The Significance of Absence of Coronary Calcification by Multidetector Row Computed Tomography (MDCT) in Patients Suspected of Coronary Artery Atherosclerosis

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Abstract

Background: Coronary artery disease continues to be one of the leading causes of morbidity and mortality, a reliable and reproducible non-invasive diagnostic test for the detection and grading of coronary artery stenosis is multidetector row computed tomography (MDCT) coronary angiography. The presence of coronary artery calcium (CAC) is almost 100% sensitive for the presence of atherosclerotic coronary plaque and increasing calcium scores are associated with an increasing likelihood of both obstructive disease and severity of coronary artery disease (CAD). Objective: To see the significance of absence of calcification in the coronary arteries and it’s correlation with the degree and the frequency of coronary atherosclerosis. Patients and methods: This prospective study was carried out at CT-angiography department in Slemani cardiac specialty hospital, Kurdistan region/Iraq from Nov. 13th 2013 to Aug. 8th 2014 in total 118 sequential patients (Their age range was between 40-78 years, with an average age of 53 years. 79 cases were female and 39 cases were male) were underwent computed tomography coronary angiography scanning (CTCA). Results: According to the Statistical Package for the Social Sciences 21 (SPSS) Regarding the calcification and its relation to the atheroma: (among the 118 cases with zero calcification, only 4 cases showed presence of atheroma (3.39%) and among them only in one case the atheroma was significant, which means less than one percent (0.85%) of the cases showed significant stenosis that needed intervention). Conclusion: Absence of CAC is highly sensitive for exclusion of coronary artery atherosclerosis, but it does not totally exclude it and most of the degree of the stenosis (if present) is non-significant.

Keywords

Coronary Artery Disease, Coronary CT Angiography, Coronary Calcium Index

1. Introduction

Coronary artery disease (CAD) is the leading cause of death worldwide. With the need for a non-invasive test to detect the disease, more attention was directed to coronary artery CT angiography [1, 2], which is a reliable, reproducible, non-invasive diagnostic test for the detection and grading of coronary artery stenosis [3-5], approaching the accuracy of traditional invasive diagnostic techniques [6-18], by atherosclerotic plaque characterization[19 - 23], having the advantage of demonstrating the vessel-wall atherosclerotic plaque& assessment of luminal patency. The assessment of plaque size and composition may have significant clinical implications [24]. A system devised by Stary et al classifies atherosclerotic lesions according to their histologic composition and structure [25]. Because the spatial resolution

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is inadequate for precise grading, coronary stenosis are often graded with semiquantitative descriptors such as normal, mild (≤ 50%), moderate (50–70% stenosis), severe (>70% stenosis), and totally occluded [26]. The presence of calcification in the epicardial coronary arteries indicates that the patient has coronary atherosclerosis [27, 28]. CT reliably detects arterial calcification and allows quantification [29, 30]. Coronary calcium load has been found to progress over time [31, 32]. Calcium has a high attenuation coefficient; a threshold of 90 or 130 HU (Hounsfield unit) [33]. Calcium load is determined semi-automatically with post-processing algorithms. The Agatston calcium score [34] is the most widely employed semi quantitative method in EBCT & a modified Agatston score equivalent versions used in MDCT [35] which is the sum of all calcium clusters scores. The ACC/AHA (American college of cardiology / American heart association) have summarized the role of CT calcium scoring [36]. Essentially, a negative CT indicates that the presence of atherosclerotic plaque, including unstable plaque, is very unlikely. A positive CT confirms the presence of a coronary atherosclerotic plaque. The greater the amount of calcium, the greater the likelihood of occlusive coronary artery disease; however, there is not a one-to-one relationship and the overall true plaque burden is underestimated [37, 38]. Increasing calcium scores are associated with an increasing likelihood of both obstructive disease, and an increased severity (number of vessels involved) of coronary artery disease (CAD) [39, 40]. Among emergency department patients with chest pain, a zero calcium score was associated with a very low risk of cardiovascular events [41]. The aim of the study was to evaluate the significance of absence of calcification in the coronary arteries with regard to it's correlation with the degree and the frequency of coronary atherosclerosis.

2. Patients and Methods

This prospective study was carried out at CT-angiography department in Sulaimanmyna Heart specialty hospital, Kurdistan region/Iraq from Nov.13th 2013 to Aug.8th 2014 in total 118 sequential patients underwent CTCA scanning. All patients were referred for CTCA with history and clinical suspicion of CAD. This study was based on patients with absent calcification in their coronary artery, so we included only patients with calcium score zero during that period and we excluded all those patients with calcium scoring > zero & patients with previous angioplasty and stenting. All images were obtained by 2011 Philips Brilliance 64-slice MDCT system/Netherland. All patients were instructed to avoid caffeine and smoking for 48 hours prior the procedure to avoid cardiac stimulation& avoid eating solid food 4 hours and to increase fluid intake prior to the study. Standard precautions with regard to contrast allergy history and renal function were taken. All the involved patients were pretreated with Beta-blockers (Concor 10mg) by oral administration. The mean heart rate of our patients was between 56-62 bpm. First calcium scoring were done with non-contrast CT, calcium scoring was quantified using the scoring algorithm proposed by Agatston et al. [42], and calcium scores were divided into the following categories: 0, 1–10, 11–100, 101–400, 401–1000, and ≥1000. CTCA done using intravenous rout “omnipaque 350 contrast” administration, and a dose of 90cc/15sec, at a rate of 6ml/sec, by auto-injector, followed by 30cc/0.5sec normal saline. Spiral (helical) technique started by 0.9mm slice thickness for axial section, then utilizing multiplanar reconstruction by 0.6mm for maximum intensity projection and multiplanar reformat (MIP and MPR) to evaluate all major coronary arteries and side branches. The images were interpreted by 5 years experienced specialist radiologist and were confirmed (as a double blinded reading) by another experienced specialist radiologist. The SPSS used in the analysis was SPSS 21 and the data entry was performed through Microsoft Excel spreadsheet as well as some analysis performed via excel program.

3. Results

This study was carried out for imaging 118 serial patients underwent CT-angiography by 64-slice CT machine.

Table 1. Age group and its frequency.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 - 49 Years</td>
<td>46</td>
<td>38.98%</td>
</tr>
<tr>
<td>50 - 59 Years</td>
<td>41</td>
<td>34.75%</td>
</tr>
<tr>
<td>60 - 69 Years</td>
<td>25</td>
<td>21.19%</td>
</tr>
<tr>
<td>70 - 79 Years</td>
<td>6</td>
<td>5.08%</td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

Table 2. Age incidence and its significance.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Normal</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>40 - 49 Years</td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td>50 - 59 Years</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>60 - 69 Years</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>70 - 79 Years</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3. Mean age and its significance.

<table>
<thead>
<tr>
<th>Number</th>
<th>Mean age</th>
<th>SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>114</td>
<td>53.77</td>
<td>8.7</td>
</tr>
<tr>
<td>Stenotic</td>
<td>4</td>
<td>50.75</td>
<td>6.8</td>
</tr>
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</table>

The age range of the study participant was between (40-78 years) with mean age of (53.67 ± 8.64 years). The gender distribution was 79 female (66.9%) and 39 male (33.1%). The risk factors among the patients, 59 cases (50.00%) had hypertension, 25 cases (21.19%) had diabetes mellitus, 21
cases (17.80%) were smokers, while 22 (18.80) cases had normal lipid profile. In this study 118 patients were with calcium score zero, of these only 4 patients (3.39%) had stenosis by non-calcified atheroma in their coronary artery upon coronary artery catheterization carried out because of the high probability of having CAD in spite of their normal CTA. Among these 4 patients, 2 cases were hypertensive, 3 cases had high lipid profile, none of them had diabetes mellitus and none of them were smoker.

Regarding the calcification and its relation to the atheroma: (among the 118 cases with zero calcification, only 4 cases showed presence of atheroma (3.39%) and among them only in one case the atheroma was significant, which means less than one percent (0.85%) of the cases showed significant stenosis that needed intervention).

<table>
<thead>
<tr>
<th>Variable</th>
<th>CTCA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Abnormal</td>
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<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>57</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>Yes</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>89</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>93</td>
</tr>
<tr>
<td>High Lipid profile</td>
<td>Yes</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>95</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>77</td>
</tr>
</tbody>
</table>

### 4. Discussion

Coronary segments with a luminal obstruction of greater than 50% are likely to have some calcification that is detectable with electron-beam CT (EBCT). In one trial, a 0 calcium score had a 100% predictive value in the exclusion of angiographic evidence of obstructive epicardial coronary lesions.

As it is shown in tables (1, 2, and 3), the age range of the participants was between 40-78 years, the age had no significant difference. The higher the calcium score, the more likely the presence of angiographic obstructive disease,[43] a calcium score >371 had a 90% specificity in the detection of a luminal obstruction of > 70%. Specificity tends to decrease with advanced patient age, but it increases with the number of calcified vessels and the total calcium score.[44, 45]. These results indicate that the CAC score is a very promising measurement to improve cardiovascular risk stratification in the elderly. Abbott et al. [46] reported no death occurred in patients with a CAC score < 10, also Vliegenthart et al. [47], found that the death rate increased significantly as the CAC score increased ($P < 0.001$). Absence of CAC was highly accurate for exclusion of CAD in subjects older than 50 years (negative predictive value = 98%). The authors concluded that the presence of CAC on MDCT in symptomatic patients is accurate for prediction of obstructive CAD and that its absence is associated with a high negative predictive value for exclusion of CAD [48].

In this study, among 118 sequential patients who underwent CT-angiography by 64-slice CT machine, the sex distribution consisted of 79 female (66.9%) and 39 male (33.1%) (table 1). Among these 118 patients 4 showed stenosis in their coronary artery, with these 4 patient 2 of them were female 50% and the other 2 were male 50% with a probability value of (p-value=0.463) for gender significance (table 4). And this finding goes with Raggi et al. who found no difference in all-cause mortality after 5 years of follow-up in over 4,000 women and over 6,000 men with a very low CAC score (< 10); 1.6% vs. 1.5% [49]. Four studies have specifically compared the prognosis for men and women in the absence of CAC. And The annual CHD event rate was very similar in women and men. Thus, absent or very low CAC score carries the same prognostic value in both genders [45].

Regarding risk factors among our 118 patients, 59 cases (50.00%) had hypertension, while among the 4 patients with coronary artery stenosis only 2 of them had hypertension, which indicate 50% chance of hypertension among non-stenotic coronary artery patients and also stenotic coronary artery patients with a p-value of (1.00) (Table 2), (table. 3) and (Table 4), as a result it shows no any significant correlation.

While according to other studies; Coronary artery disease is a major complication of hypertension[50] and usually remains silent until a catastrophic clinical event occurs. [51] As its primary determinant is coronary atherosclerosis, [52] a marker that can indicate which hypertensive individuals have the greatest potential for developing coronary atherosclerosis is particularly useful. Coronary calcification is well recognized as a marker of atherosclerosis [53], but not as a reliable indicator of coronary stenosis because calcification may occur before the atheroma narrows the lumen of coronary vessels [53]. The observation that hypertension promotes coronary calcium deposit, an anatomic marker of coronary atherosclerosis, supports the concept that hypertension is an important pathogenic factor in the development of coronary disease [54].

The precise mechanisms of the interrelationships between coronary atherosclerosis, calcification, and hypertension are complex. Hypertension may participate in the atherogenic process through the arterial wall trauma induced by the rise in arterial pressure and/or particular coexistent sharing conditions [54]. Furthermore, calcification of the atheroma is an active process in which osteopontin [55] a protein involved in mineralization, may play an important role [56] and high expression of the gene for osteopontin may be
induced by stimuli related to the arterial wall trauma [57].

Our study showed that the 4 patient with coronary artery stenosis among 118 patients had no history of diabetes mellitus and no smoking. While among 114 patients of no coronary artery stenosis showed 25 cases (21.19%) had diabetes mellitus, 21 cases (17.80%) were smokers, with a P-value of (0.29) and (0.34) for diabetes and smoking respectively (Table 4).

In comparison to other studies worldwide we concluded that Patients suffering from diabetes type–2 have been shown to harbor larger amounts of CAC than non-diabetic patients with the metabolic syndrome [58] and subjects of similar age and otherwise similar risk factor profile [58, 59]. The extent of CAC in patients with type-2 diabetes is similar to that of patients with established CAD but without diabetes, diabetic women harbor as much CAC as diabetic men [60, 61], and younger diabetic individuals have a plaque burden comparable to that of older non-diabetic individuals [62]. Wong et al. performed CAC screening and stress myocardial perfusion imaging (MPI) in 1043 patients, 313 of whom were affected by either diabetes mellitus (N = 140) or the metabolic syndrome (N = 173) [63].

In patients with a CAC score < 100, the prevalence of stress induced MPI abnormalities was very low (~ 2%). However, in the presence of a metabolic disorder (diabetes mellitus or the metabolic syndrome) a CAC score between 100 and 399 or greater than 400 was associated with a greater incidence of ischemia than in patients without a metabolic disorder (13% vs. 3.6%, $P < 0.02$, and 23.4% vs. 13.6%, $P = 0.03$, respectively) [63].

While regarding smoking and its impact according to other studies we found that Smoking was independently associated with angiographic disease but not with coronary calcium score. Smoking is a risk factor for coronary arterial thrombosis irrespective of plaque morphology [64], and it may lead to clinical symptoms at earlier stages of coronary artery disease than in nonsmokers [65]. Accordingly, smokers with a comparably low coronary plaque burden and little or no calcification may become symptomatic.

Regarding lipid profile ; in our study showed only 19 patients among total 114 patients with no stenosis had high lipid profile (table 3), while among the 4 patients with stenosed coronary artery 3 (75%) of them had high lipid profile with P-value of (0.003) according to (Table 4), means the lipid profile has an impact on the CAD.

In comparison to a study of 6093 patients for whom CAC by EBCT, lipids, personal health history, and body morphology were recorded, A low density lipid (LDL cholesterol >160 mg/dl) had a 62% increase in odds for the presence of calcified plaque [66]. CAC, once identified, seems to progress at a measurable, annual rate of approximately 30% in CAC volume on annual EBCT examinations [67].

Considerable interest exists in identifying and quantifying CAC as a marker for CAD. In the general population, a high coronary calcium score (>100) on electron beam computed tomography (EBCT) carries a relative risk for future CAD events of approximately 10 times compared with those with a score <100 [68,69]. Furthermore, it seems that a sufficiently high CAC score (>300) modifies the risk for future CAD events above that predicted by the conventional Framingham risk prediction [70].

The absence of detectable CAC is associated with a low future event rate; however, this rate is not zero. Approximately 5% of patients with a CAC score of zero will incur a myocardial infarction or cardiac death in the next 5 to 7 years after EBCT [71, 72]. This suggests that atherosclerotic plaque can exist without a sufficient amount of calcification to be detected by EBCT. This plaque, although uncommon, is thought to be lipid laden and potentially prone to plaque rupture and thrombosis [73].

It is clear from many studies that in all kinds of populations, even in high-risk populations such as diabetic patients, and in both symptomatic and asymptomatic patients, the absence of coronary artery calcium (zero calcium score) excludes most clinically relevant CAD [48].

Thus, the absence of CAC may be an important modifier of the risk of events even in the presence of cardiovascular risk factors. The high negative predictive value of a zero CAC score is extremely valuable, considering that a large number of asymptomatic individuals have no CAC. In various studies, absence of CAC was noted in 26–92% of individuals, depending on the age of the individuals. Hence, a zero CAC score may have important implications in daily clinical practice and on a population level [48].

Bottom line; our research is in agreement with the worldwide studies regarding age incidence, gender, risk factors “like diabetes, smoking and lipid profile”, while we couldn’t get the same outcome regarding hypertension and its significance on CAD; this may be due to the small sample size or we didn’t concentrate on the level of the blood pressure, it’s duration or whether it is controlled or not.

After all, we found that regardless of the risk factors, the impact of calcification and its relation to the atheroma is that among the 118 cases with zero calcification, only 4 cases showed presence of atheroma (3.9%) and among them only in one case of the atheroma was significant, which means less than one percent (0.85%) of the cases showed significant stenosis that needed intervention.
5. Conclusion

1. Absence of coronary artery calcification is highly sensitive for exclusion of coronary artery atherosclerosis.
3. Absence of CAC with absence of known risk factors for coronary artery atherosclerosis like; hypertension, diabetes mellitus, smoking and hyperlipidemias probably excludes coronary artery atherosclerosis.
4. In the absence of CAC with the presence of stenosis, most of the degree of the stenosis is non-significant.

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