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The Diagnostic Value of the Relationship between Lipid Profile, the Different Grades of Coronary Calcification and Stenosisin Patients with Possible CAD

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Abstract:

Background: Coronary calcification is an important risk factor for adverse outcomes in the general population [(1, 2).]

Coronary calcification causes reduction in the vascularcompliance [(3).]

Prediction of the severity of CAD is valuable due to the increased risk for cardiovascular events

CT scan of the coronary arteries allows assessment of the degree of coronary calcification as well as the degree of stenosis and the type of plaque (calcific or non-calcific)[(6)]

Objectives: To investigate the relationship between the lipid profileparameters and thedifferent grades of coronary calcification,using MSCT and correlate them withthe significance of coronary stenosis during coronary angiography in patients suspected to have coronary artery disease.

Subjects and Methods: Our study included 300 adult symptomatic patients, in the period between January 2017 and February 2018. Lipid profile for each patient was registered, calcium score was calculated for each patient, including areas with a density above 130 HUusing (Agatston score),we divided the study population into 2 categories (one group having calcium score above 400 and the other group having calcium score below 400)for a better correlation. After calculating the calcium score, coronary catheterization was done for the assessment of the significance of coronary stenosis,significant lesions were defined as greater than 70% reduction in the luminal diameter, the time interval between catheterization and CT scan was not more than one week.

The correlation between the lipid profile parameters and the degree of coronary calcification as well as the significance of coronary stenosis was established.

Results: Serum cholesterol, LDL and triglycerides had a strong positive correlation with the total calcium score, whereas HDL had a strong negative correlation with the total calcium score (p value <0.001).

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Serum cholesterol, LDL and Triglycerides were also significantly higher in the group of patients having significant lesions (p value<0.001), whereas HDL level was significantly lower in the group of patients having significant stenosis (p value<0.001).

Age was significantly higher in the group of high calcium score (agatston score >400), the number of hypertensive and diabetic patients was higher in the group of patients with high calcium score (agatston score>400),the number of patients with a positive family history of ischemic heart diseases was higher in the group of highcalcium score (agatston score>400).

Conclusion:dyslipidemia was found to be an important predictor for coronary calcification (detected by CT scan) as well as the presence of significant coronary artery stenosis (detected by coronary angiography)

Introduction

Coronary calcification is an important risk factor for adverse events in the general population. Many risk factors have been identified,contributing to the initiation and progression of coronary calcification.

Trials were done to controlcoronary calcification with medical therapy,but failed. Drug-eluting stents and devices for plaque modification have modestly improved to overcome calcification in the coronaries, but the adverse event rates are still high.

Innovative pharmacologic and device-based approaches are needed to improve the poor prognosis of patients with extensive coronary calcification

Coronary calcificationreduces the vascular compliance, vasomotor reaction, with impaired myocardial perfusion and is associated with worse outcomes in the general population (5).

Methods for Detection of coronary calcification

1-MDCT: is the only noninvasive test with high sensitivity and specificity for calcium detection, capable of quantifying calcium score(10). In large-scale observational studies, CT-scan–based calcium scores added prognostic value for predicting cardiac death and myocardial infarction(11).

Noninvasive assessment of calcium score is reasonable for cardiovascular risk assessment in asymptomatic patients with intermediate pretest probability for CAD (12).

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A calcium score of >0 suggests some underlying atherosclerosis, whereas scores ≥400 should prompt risk factor modification and further diagnostic evaluation[15]. Asymptomatic persons without traditional risk factors but with a documented calcium score ≥400 might have a worse cardiovascular prognosis than those with ≥3 risk factors but no CT-detected coronary calcification[15].

2-Coronary angiography: has a low to moderate sensitivity compared with gray-scale intravascular ultrasound (IVUS) and CT for detection of coronary calcification, but is very specific.Angiographic detection of coronary calcification is often classified into 3 groups: **none/mild**, **moderate**, and **severe**. Severe calcification is most commonly defined as radio-opacities seen without cardiac motion before contrast injection, usually affecting both sides of the arterial lumen, and moderate calcification as radio-opacities noted only during the cardiac cycle before contrast injection [48].

3-Intravascular ultrasound: is more accurate than cine-angiography for calcium detection, with sensitivity of 90% to 100% and specificity of 99% to 100% [17]. The signature of calcified plaque on grayscale IVUS is a bright echo with acoustic shadowing [18], and the extent of calcification can be graded by several metrics. The arc of calcium is classified as **none**, **1 quadrant** (0° to 90°), **2 quadrants** (91° to 180°), **3 quadrants** (181° to 270°), or **4 quadrants** (271° to 360°). Calcium location is defined as superficial if present in the intimal-luminal interface, deep if within the medial-adventitial border or closer to the adventitia than the lumen, or both superficial and deep. Deposits can be assessed relative to the thickest plaque accumulation as **concordant** (center of calcium arc ≤45° of thickest plaque accumulation), **perpendicular** (center of calcium arc 45° to 135° from thickest plaque accumulation), or **opposite** (center of arc of calcium ≥135° from thickest plaque accumulation). Finally, the calcium length can be measured [19].However, because ultrasound does not penetrate calcium, calcium thickness cannot be determined, and volume cannot be calculated.

Radiofrequency analysis of the IVUS signal allows for in vivo characterization of coronary plaque components, including fibrotic plaque, fibro-fatty plaque, necrotic core, and dense calcium [20].

4-Optical coherence tomography (OCT):provides higher-resolution imaging (10 to 20 μm) than grayscale IVUS (150 to 200 μm). Optical coherence tomography detects calcium as low-intensity, low-attenuation areas with sharp borders. The sensitivity (95% to 100%) and specificity (97% to 100%) of OCT for coronary calcification[21].Moreover, because light penetrates calcium, OCT can in many cases assess calcium thickness and measure calcium volume [21].

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Methods for ssessment of the degree of Coronary stenosis.

1- Coronary angiography:

A coronary angiogram shows the geometry of the lumen of the vessels, but not the vessel wall and plaque [22]. However, it provides limited information about the surface of the atherosclerotic plaque either smooth or irregular and calcifications of the vessel wall. Several studies described that the majority of culprit lesions in patients with unstable angina had a characteristic angiographic appearance. These lesions have been termed Ambrose type II lesions. However, these characteristics describe the plaques that have already ruptured, rather than those at risk to rupture. [23]

The extent of fluoroscopic calcifications is a marker of the overall atherosclerotic disease burden and, therefore, has a prognostic value.[24]

2- CT angiography:

Contrast-enhanced CT scans of the coronary arteries allow the visualization of non-calcified atherosclerotic plaque in lesions that are not associated with a significant stenosis. Detection, quantification, and characterization of coronary plaque by CT are currently the subjects of intense evaluation, helping in the risk stratification of the studied population. CT measurements can further characterize the different types of non-calcified plaque, because lipid-rich plaque is, on average, associated with lower Hounsfield attenuation numbers than fibrous plaques (14 to 72 HU for lipid-rich plaques and 90 to 121 HU for fibrous plaques)[25]

Whereas , coronary calcification can be reliably detected by CT at a relatively low radiation dose, and coronary calcium has clearly been shown to be associated with an increased risk of future coronary artery disease events in asymptomatic individuals, available clinical data are rare for the detection of non-calcified plaque by contrast-enhanced CT.

The Predictive value of MDCT for the presence of significantly obstructive coronary artery lesions is around 80% in most comparative studies [29]. MDCT does not render "projections" but "sections" of the coronary arteries with any angulation and, in a retrospective way, after the whole cardiac volume has been acquired.

Images obtained from MDCT may include cross-sectional views of the vessels. Which are not available in angiographic studies, this allows a more detailed analysis of the lesions [30].

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3- Intravascular Ultrasound (IVUS):

Intravascular ultrasound provides imaging of the vessel wall , plaque size, and plaque morphology.(32)

During cardiac catheterization, a miniature ultrasound catheter is placed distal to the target lesion site, and then withdrawn during continuous imaging, resulting in a series of cross-section images. The vessel wall of each cross-section can be described by the signal characteristics on a continuum from echo-dense (bright echo signal) to echo-lucent (faint echo signal). The measurement of lumen area, intima-media area, and external elastic membrane (EEM) area allows assessment of the state of arterial remodeling and plaque burden. Several IVUS studies have demonstrated the effectiveness of ultrasound imaging in predicting the composition of the atherosclerotic plaque when compared with histology.(33)

Advances in data acquisition and analysis in intravascular ultrasound information allowed a more detailed description of vessel wall and plaque morphology.(34) In particular, radio-frequency analysis has been used for the characterization of plaque structures such as the lipid pool and fibrous cap.(34)

Subjects and Methods

Patient selection:

Our study was carried out on 300 adult patientsof both sex groups, suspectedof having coronary artery disease and scheduled for coronary angiography at KobriElkobba military hospital during the period between January 2017 and February 2018.

All patients volunteered to undergo non enhanced CT of the heart for calculation of calcium score after taking a written consent to participate in the study,followed by coronary angiography , provided that they were not on lipid lowering therapy,

The mean age of the studied population was 55.40 (± SD 9.59) years and the majority of patients (86.7%) were males.

Patients who had undergone prior bypass surgery or prosthetic heart valves or pacemakers were excluded, for the possibility of streak artifacts from metal implants, also those with liver or kidney impairment, or facing difficulties in performing CT scan (inadequate breath holding and claustrophobia) were excluded from the study, women in the child bearing period were eligible with documentation of negative pregnancy test.

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Non-contrastenhanced CT which was done 24hrs to 1 week before coronary angiography depending upon the patient risk profile and clinical presentation

All participants underwent measurement of coronary calcium using Multi-Detector CT (MDCT) at baseline using Agatstonscore. Tissue densities ≥ 130 Hounsfield units were set as the attenuation level for a calcified plaque.

We used a dual source scanner (Somatom Definition Flash) using two X-ray sources which would yield better visualization of the coronary tree, ECG triggering was set to 75% of the RR interval.

Agatston score was used to calculate the sum of calcification in all coronaries as well as the calcium score in each vessel separately after reconstructing slices of 3 mm in thickness,beginning 1 cm below the carina and progressing caudally to include the proximal coronary arteries.The coronary calcification was calculated based on the area and density for each of the major coronary arteries: LMT, LAD, LCX, and RCA

The images were evaluated by four experienced observers, who had no knowledge of the clinical data. Two contiguous pixels with an attenuation coefficient >130 Hounsfield units were defined as a calcium deposit .The calcification was scored on a vessel by vessel and a total score was obtained for all vessels

All studies performed were scored independently by the observers to assess inter-observer variations

The collected data were analyzed on dedicated software platforms.

Routine laboratory investigations with special concern to:

- Fasting Blood sugar level,Fasting plasma lipid profile including (Total Cholesterol ,Triglycerides , HDL , LDL)to assess the interaction between the cardiovascular risk factors and the degree of coronary calcificationas well as the significance of coronary stenosis.

Coronary angiography was performed in different projections after discussing the risk-benefit ratio of the procedure and obtaining signed informed consent, allpatients werebrought to the cardiac catheterization laboratory,Mild conscious sedation was commonly used, and Oxygen saturation was constantly monitored.

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The vascular access site was cleansed with an antibacterial solution and covered with surgical drapes.

A percutaneous radial artery approach was occasionally used in patients with severe peripheral vascular disease or when the groin approach was not possible or technically difficult.

Coronary angiograms were obtained with the use of pre shaped (usually Judkins, but occasionally Amplatz, multipurpose or other) 6 French diameter diagnostic catheters. After engaging the ostium of the coronary artery it was confirmed that the tip of the catheter was free, and not against the wall of the artery, under a sub-intimal plaque. This was accomplished by confirming that the pressure was not damping and with the use of a test injection using a small amount of contrast material [35].

Various views or projections of the coronary angiograms were obtained by rotating the x-ray video camera around the patient.

The cinegrams were interpreted by 2 experienced cardiologists who had no knowledge about the CT findings

The vessels were subdivided anatomically as described for CT and the condition of each vessel was described by one of the following categories , mild (<50% luminal stenosis) , borderline (50-70% luminal stenosis) and significant (>70% luminal stenosis) , diseased vessels were defined as those having luminal stenosis >50% , and significantly stenotic vessels were defined as those having >70% luminal narrowing

The analysis of data included:

- Initial assessment of the lipid profile parameters and quantification of the amount of calcification by agatston score using a non-contrast enhanced CT scan.
- The included subjects were then categorized into two groupsfor better data analysis , the first group was for those with calcium score less than 400 (low calcium score) and the other group was for those with calcium score more than 400 (high calcium score group) ,.
- The severity or degree of stenosis was measured angiographicallyby comparing the area of narrowing to an adjacent normal segment, and as a percentage reduction and calculated in the projection which demonstrates the most severe narrowing [35].
- The patient was considered to have significant stenosis, if ≥ 1 plaque is causing >70% luminal narrowing.

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- Analysis of the data obtained by correlating the lipid profile parameters, calcium score and the presence of significant stenosis, using specific statistical programs.

Data were analyzed using Statistical Program for Social Science (SPSS). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were used:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (X2) test of significance was used in order to compare proportions between two qualitative parameters.
- Pearson's correlation coefficient (r) test was used for correlating data.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:
  - Probability (P-value)
  - P-value <0.05 was considered significant.
  - P-value <0.001 was considered as highly significant.
  - P-value >0.05 was considered insignificant.

RESULTS

Patient demographics

The clinical characteristics of patients are summarized in (**Table 1)**, the total number of the studied population was 300 patients,the mean age of the study group was (55.40±9.59), 86.7% were males and 13.3% were females, 59% were hypertensive, 47.7% were diabetic, 48.7% were smokers, 5.7% had a family history of ischemic heart diseases.

Table (1): Baseline Characteristic data of the study group.

Characteristic data	Total (N=300)
gender	
Female	40 (13.3%)
Male	260 (86.7%)
Age (years)	31-78 (55.40±9.59)
HTN	177 (59.0%)
DM	143 (47.7%)
Smoking	146 (48.7%)
Family history of ischemic heart disease	17 (5.7%)

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The mean age of the study group was (55.40±9.59), 86.7% were males and 13.3% were females, 177 (59%) patients were hypertensive, 143 (47.7%) patients were diabetic, 146 (48.7%) patients were smokers, 17 (5.7%) patients had a family history of ischemic heart disease

Lipid profile parameters of the studied population were summarized in **(table 2),**the mean total cholesterol was 242.92 ± 43.25, mean LDL cholesterol level was 153.12 ± 31.01, mean HDL cholesterol was 50.91±17.04, the mean serum triglycerides level was 197.88±51.18.

Table (2): Lipid profile parameters ofthe patients included in the study.

Lipid Profile	Total (N=300)
S. Cholesterol	155-350 (242.92±43.25)
LDL	89-230 (153.12±31.01)
HDL	26-159 (50.91±17.04)
S. Triglycerides	90-340 (197.88±51.18)

LDL=Low density lipoprotein, HDL = High density lipoprotein, SD=Standard deviation.

The clinical data of the patients are also characterized in both groups of calcium score (the high calcium score group and the low calcium score group) , summarized in (**table 3**) ,Age was significantly correlated with the total calcium score **(fig1)** and the higher age group of patients was markedly distributed in the group of high calcium score (p value <0.001)**(fig2)** ,the number of hypertensive and diabetic patients was significantly higher in the group of higher calcium score , family history of ischemic heart diseases was strongly positive in the group of higher calcium score (p value 0.011) **(fig3)**. Sex difference and smoking had no significant difference betweenbothcalcium score groups.

Table (3): Comparison between the effect of demographic data on Calcium score in both groups <400 and >400 according to baseline data.

Characteristic data	Ca score <400 (N=200)	Ca score >400 (N=100)	t/x2#	p-value
Age (years) Mean±SD Range	52.50±8.42 31-75	61.21±9.19 40-78	67.103	<0.001
Sex Female Male	27 (13.50%) 173 (86.50%)	13 (13.00%) 87 (87.00%)	0.014#	0.904
HTN	103 (51.50%)	74 (74.00%)	13.952#	<0.001
DM	84 (42.0%)	59 (59.00%)	7.057#	0.008

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Smoking	96 (48.00%)	50 (50.00%)	0.107#	0.744
Family history	6 (3.00%)	11 (11.00%)	6.555#	0.011

Age was significantly higher in the calcium score group >400 (p value <0.001) ,the number of hypertensive and diabetic patients was significantly higher in the calcium score group>400, family history of ischemic heart diseases was strongly positive in the calcium score group >400 (p value 0.011) . Sex difference and smoking had no significant difference in their effect between both groups.

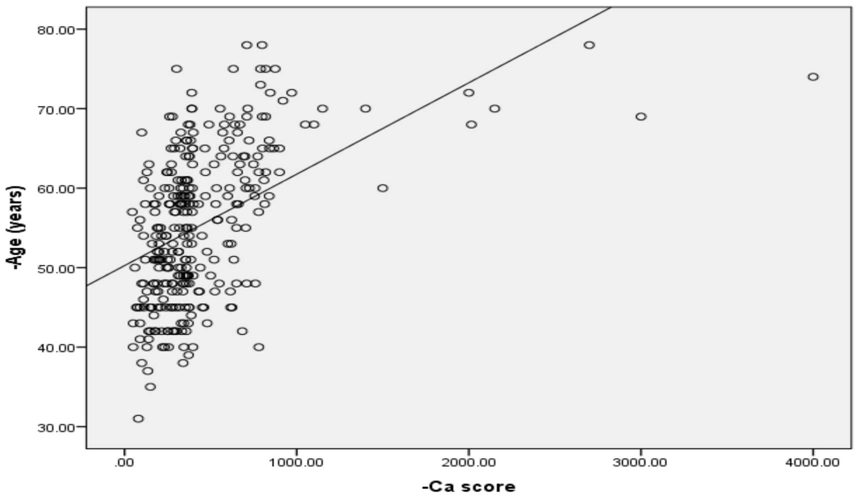

Figure (1): Scatter plot between Ca score and age (years) showing a significant positive correlation between age and the total calcium score.

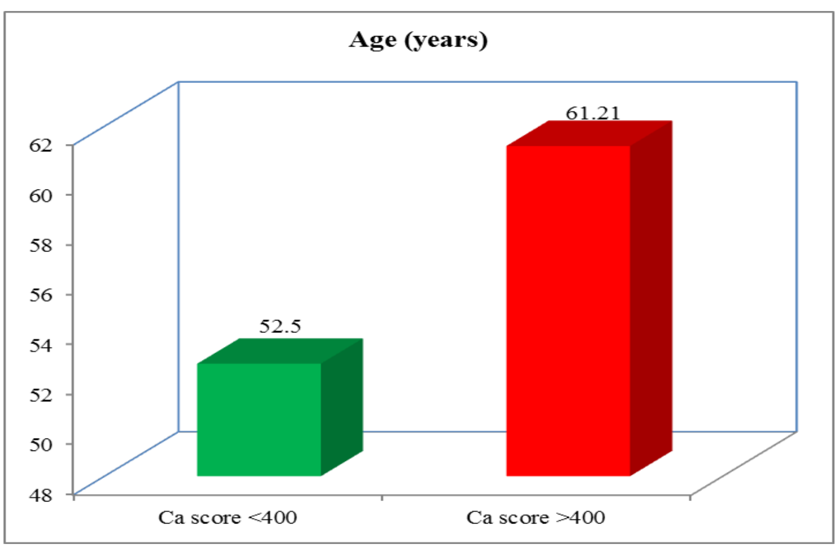

Figure (2): Bar chart showing the difference between both calcium score groups as regarding the age of the included patients , a significant distribution of the advanced age patients in the calcium score group>400.

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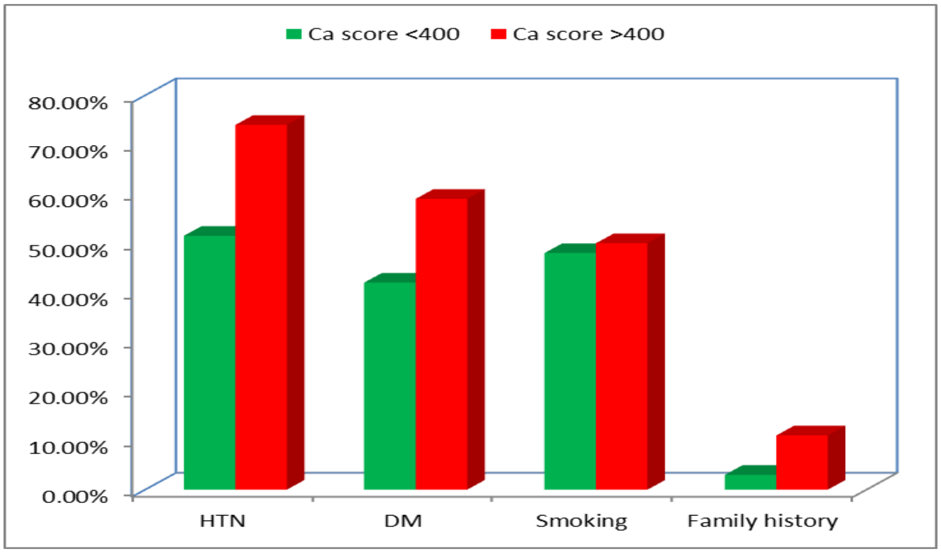

Figure (3): Bar chart showing thedistribution of the different risk factors between both calcium score groups.

Calcium score distribution of the study group was summarized in (**table 4);**calcium score in the study group was ranging from 45-4000.

200 cases had low calcium score (calcium score<400) and 100 cases had high calcium score(calcium score>400)

Table (4): Ca score distribution of the study group.

Ca score	**Total (N=300)**
<400	200 (66.7%)
>400	100 (33.3%)
Range [Mean±SD]	45-4000 (447.16±406.80)

This table shows that 200 cases were distributed in the subgroup <400 Cacium score and 100 cases were distributed in the subgroup >400 Calcium score, calcium score in the study group was ranging from 45-400.

The relationship between the different lipid profile parameters and the total calcium scorewas summarized in (**table 5)** , there was a significant positive correlation between the total cholesterol level and the total calcium score **(fig4)** , a significant positive correlation was detected between LDL and the total calcium score **(fig5)** , a significant negative correlation between HDL and the total calcium score **(fig 6)** , a significant positive correlation was detected between triglycerides and the total calcium score **(fig7)**

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Table (5): Comparison between both Calcium score groups (<400 and >400) according to lipid profile parameters

Lipid Profile	Ca score <400 (N=200)	Ca score >400 (N=100)	t-test	p-value
S. Cholesterol				
Mean±SD	227.15±38.33	274.48±34.45	108.595	<0.001
Range	155-350	190-340		
LDL				
Mean±SD	141.18±27.26	177.01±23.38	126.286	<0.001
Range	89-210	120-230		
HDL				
Mean±SD	56.82±17.63	39.09±6.39	94.725	<0.001
Range	39-159	26-61		
S. Triglycerides				
Mean±SD	174.43±35.37	244.78±45.41	216.974	<0.001
Range	90-320	145-340		

Total cholesterol, LDL cholesterol, and serum triglycerides were significantly higher in the group of high calcium score (> 400) than the group of lower calcium score (< 400) (P value < 0.001). HDL was significantly lower in the group of high calcium score (>400), P value < 0.001

LDL = Low density lipoprotein, HDL = High density lipoprotein

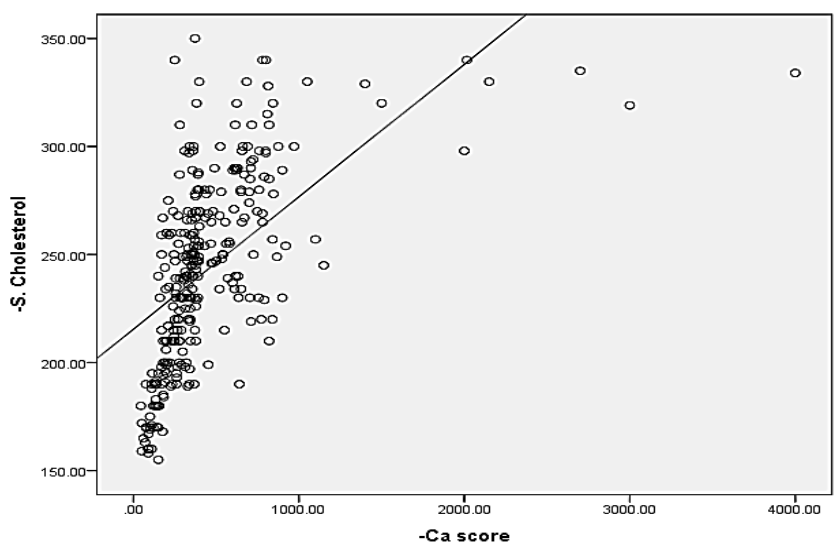

Figure (4): Scatter plot between Ca score and S. cholesterol showing a significant positive correlation.

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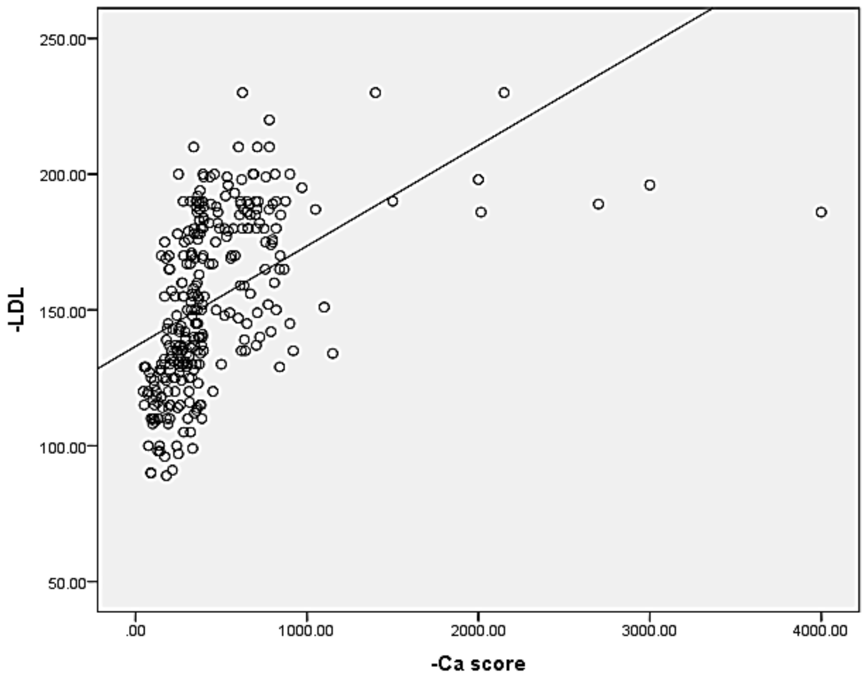

Figure (5): Scatter plot between Ca score and LDL showing a significant positive correlation

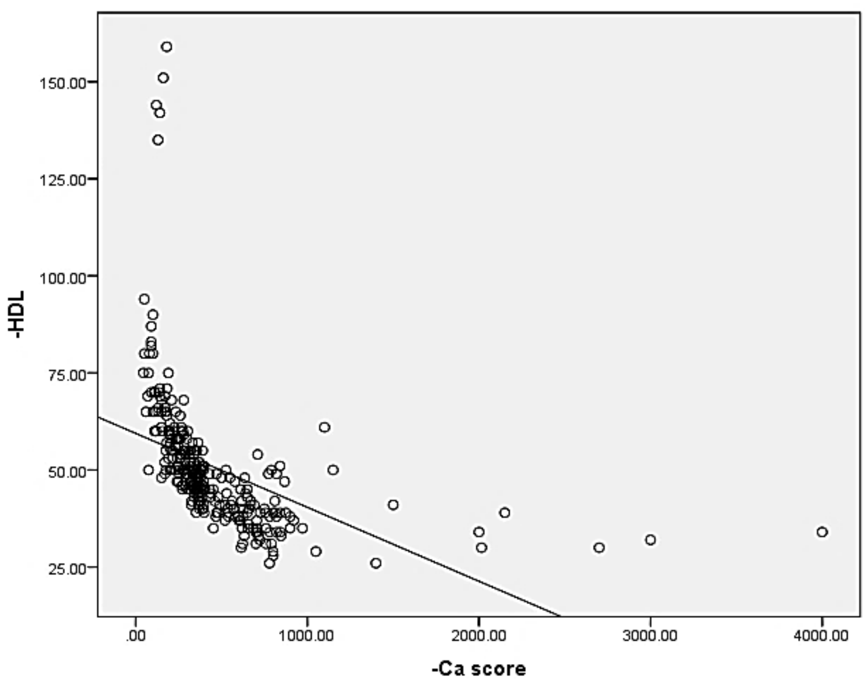

Figure (6): Scatter plot between Ca score and HDL showing a significant negative correlation

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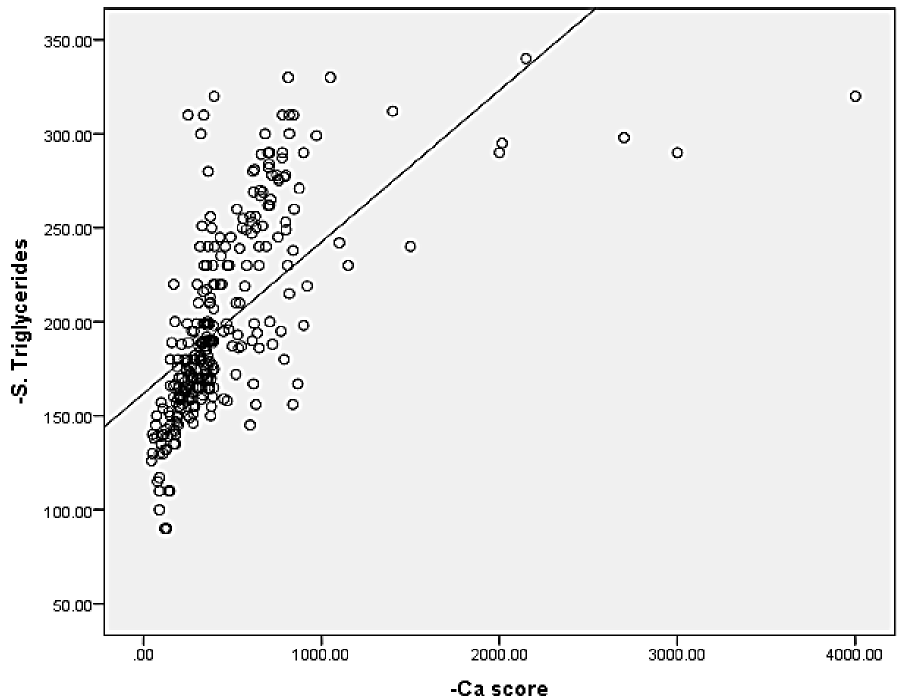

Figure (7): Scatter plot between Ca score and S. Triglycerides showing a significant positive correlation.

The relationship between the different lipid profile parameters and the significance of stenosiswas summarized in (**table 6, fig8)**, Serum cholesterol, LDL and Triglycerides were significantly higher in the group of patients having significant coronary stenosis, whereas HDL level was significantly lower in that group.

Table (6): Comparison between non-significant stenosis and significant stenosis according to the lipid profile parameters.

Lipid Profile	**Non significant stenosis (N=156)**	**Significant stenosis (N=144)**	**t-test**	**p-value**
S. Cholesterol				
Mean±SD	214.21±31.47	274.03±31.04	274.264	<0.001
Range	155-350	189-340		
LDL				
Mean±SD	128.85±17.11	179.42±18.83	593.689	<0.001
Range	89-180	127-230		
HDL				
Mean±SD	58.58±19.59	42.59±7.57	84.325	<0.001
Range	33-159	26-60		

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S. Triglycerides Mean±SD Range	164.28±27.95 90-284	234.28±45.42 159-340	262.848	<0.001

Serum cholesterol, LDL and Triglycerides were significantly higher in the group patients having significant stenosis (p value<0.001), whereas HDL level was significantly lower in the group of patients having significant stenosis (p value<0.001).

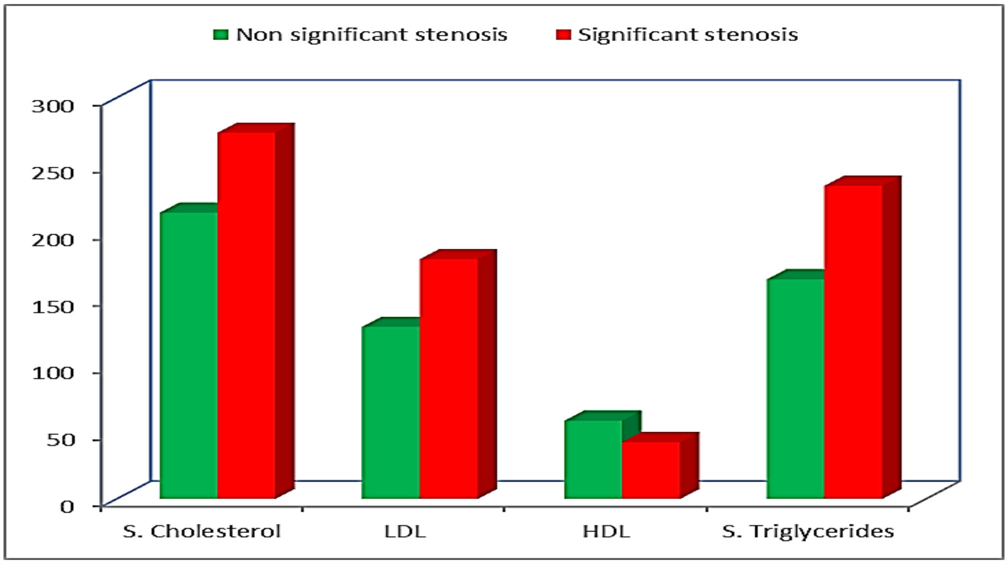

Figure (1): Bar chart between the significance of stenosis and lipid profile parameters

Discussion

High-resolution, contrast enhanced computed tomography of the coronary arteries allows the evaluation not only of the degree of coronary stenosis, but also evaluates coronary plaques, the degree and pattern of calcification. [36]

The main purpose of this study was to explore the relationship between the lipid profile parameters and thedegree of coronary calcification as well as the severity of coronary stenosis.

There was a significant relation between the different lipid profile parameters and the degree of calcification , as a positive correlation was found betweenLDL , total cholesterol , serum triglycerides and the degree of calcification (P < 0.001) ,Whereas HDL cholesterol had a significant negative correlation with the degree of calcification (P < 0.001),which was supported by the results of*Richard A. Kronmal et al*,that studied the relationship between dyslipidemia and incident coronary calcification[41].

A significantpositive correlation was found between different risk factors including age, hypertension, diabetes, family history of IHD and the presence of as well as the degree coronary calcification; however smoking had a non-significant effect on coronary calcification. In agreement with the previous finding , studies done by *Mazzone T et al* , N.D. *Wong et al* , *H. Eisenberg, et al* who found a significant relation between individual risk factors including age, hypertension, dyslipidemia, diabetes and the presence as well as the degree of coronary calcification [(42,43,44)]

We found also that the total cholesterol, LDL, and TG levels were significantly higher in the group of patients who had significant stenosis thaninthe group of patients havingnon-significant stenosis ($P < 0.001$), whereas HDL cholesterol was significantly lower in the group of patients having significant stenosis. This is supported by the results of *Shipilova etal*.that found a positive linear correlation between the severity of stenosis on one hand, and the total cholesterol, LDL cholesterol and serum triglycerides on the other hand, negative linear correlation between HDL cholesterol and severity of stenosis was also found.[(45)].The study done by *Ladeia AM, et al*found that Lower HDL-C was associated with more severe and intensive CAD[(46)]supporting our findings about the negative correlation between HDL and the severity of CAD

In contrast to our results, a study done by *M F Reardon et al.*on65 men and 42 women and noted that only LDL and TGs have the only positive correlation with the stenosis severity, whereas no relation could be detected between HDL and the severity of stenosis, total cholesterol did not account also for changes in stenosis severity in women.[(47)]

Conclusions

Dyslipidemia has a strong correlation with the degree of coronary calcification as well as the degree of stenosis, as revealed by multi-detector computed tomography and coronary angiography.

Other risk factors including age, hypertension,and diabetesare strongly correlated with the degree of coronary calcification as well as the degree of stenosis.

MSCT is the best modality for detecting and calculating the degree of coronary artery calcification.

Recommendations

1- MDCT scan of the coronaries can be used for visualization and assessment of coronary calcifications as well as risk stratification of the patients with intermediate pretest probability for coronary artery diseases.

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2- Lipid profile analysis before non-invasive assessment of patients with intermediate probability for CAD is very important for a further risk stratification of the patients.

Limitations

1- Our study included patients who underwent coronary assessment for clinical indications, however many asymptomatic patients have an abnormal lipid profile, so that the relation between dyslipidemia and coronary stenosis in these subjects is not well established.

2- A limited number of female patients were included in our study, which led to inadequate assessment of sex differences as regards incidence of the different risk factors, coronary calcification and stenosis.

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