreement with these results, 122 patients without MVC have also a reduced CVR (87.8% of patients with a reduced CVR and the 87.1% of patients without MVC) (Table IV). Analysing data obtained, a relationship statistically significative ($p<0.05$) (Table

Table III. Data Collection Form used in this study.

NAME AND SURNAME				**CASE NUMBER**					
ADDRESS				**TELEPHONE**					
DATE OF BIRTH				**AGE**	*(years)*				
CARDIOVASCULAR RISK	*(%)*			**PRESENCE OF MVC**	*Yes*		*No*		
DIABETES MELLITUS	*No*	*1*	*2*	**TREATMENT OF DIABETES**					
SYSTEMIC ARTERIAL HYPERTENSION	*Yes*	*No*		**TREATMENT OF HYPERTENSION**					
SMOKING	*Yes*	*No*		**PREVIOUS VASCULAR EVENTS**	*Yes*		*No*		
NO. OF PREGNANCIES				**TOTAL MONTHS OF BREASTFEEDING**					
PRIMARY OVARIAN INSUFFICIENCY	*Yes*	*No*		**HORMONE REPLACEMENT THERAPY**	*Yes*		*No*		
FAMILY PLANNING METHOD				**AGE OF LAST MENSTRUATION**					
WEIGHT	*(kg)*	**HEIGHT**	*(cm)*	**BMI**	*(kg/m²)*				
WAIST	*(cm)*	**HIP**	*(cm)*	**WAIST/HIP RATIO**					
TOTAL CHOLESTEROL	*(mg/dl)*	**HDL**	*(mg/dl)*	**LDL**	*(mg/dl)*	**NO HDL**	*(mg/dl)*		
TRIGLYCERIDES	*(mg/dl)*	**GLUCOSE**	*(mg/dl)*	**INSULIN**	*(µUI/ml)*	**HOMA**			
TSH	*(mUI/L*	**CREATININE**	*(mg/dl)*	**DRUGS**					
BI-RADS	*0*	*1*	*2*	*3*	*4ª*	*4b*	*4c*	*5*	*6*
FOLLOW-UP	*0*	*1*	*2*	*3*	*4ª*	*4b*	*4c*	*5*	*6*
MAMMARIAN BIOPSY	*Benign*		*Malign*	**HISTOPATHOLOGICAL DIAGNOSIS**					
T-SCORE *Lumbar segment* *Hip*				*Normal* *Osteopenia* *Osteoporosis*					

Observations: Dr. Imelda Hernández Marín (JSBRH)/Dr. Ana Carolina Salazar Romo assigned to the Department of Human Reproduction Biology (R5BRH).

Table IV. Percentages of MVC in the overall population and in the subpopulations defined in according to CVR evaluation.

			MVC		
			Yes	No	Total
CVR	High (>7.50%)	No.	49	18	67
		% on HCR pop.	73.1%	26.9%	100.0%
		% on MVC pop.	74.2%	12.9%	32.5%
		% of total	23.8%	8.7%	32.5%
	Low (<4.99%)	No.	17	122	139
		% on HCR pop.	12.2%	87.8%	100.0%
		% on MVC pop.	25.8%	87.1%	67.5%
		% of total	8.3%	59.2%	67.5%
Total		No.	66	140	206
		% on HCR pop.	32.0%	68.0%	100.0%
		% on MVC pop.	100.0%	100.0%	100.0%
		% of total	32.0%	68.0%	100.0%

V) between MVC and CVR emerges strongly by this work as confirmed also comparing CVR means in patients with or without MVC (Figure 1). Although a statistically significant relationship was found between CVR and presence of MVC, the variable responsible of this association is not connected to the lipid profile of patients. Indeed, all lipid profiles data (total cholesterol, LDL, HDL, and triglycerides) were resulted not statistically related ($p>0.05$) to the presence of MVC, probably because a statins treatment was not considered within the exclusion criteria (Table V). Interestingly, a diagnosis of metabolic syndrome in almost 50% of patients was resulted. However, according to the statistical analysis, the relationship of this diagnosis with presence of MVC was not corroborated. Another factor analysed, that was resulted not connected to the presence of MVC, is the smoking. Indeed, this last, representing one of the most important factors in the calculation of CVR, is present only in the 8.7% of patients. Analysing then the BMI of these patients, also in this case, a statistically significative connection to the presence of MVC was not found though only 19.9% of all patients have reported a BMI within normal threshold. Among factors that were found related to MVC presence, in a statistically significative way, there are: hypertension, age and diagnosis of Type 2 Diabetes Mellitus. Indeed, this last, representing also a variable used for CVR calculator of AHA, seems to have a statistically significant relationship not only with CVR but also with the presence of MVC, as reported in Table V. In this regard, 54% of all patients (n=111 of 206) have shown alterations of carbohydrates metabolism and about the 30% of the total population (n=62) is resulted insulin resistant while the 23.7% (n=49) have received a diagnosis of Type 2 Diabetes Mellitus (Table VI). Another variable of CVR calculation, which could explain the statistically significant relationship

Table V. Statistical analysis of the analyzed correlations.

	Sensibility	Specificity	Predictive (+) value	Predictive (-) value	Relative Risk	Odds Ratio	IC 95%	*p*-value
CVR	0.7424	0.8714	0.7313	0.8776	5.9740	19.53	9.31-40.9	**<0.05**
Metabolic Syndrome	0.6060	0.5714	0.4000	0.7547	0.6132	2.051	1.13-3.72	**>0.05**
T2 Diabetes Mellitus	0.3787	0.8285	0.5102	0.7388	1.954	0.339	0.175-0.659	**<0.05**
Insulin resistance	0.3041	0.4022	0.2482	0.5952	0.5781	0.447	0.252-0.847	**>0.05**
Hypertension	0.5151	0.7642	0.5074	0.7697	2.204	1.472	0.793-2.73	**<0.05**
Total Cholesterol	0.3181	0.4928	0.2282	0.6052	0.5781	0.447	0.242-0.827	**>0.05**
LDL	0.2575	0.5395	0.2098	0.6048	0.5310	0.407	0.213-0.775	**>0.05**
HDL	0.6818	0.4071	0.3515	0.7307	1.305	1.472	0.793-2.73	**>0.05**
Triglycerides	0.3939	0.6214	0.3291	0.6850	1.004	1.067	0.585-1.945	**>0.05**
Smoking	0.1060	0.9214	0.3888	0.6861	1.230	0.719	0.265-1.949	**>0.05**
Aging								**<0.05**
BMI								**>0.05**

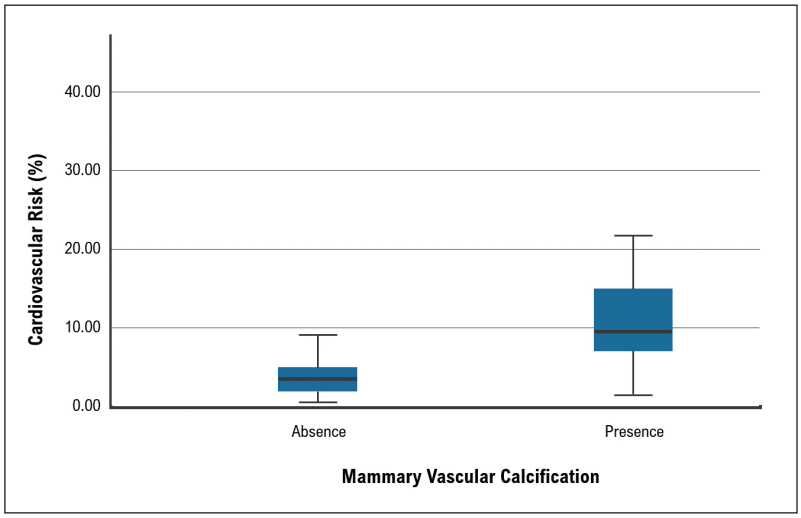

Figure 1. Comparison between CVR means of patients with and without MVC.

Table VI. Percentages of MVC in the overall population and in the subpopulations with or without Type 2 Diabetes Mellitus diagnosis.

			MVC		
			Yes	No	Total
Type 2 Diabetes Mellitus	Yes	No.	25	24	49
		% on T2DM pop.	51.0%	49.0%	100.0%
		% on MVC pop.	37.9%	17.1%	23.8%
		% of total	12.1%	11.7%	23.8%
	No	No.	41	116	157
		% on T2DM pop.	26.1%	73.9%	100.0%
		% on MVC pop.	62.1%	82.9%	76.2%
		% of total	19.9%	56.3%	76.2%
Total		No.	66	140	206
		% on T2DM pop.	32.0%	68.0%	100.0%
		% on MVC pop.	100.0%	100.0%	100.0%
		% of total	32.0%	68.0%	100.0%

between CVR and presence of MVC, is the systemic arterial hypertension diagnosis. Indeed, this clinical condition, involving one third of the cases included in this study, is mainly reported in MVC patients as shown in (Table VII). As previously reported, also the age of patients is a factor, emerging from this study in a statistically significant way (Table V) that should be taken in consideration. Indeed, as shown in this paper, the cases of MVC increase proportionally with the age of patients, confirming the importance of this parameter to understand the relationship between MVC and CVR as shown in Figure 2 that represent the MVC case distribution according to the age of patients.

Table VII. Percentages of MVC in the overall population and in the subpopulations with or without Systemic Arterial Hypertension diagnosis.

			MVC		
			Yes	No	Total
Systemic Arterial Hypertension	Yes	No.	34	33	67
		% on SAH pop.	50.7%	49.3%	100.0%
		% on MVC pop.	51.5%	23.6%	32.5%
		% of total	16.5%	16.0%	32.5%
	No	No.	32	107	139
		% on T2DM pop.	23.0%	77.0%	100.0%
		% on MVC pop.	48.5%	76.4%	67.5%
		% of total	15.5%	51.9%	67.5%
Total		No.	66	140	206
		% on T2DM pop.	32.0%	68.0%	100.0%
		% on MVC pop.	100.0%	100.0%	100.0%
		% of total	32.0%	68.0%	100.0%

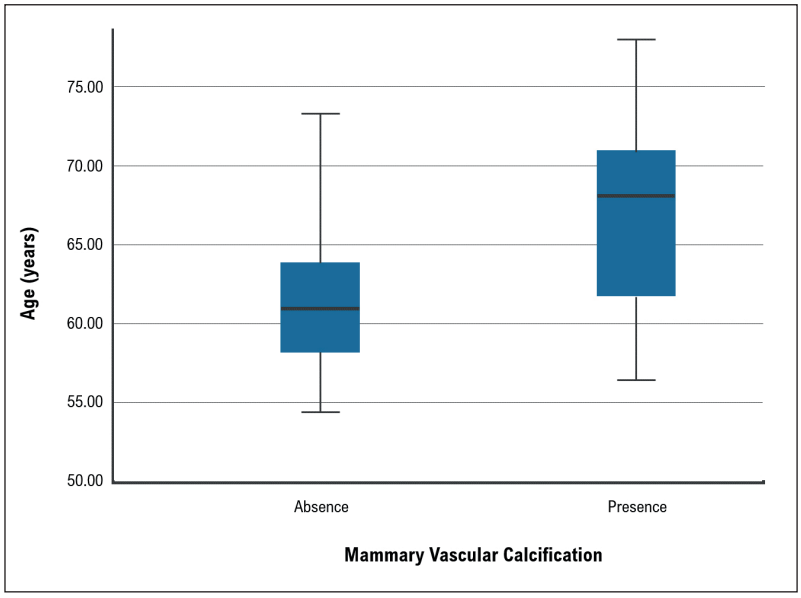

Figure 2. MVC case distribution according to the age of patients.

DISCUSSION

Cardiovascular complications represent the first cause of mortality in the population and the identification of finding tools for patients at high risk of acute coronary attack is essential. At this regard, one of the most interesting opportunities could be offered to physicians by the application breast mammography. In the last years, indeed, the interest for the alternative uses of this diagnostic method, representing the most important routine exam for women over 40 years of age as oncological screening, is grown, considering its ability to reveal abnormalities related to diseases not only of the mammary gland. Among these changes, there are the MVC, predictably associated with others arterial calcifications e.g. at coronary level, easily detectable, associated in several studies to an increased CVR[2]. For this reason, MVC increasingly have attracted the attention of scientific community as predictive markers of potential cardiovascular events[7,8,12]. Considering the pathological impact of arterial calcifications and the clinical importance of the breast cancer screening program in the world, it is evident how much could be important the adoption of MVC as CVR marker. Several studies and metanalysis have also confirmed the relationship between MVC, cardiovascular diseases[2,6,9,13-16]. For this reason, the aim of this study was been to evaluate the potential application of MVC presence as CVR marker. Although a statistically significant relationship between CVR and presence of MVC in this study was found, the variables responsible of this association seem to be: age, diagnosis of Type 2 Diabetes Mellitus and Systemic Arterial Hypertension. On the contrary, interestingly, this relationship seems to be not influenced by lipid parameters despite although the correlation between CVR and lipid profile has been repeatedly demonstrated. However, an explanation clarifying this aspect could be the lack of data related to treatments with lipid-lowering agents. For this reason, a correlation between MVC, dyslipidaemia and CVR cannot be excluded by this study.

CONCLUSIONS

Thanks to these data, we can confirm the correlation between MVC and CVR even if it is essential to consider the possible impact of several factors like, age, hypertension and type 2 diabetes diagnoses in the CVR evaluation. Obviously, further studies at this regard are fundamental to confirm these preliminary data.

Conflicts of interest:
The Authors declare that they have no conflict of interests.

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