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Determining factors in the development of coronary plates and obstructions

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ABSTRACT

Introduction: Coronary artery disease is the largest cause of mortality in the world. The main risk factors for its development include systemic arterial hypertension and type 2 diabetes mellitus. **Objective:** To search for predictors of the development of plaques and obstructions in coronary arteries and to determine whether the exercise test is a reliable pretest for coronary angiotomography. **Methods:** 883 computed tomography reports of coronaries were analyzed. Sociodemographic information, health conditions and results of the exercise test from patients were collected, along with calcium score, percentile and number of arterial segments with significant obstruction. The data were analyzed using descriptive and inferential statistics. Significance was considered for $p<0.05$. **Results:** It observed that the statistically significant predictors to the calcium score were male, being over 60 years old, having type 2 diabetes mellitus and systemic arterial hypertension. There was no relationship with high BMI and coronary obstruction. Regarding the exercise test, it was possible to observe that the majority of individuals who were positive in the exercise test, did not have a positive calcium score or significant coronary obstructions. **Conclusion:** The predictors for the development of coronary plaques and obstructions were male, aged ≥60 years, having type 2 diabetes mellitus and systemic arterial hypertension.

Keywords: cardiovascular diseases; coronary disease; angiography; atherosclerosis; life style.

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INTRODUCTION

Coronary artery disease (CAD) is the main cause of mortality in the world, responsible for 7.25 million deaths, which corresponds to 12.8% of the total deaths per year[1]. Knowing that in at least half of people with CAD, acute myocardial infarction is the first manifestation, the identification of asymptomatic individuals is crucial for effective prevention and the correct development of therapeutic goals[2].

The main risk factors for the development of coronary heart disease include age, sex, family history, systemic arterial hypertension (SAH), smoking, dyslipidemia, overweight and type 2 diabetes mellitus (DM2)[3]. The leading cause of death in individuals with diabetes is cardiovascular disease, accounting for half of deaths from diabetes in most countries[4].

Knowing the high incidence of CAD, it is important to identify the determinants related to the disease and its correct diagnosis, so that prevention and consequent implementation of actions to reduce the indexes found are elaborated.

Thus, this study aimed to detect the predictors for the development of coronary plaques and obstructions detected by computed tomography of coronary arteries, a gold standard exam in the area, in addition to determining if the stress test is a reliable pretest for coronary angiotomography.

METHODS

This study was approved by the Ethics and Research Committee of the Centro Universitário de Maringá (Process No. 1,359,730).

Sample

Quantitative, observational and retrospective study, carried out by analyzing 1048 reports of computed tomography (TCcor) exams composed of coronary angiography (CA) and calcium score (CS) of patients referred for CAD investigation in January 2012 to December 2014 at a reference imaging clinic, located in the city of Maringá - Paraná, this sample being the total number of tests performed in this period. Due to the retrospective characteristic of the collected data, there was no need to collect signatures for the informed consent form.

Of the 1,048 reports of TCcor exams, 883 were selected for analysis, since the others were excluded because they fit the exclusion criteria. Examinations with unavailability of data were excluded from the study, in addition to those that contained as an indication for carrying out: assessment of cardiac masses; congenital heart disease; valve disease, post stent placement, post cardiac transplant and post coronary revascularization. The selected reports were those that indicated risk stratification for coronary heart disease.

Assessed variables

The data collection of the reports was based on the identification and capture of four pieces of information: result of CS, CA, description of predictive factors and result of exercise stress test (ST).

The CS, measured in a Hounsfield unit (HU), was classified as negative if =0, and positive >0. The CA assessed the percentage of obstruction in 56 coronary segments (14 coronary arteries divided into four segments each, with the artery ostium, proximal, middle and distal branch), was classified according to the number of segments with significant luminal obstruction: none obstructed segment; one to three segments; four or more segments, being considered "without significant luminal reduction" when the obstruction was below 50%, and "with significant luminal reduction", obstruction of 50% or more of the coronary artery[5].

The Hounsfield scale used in the examination is a quantitative scale that describes radiodensity. The radiodensity of distilled water and air under standard conditions of temperature and pressure corresponds respectively to 0 and -1000 HU.

Among the factors intrinsic to the patient, the following information was collected from the reports: age, sex, body mass index (BMI) (Kg/m^2), smoking, family history and presence of associated chronic diseases (DM2, dyslipidemia and SAH).

The result of the exercise stress test was included in the TCcor report for patients who had previously undergone ST before TCcor. The result of the stress test can be positive, inconclusive or negative for myocardial ischemia.

Statistical Analysis

The data were tabulated in a Microsoft Office Excel spreadsheet and in order to investigate the associations between the CS result and the number of segments with significant luminal reduction, with the possible predictive factors, the odds ratios were calculated. Subsequently, using the methodology proposed by Hosmer and Lemeshow[6], the factors that showed at least a moderate association ($p>0.25$) with the TCcor result were selected using the chi-square test. Such factors were included in the multivariate model, which estimates the odds ratio considering the possible interactions between the variables.

The χ^2 score test was applied to verify the assumption of proportional odds. Both for univariate analyzes and for the adjusted multivariate model, there was sample evidence that the proportional odds model was adequate to adjust the data, considering a 5% level of significance. Statistical analyzes were performed using the SAS (Statistical Analysis System) software, version 9.3.

Aiming to evaluate the possible association between the result of st with the number of obstructions in the arteries, as well as the CS, the chi-square test (χ^2) was applied in both situations, setting the level of 5% of significance, with the aid of the R (R Development Core Team) statistical environment.

RESULTS

The results presented in Table 1 show that 48.92% of the evaluated exams presented a negative result for CS. It is noted that male patients have almost twice the chances of obtaining a positive CS result compared to women with (odds ratio OR=1.98). It was also found that the chances of individuals who are 60 years old or older to have positive CS represent five times more chances compared to those between 40 and 60 years old (OR=5.03), while individuals younger than 40 years old had chances significantly smaller.

It is estimated that patients with SAH are twice as likely to obtain a positive calcium score as compared to non-hypertensive patients (OR=2.01). Those with DM2 are 153% more likely to have a positive outcome compared to their peers. The presence of dyslipidemia is also a factor that significantly increases the patient's

chances of having a positive CS (OR=1.56). It was found that patients who declared to be ex-smokers are almost twice as likely (OR=1.91) to obtain a positive calcium score.

It is also possible to notice that the factors sex, age, SAH, DM2, dyslipidemia and ex-smoking, have a significant association with the result of CS, considering a level of 5%. In addition to these variables, BMI was also included in the multivariate logistic regression model, as it presented at least a moderate association, with a p-value of 0.09, less than 0.25.

It can be seen in Table 2, the male gender, the age above 60 years and the presence of chronic diseases SAH and DM2 remained as determining factors, considering the significant increase in the chances of obtaining a positive result for CS, when analyzed together, while the age of less than 40 years remained a determining factor of protection. It is noteworthy that the estimated odds ratios for male individuals were much higher in the joint analysis, with men being about four times more likely to have a positive CS when compared to women (OR=4.15).

Just as the univariate and multivariate analysis of factors related to CS was performed, the same method was used to analyze the percentage of coronary obstruction.

Table 2: Multivariate analysis of the calcium score (CS).

Factors	Adjusted OR	CI 95%	P value
Sex			
Female	1.00	-	-
Male	4.15	2.86-6.03	<0.01*
Age			
< 40 years	0.06	0.01-0.25	<0.01*
40 |- 60 years	1.00	-	-
≥ 60 years	6.98	4.85-10.06	<0.01*
BMI			
Underweight	-	-	-
Normal	1.00	-	-
Overweight	1.42	0.96-2.09	0.08
Obesity	1.32	0.86-2.04	0.21
Systemic Arterial Hypertension			
No	1.00	-	-
Yes	1.38	0.99-1.91	0.05*
Type 2 Diabetes Mellitus			
No	1.00	-	-
Yes	1.74	1.14-2.67	0.01*
Dyslipidemia			
No	1.00	-	-
Yes	1.24	0.90-1.71	0.19
Ex-smoker			
No	1.00	-	-
Yes	1.34	0.87-2.06	0.18

*Statistically significant values for p≤0.05.

BMI: body mass index; CI: confidence interval; OR: odds ratio.

Table 1: Univariate analysis of the result of the calcium score (CS).

Factors	CS		Gross OR	CI 95%	P value	P value χ^2 test
	Negative	Positive				
Sex						
Female	173	114	1.00	-	-	<0.01*
Male	259	337	1.98	1.48-2.63	<0.01	
Age						
<40 years	52	2	0.06	0.02-0.26	<0.01	<0.01*
40l-60 years	296	185	1.00	-	-	
≥60 years	84	264	5.03	3.70-6.83	<0.01	
BMI						
Underweight *	0	3				0.09
Normal	125	105	1.00	-	-	
Overweight	186	204	1.31	0.94-1.81	0.96	
Obesity	121	139	1.37	0.96-1.95	0.96	
Systemic Arterial Hipertension						
No	251	184	1.00	-	-	<0.01*
Yes	181	267	2.01	1.54-2.63	<0.01	
Type 2 diabetes mellitus						
No	379	333	1.00	-	-	<0.01*
Yes	53	118	2.53	1.78-3.62	<0.01	
Dyslipidemia						
No	251	212	1.00	-	-	<0.01*
Yes	181	239	1.56	1.20-2.04	<0.01	
Smoker						
No	389	403	1.00	-	-	0.74
Yes	43	48	1.08	0.70-1.66	0.74	
Ex-smoker						
No	379	356	1.00	-	-	<0.01*
Yes	53	95	1.91	1.32-2.75	<0.01	
Family history						
No	315	333	1.00	-	-	0.76
Yes	117	118	0.95	0.71-1.29	0.76	

*Statistically significant values for p ≤0.05.

BMI: body mass index; CI: confidence interval; OR: odds ratio.

Table 3 shows the univariate analysis and Table 4 the multivariate analysis, related to the degree and number of segments with significant luminal reduction.

Regarding the number of blocked artery segments, 77.91% of the exams evaluated did not present any obstruction, 18.57% had 1 to 3 obstructed segments and only 3.52% had 4 or more. It is estimated that the chances of a male patient having a higher number of obstructions are 70% greater than the chances of women. As for age, it is observed that the chances of having more obstructed segments significantly increase for patients over 60 years of age compared to those who are in the 40 to 60 age group, and even for individuals under 40 years of age, the chances are one third in relation to the aforementioned range. It is also possible to note that patients who have SAH, DM2 and dyslipidemia have significantly greater chances that the number of obstructions is greater, when compared to those who do not have these diseases. Still, it is estimated that ex-smokers have a 50% greater chance of presenting a greater number of obstructions than those who have not smoked in the past. No other characteristic provided significant differences in the ratio of chances of presenting a greater number of obstructions.

All the factors mentioned above, sex, age, SAH, DM2, dyslipidemia and ex-smoker, are significantly associated with the number of obstructions at the 5% level of significance, according to the chi-square test. The other factors that presented p value >0.25, were not included in the multivariate ordinal logistic model, the results of which are shown in Table 4.

Only the variables male gender, age over 60 years and the presence of DM2, remained as predictive factors for presenting a greater number of obstructed artery segments, with the significance level set at 5%, indicated in Table 4. The difference in odds ratio of the other characteristics were not significant.

Among the patients who presented negative results for the calcium score, (97.22%) did not present any segment of artery with obstruction, while for those who obtained positive CS, a total of 40.57% had 1 or more segments of arteries with degree of obstruction greater than 50%.

It was found that, at 5% level of significance, there is sample evidence that confirms the significant association between the result of the calcium score and the number of blocked artery segments.

Table 3: Univariate analysis of the number of coronary obstructions.

Factors	Number of coronary obstructions			Gross OR	CI 95%	P value	χ^2 test
	0	1 to 3	4 or more				P Value
Sex							
Female	240	41	6	1.00	-	-	0.01*
Male	448	123	25	1.70	1.18-2.44	<0.01	
Age							
<40 years	51	3	0	0.33	0.10-1.08	<0.01	<0.01*
40l-60 years	408	63	10	1.00	-	-	
≥60 years	229	98	21	2.91	2.09-4.06	<0.01	
BMI							
Underweight*	3	0	0				0.46
Normal	179	41	10	1.00	-	-	
Overweight	309	73	8	0.90	0.61-1.33	0.97	
Obesity	197	50	13	1.13	0.74-1.71	0.97	
Systemic Arterial Hypertension							
No	361	66	8	1.00	-	-	<0.01*
Yes	327	98	23	1.84	1.33-2.54	<0.01	
Type 2 Diabetes Mellitus							
No	585	113	14	1.00	-	-	<0.01*
Yes	103	51	17	3.19	2.24-4.56	<0.01	
Dyslipidemia							
No	380	74	9	1.00	-	-	<0.01*
Yes	308	90	22	1.70	1.23-2.34	<0.01	
Smoker							
No	621	143	28	1.00	-	-	0.51
Yes	67	21	3	1.28	0.78-2.10	0.33	
Ex-smoker							
No	581	133	21	1.00	-	-	0.04*
Yes	107	31	10	1.50	1.01-2.22	0.05	
Family history							
No	502	122	24	1.00	-	-	0.82
Yes	186	42	7	0.90	0.63-1.30	0.58	

*Statistically significant values for p≤0.05.

BMI: body mass index; CI: confidence interval; OR: odds ratio.

In the analysis between the relationship between exercise testing and the result of TCcor, 241 exams were included, since of the 883 complete exams, 241 had performed the ST prior to the coronary angiotomography exam.

In general, most patients who underwent ST had a positive result (69.29%), 20.74% had an indefinite result and the smallest part (9.95%), a negative result for myocardial ischemia.

As for the number of obstructions, it is observed that most had no obstruction with a degree greater than 50%, 14.93% had significant obstruction in 1 to 3 coronary segments, and 3.73% had more than 4 segments with obstruction. As for the calcium score, 52.28% of the individuals had a negative result and 47.71% positive.

When stress testing is related to TCcor, most patients presented positive ST for myocardial ischemia and did not present any obstruction. Only 13.68% of the individuals confirmed the test was positive and had coronary obstructions (3.31% with 4 or more obstructions and 10.37% with 1 to 3 obstructions).

If we observe the relationship between ST and calcium score, the discrepancy was smaller, since 35.68% had positive ST and negative CS, whereas 33.60% had positivity in the 2 tests.

No statistically significant difference was found in the relationship between CTcor and CS with ST.

DISCUSSION

Among the main findings of this study, the relationship of risk for the development of coronary obstructions in elderly male individuals with type 2 diabetes mellitus stands out, as well as the low relationship between the presence of coronary obstruction and positivity in the effort.

Table 4: Multivariate analysis of the number of obstructions.

Factors	Adjusted OR	CI 95%	P value
Sex			
Female	1.00	-	-
Male	2.47	1.66-3.67	<0.01*
Age			
<40 years	0.37	0.11-1.24	0.11
40l-60 years	1.00	-	-
≥60 years	2.91	2.04-4.14	<0.01*
Systemic Arterial Hypertension			
No	1.00	-	-
Yes	1.25	0.87-1.79	0.22
Type 2 Diabetes Mellitus			
No	1.00	-	-
Yes	2.36	1.60-3.49	<0.01*
Dyslipidemia			
No	1.00	-	-
Yes	1.37	0.97-1.94	0.08
Ex-smoker			
No	1.00	-	-
Yes	1.09	0.71-1.67	0.70

*Statistically significant values for p≤0.05.

BMI: body mass index; CI: confidence interval; OR: odds ratio.

Cardiovascular diseases continue to be the main cause of mortality and morbidity worldwide and the detection of their predictive factors, in particular for CAD, has been of great importance for the development of primary prevention strategies[7]. The calcium score and coronary angiography, which make up the TCcor, have been shown to be an ally in the diagnosis and investigation of coronary atherosclerotic diseases, since they are more accurate than other diagnostic methods[8].

The result of this research indicates that there is a significant association for calcium score and coronary obstructions, since coronary artery calcification (CAC) is most often related to a greater degree of stenosis and number of obstructed segments. The CS examination can contribute to the diagnosis of CAD, since the cost of the CS examination performed in isolation is lower, making it more accessible to the population. This indication corroborates the study carried out by Ferreira et al.[9] who, when analyzing the cost-effectiveness of diagnostic methods such as stress testing, myocardial scintigraphy, echocardiography, TCcor, CS and catheterization, concluded that angiotomography can be reserved for individuals with calcium score >0, and TCcor was considered the most cost-effective method among the analyzed tests, and can be used as a first-line test.

In contrast, work carried out with 291 patients undergoing coronary angiotomography, determined that an CS=0 does not rule out the occurrence of significant stenosis, however this result was restricted to individuals with acute coronary syndrome[10].

The minority of individuals had CS equal to 0 and with 1 to 3 coronary obstructions, in contrast, no report had a total absence of CAC associated with 4 or more affected segments. Coronary CS provides important prognostic information that is essential to alter clinical management, therefore, performing CS alone is more indicated when the objective is to stratify cardiovascular risk in asymptomatic patients, while CA provides a detailed assessment of the anatomy of coronary arteries with excellent accuracy. The results obtained from the CA are incremental when compared to the CS, so currently coronary angiotomography is not indicated when the goal is only stratification of global cardiovascular risk in asymptomatic patients[11].

Regarding the degree of coronary obstruction, in this study it was possible to observe that more than half of the individuals submitted to the exam did not present any obstructed artery among the 56 analyzed segments, although this research did not calculate the predictive values, this finding is similar to the study Accuracy[12], where it was concluded that the negative predictive value of TCcor (99%) was greater than the positive predictive value, situated between 48% and 64%.

In this research it was possible to observe that both in the association of CS and in coronary stenosis, the individual belonging to the male sex is a strong determinant for a higher risk of CAD, in contrast, a study similar to this one did not find any relationship between the

male sex and the presence of coronary obstructions after analysis of 355 TCcor reports. The same occurred in the variables smoking and hypertension, which in the study cited found a significant relationship between these factors and obstruction of coronary artery light. The only predictive factor that resembled this research was the association of DM2 with the positive result for coronary stenosis[13].

On the other hand, Won et al.[14] confirmed the relationship between males and the risk of CAD. After evaluating 1690 patients with coronary artery occlusions, the researchers concluded that although women were significantly older and hypertensive than men, male subjects had a higher prevalence of coronary obstructions, a statistically significant result when compared to females.

The same hypothesis was confirmed when compared to a cross-sectional and prospective study, which used TCcor reports from 509 patients and analyzed the predictive factor for coronary heart disease risk. Oliveira et al.[15] concluded that belonging to the male gender is a determining factor for significant obstructions and CS≥100. While SAH was a factor related to partially calcified plaques. In the same study, they identified that among the main determining factors for the development of CAD was dyslipidemia, although in the present study we did not find a significant relationship between dyslipidemia and the presence of calcification and coronary stenosis. When associated with the other predictive factor, this variable, analyzed individually, presented significance for both the development of CAC and for coronary obstructions.

Changes in blood cholesterol levels have a strong relationship with the development of coronary diseases, mainly in the formation of atherosclerotic plaques, and HDL (high density lipoprotein) works as a protector for the evolution of CAD[16-21]. This fact partially corroborates with the present research, since dyslipidemia was correlated with both the presence of calcification and coronary obstruction when analyzed in isolation, however, when related to the other predictive factors, this was not significant.

It was possible to observe that both in the relationship between CS and CA, DM2 was statistically significant as a high potential determinant for the development of CAD. A study carried out with 90 diabetic individuals between 40 and 65 years of age, using TCcor as an evaluation, demonstrated that asymptomatic diabetic patients had a high prevalence of coronary obstructions, affecting two or more coronary segments[22]. So also in a study carried out with 3,544 individuals that associated DM2 and precordial pain indicative of myocardial ischemia, found a relationship between hyperglycemia and pain suggestive of CAD[23].

The finding that there is a higher mortality due to cardiovascular factors in the diabetic population, and that those using insulin have a higher risk of events has already been described[24]. The predisposition of diabetics for CAD is not yet clear, since some researchers suggest the potential direct effect of endothelial dysfunction to insulin[25], and others show that the use of insulin is a marker of severity and duration of DM2. With greater severity, these individuals are likely to have more hyperglycemic crises that generate a consequent increase in oxidative stress and the presence of atherogenic particles in the vascular endothelium[26].

Although none of the analyzes in the present study showed a significant relationship between BMI and risk for coronary atherosclerotic diseases, a prospective study conducted with 3275 adults between 18 and 30 years old, confirmed through TCcor that the presence of obesity and also fat abdominal pain for a long time is associated with coronary heart disease, and preventing or delaying the onset of obesity in young adults can decrease the risk of developing atherosclerosis[27]. In order to prevent the individual from being overweight and consequently preventing the risk for the development of CAD, it is important to practice physical exercises, since another study carried out with 4872 individuals demonstrated that the improvement of physical fitness is favorable for the prevention of cardiovascular disease risks. however, this improvement caused by exercise was observed through the relationship with myocardial hypertrophy, but there was no significant association when associated with the calcium score[28].

However, it is noteworthy that in this study, despite the BMI having no significance for the development of CAC and coronary obstructions, individuals with overweight and obesity were more likely to have CAD risks through the analysis of odds ratios.

For the age factor, in this research the relationship with CS and CA was statistically significant for individuals aged 60 years or older to develop an accumulation of calcified plaques and consequent coronary obstructions. In a survey carried out through the analysis of 1,850 participants that aimed to determine the predictors for arterial aging, they did not find a relationship between the factors age, sex and ethnicity with the calcium score when analyzed in isolation, however, it was possible to conclude that healthy arterial aging is influenced by the long-term maintenance of modifiable risk factors[29].

Many recent studies show the genetic relationship as a predictor for coronary artery disease[14,30-32], a factor that despite being widely cited in the literature, has not been explored in this study, so this predictive factor is not yet well understood, it was noted that other studies published did not find this association[33,34].

Even if an individual has no predictive factor, research shows that a 50-year-old with no exposure to risk factors has a 6% chance of developing CAD in 10 years. The knowledge of the modifiable determinants allows the creation of efficient preventive strategies for the development of health actions, aimed at promoting the quality of life in the population[33,35].

Regarding the ST, despite being an accepted test for the diagnosis of cardiovascular diseases, it is also used in the prognostic determination in the medical field for the detection of myocardial ischemia, in this study this fact was not confirmed, since the majority of patients with positive results in ST they did not present coronary artery obstructions. This finding is similar to the research carried out by Oliveira[36], where the specificity of the stress test was high (93%),

however, the sensitivity was low in asymptomatic patients, concluding then a low accuracy of the test to detect myocardial ischemia.

It is noteworthy that of the small part of the individuals in this study who presented negative ST, most did not have any coronary obstruction, however a small percentage of these individuals, even with the negativity in the exercise test, presented from 1 to 3 coronary obstructions. None of these with negative ST had 4 or more obstructions, thus proving the specificity of the exercise test.

Fornitano and Godoy[37] proved after the evaluation of 165 patients, that when an individual presents a double product (resulting from the multiplication of systolic blood pressure by the heart rate, which evaluates ventricular function), this data can be considered an important variable to predict the absence significant obstructive coronary disease, even when the exercise test is positive for myocardial ischemia. This information can be useful in complementing the ST even when positive, so that the individual can be referred to a higher cost exam, such as TCcor.

Despite the results, this study has some limitations that deserve to be highlighted. The design is transversal, which prevents inferring causality; these are the results of a single population group, preventing their generalization. Therefore, it is suggested that studies with larger samples and in different regions be performed, so that it can be proved that DM2 is a more significant predictor than other factors, such as hypercholesterolemia, overweight and SAH, and that ST is not a reliable pre-test for referral to perform TCcor.

The investigation of the data allowed us to conclude that the main predictive factors associated with the development of arterial calcification and obstruction of the coronary arteries were age ≥60 years, belonging to the male gender and presenting DM2. Regarding CS, the main predictive factors were the same, with the inclusion of the predictive factor SAH. It was also possible to conclude that the CS and the CA present a statistically significant association.

Regarding the ST, there is no evidence to state that both the number of obstructions and the result of the calcium score are significantly associated with the result of the exercise test, for the patients who performed it. Therefore, it is suggested to readjust the objective of requesting the exercise test examination, since there is no relationship with coronary obstruction or altered calcium score.

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