Original Article

DOI: 10.7860/JCDR/2015/12081.5989

Internal Medicine Section

Coronary Artery Disease Risk Factors, Coronary Artery Calcification and Coronary Bypass Surgery

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ABSTRACT

Introduction: Atherosclerosis is an intimal disease which affects large and medium size arteries including aorta and carotid, coronary, cerebral and radial arteries. Calcium accumulated in the coronary arterial plaques have substantial contribution to the plaque volume. The aim of our study is to investigate the relationship between coronary artery disease (CAD) risk factors and coronary arterial calcification, and to delineate the importance of CACS in coronary artery bypass surgery.

Materials and Methods: The current study is retrospective and 410 patients admitted to our clinic with atypical chest pain and without known CAD were included. These individuals were evaluated by 16 slice electron beam computed tomography with suspicion of CAD and their calcium scores were calculated. Detailed demographic and medical history were obtained from all of the patients.

Results: In our study, we employed five different analyses using different coronary arterial calcification score (CACS) thresold levels reported in previous studies. All of the analyses, performed according to the previously defined thresold levels, showed that risk factors had strong positive relationship with CACS as mentioned in previous studies.

Conclusion: Coronary arterial calcification is part of the athero-sclerotic process and although it can be detected in atherosclerotic vessel, it is absent in a normal vessel. It can be concluded that the clinical scores, even they are helpful, have some limitations in a significant part of the population for cardiovascular risk determination. It is important for an anastomosis region to be noncalcified in coronary bypass surgery. In a coronary artery, it will be helpness for showing of calcific field and anostomosis spot.

Keywords: Colorectal cancer, Elderly, Morbidity, Mortality

INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in the developed countries and according to the 1999 WHO data, they will account for the most of the morbidity and mortality throghout the world in 2020 [1].

Atherosclerosis is an intimal disease which affects large and medium size arteries like aorta and carotid, coronary, cerebral and radial arteries [2]. Local endothelial injury, inflammation, oxidative stress and calcification take part in the pathogenesis of atherosclerosis [2]. Calcification is the accumulation of calcium salts in the tissues [3]. Calcium accumulated in the coronary arterial plaques makes an important contribution to the plaque volume [3,4]. In histopathological studies, coronary artery calcification has shown to have an important role in the formation of atherosclerosis and there is a strong relationship between coronary arterial calcification and plaque burden [3,5].

In coronary arterial systems of patients with zero coronary calcium scores, the possibility of soft plaque or plaques with stenotic lesions, is very low [5,6]. The risk of stenotic coronary lesions increases with higher coronary calcification levels [6]. The zero calcium scores in coronary calcium scanning have higher negative predictive values showing the absence of atherosclerosis and indicating a better prognosis at short and long term [7].

Electron beam computed tomography (EBCT) which measures coronary calcification density is an important tool in calculation of coronary arterial calcification score (CACS) [8]. CACS is calculated by Agatston method in which multiplication of plaque area and density is used for calculation [8]. The total CACS is calculated according to the Agatston scoring system by using summation of total area and score of the calcified plaques in four main coronary arteries [8].

In the 2010 ACCF/AHA guidelines for assessment of cardiovascular risk in asymptomatic patients, CACS has a class IIa indication, with level of evidence B for cardiovascular risk stratification in individuals with intermediate risk by the Framingham risk score [9,10].

The aim of our study is to investigate the relationship between coronary artery disease (CAD) risk factors (Age, gender, hypertension, hypercholesterolemia, diabetes mellitus, smoking, obesity, low HDL levels and family history of CAD) and coronary arterial calcification, and to show importance of CACS in coronary artery bypass surgery. In our study we employed five different analyses using four different CACS thresolds (various values like 0, 0-100, 100-400 and >400 and, thresold 130 and thresold 0, and according to the percentile values) mentioned in the previous studies.

MATERIALS AND METHODS

Subject

Our study is retrospective and 410 patients who was admitted to Florance Nightingale Hospital Cardiology Clinic with atypical chest pain and without known CAD, were included in the study. Patients with history of coronary bypass surgery, myocardial infarction and percutaneous coronary intervention, metobolic calcium disorders, high urea-creatinine levels or kidney failure, thyroid gland dysfunction, active infection and malignity, were excluded. The calcium scores were calculated by 16 slice EBCT with suspicion of CAD. The 146 (35.6%) of patients were females and the 264 (64.4%) were males and the mean age was 53.3±23.4 y.

Coronary CT Scanning and CACS Measurements

The examination of coronary arteries was performed without using contrast material by 16 slice MDCT at 1.5 mm collimation with spiral axial slices. The diastolic phase images were reconstructed by retrospective ECG (Electrocardiography) gating with the help of a special computer programme and CACS values were calculated by Agatston method.

In previous studies, different thresold levels for CACS were defined in order to determine the patients at low, medium or high risk for CAD [11,12]. In our study, the patients were evaluated in five different ways according to the several CACS thresolds mentioned in the previous studies [11,12]. First, the patients were allocated into four CACS groups which were 0, 0-100, 100-400 and >400. Secondly, percentile values of five CACS groups, which are 10, 25, 50, 75, and 90 were evaluated. In the next evaluation, the patients were assessed according to their CAD or myocardial infarction risks namely having low, intermediate or high risk. In the forth step, the patients were allocated into two groups according to the CACS 130 thresold level. Finally, two groups in terms of CACS zero thresold level, were compared. The correlation of risk factors between all CACS groups were investigated.

Coronary Risk Factors

Detailed demographic and medical history of the study group were obtained from the medical records of our instutition. If subjects were current smokers, they were considered to have a positive history of cigarette smoking. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and/or being under antihypertensive therapy. Diabetes mellitus (DM) was self-reported by patients under antidiabetic therapy. Hypercholesterolemia was characterized by fasting serum low-density lipoprotein (LDL) cholesterol level ≥140 mg/dl or being under lipid-lowering theraphy. The subjects were assumed to be obese if their BMI (Body mass index) was 30 or above. The family history of CAD was accepted as positive if father or a first degree male relative had CAD before 55-year-old and if mother or a first degree female relative had CAD before 65-years-old. The age, as a risk factor, was defined to be younger than 45-year-old for males and 55-year-old for females. High-density lipoprotein (HDL) cholesterol levels lower than 40 mg/dl was accepted as a risk factor.

STATISTICAL ANALYSIS

The data analysis were performed electronically by SPSS (Statical Package for Social Science) Statistics 17.0 package programme. The mean, standart deviation, frequency and percentage measurements were utilized in descriptive statistics of data. In analysis of categorical data, Chi-square test was used, if Chi-squre test conditions were not provided, Fisher's exact test was then utilized. The Pearson's correlation analysis was used to test the correlation between variables. Tests were performed within a confidence interval of 95%.

RESULTS

One hundred and forty six (35.6%) of patients were females and the 264 (64.4%) were males and mean age was 53.3±23.4 y. The mean value of CACS was 118±486,7 (0-1517). 233 (56.8%) of the patients had hypertension, 120 (29.3%) had DM, 217 (52.9%) had hyperlipidemia, 159 (38.8%) had positive family history for CAD and 244 (59,5%) had smoking history. The 158 (38,5%) of the patients were obese.

In the first analysis, patients were divided into four groups according to their CACS levels (0, 0-100, 100-400, and >400). A correlation analysis was done between CACS groups for conventional risk factors. There was a statistically significant difference between four CACS groups for age risk factor which is being male >45 and female >55-year-old. When the groups were compared for gender, CACS were significantly higher in males. The comparison of groups for smoking, hypertension, hypercholesterolemia, DM, obesity and low HDL cholesterol levels, also revealed statistically significant results. There was not any significant difference between groups according to the family history of CAD (p:0.307) [Table/Fig-1].

In the second analysis, patients were evaluated in five groups according to their CACS percentile values (10, 25, 50, 75, 90). A correlation analysis between groups was performed for risk factors. The analysis showed statistically significant difference between groups for age (male >45 and female >55-years-old), hypertension, family history of CAD, hypercholesterolemia, DM, obesity, low HDL cholesterol levels and smoking [Table/Fig-2].

In the third step, the patients were allocated into low, medium and high risk groups for CAD or history of myocardial infarction. Again, a correlation analysis between these groups for risk factors was done. In this analysis of risk status, we showed a statistically significant difference between risk factor groups of age (being male >45 and female >55-year-old), hypertension, family history for CAD, hypercholesterolemia, DM, obesity, low HDL cholesterol levels and smoking [Table/Fig-3].

In the fourth evaluation, the patients were divided into two groups according to the CACS 130 thresold level (CACS; <130 (Group 1) and >130 (Group 2)) and correlation between groups for risk factors was examined. In the analysis of two groups for age, hypertension, hypercholesterolemia, DM, obesity, low HDL levels and smoking, we found a statistically significant difference between two groups. There was not any statistically significant difference between groups according to the family history of CAD [Table/Fig-4].

In the fifth analysis, the patients were allocated into two groups according to CACS 0 thresold level (CACS: 0 (Group 1) and >0 (Group 2)) and correlation between the groups for risk factors was evaluated. This analysis also showed a statistically significant difference between the groups for the risk factors of age, hypertension, hypercholesterolemia, DM, obesity and smoking. We did not find any statistically significant difference between groups for family history of CAD and low HDL cholesterol levels [Table/Fig-5].

	Group 1	Group 2	Group 3	Group 4	p-value
Males >45-year-old	48 (44.9%)	55 (70.5%)	50 (90.9%)	23 (95.8%)	$0.001^{1,2,3,4,5}$
Females >55-year-old	14 (24.1%)	28 (59.6%)	20 (80%)	15 (93.8%)	$0.001^{1,2,3,4,5}$
Sex (M/F)	93/72	78/47	60/20	33/7	$0.001^{1,2,3,4,5}$
Family history for CAD	61 (37%)	46 (36.8%)	31 (38.8%)	21 (52.5%)	0.307
Smoking	80 (48.5%)	73 (58.4%)	62 (77.5%)	29 (72.5%)	$0.001^{2,3,4}$
Hypertension	64 (38.8%)	77 (61.6%)	61 (73.6%)	31 (77.5%)	$0.001^{1,2,3,4}$
Hypercholesterolemia	67 (40.6%)	68 (54.4%)	58 (72.5%)	24 (60%)	$0.001^{1,2,3,4}$
Diabetes mellitus	26 (15.8%)	38 (30.4%)	39 (48.8%)	17 (42.5%)	$0.001^{1,2,3,4}$
Obesity	44 (26.7%)	50 (40%)	44 (55%)	20 (50%)	$0.001^{1,2,3,4}$
Low HDL levels	51 (30.9%)	44 (35.2%)	31 (38.8%)	22 (55%)	$0.038^{3,4,5}$

[Table/Fig-1]: The patient characteristics and analysis of CACS groups; CACS 0 (Group 1), 0-100 (Group 2), 100-400 (Group 3) and >400 (Group 4). In subgroup analysis ^{1} p<0.05 between group 1 and group 2^{2}, p<0,05 between group 1 and group 3^{3}, p<0,05 between group 1 and group 4^{4}, p<0,05 between group 2 and group 3^{5}, p<0,05 between grup 2 ile grup 4 arasında p<0.05

	Group 1	Group 2	Group 3	Group 4	Group 5	p-value
Males >45-year-old	63 (48.8%)	22 (73.3%)	34 (89.5%)	36 (90%)	21 (77.8%)	0.001[1,2,3,4]
Females >55-year-old	21 (30.4%)	9 (69.2%)	12 (66.7%)	16 (80%)	19 (73.1%)	0.001[1,2,3,4]
Sex (M/F)	115/83	30/13	38/18	48/12	33/20	0.006[2,3,4]
Family history for CAD	74 (37.4%)	13 (30.2%)	16 (28.6%)	25 (41.7%)	31 (58.5)	0.012 [4,7,8]
Smoking	101 (51%)	26 (60.5%)	34 (60.7%)	45 (75%)	38 (71.7%)	0.001[2,3,4]
Hypertension	82 (41.4%)	29 (67.4%)	38 (67.9%)	47 (78.3%)	37 (69.8%)	0.001[1,2,3,4]
Hypercholesterolemia	81 (40.9%)	22 (51.2%)	39 (69.6%)	42 (70%)	33 (62.3%)	0.001[2,3,4]
Diabetes mellitus	33 (16.7%)	16 (37.2%)	20 (35.7%)	27 (45%)	24 (45.3%)	0.001[1,2,3,4]
Obesity	56 (28.3%)	14 (32.6%)	28 (50%)	37 (61.7%)	23 (43.4%)	0.001[2,3,4,5]
Low HDL levels	59 (29.8%)	9 (20.9%)	27 (48.2%)	25 (41.7%)	28 (52.8%)	0.001[2,4,6,7]

[Table/Fig-2]: The patient characteristics and analysis according to CACS percentiles; 10 (Group 1), 25 (Group 2), 50 (Group 3), 70 (Group 4) and 90 (Group 5). In the subgroup analysis [1] p<0,05 between group 1 and group 2 [2], p<0,05 between group 1 and group 3 [3], p<0,05 between group 1 and group [4], p<0,05 between group 1 and group 5 [5], p<0,05 between group 2 and group 4 [6], p<0,05 between group 2 and group 3 7, p<0,05 between group 2 and group 5[8], p<0,05 between group 3 and group 5.

	Group 1	Group 2	Group 3	p-value
Males >45-year-old	76 (51.7%)	50 (84.7%)	50 (86.2%)	0.001[1,2]
Females >55-year-old	26 (32.5%)	26 (76.5%)	25 (78.1%)	0.001[1,2]
Sex (M/F)	133/94	64/29	67/23	0.001[1,2]
Family history for CAD	83 (36.6%)	31 (33.3%)	45 (50%)	0.041[2]
Smoking	118 (52%)	58 (62.4%)	68 (75.6%)	0.001[1,2]
Hypertension	103 (45.4%)	63 (67.7%)	67 (74.4%)	0.001[1,2]
Hypercholesterolemia	100 (44.1%)	58 (62.4%)	59 (65.6%)	0.001[1,2]
Diabetes mellitus	42 (18.5%)	41 (44.1%)	37 (41.1%)	0.001[1,2]
Obesity	71 (31.3%)	41 (44.1%)	46 (51.1%)	0.002[1,2]
Low HDL levels	66 (29.1%)	39 (41.9%)	43 (47.8%)	0.003[1,2]

[Table/Fig-3]: The patient characteristics and analysis according to CAD or history of MI; low risk (Group 1), medium risk (Group 2) and high risk (Group 3). In the subgroup analysis [1] p<0,05 between group 1 and group 2[2], p<0,05 between group 1 and group 3

	Group 1	Group 2	p-value
Males >45-year-old	114 (57.6%)	62 (93.9%)	0.001
Females >55-year-old	49 (43.8%)	28 (82.4%)	0.001
Sex (M/F)	184/126	80/20	0.001
Family history for CAD	118 (38.1%)	41 (41%)	0.600
Smoking	168 (54.2%)	76 (76%)	0.001
Hypertension	156 (50.3%)	77 (77%)	0.001
Hypercholesterolemia	149 (48.1%)	68 (68%)	0.001
Diabetes mellitus	74 (23.9%)	46 (46%)	0.001
Obesity	105 (33.9%)	53 (53%)	0.002
Low HDL levels	102 (32.9%)	46 (46%)	0.018

[Table/Fig-4]: The patient characteristics and analysis according to CACS; <130 (Group 1) and >130 (Group 2)

	Group 1	Group 2	p-value
Males >45-year-old	48 (44.9%)	128 (81.5%)	0.001
Females >55-year-old	14 (24.1%)	63 (71.6%)	0.001
Sex (M/F)	93/72	171/74	0.001
Family history for CAD	61 (37%)	98 (40%)	0.537
Smoking	80 (48.5%)	164 (66.9%)	0.001
Hypertension	64 (38.8%)	169 (69%)	0.001
Hypercholesterolemia	67 (40.6%)	150 (61.2%)	0.001
Diabetes mellitus	26 (15.8%)	94 (38.4%)	0.001
Obesity	44 (26.7%)	114 (46.5%)	0.001
Low HDL levels	51 (30.9%)	97 (39.6%)	0.073

[Table/Fig-5]: The characteristics of patients and analysis due to CACS; 0 (Group 1) and >0 (Group 2)

DISCUSSION

The aim of our study is to demonstrate the relationship between CACS and CAD risk factors and to delineate the importance of CACS in coronary artery bypass surgery.

Today, cardiovascular disease is the most important cause of morbity and mortality in the developed countries. CAD is the most common form of CVD and related to higher morbidity and mortality rates [13]. Coronary arterial calcification is a part of atherosclerotic process and although it can be detected in atherosclerotic vessel, it is absent in normal vessel.

When it is compared with conventional risk factors, CACS alone was shown to have a higher prognostic value as a CAD risk factor reported in previous studies [9]. In a meta-analysis of six studies among 27622 asymptomatic subjects performed by ACCF/AHA, global cardiovascular risk was reported to increase in direct proportion to CACS score [9].

In asymptomatic individuals, global cardiovascular risk scores should constitute the first step in cardiovascular risk stratification [9,10]. 2007 twelve asymptomatic subjects, in an expert consensus report of ACCF/AHA, reported to be at intermediate risk by the Framingham risk score, were evaluated as better candidates for CACS in order to straighten the stratification which has a potential to change the clinical practice [10].

Nevertheless, more than one half of the acute coronary syndromes and sudden cardiac deaths are seen among previously asymptomatic patients [14]. In a study of Greenland and collegues, it was shown that before the acute event, 50% of the patients with acute coronary syndrome were in the intermediate risk group according to the Framingham risk score [14].

It can be concluded that the clinical scores, even they are helpful, have some limitations in a significant part of population for cardiaovascular risk determination [9]. These limitations are more common in younger individuals and female patients [9]. In clinical setting, CACS seems to provide important prognostic data in asymptomatic subjects [9]. As a result, some laboratory and imaging tests like CACS, together with clinical risk scores, can be useful for risk stratification in asymptomatic patients [9].

In some previous studies, various statistical analyses were

were performed between CACS and CAD risk scores according to different CACS thresold levels [9,11,12]. In our study, we employed five different analyses using different CACS thresold levels reported in these previous studies. All of the analyses, performed according to the previously defined thresold levels, showed that risk factors like age, gender, smoking, hypercholesterolemia, DM, obesity and hypertension had a strong positive relationship with CACS as mentioned in those studies. The analyses of lower HDL levels and family history revealed different results.

In four of five analyses, there was a statistically significant correlation between lower HDL levels and CACS but when we made a comparison between CACS 0 and CACS >0 groups, we could not find any significant relationship. Until now there were different results in the literature about the relationship between lower HDL cholesterol levels and CACS. Orakzai and collegues could not find any significant relationship between lower HDL cholesterol levels and CACS, however, in a study of Detrano and collegues among 1461 patients, it was reported that there was a strong positive correlation between these paramaters [15,16].

The correlation between family histroy and CACS revealed various results in our five different analyses. In the two analyses with risk and percentile groups there was a significant correlation, however, in other analyses there was not any statistically significant relationship between groups. The relationship between positive family history and coronary calcification, compared with other risk factors, was recalled lesser in previous studies. In MESA study, family history was found to be related to severe coronary artery calcification. A previous study in 312 patients showed that there was not any statistically significant correlation between family history and CACS [17].

In some studies it was demonstrated that CACS has a strong association with major cardiovascular events (all-cause death, cardiac death, and non fatal AMI) during the follow-up period [10]. The risk of a cardiovascular event in a patient increases as the amount of calcium in the coronary arteries increases [9]. In the Multi Ethnic Study of Atherosclerosis (MESA) study, it was shown that CACS has a predictive power for coronary events and a two fold increase in CACS leads 26% increase in CVD risk [18].

In a study, Lange and collegues reported a strong positive correlation between different CACS values for hypertension, DM and mean LDL cholesterol levels [19]. Harvey and collegues showed a statistically significant correlation between age and CACS [20]. Similiar to the previous studies, all of the analyses revealed significant correlation between obesity and CACS [16].

Raggi and collegues evaluated the CAC in diabetic and non-diabetic patients without CAD. This study showed that there was not any significant difference in five year survival between diabetic and non-diabetic patients in the absence of CAC (CACS:0), however, in the presence of CAC (CACS >0), the diabetic patients were shown to have a higher death risk than the nondiabetic ones [21].

CACS was reported to have an excellent negative predictive value to show the absence of significant CAD (96 to 100%) in the initial studies, however, it was found to have moderate positive predictive value [22]. Although it has higher predictive value for myocardial infarction and cardiovascular mortality in asymptomatic individuals, screening of all asymptomatic subjects is not recommended because it has harmful effects and is not cost effective [22].

When the CACS values smaller than 100 was compared with nuclear stress test and coronary angiography, a significant correlation with perfusion abnormality smaller than 2 percent and obstructive CAD smaller than 3%, were detected, respectively. In a study of Mautner and collegues, calcium deposition was detected in 93% of lesions with luminal stenosis greater than 75%, however, calcium deposition was only detected in 14% of lesions with luminal narrowing smaller than 25% [23].

CONCLUSION

It is important for an anastomosis region to be noncalcific in coronary bypass surgery. In our study we showed that coronary calcification increased with the number of risk factors independent of anatomic region. Developing tomographic coronary calcium screening tests can define the regions with dense coronary calcification, anatomically. This will be important in especially procedures like thoracotomy except median sternotomy and determination of surgical area and anastomosis region distant from calcification in off-pump coronary artery bypass surgery.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Nov 20, 2014**
Date of Peer Review: **Feb 18, 2015**
Date of Acceptance: **Mar 19, 2015**
Date of Publishing: **May 01, 2015**