İntima-media kalınlığı, koroner kalsiyum skorlama ve koroner arter hastalığının ilişkisi

The relationship of intima-media thickness, coronary calcium score and coronary artery disease

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Abstract

Background: The aim of this study is to compare the values of carotid artery intima-media thickness (CIMT) and coronary artery calcium scoring (CACS) in determining extention and severity of coronary artery disease (CAD) that diagnosed via coronary CT angiography in patients without known diagnosis of CAD previously.

Methods: 184 patients were included in the study. All patients were undergone CACS examination with 64-detector MDCT scanner for coronary angiography examination. Following angiography examination, CIMT was measured for all patients using B-mode ultrasound device with a 7.5 MHz linear probe. According to the results of coronary CT angiography, patients were classified as normal, mild CAD, moderate CAD, significant stenotic CAD, severely stenotic CAD. The significant difference of calcium score and CIMT levels between these groups was examined with statistical analysis.

Results: Calcium score and CIMT showed significant increase in patients with CAD. They were also found valuable in predicting stenotic CAD, however CACS was found to be more decisive than CIMT for prediction of stenotic CAD. The best cut-off point for CIMT to predict stenotic CAD was 0.88mm.

Conclusion: CACS and CIMT measurements are valuable in determining extention of CAD, however CACS has a better correlation with extention and severity of CAD compared with CIMT. When we evaluated the patients with zero calcium score alone, we found no significant difference in terms of the average CIMT between the group of existing CAD, and the group of non-existing CAD

Keywords: Calcium score, intima-media thickness, coronary artery disease, coronary CT angiography.

Öz

Amaç: Bu çalışmanın amacı daha önce bilinen koroner arter hastalığı (KAH) tanısı olmayan olgularda karotid arter intima-media kalınlığı ve koroner arter kalsiyum skorlamanın koroner arter BT anjiografi incelemesi ile belirlenen koroner arter hastalığının yaygınlığını ve derecesini belirlemedeki değerlerini karşılaştırmaktır.

Materyal-Metod: Çalışmaya 64-dedektörlü çok kesitli bilgisayarlı tomografi (ÇKBT) anjiografisi çekilen ve koroner arter kalsiyum skorlama tetkiki yapılan 184 hasta dahil edildi. Anjiografi incelemesinin ardından 7.5 MHz lineer prob kullanılarak B-mod ultrason cihazı ile tüm hastalara karotid arter intima-media kalınlığı ölçümü yapıldı. ÇKBT anjiografi sonuçlarına göre hastalar normal, hafif KAH, orta KAH, anlamlı stenotik KAH ve şiddetli stenotik KAH olarak sınıflandırıldı. Gruplar arasındaki carotid arter intima media kalınlığı ve kalsiyum skoru düzeylerinde anlamlı fark olup olmadığı istatistiksel analiz ile incelendi.

Bulgular: Kalsiyum skoru ve intima-media kalınlıkları KAH olan hastalarda önemli bir artış gösterdi. Ayrıca her ikisi de KAH öngörmede değerli bulundu. Ancak stenotik KAH'nı öngörmede intima-media kalınlığına göre kalsiyum skorunun daha belirleyici olduğu görüldü. Karotid arter intima-media kalınlığı değeri için stenotik KAH'nı öngörmede en iyi kesim noktası 0.88 olarak saptandı.

Sonuç: Karotid arter intima-media kalınlığı ve kalsiyum skoru KAH'nın yaygınlığını öngörmede değerlidir ancak kalsiyum skoru intima-media kalınlığına gore KAH yaygınlığı ve şiddeti ile daha iyi korelasyon göstermektedir. Sadece kalsiyum skoru sıfır olan hastalar değerlendirildiğinde KAH olan ve KAH olmayan gruplar arasında ortalama intima-media kalınlıkları açısından anlamlı fark saptanmadı.

Anahtar kelimeler: Kalsiyum skorlama, intima-media kalınlığı, koroner arter hastalığı, koroner BT anjiografi

Introduction

Atherosclerosis starts in childhood and adolescence it shows quiet and slow progression. Clinical sings usually expose in adulthood and may cause serious clinical conditions leading to high morbidity and mortality (1).

To predict the cardiovascular disease risk of asymptomatic individuals, some scales are used such as Framingham risk classification (FRS) (2), European Systemic Risk Assessment (3) etc. Limitations of these methods have brought the usage of different diagnostic tools to identify asymptomatic individuals. Being able to predict the global coronary artery disease (CAD) risks and having a strong relationship with the total atherosclerotic plaque burden, it is led the usage of Coronary Artery Calcium Score (CACS) as a different diagnostic tool (4). CIMT is also being used as parameter in determining atherosclerosis (5).

The purpose of this study was to compare the values of CIMT and CACS in determining extension and severity of CAD.

Materials and Methods

In this study, patients referred for CT angiography to our clinic from our cardiology department between August 2009 and May 2010 were discussed. 93 women, 91 men were included in the study for a total of 184 patients. The Local Ethic Committee approved this prospective study and waived the requirement for informed patient consent. The main symptoms of the patients were chest pain (n=78), atypical symptoms like palpitation, dyspnea, left arm numbness (n=75) and asymptomatic cases with existing risk factors (n=31). We have not included patients with known CAD (coronary artery disease) and/or patients who had gone coronary artery bypass graft or stent surgery previously.

Patients were asked to report age, gender, smoking, diabetes mellitus, hypertension, dyslipidemia, family history of CAD and drugs which were in use. Genetic predisposition was considered positive if there were a family history of a cardiovascular event in a parent under 55 years of age for males and under 65 years of age for females. Patients' body weight in kilograms and height in meters were measured.

Weight/(height)² formula was used for the calculation of body mass index.

Pulse and blood pressure were measured prior to coronary artery angiography examination. Patients with heart rate over 75 beats per minute were premedicated with 40 mg propranolol one hour before the examination. All patients were given sublingual nitroglycerin just before the angiography examination.

All patients were undergone CACS examination with 64-detector MDCT scanner (Aquillon 64, Toshiba Medical Systems, Tochigi, Japan) and then using the method of retrospective ECG gating coronary angiography examination was performed.

CACS examination was performed without using contrast agent. For all examinations we used 3mm slice thickness and 2.4mm table movement, 55 mA, 120 kV, 0.5 s gantry rotation time. Lying in supine position a topographical image and from 1cm below the carina axial sections were obtained including the whole heart with prospective ECG triggering.

Immediately after CACS, using parameters of 0.5mm slice thickness, 400 mAs, 120 kV, gantry rotation time of 400 ms, coronary CT angiography was performed. With high iodine concentration (350-400mg/ml), 80-85 ml of nonionic contrast medium was given with a speed of 5 ml/sec from the right antecubital vein using 20-gauge IV cannula. Following intravenous injection of contrast agent, 20 ml physiological saline with a speed of 5 ml/sec was given. Automatic bolus tracking method was used for determining the delay time. Region of interest (ROI) was placed proximal to the descending aorta and the threshold value was determined as 180 HU.

Images were reconstructed in various phases of cardiac cycle to obtain the best images. Automatically generated by the device, images were obtained 75% of RR interval reconstructions that were the best in majority of cases, for the other cases reconstructions were made in additional phases determined by the operator. Reconstructed images were transferred in a workstation (Vitrea 2 workstation, INC. vital image. Plymouth, Minnesota, USA). İnitially axial base images and oblique multiplanar images were assessed. Then a detailed study was made using curved multiplanar reformatted images (CPR), thin and thick maximum intensity projection (MIP) and volume rendering (VR) methods (Figs. 1, 2). Coronary plaques were defined as structures ≥1mm² within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding tissue. For each patient, the number of affected segments and the location of coronary plaques were recorded. For coronary stenoses analysis, the minimal luminal diameter of the stenotic segment was visually compared to the adjacent proximal and distal nonstenotic reference segment with regard to coronary luminal narrowing (6).

Following angiography examination, CIMT was measured for all patients. Toshiba ultrasound device (Xario, Toshiba Medical Systems, Japan) with a 7.5 MHz linear probe was used. Measurements were taken from the posterior wall of common carotid artery 1.5cm proximal to the carotid bifurcation. Three CIMT measurements were taken manually from each carotid artery wall and arithmetic average values of six measurements were used in statistical analysis.

According to the results of MDCT angiography, patients were classified as normal (Grade 0), mild CAD (Grade 1), moderate CAD (Grade 2), significant stenotic CAD (Grade 3), severely stenotic CAD (Grade 4). 1-19% stenosis of coronary arteries, segment affected less than 2cm, one or two vascular

disease were determined mild CAD. 20-49% stenosis, segment affected longer than 2cm, three or more vascular disease were determined as moderate CAD. Except left main coronary artery presence of 50-69% stenosis were determined as significant stenotic CAD. In the presence of stenosis 70% or more and for left main coronary artery stenosis ≥ 50% were considered to be severely stenotic CAD.

The amount of calcium in the coronary arteries was determined using the Agatston scoring system. On axial slices, calcium score was calculated automatically by the computer software program, and patients were separated into 5 groups according to Agatston score as 0 calcium score (Stage 0), 1-10 (Stage 1), 11-100 (Stage 2), 101-400 (Stage 3), >400 (Stage 4).

Data analysis was performed using SPSS for Windows 11.5 package program.The significant difference of calcium score and CIMT levels between two groups was examined with Mann-Whitney U test. Kruskal-Wallis test was used for determine the difference between more than two groups. The value of CIMT predicting the existence and the extent of CAD was evaluated with ROC analysis. The area under the curve and 95% confidence intervals were calculated. $p < 0.05$ was considered statistically significant for the results.

Results

In this study 184 patients, mean age of 54±11 years (min-max: 16-82 years) were included. 91 of the patients were male (49%), 93 of them were women (50%). In 72 of 184 (39%) cases had smoking history, 59 (32%) of the cases had genetic predisposition, 39 (21%) of the cases had diabetes, 84 (45%) of the cases had hypercholesterolemia, 85 (46%) of the cases had hypertension.

Mean calcium score was found 71 (min-max:0-1064) for all cases. In 118 (64%) cases stage 0 calcium score was found. In 15 (8%) of the cases stage 1 score, in 25 (13%) of the cases stage 2 score, in 21 (11%) of the cases stage 3 score and in 9 (4%) of the cases stage 4 calcium score were detected.

When patients were evaluated for CAD, 90 (48%) of them were normal. 21 patients (11%) were grade 1 CAD, 53 patients (28%) were grade 2 CAD, 8 patients (4%) were grade 3 CAD, 12 patients (12%) were grade 4 CAD.

CIMT values were found between 0.38mm and 1.51mm and the average value was calculated 0.79mm.

All of the patients were divided into two groups as CAD (grade 1, 2, 3, 4) and non-CAD (grade 0). The mean age of the patients with CAD was 59 and for the non-CAD group it was 48. Age of patients with CAD was significantly higher ($p<0,001$). When CIMT was considered for both groups, the average value of CIMT in the group non-CAD was found 0.71mm, while in the group with CAD it was 0.87mm and the difference was statistically significant ($p<0.001$) (Table 1). Calcium score and CIMT showed significant increase in patients with CAD.

When the patients were evaluated in terms of stenotic CAD (grade 3,4) the mean age was 62, in non-stenotic group the mean age was 53,2 and the difference was significant ($p<0.001$). In the group of stenotic disease average calcium score was 312 and the average CIMT was 0.99mm. Calcium score and CIMT was found valuable in predicting stenotic disease ($p<0.001$) (Table 2). Analyzing p-values (or Wald statistic) of CACS and CIMT, CACS was found to be more decisive than CIMT (Table 3).

The area under the curve for CIMT was 0.778 (95% confidence interval 0.682-0.894). The best cut-off point for the value of CIMT was 0.88mm (Fig. 3).

CAD was detected at any level (grade 1-4) in 23% of the patients with 0 calcium score and stenotic disease

was detected in 0,8% of the patients with 0 calcium score. The average value of CIMT in patients with grade 0 CAD was 0.71mm, the average value of CIMT in patients with CAD at any level (grade 1-4) was 0.72mm. No statistically significant difference was detected between the two groups.

Discussion

Studies show that, 40-60% of the patients are being classified wrong with using the traditional risk determining methods (7). For this reason, alternative risk determining methods are investigated and CIMT measurement and coronary calcium scoring methods are among emphasized. Differently from the other methods, both of them are direct indicators of subclinical atherosclerosis (8).

In our study, we compared the value of coronary artery calcium scoring and CIMT predicting the presence and severity of coronary artery disease identified via CT angiography. We found a positive correlation between the presence and severity of coronary artery disease, with both CIMT and CACS. CACS had a quite good correlation (r=0.816), however a moderate correlation (r=0.499) was found between CIMT and the severity of the disease. Terry et al. (9) had found the similar results in their study in which they investigated the value of CIMT and CACS determining the prevalent coronary artery disease using helical CT. Also Sees et al. (10) compared the CACS detected via Electron-beam CT (EBCT) and presence of carotid plaque to determine coronary heart disease. They have found that CACS is more valuable in predicting coronary artery disease.

In many publications, CIMT is stated as a reference method that can be used to determine the extent of atherosclerosis, and is now also being used in a wide range of radiological and clinical trials [11-13]. Salonen et al. (14) were detected 11% increase in the risk of acute myocardial infarction for each 0.1mm increase in CIMT. In our study, CIMT had been found valuable in the sense of predicting the presence and severity of coronary artery disease. The best cut-off point for stenotic disease was 0.88mm. Coskun et al. (15) studied 100 patients with stable angina pectoris and they found that the mean value of CIMT was significantly higher in patients with stenotic CAD and the best cut-off point for stenotic disease was 1mm. We found CIMT valuable in predicting prevalent disease, although the correlation between CIMT and severity of the disease was moderate. Adams et al. (16), found a weak correlation ($r<0.30$) between CIMT and CAD in their cross-sectional study similar to our results.

Large patient populations are available about the prognostic value of CIMT and calcium score and they have found calcium score more valuable than CIMT predicting coronary events, similar to our results. As an example, Newman et al. (17) evaluated 559 adults, between the ages of 70-99. They studied CACS detected via EBCT and IMT measured from internal carotid artery (ICA) and external carotid artery (ECA). They followed-up these patients for 5 years. A total of 127 cardiovascular events had been occurred in this population and cardiovascular event incidence was significantly higher in the group that calcium scores and CIMT measures were high. However, ICA-IMT and cardiovascular events were not associated. CIMT was found to be valuable in predicting stroke, but calcium score was found more valuable in predicting myocardial infarction. Multiethnic Study of Atherosclerosis group (MESA) made a study with the total number of 6698 asymptomatic individuals between the ages of 45-84 (18). They compared CACS and CIMT in terms of predicting cardiovascular disease and CACS was found more closely associated with CAD. They suggested that, CACS is more valuable than CIMT in the moderate risk group, according to the FRS.

Zero score cannot exclude CAD completely. CAD, at any stage, was identified in 23% of patients with zero calcium score in our study. CIMT may have an important role in patients with zero calcium score. However, in our study, when we evaluated the patients with zero calcium score, we found the average CIMT 0.72mm in the group of CAD, and the average CIMT was 0.71mm in the group of non-CAD. There was no significant difference between groups. Lester et al. (1) examined 89 patients with zero calcium score, between the ages of 36-59. In their study, CIMT could demonstrate coronary atherosclerosis in 47% of the patients with zero calcium score. They suggest that, though CACS and CIMT are both indicators of subclinical atherosclerosis, calcification is of a later stage. Because of this reason, especially in the young age group zero calcium score is not reliable and CIMT is more decisive in this group. The difference among the results can be attributed to the fact that the patient population in our study is elder than Lester et al.'s population. Moreover, number of patients existing CAD with zero calcium score in our study is limited.

There are some limitations of our study. It is a small cross-sectional study. Patients' demographic characteristics are based on only the history taken from the patients.

In conclusion, CACS and CIMT measurements are valuable in determining extension and severity of CAD, however CACS has a better correlation. In addition, coronary artery disease can be existing in patients with zero calcium score, and, to our results, CIMT is not valuable in predicting CAD in patients with zero calcium score.

Table 1: Evaluation of demographic and clinical c haracteristics of patients with CAD and without CAD

	CAD grade 0	CAD grade 1-2-3-4	p
Age (mean)	48,4	59,8	<0,001
Ca score			
Mean(min-max)	0(0-0)	139(0-1064)	<0,001
CIMT			
Mean(min-max)	1,71(0,38-1,2)	0,87(0,51-1,51)	<0,001

CAD Coronary artery disease
CIMT Carotid intima-media thickness

Table 2: Comparison of demographic and clinical characteristics of patients with stenotic CAD

	CAD grade 0-1-2	CAD grade 3-4	p
Age (mean)	53,2	62,2	<0,001
Calcium score			
Mean(min-max)	41,6(0-940)	312(0-1064)	<0,001
CIMT			
Mean(min-max)	0,77(0,38-1,41)	0,99(0,59-1,51)	<0,001

CAD Coronary artery disease

CIMT Carotid intima-media thickness

Table 3: Comparison of the groups of CAD grade 0-1-2 and CAD grade 3-4 with multivariate logistic regression analysis

	Wald	p
Age	0,486	0,486
Gender (Male)	4,241	0,039
CIMT	4,527	0,033
Calcium score	7,716	0,005

CIMT Carotid artery intima-media thickness

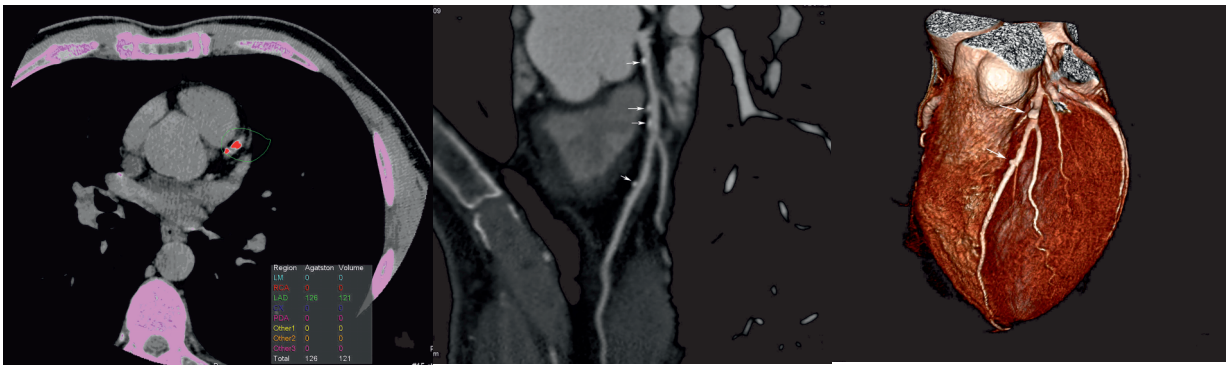

Fig. 1. a -c. 45 year -old male patient's calcium score measurement (a) and coronary CT angiography examination CPR (b) and 3D VR (c) images. Calcium score measurement shows the total calcium score of 126. There is multipl calci fic plaque formations in LAD (white arrows). Patient's CIMT was 0.7mm.

CPR Curved planar reformation

VR Volume rendering

LAD Left anterior desending

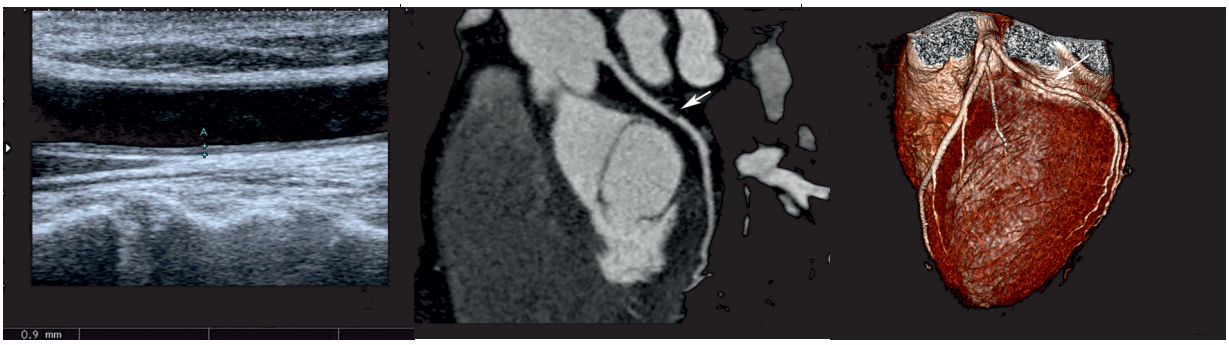

Fig. 2. a-c. 52 year-old male patient's CIMT measurement (a) and coronary CT angiography examination CPR (b) and 3D VR (c) images. Patient's CIMT is 0.9mm. There is a non-calcified plaque in circumflex artery (white arrows). Calcium score of this patient was 82.

CPR Curved planar reformation

VR Volume rendering

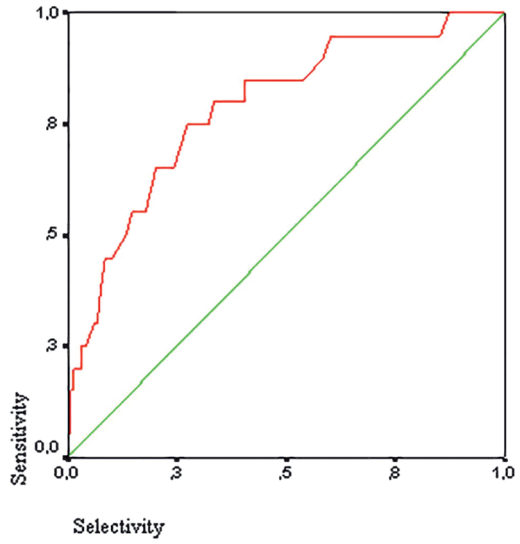

Fig. 3. Roc curve of CIMT predicting stenosis

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