THE ASSOCIATION BETWEEN PLASMA LIPIDS AND CORONARY PLAQUE DENSITY (DETECTED BY MSCT ANGIOGRAPHY)

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ABSTRACT

Background: Coronary artery disease (CAD) is a prevalent symptom of cardiovascular disease, which is a major worldwide health problem. Dyslipidemia significantly contributes to CAD development and progression. This study aimed to investigate whether a correlation exists between dyslipidemia, the different lipid levels and the density of coronary plaques in individuals presenting with chest pain with low to intermediate PTP for CAD, utilizing multidetector computed tomography (MDCT) imaging.

Methods: this study is an observational cross-sectional study on one hundred patients with varying degrees of coronary stenosis , detected by MSCT in the cardiac CT Unit in Kobri Elkobba military specialized heart hospital , Cairo , Egypt . A full diagnostic workup was done for all patients , including history , laboratory tests , clinical examination , ECG and finally MSCT for identification of the coronary plaque characteristics , including plaque plaque density , morphology , presence of calcification and finally the severity of coronary stenosis .

Results: The mean total cholesterol was 237.51 ± 60.03, LDL cholesterol was 145.75 ± 30. HDL cholesterol was 44.66 ± 15.29, triglycerides level was 176.81 ± 35.66. A highly significant negative correlation was found between cholesterol, LDL and triglycerides on one hand and the mean plaque density on the other hand (P value < 0.001) , on the other hand a significant positive correlation was found between HDL cholesterol and the mean density of the plaques. A strong positive correlation was found between the total cholesterol, LDL, Triglycerides on one hand and the presence of non-calcified plaques , however a negative correlation was found between HDL and the presence of non-calcified plaques (P value <0.001)

significant lesions were mostly present in patients with higher total cholesterol, LDL, triglycerides, LDL/HDL ratio. HDL level was significantly lower in the subgroup of significant lesions.

Conclusion: There was a significant correlation between plasma lipid parameters on one hand and plaque density , presence of non-calcified plaques , as well as the significance of coronary stenosis on the other hand .

Keywords: vulnerable plaques , plaque density , Coronary artery disease, Lipid profile, MDCT.

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Introduction

Low density lipoprotein (LDL) cholesterol is responsible for transporting cholesterol from the liver to the tissues of the body. Dyslipidemia is an important correctable, risk factor for coronary artery disease. There is strong, independent, continuous and graded relationship between total cholesterol or LDL cholesterol level and risk for coronary artery disease events **(1).**

Coronary lesion development starts relatively early in life; macrophages accumulate at future plaque sites and by incorporating cholesterol, become foam cells. In advanced lesions, further cell accumulation leads to formation of a lipid rich core which is separated from the lumen by a fibrous cap . The size of the lipid pool within an atherosclerotic plaque and the thickness of the overlying fibrous cap are important characteristics predicting the stability of advanced plaques. It is also known that vulnerable plaques are characterized by a large lipid pool with thin fibrous cap with a characteristic lower plaque density due to the higher fat content **(2).**

Contrast-enhanced high-resolution computed tomography (CT) scans of the coronary arteries allow the evaluation not only of the degree of coronary stenosis, but also of coronary plaques either calcified or non-calcified even if not associated with significant stenosis. CT measurements can potentially contribute to the further characterization of non-calcified coronary plaque, since a lipid-rich plaque is associated with a lower CT hounsefield attenuation numbers than fibrous plaques **(3).**

Aim of the work

As lower density plaques (vulnerable plaques) are very hazardous and risky due to their higher fat content with more susceptibility of plaque rupture and thrombosis, so that our study aimed to detect the correlation between the different levels of plasma lipids and the different plaque densities detected by cardiac CT among symptomatic statin naïve patients.

Patients and methods

Patient selection:

The current study included 100 patients of mean age 54.34 ±11.04 with detectable coronary artery plaques as revealed by coronary multi-detector computed tomography (MDCT) in the period between january 2022 and May 2022, done in Kobri Elkobba military hospital.

Exclusion criteria:

The study excluded patients with:

1- contrast allergy.

2- normal coronary angiography on MDCT

3- Heart rate more than 80 beats /min.

4- Renal impairment .

5- Severe coronary calcification .

6-liver dysfunction .

7-inadequate breath holding.

Methods:

All patients were subjected to:

1. **Full history taking clinical examination fulfilling the following data:**

- Age
- Sex
- Hypertension
- Diabetes mellitus
- Smoking
- Cardiac examination
- Family history of CAD

2. **12 Lead ECG .**
3. **Routine laboratory investigations , including:**

- Complete blood picture.
- Random Blood glucose level.
- Serum creatinine.
- Complete Lipid profile.

Total serum cholesterol, serum low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and serum triglycerides (TG), according to NCEP ATP III **(4)** Blood samples were collected in the morning after a 12-hour fasting period, during the second and third visits, and lipid measurements were performed.

In the alternate-day regimen group (group B), samples were obtained in the morning when the patient did not receive the pill. Serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured colorimetrically on Synchron Cx5 (Beckman Coulter Instruments Inc., CA, USA) using Beckman Coulter reagents.

Total cholesterol was measured by the cholesterol oxidase method, HDL cholesterol with a homogeneous assay, and triglycerides by enzymatic hydrolysis followed by the measurement of free glycerol.

For the assay of HDL, precipitation of LDL-C and very low-density lipoprotein cholesterol (VLDL-C) was performed by phosphotungistic acid in the presence of magnesium ions; they were then removed by centrifugation. The cholesterol in HDL-C fraction, which remains in the supernatant, was assayed in the same way as total cholesterol on Beckman Coulter Synchron Cx5 autoanalyzer. The

precipitating reagents used for the determination of HDL were purchased from Quimica Clinica Aplicada (QCA 43870–Amposta, Trragona, Spain). LDL-C concentrations were calculated according to the Friedewald equation.

If any patient had a triglyceride level above 300 mg/dl, LDL-C was measured directly by ultracentrifugation (β-quantification; direct LDL-C). High-sensitivity CRP was quantified by means of high-sensitivity immunophelometry (hs-CRP; Dade Behring, Inc). Standardization was conducted according to the recommendations of the International Federation of Clinical Chemistry with reagents and standards from Beckman Coulter. In brief, the analysis was done using the SPECTROPHOTOMETER for serum Cholesterol, serum Triglycerides and HDL, while the LDL is calculated using the FRIEDEWALD FORMULA **(5).**

4. Coronary multi-detector computed tomography (MDCT):

The CT angiography was performed to all patients utilizing a dual source scanner (Somatom Definition Flash) using two X-ray sources which would yield better visualization of the coronary tree at relatively high heart rates (above 70 bpm) and all coronary arteries were evaluated at different phases of the cardiac cycle by acquisition of thin slice sections (0.6 mm) till reaching the optimum phase for reconstruction of MRP, MIP and VR images. The available data which were collected are analyzed on dedicated software platforms. All scans were preceded by non-contrast enhanced scan for coronary calcium score (sequential scan with 32 x 0.6 mm collimation, tube current 60 mAs at 120 kV) , this was done to rule out patients with dense coronary calcification (total score above 1000). All included patients received intravenous non ionic iso-osmolar contrast medium, the time delay up to coronary filling will be calculated using the test bolus technique, a bolus of 10 ml of the contrast agent was injected intravenously at a rate of (5 ml/s). Then angiography was done injecting 60 ml of the same contrast agent at a rate of 6 ml /s, the whole process was ECG gated retrospectively.

- Plaque density was measured in Hounsfield units for each plaque , mainly at the proximal and mid segments of the main coronary arteries to avoid artifacts.

Obtained data were correlated with patients fasting lipid profiles. The relationship between each parameter and the total plaque density in the proximal coronary segments was done.

The analysis also included:

- coronary calcium score.
- Coronary plaque density in Hounsfield units, as fat rich plaques are characterized by much lower values , usually negative ,however the fibrous and calcific plaques have high positive values .
- Non-calcified plaque is defined as a lesion with a radio-density greater than the neighboring soft tissue and lower than the luminal contrast, while, calcified component is defined as a lesion with a radio-density greater than the luminal contrast .
- Stenosis is considered significant if it causes ≥ 50% stenosis of the left main coronary and/or ≥ 70% stenosis of the other coronary branches which is detected by visual inspection.
- The patient is considered to have significant stenosis, if ≥ 1 plaque is causing significant stenosis **(6).**

Results

The study was carried out on one hundred patients at Kobri Elkobba military hospital in the period between January and September 2022. All patients were not on statin therapy and underwent MSCT scan of the coronary arteries, The mean age of the studied population was 54.34 ± (11.04).

Table (1): Characteristics of the study group

		N
Age		54.34 ± 11.04
Sex	Female	20
	Male	80
HTN		61
DM		45
Smoking		50
Family history		41

DM = Diabetes mellitus, HTN= Hypertension, N = Number

Table (1) shows the baseline characteristics. The mean age of the study group was (54.34±11.04), eighty of them were males, sixty-one patients were hypertensive, forty-five patients were diabetic, fifty patients were smokers and forty-one patients had a family history of ischemic heart disease.

Table (2): Baseline lipid parameters of the study group.

	Range	Mean ± SD
Total Cholesterol	142.0 - 400.0	237.51 ± 60.03
LDL level	76.0 - 220.0	145.75 ± 30.12
HDL level	22.0 - 81.0	44.66 ± 15.29
Serum Triglycerides	90.0 - 350.0	176.81 ± 35.66
LDL /HDL ratio	1.1 - 6.9	3.63 ± 1.36
LDL/cholesterol ratio	0.3 - 1.0	0.63 ± 0.14

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

Table (2) showing lipid profile parameters in the study group. The mean total cholesterol was 237.51 ± 60.03, LDL cholesterol was 145.75 ± 30. HDL cholesterol was 44.66 ± 15.29, triglycerides level was 176.81 ± 35.66.

Table (3): Correlation between lipid parameters and the mean density of plaques.

	Mean density by HU	
	R	P-value
S. Cholesterol	-0.715	<0.001*
LDL	-0.403	<0.001*
HDL	0.842	<0.001*
S. Triglycerides	-0.514	<0.001*
LDL /HDL	-0.761	<0.001*

LDL = Low density lipoprotein, HDL = High density lipoprotein.

Table (3) A highly significant negative correlation was found between cholesterol, LDL and triglycerides on one hand and the mean plaque density on the other hand, P value < 0.001 , on the other hand a significant positive correlation was found between HDL cholesterol and the mean density of the plaques.

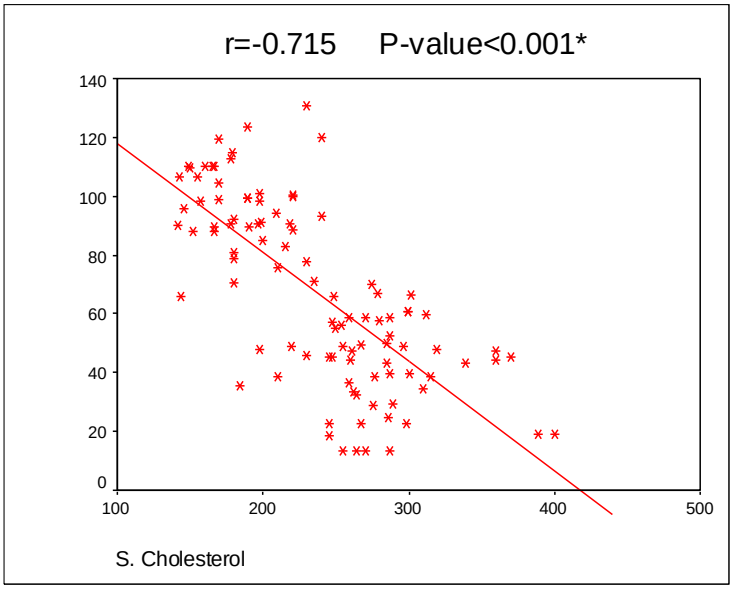


Fig. (1): a negative correlation between cholesterol and the mean plaque density

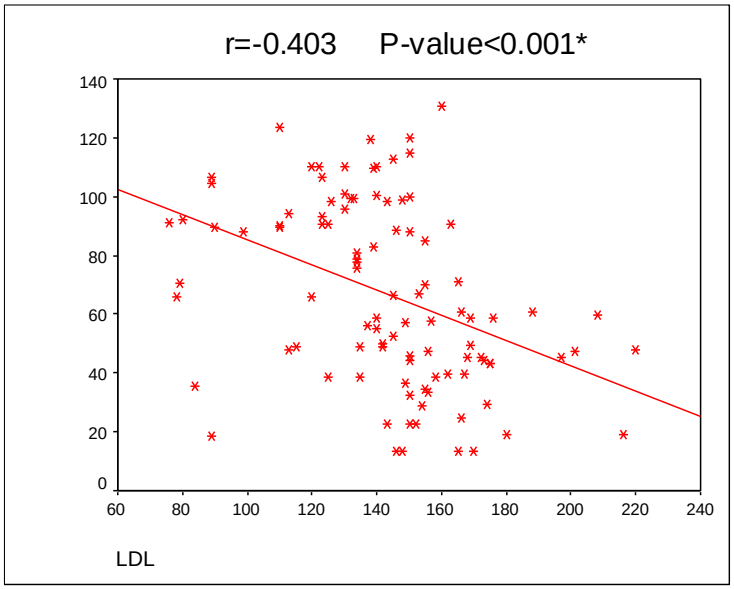


Fig. (2): a negative correlation between LDL and the mean plaque density.

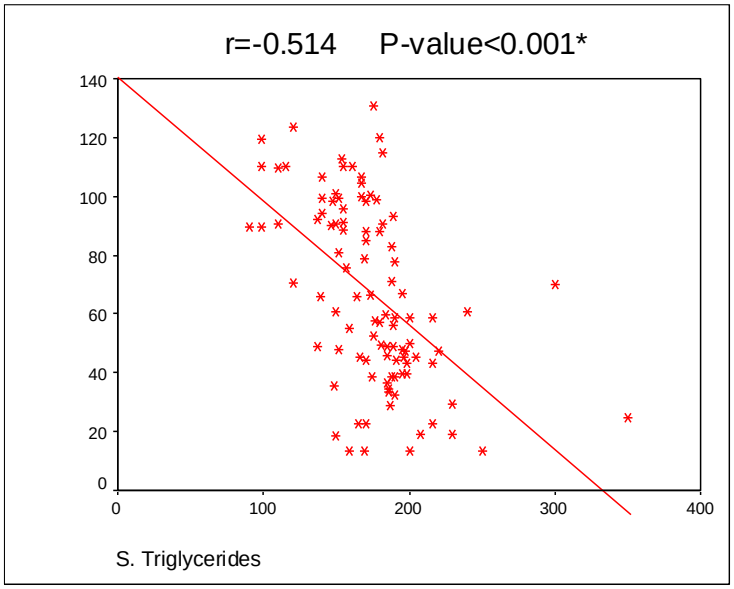


Fig. (3): a negative correlation between serum triglycerides and the mean plaque density .

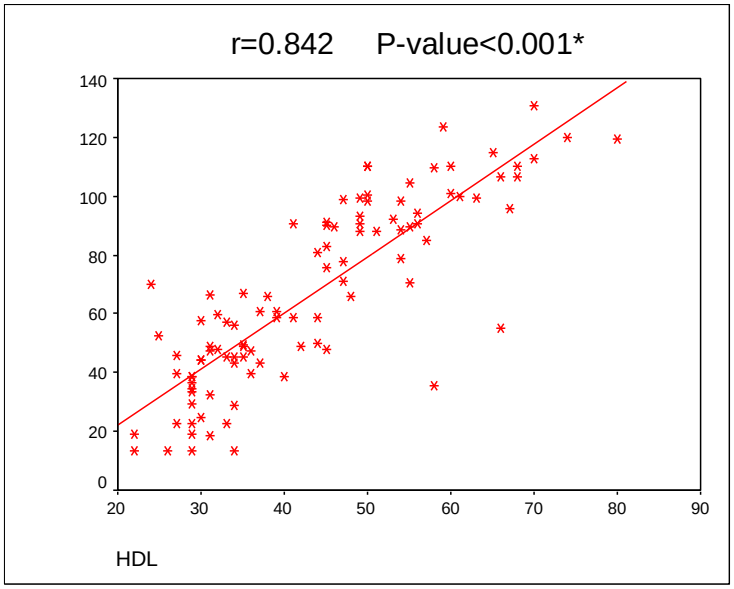
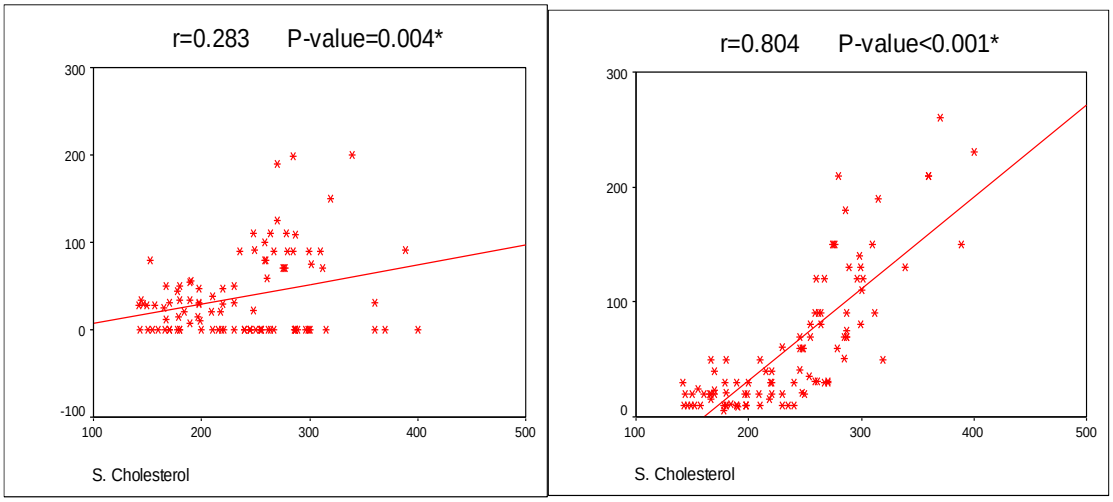


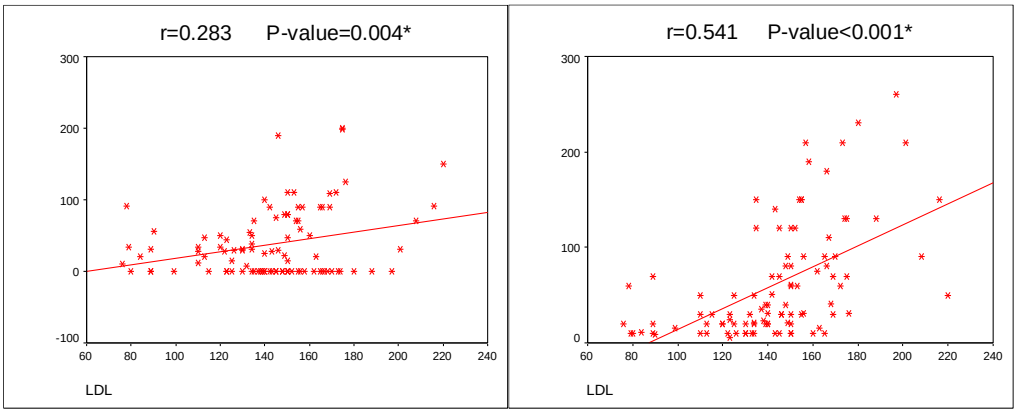
Fig. (4): a positive correlation between HDL cholesterol and the mean plaque density.

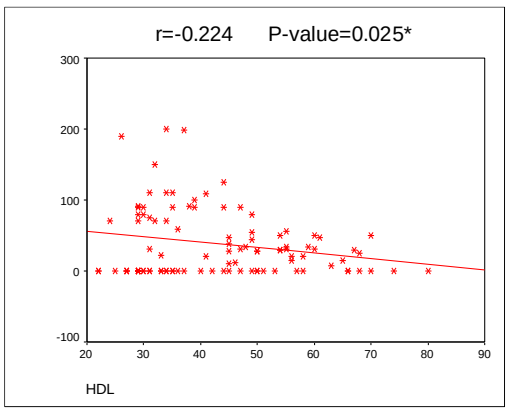
Table (4) correlation between the different lipid profile parameters and the presence of non-calcified versus calcified plaques

	Calcified plaques		**Non Calcified plaques**	
	r	P-value	r	P-value
S. Cholesterol	0.283	0.004*	0.804	<0.001*
LDL	0.283	0.004*	0.541	<0.001*
HDL	-0.224	0.025*	-0.683	<0.001*
S. Triglycerides	0.154	0.127	0.551	<0.001*
LDL /HDL	0.234	0.019*	0.772	<0.001*
LDL/chol	-0.096	0.342	-0.418	<0.001*

Table (4): showing the correlation between the different lipid profile parameters and the presence of non-calcified versus calcified plaques. A strong positive correlation was found between the total cholesterol, LDL, Triglycerides on one hand and the non-calcified plaque volume on the other hand, however a negative correlation was found between HDL and the non-calcified plaque volume.







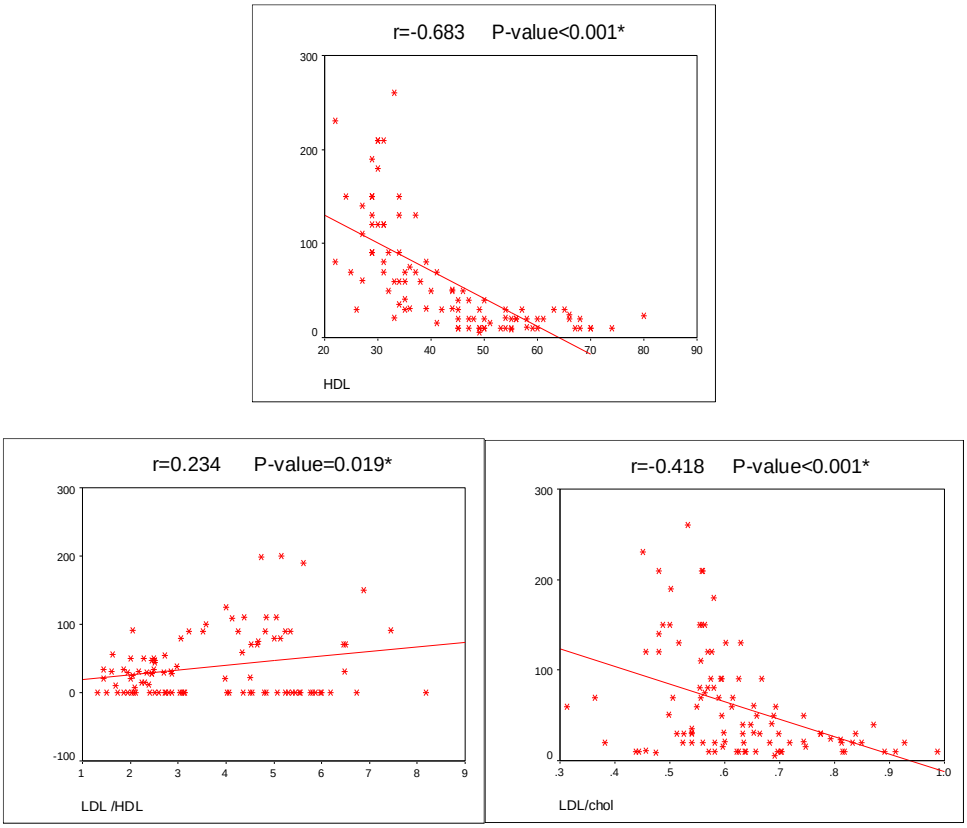


Figure (5): showing the correlation between the different lipid profile parameters and the presence of non-calcified versus calcified plaques. A strong positive correlation was found between the total cholesterol, LDL, Triglycerides on one hand and the non-calcified plaque volume on the other hand, however a negative correlation was found between HDL and the non-calcified plaque volume.

Table (5): Correlation between lipid profile parameters and the calcium score.

	Ca score	
	r	P-value
S. Cholesterol	0.593	<0.001*
LDL	0.469	<0.001*
HDL	-0.573	<0.001*
S. Triglycerides	0.420	<0.001*
LDL /HDL	0.589	<0.001*
LDL/chol	-0.230	0.080

LDL = Low density lipoprotein, HDL = High density lipoprotein

Table (5) shows the correlation between lipid profile parameters (total cholesterol, LDL cholesterol, HDL cholesterol and serum triglycerides) and calcium score. There was a highly significant positive correlation between total cholesterol, LDL cholesterol, and serum triglycerides on one hand and the calcium score ,P < 0.001.On the other hand There was a significant negative correlation between HDL cholesterol and the calcium score,P < 0.001.

Table (6): Correlation between lipid profile parameters and and plaque eccentricity.

Plaque Morphology	**S. Cholesterol**							
	Negative			Positive			**T-test**	
	Mean	±	SD	Mean	±	SD	t	P-value
Eccentric	253.69	±	61.73	235.09	±	59.20	1.051	0.296
Concentric	218.85	±	52.34	275.39	±	55.79	-4.971	<0.001*

Plaque Morphology	**LDL**					
	Negative		Positive		**T-test**	
	Mean ± SD		Mean ± SD		t	P-value
Eccentric	145.00 ± 30.95		142.61 ± 29.01		0.275	0.784
Concentric	137.60 ± 27.79		153.73 ± 29.16		-2.685	0.009*
Plaque Morphology	**LDL /HDL**					
	Negative		Positive		**T-test**	
	Mean ± SD		Mean ± SD		t	P-value
Eccentric	4.22 ± 1.62		3.66 ± 1.63		1.165	0.247
Concentric	3.27 ± 1.50		4.67 ± 1.50		-4.386	<0.001*

Plaque Morphology	**HDL**				
	Negative		Positive	**T-test**	
	Mean ± SD		Mean ± SD	t	P-value
Eccentric	38.46 ± 14.58		44.09 ± 13.39	-1.399	0.165
Concentric	47.18 ± 13.16		35.61 ± 11.08	4.347	<0.001*

Plaque Morphology	**S. Triglycerides**				
	Negative		Positive	**T-test**	
	Mean ± SD		Mean ± SD	t	P-value
Eccentric	201.92 ± 64.36		170.29 ± 30.32	2.935	0.004*
Concentric	166.33 ± 31.15		190.79 ± 44.31	-3.197	0.002*

Table (6): showing the relation between serum cholesterol, HDL, LDL , LDL/HDL ration and triglycerides with the coincident plaque morphology , where the higher cholesterol , LDL , ratio and triglycerides were more associated with the presence of concentric plaques , however lower HDL levels were more associated with the presence of of concentric plaques .

Table (7): showing the relation between the lipid profile parameters and the presence of either significant or non-significant lesions.

Lipid parameter	**Stenosis**				
	Non significant lesions		Significant lesions	**T-test**	
	Mean ± SD		Mean ± SD	t	P-value
S. Cholesterol	198.81 ± 36.53		290.95 ± 40.78	-11.854	<0.001*
LDL	129.10 ± 21.86		162.00 ± 27.21	-6.698	<0.001*
HDL	50.76 ± 12.70		33.14 ± 6.18	8.297	<0.001*
S. Triglycerides	155.90 ± 25.82		199.95 ± 36.56	-7.066	<0.001*
LDL /HDL	2.77 ± 1.12		5.07 ± 1.24	-9.682	<0.001*

LDL = Low density lipoprotein, HDL = High density lipoprotein, N=Number.

Table (7): a significantly higher total cholesterol, LDL, triglycerides, LDL/HDL ratio was found in the subgroup of significant lesion. HDL level was significantly lower in the subgroup of significant lesions.

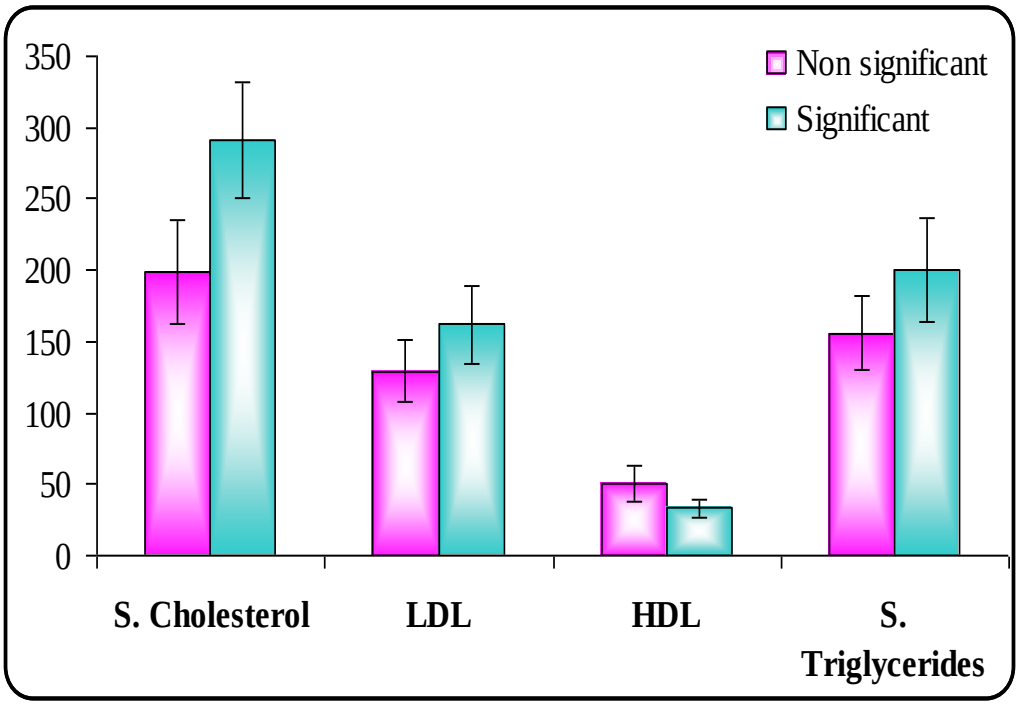


Fig. (6): Shows lipid profile parameters in the 2 subgroups classified according to the significance of stenosis.

Discussion

Dyslipidemia is an important correctable, risk factor for coronary artery disease. There is strong, independent, continuous and graded relationship between total cholesterol or LDL cholesterol level and risk for coronary artery disease events **(7).**

Contrast-enhanced high-resolution computed tomography (CT) scans of the coronary arteries allow the evaluation not only of the degree of coronary stenosis, but also of coronary plaques either calcified or non-calcified even if not associated with significant stenosis **(8)**

Our study was coducted in Kobri Elkobba military hospital in the period between January and september 2022 , It included 100 consecutive patients referred for MDCT which revealed coronary atherosclerosis along with lipid profile analysis without being on statin therapy, the mean age of the studied population was 54.34 ± 11.04, and there were 69 (69%) male patients.

Our study showed highly significant negative correlation between total cholesterol, LDL cholesterol, and serum triglycerides on one hand and the mean density of the plaques on the other hand, ($P < 0.001$ for all). There was a significant positive correlation between HDL cholesterol and the mean density of the plaques ($P < 0.001$).These findings were supported by the prospective study done by Philipp Sebastian who used intravascular ultrasound-virtual histology (IVUS-VH) for assessment of coronary plaque composition in about 990 patients from 42 centres. They demonstrated a significant correlation between plaque components and lipid profile parameters, where patients with high total cholesterol, LDL cholesterol and serum triglycerides levels on one hand and low HDL cholesterol levels on the other hand, have non-calcified lesions more than calcified lesions **(9)**

We also found that the mean serum total cholesterol level, LDL, and triglycerides were higher in the subgroup having non-calcified plaques than the subgroup having calcified plaques ($p<0.001$ for all). HDL cholesterol was lower in the subgroup having non-calcified plaques than the subgroup having calcified plaques ($P = 0.025$). This is in accordance with previous studies which stated that higher total serum cholesterol, LDL cholesterol and serum triglycerides on one hand and lower HDL chlesterol on the other hand played an important roles in the development of calcified plaques and non-calcified plaques, Also they were emerged as the only significant predictors of the absolute non-calcified plaque count and the relative predominance of calcified plaques, mixed plaques and non-calcified plaques **(10)**

Two prior studies investigated the prevalence and characteristics of clearly discernible noncalcified coronary plaques in a patient population with suspected significant coronary artery disease (CAD) by using 64-slice computed tomography (CT). They indicated that noncalcified coronary plaques, alone or in combination with calcifications, can be detected in a high proportion of patients investigated by CT angiography for suspected CAD. Patients with noncalcified plaques

were characterized by significantly higher total cholesterol, low-density lipoprotein, and C-reactive protein levels **(10, 11).**

In our study, we found also that the total cholesterol, LDL cholesterol, and serum triglycerides were significantly higher in the subgroup with significant stenosis than the subgroup with non-significant stenosis ($P < 0.001$ for all). HDL cholesterol was significantly lower in the subgroup with significant stenosis than the subgroup with non –significant stenosis ($P < 0.001$). In contrast to our results, two other studies which analyzed serial IVUS studies of 60 left main coronary artery atherosclerotic plaques during ≥12 months of follow-up (18.3±9.4 months) and stated that there is no significant correlation between lipid profile parameters and atheroma burden on static assessment. Where as in serial evaluation - in accordance to our study - they found a significant positive linear correlation between total cholesterol, LDL cholesterol and serum triglycerides on one hand, and the progression of atheroma (greater annual increase in plaque and media cross sectional area) and greater annual decrease in lumen cross sectional area on the other hand , HDL cholesterol had also a significant negative linear relation with annual changes in plaque and media cross sectional area **(12, 13).**

Our study showed highly significant positive correlation between total cholesterol, LDL cholesterol, and serum triglycerides on one hand and the degree of calcification detected by ca score using the Agatson score on the other hand, ($P < 0.001$ for all). There was a significant negative correlation between HDL cholesterol and the degree of calcification detected by ca score using the Agatson score ($P < 0.001$). This finding was supported by the rsults of **Kronmal et al. (14)** in the MESA cohort, which studied the cardiovascular risk factors associated with both the risk of developing incident coronary calcium and increases in existing calcification. However LDL and HDL have no significant role in the progression of calcification . Against this result , **Yadon Arad**, **et al.(15)** In univariate correlation,all lipid profile parameters were strongly correlated with calcium score except LDL cholesterol($p=0.15$) which became significantly positively correlated with calcium score in the multivariate correlation($p=0.01$), HDL was strongly negatively correlated with calcium score in the univariate correlation (<0.001) and became borderline in correlation with calcium score in the multivariate analysis ($p=0.04$) .

Conclusion

Total serum cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and serum triglyceride levels have a strong, independent, correlation with coronary plaque density , plaque vulnerability and the degree of calcification , besides the degree of coronary stenosis , as revealed by multi-detector computed tomography

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