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Frequency and extent of coronary atherosclerotic plaques in patients with a coronary artery calcium score of zero: assessment with CT angiography

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PURPOSE
We aimed to evaluate the frequency and extent of coronary atherosclerotic plaques in patients with a coronary artery calcium (CAC) score of zero and establish the demographic characteristics and the cardiovascular risk factors that affect the formation of atheromatous plaques.

MATERIALS AND METHODS
Coronary computed tomography (CT) angiography was performed in 288 cases with a CAC score of zero. The plaques that were detected using coronary CT angiography were categorized into two groups: nonsignificant (<50%) and significant (≥50%). Based on the coronary CT angiography results, the patients who had plaque and those who did not have plaque were compared in terms of the demographic characteristics and the presence of cardiovascular risk factors.

RESULTS
Noncalcified plaques were detected in 50 cases (17.4%) on CT angiography, of which six cases (2.1%) had significant stenosis. The plaques were localized most frequently (38.2%) in the proximal left anterior descending artery. When all the plaques considered 50% of the plaques were localized in the proximal segments, 42.7% were in the mid-segments, and 7.3% were in the distal segments. Hypertension was a significant risk factor for coronary artery disease in both genders, and smoking was a significant risk factor in females. Additionally, diabetes mellitus was a borderline significant risk factor in both genders.

CONCLUSION
In patients with a CAC score of zero, the frequency of noncalcified plaques is too high to be ignored. The distribution of these plaques in the coronary artery is similar to calcified plaque localizations. Patients who have a CAC score of zero and cardiovascular risk factors need to be evaluated with additional tests for the detection of noncalcified plaques.

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Because most cardiovascular events occur in patients with low or moderate risk, the need to establish new methods that can evaluate coronary atherosclerosis during the subclinical stage has arisen in recent years. These new methods have improved upon conventional cardiovascular risk factor scoring models, such as the Framingham risk score (1). Studies have indicated that the coronary artery calcium (CAC) load, which is an indicator of subclinical atherosclerosis, is directly proportional to the amount of coronary plaque. In addition, the CAC load provides information on the risk and prognosis of coronary artery disease (CAD) and the serological and demographical risk factors for patients with moderate risk. Studies have demonstrated that there is a strong relationship between wall calcification in the coronary arteries, CAD, and coronary artery calcification, which occurs in atherosclerosis and is only observed in atherosclerotic arteries but not in normal arteries (2, 3). CAC scoring was first evaluated by electron beam computed tomography (CT). In early studies that were conducted in this field, electron beam CT was used in a limited number of centers and was costly; therefore, the CAC score was not accepted for widespread use (4). However, the implementation of multidetector CT at the end of the 1990s resulted in the widespread use of CAC scoring (5).

Because noncalcified plaques can be found in cases of CAD in addition to calcified plaques, the CAC score examination has numerous limitations in detecting coronary atherosclerosis. Recent studies found varying degrees of noncalcified plaques using coronary CT angiography in patients with a CAC score of zero (6–8). Acute coronary syndromes frequently result from the rupture of these noncalcified small plaques, which are generally not flow-limiting and do not cause stenosis (9). Calcification is a marker of plaque stability, whereas an unstable plaque is characterized by a large lipid core, a thin fibrous cap, and inflammation. An unstable plaque has been termed the "vulnerable plaque". The early detection of these plaques is important because they have a tendency to rupture but respond to medical treatment (10).

In studies that used catheter angiography to detect the presence of CAD in patients with a CAC score of zero, the negative predictive value of a CAC score of zero in excluding significant coronary artery stenosis was approximately 100% (11). However, there are limitations to catheter angiography because this method provides information only on the lumen and cannot demonstrate the changes that occur on the arterial wall during the early stages due to positive arterial remodeling. Therefore, the presence of atherosclerotic plaques may not be accurately detected using this test method. To date, the use of coronary CT angiography in the imaging of the coronary arteries continues to increase. Coronary CT angiography is a noninvasive imaging method that can be used to evaluate the arterial wall and the arterial lumen in contrast to catheter angiography. Calcified and noncalcified plaques can be detected by coronary CT angiography with a high accuracy. Studies have indicated that the negative predictive value of coronary CT angiography in detecting coronary atherosclerosis is high (5, 12). This value was reported to be 90% for the detection of atherosclerotic plaque and over 95% for the detection of significant stenosis. As a result, coronary CT angiography has become a noninvasive diagnostic option for detecting critical coronary artery stenosis in patients with low or moderate risk.

The aim of this study was to evaluate the frequency and extent of coronary atherosclerotic plaques in patients with a CAC score of zero using 64-slice coronary CT angiography and establish the demographic characteristics and the cardiovascular risk factors that affect the formation of atheroma plaques in these patients.

Materials and methods

Patient population

A total of 1045 cases of CAD that were known or based on suspicion underwent a coronary CT angiography examination from December 2008 to March 2011 at our institution. Overall, 242 patients who did not undergo a CAC score examination before coronary CT angiography and who had a coronary stent or by-pass grafts were excluded from the study. In the CAC score examination that was conducted immediately before coronary CT angiography, a total of 288 cases (130 females, 158 males; mean age, 47.6±12.3 years [range, 18–78 years]) with no detection of calcified plaques in the coronary arteries (CAC score=zero) were included in the study. Cases were excluded from the study when the CAC score was above zero, the coronary CT angiography examination was suboptimal, and the coronary arteries could not be sufficiently evaluated.

Of the 288 cases that were included in the study, the reasons for a referral to our clinic for a coronary CT angiography examination were chest pain (n=98), atypical complaints (n=64), and asymptomatic but present risk factors for CAD (n=126). The demographic information and the risk factors that were present for CAD (diabetes, hypertension, family history, smoking, and hyperlipidemia) were obtained from the forms that were filled in by the patients before the test and from the medical records in the hospital information system. The demographic and clinical characteristics of the patient population that was included in the study are provided in Table 1. Informed consent was obtained from all of the patients, and the study was approved by the local ethics committee of our hospital.

Multidetector CT data acquisition

A 64-detector CT scanner (Aquilion, Toshiba Medical Systems, Tokyo, Japan) and the same protocol were used for the examination of the patients. First, anteroposterior and lateral scanogram images were obtained to determine the position of the heart and the borders of the examination area. In the CAC score examination, an area from the carina level to the heart base was scanned with prospective ECG triggering at a slice thickness of 3 mm (tube voltage, 120 kV; tube current, 300 mA). In the coronary CT angiography examination, an 80–100 mL iodinated contrast agent (Iomeron, Iomeprol 400 mgI/mL, Bracco, Italy or Iopromid, Ultravist 370 mgI/mL, Schering AG, Berlin, Germany) was administered through an 18–20 G cannula, which was placed inside the right antecubital vein. Then, 40 mL saline was administered at the same rate. The optimal scan time was determined using the automatic bolus tracking method (Sure Start, Toshiba Medical Systems). The region of interest was placed over the descending aorta, and an adjustment was made to ensure that the scanning would automatically start when the maximum contrast reached 180 Hounsfield unit (HU). The coronary CT angiography examination parameters were as follows: collimation, 64×0.5 mm; tube voltage, 120 kV; tube current, 400–500 mA; tube rotation time, 400 ms; slice thickness, 0.5 mm; and increment, 0.3 mm. A retrospective ECG-gated technique was used for the reconstruction of the images. The raw data that were obtained from the coronary CT angiography examination were reconstructed at the 75% phase (mid-diastolic phase) of the R-R interval using a slice thickness of 0.5 mm and an increment of 0.3 mm. For the cases in which this phase was not optimal for the image analysis, additional reconstructions were obtained at the 35%–85% phase of the R-R interval.

Multidetector CT image analysis

The Agatston method was used in the quantification of the CAC score. The left main coronary artery (LMCA), the left anterior descending (LAD) artery, the left circumflex (LCX) artery, and the right coronary artery (RCA) were examined for the presence of calcified plaque in the noncontrast axial slices throughout their entire trace. The foci of the CAC were detected by one of two experienced radiologists and scored using semi-automatic commercial software to detect at least three contiguous pixels (voxel size, 1.03 mm^3) with a peak density ≥130 HU within a coronary artery.

Table 1. Demographic and clinical characteristics of study patients (n=288)

Characteristics	Result
Male/female, n (%)	158/130 (55/45)
Mean age (years), mean±SD (range)	47.6±12.3 (18–78)
Diabetes mellitus, n (%)	60 (20.8)
Hypertension, n (%)	121 (42.0)
Family history, n (%)	101 (35.1)
Smoking, n (%)	92 (31.9)
High LDL, n (%)	104 (36.1)
High total cholesterol, n (%)	133 (46.2)
Low HDL, n (%)	148 (51.4)
High triglyceride, n (%)	78 (27.1)
Body mass index (kg/m^2), mean±SD	28.7±3.6

HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; SD, standard deviation.

Two- and three-dimensional images were rendered using multiplanar reformatting, curved planar reformatting, maximum intensity projection, and volume rendering methods by transferring the obtained axial CT angiography images to a separate workstation (Vitrea 2, Vital Images, Plymouth, Minnesota, USA). A modified American Heart Association classification that divided the coronary arterial system into 16 segments was used in the evaluation of the coronary arteries. In the coronary CT angiography images, each coronary artery segment was evaluated for the presence of a wall irregularity and/or the presence of an atherosclerotic plaque. The composition (calcified, noncalcified/soft, or mixed) of the plaques was established. Only the cases that had soft plaques (Agatston score=zero) were included in the study. The degree of stenosis that was caused by the plaques was found by comparing the lumen diameter of the narrowest segment with that of a more proximal or distal normal segment. Stenoses were classified as nonsignificant in cases with a mean lumen diameter reduction of <50% or significant in cases with a mean lumen diameter reduction of ≥50% in two orthogonal projections. The patient groups with or without plaque as observed in coronary CT angiography were classified according to the demographic characteristics and the cardiovascular risk factors and were statistically compared.

Statistical analysis

Statistical analyses were performed using a commercially available software (Statistical Package for Social Sciences, version 15.0, SPSS Inc., Chicago, Illinois, USA). The continuous variables were expressed as the mean±standard deviation (SD). The differences in the mean values between the two groups were compared using the unpaired t test. Comparisons of the categorical variables between the two groups were performed using the chi-square test. Multiple logistic regression analyses were used to assess the associations with the presence of coronary plaque. These analyses were performed for the entire study population and the gender-specific population. The 95% confidence interval was calculated for each odds ratio. Values of $P < 0.05$ were considered significant.

Results

In 238 of 288 cases (82.6%) CT angiography was normal and 50 cases (17.4%) had noncalcified plaques. Of the cases with noncalcified plaques, 44 (15.3%) had nonsignificant (<50%) stenosis (Figs. 1, 2) and six (2.1%) had significant (≥50%) stenosis (Figs. 3, 4). A total of 68 noncalcified plaques were detected in 50 cases. In total, 44 cases with nonsignificant stenosis had 59 plaques, and six cases with significant stenosis had nine plaques. One (1.5%) of the plaques was localized in the LMCA, 47 (69.1%) plaques were in the LAD artery, seven (10.3%) plaques were in the LCX artery, and 13 (19.1%) plaques were in the RCA. When the segment basis was evaluated, the plaques were most frequently localized in the proximal segment of the LAD artery (38.2%), followed by the mid-segment of the LAD artery (26.4%). Following the LAD artery, the most frequent plaque localization was the mid-segment of the RCA (16.2%). When all the plaques considered 50% of the plaques were localized in the proximal segments, 42.7% were in the mid-segments, and 7.3% were in the distal segments.

When an evaluation was performed based on whether the patients were symptomatic, 56.2% of the cases were observed to be symptomatic (chest pain or atypical complaints) and 43.7% were observed to be asymptomatic with risk factors for CAD. Complaints of chest pain were observed more frequently in cases with atherosclerotic plaque as detected by coronary CT angiography; however, the differences between the two groups were not statistically significant ($P = 0.76$).

Figure 1. a, b. A 54-year-old asymptomatic woman with three risk factors, which are diabetes mellitus, family history, and smoking. Curved planar reformatted **(a)** and volume-rendered **(b)** CT angiography images show a noncalcified soft plaque (*white arrows*), which is causing a nonsignificant (<50%) stenosis in the proximal segment of the RCA (Ao, aorta; LADA, left anterior descending artery; RCA; right coronary artery).

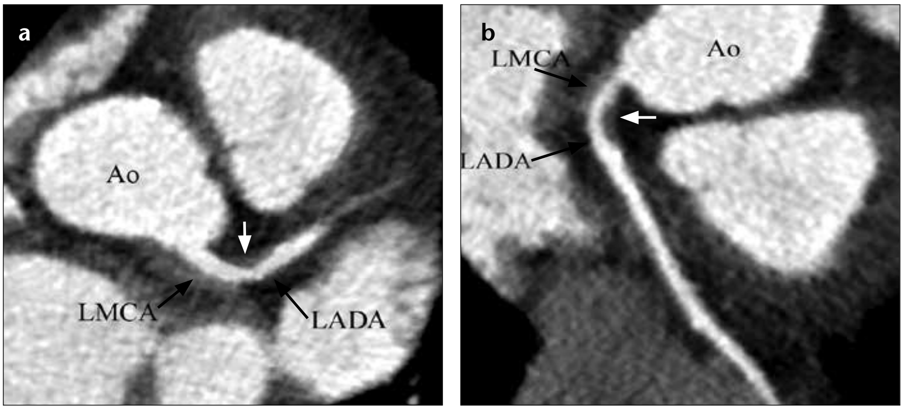

Figure 2. a, b. A 67-year-old woman presented with angina pectoris and two risk factors, which are diabetes mellitus and hypertension. Axial **(a)** and curved planar reformatted **(b)** CT angiography images reveal a noncalcified soft plaque (*white arrows*), causing a nonsignificant (<50%) stenosis in the LMCA and the proximal segment of the LAD artery (Ao, aorta; LADA, left anterior descending artery; LMCA, left main coronary artery).

Table 2. Baseline characteristics and prevalance of cardiovascular risk factors of study patients with (+) or without (-) plaques in coronary CT angiography

	Entire cohort (n=288)			Males (n=158)			Females (n=130)		
	Plaques (-)	Plaques (+)	*P*	Plaques (-)	Plaques (+)	*P*	Plaques (-)	Plaques (+)	*P*
N (%)	238 (82.6)	50 (17.4)	-	126 (79.7)	32 (20.3)	-	112 (86.2)	18 (13.8)	-
Male	126 (53)	32 (64)	0.153	-	-	-	-	-	-
Age (years)	46.6 ±12.6	52.5±9.8	0.05	42.9±11.9	49.7±9.6	0.03	50.75±12.17	55.9±9.2	0.089
Diabetes mellitus	44 (18.5)	16 (32.0)	0.032	18 (14.3)	9 (28.1)	0.063	26 (23.2)	7 (38.9)	0.156
Hypertension	89 (37.9)	32 (64.0)	0.001	45 (35.7)	19 (59.4)	0.015	44 (39.3)	13 (72.2)	0.009
Family history	80 (33.6)	21 (42.0)	0.259	39 (31)	13 (40.6)	0.298	41 (36.4)	8 (44.4)	0.524
Smoking	70 (29.4)	22 (44.0)	0.044	44 (34.9)	12 (37.5)	0.785	26 (23.2)	10 (55.6)	0.004
High LDL	81 (34.0)	23 (46.0)	0.109	44 (65.1)	15 (/71.9)	0.467	37 (33)	8 (44.4)	0.345
High total cholesterol	104 (43.7)	29 (58.0)	0.065	53 (42.1)	20 (62.5)	0.038	51 (45.5)	9 (50)	0.724
Low HDL	119 (50.0)	29 (58.0)	0.304	82 (65.1)	23 (71.9)	0.467	37 (33)	6 (33.6)	0.980
High triglyceride	60 (25.2)	18 (36.0)	0.119	41 (32.5)	14 (43.8)	0.235	19 (17)	4 (22)	0.587
Body mass index	28.0±3.7	29.5±2.7	0.007	27.8±3.1	29.2±2.4	0.02	28.2±4.3	30.1±3.15	0.078

LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol.
Data are given as n (%) or mean±SD.

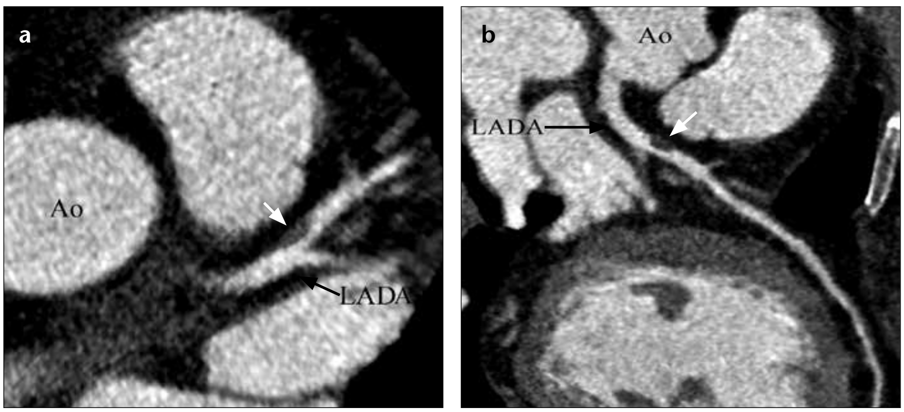

Figure 3. a, b. A 53-year-old woman presented with angina pectoris and three risk factors which are diabetes mellitus, hypertension, and hyperlipidemia. Axial **(a)** and curved planar reformatted **(b)** CT angiography images reveal a noncalcified soft plaque (*white arrows*), a significant (≥50%) stenosis in the mid-segment of the LAD artery (Ao, aorta ; LADA, left anterior descending artery).

Of the 238 patients without plaques according to coronary CT angiography, 126 (53%) were male and 112 (47%) were female. Of the 50 patients with plaques, 32 (64%) were male and 18 (36%) were female. Although the frequency of plaques was higher in males, this increase was not statistically significant (P = 0.153). The mean age of the cases with plaques (52.5 years) was higher than the mean age of the cases without plaques (46.6 years) (P = 0.05). The prevalence of the presence of diabetes, hypertension, and smoking was significantly higher in the patients with plaques compared with the patients without plaques. The demographic characteristics and the prevalence of cardiovascular risk factors are provided in Table 2.

A univariate logistic regression analysis was performed after the patient population with a CAC score of zero was divided into male and female groups. The analysis demonstrated the following significant risk factors for CAD: an increase in age every 10 years after the age of 40 for males (P = 0.051 for the ages of 41–50 [borderline significant], P = 0.005 for the ages of 51–60), hypertension (P = 0.017), and high total cholesterol (P = 0.041). For females, the risk factors were hypertension (P = 0.013) and smoking (P = 0.007). In the multivariate logistic regression analysis, the presence of hypertension (P = 0.005) in males and the presence of hypertension (P = 0.010) and smoking in females were significant risk factors for CAD, whereas the presence of diabetes was a borderline significant risk factor for both genders (P = 0.55 for both genders). The multivariate logistic regression analysis results are provided in Table 3.

A statistical analysis was conducted, which included diabetes, hypertension, smoking, and high level of low density lipoprotein (LDL) cholesterol as risk factors without considering the differences of age and gender. This analysis evaluated the relationship between an increase in the number of risk factors and the presence of CAD. The risk for CAD in cases with one risk factor increased 2.51-fold compared to cases without any risk factors; however, this increase was not statistically significant (P = 0.12). When two risk factors were present, the risk for CAD increased 4.18-fold. When three or four risk factors were present, the risk for CAD increased 9.95-fold. These increases in risk were statistically significant (P = 0.01 and P < 0.001, respectively). The correlation between an increase in the number of cardiovascular risk factors and the risk for CAD is provided in Table 4.

Discussion

The most important result of this study was the presence of coronary

Table 3. Predictors of the presence of noncalcified plaques on multivariate logistic regression analyses

Gender	Clinical parameters	Odds ratio (95% confidence interval)	*P*
Female	Diabetes mellitus	2.962 (0.978–8.970)	0.055
	Hypertension	4.598 (1.449–14.596)	0.010
	Smoking	4.205 (1.432–12.350)	0.009
Male	Diabetes mellitus	3.403 (1.241–9.333)	0.055
	Hypertension	3.345 (1.434–7.806)	0.005
	Family history	2.328 (0.961–5.644)	0.061

Figure 4. A 58-year-old man presented with angina pectoris and three risk factors, namely hypertension, smoking, and hyperlipidemia. A curved planar reformatted CT angiography image reveals a noncalcified soft plaque (*white arrows*), which is causing a significant (≥50%) stenosis in the proximal segment of the LCX artery (Ao, aorta; LCXA; left circumflex artery; OM1, first obtuse marginal artery).

atherosclerosis at a high frequency of 17.4% in patients with a CAC score of zero. In our study, we observed that noncalcified plaques caused nonsignificant stenoses (<50%) in 15.3% of the patients with a CAC score of zero and significant stenoses (≥50%) in 2.1% of these patients. The presence of noncalcified plaques in cases with a CAC score of zero has been reported at varying frequencies in the literature (1, 7, 8, 13, 14). These rates were reported to be 6.5% by Cheng et al. (7), 10% by Choi et al. (1), 12% by Sosnowski et al. (8), and 20% by Ergün et al. (13); however, Kelly et al. (14) reported a rate as high as 51%. These different rates may have resulted from the differences in the characteristics of the patient populations that were included in the studies.

In our study, we observed that plaques were most frequently localized in the proximal segment of the LAD artery (38.2%), followed by the mid-segment of the LAD artery (26.2%). The most frequent localization of plaques, following the LAD artery, was the mid-segment of the RCA (16.2%). Only one case (1.5%) had a plaque in the LMCA. When all of the plaques were considered, the plaques were most commonly (48.5%) found in the proximal segments and were least commonly (7.3%) found in the distal segments of the coronary arteries. This finding is consistent with other observations regarding the tendency of plaques to occur more proximally and indicates that this tendency was similar among the plaques that were detected in patients with a CAC score of zero (14).

In studies that have compared the results of the CAC score examination with catheter angiography findings, the negative predictive value of a CAC score of zero was high in the exclusion of significant coronary artery stenosis. Haberl et al. (3) reported that the incidence of significant coronary artery stenosis in cases with a CAC score of zero was below 1%, and Rumberger et al. (4) found a rate of 1.5%. In studies that were performed using coronary CT angiography in cases with a CAC score of zero, significant rates of coronary artery stenosis were reported to range from 0.5% to 7%, and these rates were higher compared to those in studies that were performed using catheter angiography. We established that the rate of significant stenosis in the coronary arteries was 2.1% in our study population, which had a CAC score of zero and was comprised of symptomatic (56.2%) and asymptomatic (43.7%) cases. This rate falls within the range of rates that were reported in the literature. The reported rates were 4% by Kelly et al. (14), 5% by Rivera et al. (10), and 4.9% by Ergün et al. (13). Akram et al. (15) reported

Table 4. Odds ratio of the presence of noncalcified coronary plaque to the number of cardiovascular risk factors

Risk factors (n)	Patients (n)	Patients with plaques (n [%])	Odds ratio (95% confidence interval)	*P*
0	58	4 (6.9)	1.00 (reference)	-
1	123	15 (12.2)	2.510 (0.796–7.936)	0.12
2	74	16 (21.6)	4.180 (1.330–13.141)	0.01
≥3	33	15 (45.5)	9.950 (2.988–33.110)	< 0.001

Diabetes, hypertension, smoking, and high LDL cholesterol were accepted risk factors, without considering the differences of age and gender.

a higher rate in symptomatic cases, which was 8.2%. These varying results that were reported in the literature may be due to the differences in the characteristics of the patient populations that were included in the studies or from the differences in the sensitivities of the multislice CT scanners that were used in the examinations to detect the plaques.

Atheromatous plaques are polyphasic; therefore, these plaques are typically not in the same phase. Newly formed noncalcified plaques, which are unstable, can exist in coronary segments; however, other segments may have chronic, densely calcified plaques, which are stable. In addition, new unstable components may be observed in chronic calcified plaques. Therefore, the correlation between the presence of calcification in atheromatous plaques and the severity and risk of lumen stenosis, which is caused by the plaque, is weak. There may be cases without significant lumen stenosis despite widespread CAC, and there may be cases with widespread, risky, unstable atheromatous plaques with no CAC or with a low CAC score. In post mortem studies that were aimed at establishing the prevalence of sub-clinical atherosclerosis in the general population, the incidence of noncalcified plaques in young adults was high. In a post mortem study by Strong et al. (16), plaque was detected in the RCA in 47.4% of adults 30–34 years of age, and only 2.9% of these plaques were calcified. Positive arterial remodeling is the reshaping of an artery in the early stages of coronary atherosclerosis to preserve the arterial opening and lumen diameter. This condition is caused by unstable noncalcified plaques. Positive arterial remodeling changes the flow dynamics, heightens the surface tension on the plaque surface, and increases the tendency of the plaque to rupture. Catheter angiography can inaccurately present severe lesions as mild lesions due to the preservation of the lumen diameter by positive arterial remodeling. To date, the imaging methods that are used to detect positive arterial remodeling include intravascular ultrasonography and coronary CT angiography.

The clinical importance of noncalcified plaque detection in patients with a CAC score of zero is not sufficiently clear. Motoyama et al. (9) demonstrated that the CT characteristics of plaques that were associated with acute coronary syndrome included positive arterial remodeling, low plaque density, and the presence of spotty calcification. Taylor et al. (17) reported that the incidence of acute coronary syndrome development in cases with a CAC score of zero was 0.16%. In 2009, Budoff et al. (11) reported that the prevalence of acute coronary syndrome was 0.4% in a patient population that was comprised of 25 253 cases with a CAC score of zero over a 12-year follow-up period. During a three-year follow-up of cases with a CAC score of zero, Uretsky et al. (18) reported a mortality rate of 0.4%, and the deaths occurred among cases without plaques detected in coronary CT angiography. In 2010, Russo et al. (5) found that the occurrence of cardiovascular events in cases with noncalcified or mixed type plaques was higher compared with cases that had a CAC score above 400. Therefore, comprehensive prognostic studies need to be performed in the future to determine whether coronary atherosclerosis can be excluded in cases with a CAC score of zero, whether the presence of noncalcified plaque would increase the rate of cardiac events in these cases, and whether plaque detection has clinical benefits.

It is important to determine which patients with a CAC score of zero are at risk for CAD and which coronary CT angiography results will provide beneficial information regarding this risk. Varying results were obtained in studies that examined whether patients were symptomatic or asymptomatic. In a study by Akram et al. (15), the rate of obstructive plaques in symptomatic patients with a CAC score of zero was 8.2%, whereas obstructive plaques were not detected in asymptomatic patients. However, Kelly et al. (14) and Ergün et al. (13) did not find a correlation between symptoms and obstructive and nonobstructive lesions. In our study, we did not find a correlation between the presence of noncalcified atherosclerotic plaques that were detected using coronary CT angiography in a symptomatic patient population with a CAC score of zero.

Varying results have been reported in studies that determined whether the detection of conventional cardiovascular risk factors for patients with a CAC score of zero is beneficial in estimating the presence of atherosclerotic plaque using coronary CT angiography. Nikolaou et al. (12) found that diabetes, hypertension, smoking, and obesity were significant risk factors, and diabetes and smoking were reported to be significant risks in studies by Budoff et al. (11) and Blaha et al. (19). Uretsky et al. (18) reported that the male gender, age, and smoking were risk factors, whereas Ueda et al. (20) reported that diabetes and hypercholesterolemia were risk factors. Ergün et al. (13) reported that age and diabetes were risk factors for both genders, whereas dyslipidemia was a risk factor for male patients, and family history was a risk factor for female patients. Rivera et al. (10) found that significant risk factors were the male gender and age for calcified and mixed type plaques; the male gender, diabetes, and smoking were risk factors for noncalcified plaques; and high LDL cholesterol was a risk factor for mixed type plaques. We established that the risk factors were hypertension for both genders and smoking for female patients. In addition, diabetes was a borderline significant risk factor for both genders in estimating the presence of noncalcified atherosclerotic plaque using coronary CT angiography in patients with a CAC score of zero based on the multivariate logistic regression analysis. When we evaluated the correlation between the increase in the number of cardiovascular risk factors and the risk for CAD, we found that the risk for CAD increased 2.51-fold in a case with one risk factor compared with a case with no risk factors. The risk for CAD increased 4.18–fold when the number of risk factors was two, and the risk increased 9.95-fold when the number of risk factors was three or four.

In our study, we observed that the mean age of the cases (52.5 years) with noncalcified atherosclerotic plaque, as detected by coronary CT angiography, and a CAC score of zero was higher than the mean age of the cases without plaques (46.6 years). Similarly, Kelly et al. (14) and Ergün et al. (13) found that the mean age of the cases with atherosclerotic plaque, as detected by coronary CT angiography (53 and 54.4 years, respectively), was higher than the mean age of the cases (49 and 50.4 years, respectively). The mean age of the cases with atherosclerotic plaques that caused significant stenosis, as detected by coronary CT angiography, was 54 years according to Kelly et al. (14) and 55.2 years according to Ergün et al. (13); however, we found that the mean age of these cases was 53.8 years in our study. Similar to the findings in these two studies, the results of our study demonstrated that the rate of plaque detection by coronary CT angiography in the patient population with a CAC score of zero was higher in patients over 50 years of age; however, it is difficult to determine a threshold value for the age limit because studies have reported that the risk for CAD is higher in patients 45–50 years of age (16).

Coronary CT angiography provides more diagnostic information than CAC scoring and has more independent and stronger prognostic value than conventional cardiovascular risk factors and CAC scoring. Coronary CT angiography can detect the disease at the sub clinical stage in patients with a CAC score of zero and establish the presence of severe stenosis in patients with a positive CAC score. Therefore, coronary CT angiography is more precise than the CAC score in the evaluation of CAD. The results of our study demonstrated that coronary CT angiography was more beneficial in the detection of CAD compared with the CAC score examination. In addition, coronary CT angiography should be used instead of the CAC score examination for cases with cardiovascular risk factors. However, coronary CT angiography has several disadvantages, such as a high radiation dose and the need to use an iodine contrast agent. The estimated radiation dose that patients are exposed to in coronary CT angiography ranges from 8 to 18 mSv, and this range is higher than the radiation dose in the CAC score examination (1–2 mSv). However, because of innovations in CT technology, the radiation dose in coronary CT angiography has been reduced to the same dose that is administered in the CAC score examination.

This study had some limitations. We compared the coronary CT angiography results of six cases that had atherosclerotic plaque, which caused significant stenosis (≥50%), with the catheter angiography results. For these cases, the results of both examinations were consistent with each other, and four cases were treated with a balloon angioplasty and a stent. For the cases in which plaque caused stenosis below the significant limit, treatment was initiated without the need for catheter angiography. We could not compare the coronary CT angiography results with the catheter angiography results for these patients, and we could not conduct a long-term follow-up of the cases.

In conclusion, the frequency of noncalcified atherosclerotic plaques that are detected by coronary CT angiography examination in patients with a CAC score of zero is too high to be ignored. The distribution of these noncalcified plaques in coronary arteries is similar to the distribution of calcified plaque localizations. The early detection of noncalcified plaques is important because these plaques are unstable and have a tendency to rupture but respond to medical treatment. Patients with a CAC score of zero and cardiovascular risk factors need to be evaluated by additional tests for the detection of noncalcified plaques. Coronary CT angiography can detect coronary atherosclerosis noninvasively and with a high accuracy; therefore, this method should be the preferred imaging method.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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