Association Of Lipid Profile And Inflammatory Markers With Coronary Plaque Characteristics Assessed By Multi Slice Coronary CT Angiography In patients with Coronary Artery Disease

Thesis

Submitted for fulfillment for Master Degree in Cardiology

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2019

بسم الله الرحمن الرحيم

قَالُوا

سُبْحَانَكَ لَا عِلْمَ لَنَا

إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ

الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgment

All praises to Allah and all thanks for guiding me by his mercy to fulfill this thesis, which I hope to be beneficial for people.

I would like to express my deepest gratitude to **Dr. Hisham Mohammed AboulEnein** professor of cardiology, Benha Faculty of medicine, for his meticulous supervision, stimulating valuable suggestions and his general support throughout the whole work.

I wish also to express my supreme gratitude and appreciation to **Dr.Shimaa Ahmed Mostafa** , assistant professor of cardiology , Benha Faculty of medicine, for her meticulous supervision, kind guidance, and continuous support.

Also, I would like to express my Sincere thanks and appreciation to **Dr. Hani Hassan Ebaid** ,lecturer of cardiology, Benha Faculty of medicine, for his continous encouragement and support and careful supervision throughout this study.

My thanks also extend to my colleagues who helped me in this work in its various stages.

Last but not least, none of my work would have been possible without the constant support of my family.

Abdelrahman Gamal

Contents

List of abbreviations

ABP	Arterial Blood Pressure
ACS	Acute Coronary Syndrome
ADHF	Acute Decompensated Heart Failure
AF	Atrial Fibrillation
AHA	American Heart Association
AR	Aortic Regurge
BMI	Body Mass Index
BNP	B Natriuretic Peptide
bpm	Beat Per Minute
Ca	Calcium
CABG	Coronary Artery Bypass Graft
CAC	Coronary Artery Calcium
CAD	Coronary Artery Disease
CRP	C Reactive Protein
CT	Computed Tomography
CTA	Computed Tomography Angiography
CVD	Cardio Vascular Disease
DM	Diabetes Mellitus
EF	Ejection Fraction
FD-OCT	Frequency Domain- Optical Coherence Tomography
FFR	Fractional Flow Reserve
FFRCT	Fractional Flow Reserve Computed Tomography
HDL	High Density Lipoprotein
HDL-C	High Density Lipoprotein- Cholesterol
HR	Heart Rate
Hs-CRP	High Sensitive- C Reactive Protein
HU	Hounsfield Unit
IHD	Ischemic Heart Disease
IQR	Inter Quartile Range
IVUS	Intra Vascular Ultra Sound
L	Lymphocytes
LAD	Left Anterior Descending coronary artery
LCX	Left Circumflex coronary artery
LDL	Low Density Lipoprotein
LDL-C	Low Density Lipoprotein- Cholesterol
LM	Left Main coronary artery
M	Monocytes
MDCT	Multi Detector Computed Tomography
MI	Myocardial Infarction
MLD	Minimum Lumen Diameter
MR	Mitral Regurge
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MSCT	Multi Slice Computed Tomography
N	Neutrophils
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NIRS	Near Infra-Red Spectroscope
NLR	Neutrophil to Lymphocyte Ratio
NYHA	New York Heart Association

OCT	Optical Coherence Tomography
OM	Obtuse Marginal coronary branch
PCI	Percutaneous Coronary Intervention
PEACE	Prevention of Events with Angiotensin-Converting Enzyme inhibition trial
PHS	Physician's Health Study
PREVEND	Prevention of REnal and Vascular End stage Disease study
RCA	Right Coronary Artery
ROI	Region Of Interest
RS	Raman Spectroscope
SIS	Segment Involvement Score
SPSS	Statistical Package for Social Science
TC	Total Cholesterol
TCFA	Thin Capped Fibro Atheroma
TD-OCT	Time Domain – Optical Coherence Tomography
TG	Triglycerides
TIMI	Thrombolysis In Myocardial Infarction
VH	Virtual Histology
VLDL	Very Low Density Lipoprotein
VP	Vulnerable Plaque

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Introduction

Coronary artery disease (CAD), the leading cause of mortality worldwide, places a serious economic burden on health care systems. CAD is mainly due to atherosclerosis, an inflammatory process that is based on the interaction between immune mechanisms and metabolic risk factors. Atherosclerosis is the primary cause of mortality and morbidity in cardiovascular disease (CVD) . (*Moreira et al 2015).*

Dyslipidemia is the most important risk factor for atherosclerosis and contributes to increased risk to develop CVD. Abnormal lipid levels, particularly elevated low-density lipoprotein (LDL) and decreased high-density lipoprotein (HDL), are well-established independent risk factors for CVD, including coronary artery disease *(Tsao and Donnell 2013).*

 Previous studies have demonstrated that LDL is the primary atherogenic lipoprotein and that HDL is the predominant anti-atherosclerotic lipoprotein. Therefore, measurements of total cholesterol (TC), HDL-C, and LDL-C are widely recommended *(Nakazato et al, 2013)*.

Other data suggested that non-HDL-C is a better parameter for assessing CVD risk rather than TC and HDL-C *(Li et al* **2011***).* Also, some studies suggest that lipid ratios, including TC/HDL-C and LDL-C/HDL-C ratios are risk factors with better predictive value for coronary atherosclerotic progression or regression than each lipid parameter used independently *(Kimura et al 2010)* .

The most widely tested inflammatory biomarker is high-sensitivity C-reactive protein (hs-CRP), which predicts the risk of a first myocardial

infarction (MI) in healthy individuals and future coronary events in patients with stable CAD *(Sabatine et al 2007).*

Increased CRP levels are found to be associated with the prevalence of any plaque and mixed calcified plaques, as well as significant coronary stenosis *(Rubin et al 2011).*

It is well known that both elevated CRP and specific plaque subtypes are associated with poor disease outcome *(Ridker et al 2013).*

Also neutrophil-to-lymphocyte ratio (NLR), calculated as the ratio of absolute neutrophil count and absolute lymphocyte count, has recently been considered as a potential marker for identifying individuals with a risk of CVD and associated events *(Verdoia et al 2016).*

Major advances in CAD prevention require early detection of the vulnerable plaques. Conventional X-ray coronary angiography is the current gold standard for invasive evaluation of CAD. However, it only shows the lumen of the vessel, greatly underestimating the atherosclerosis burden. A noninvasive assay to directly detect coronary atherosclerosis would therefore be beneficial. Coronary CTA provides comprehensive information noninvasively regarding the location, severity, and characteristics of coronary atherosclerotic plaques: noncalcified, calcified, and mixed plaques can be identified. A previous study showed that vulnerable plaques in diabetic patients tend to occur at multiple sites, with high atherosclerotic burden *(Chu et al 2010).*

Understanding how lipid profile, inflammatory markers and vulnerable plaques are related ,and using imaging techniques to assess this relationship may enable the early identification of vulnerable patients.

Aim of the work

The aim of this work is to study the relation between lipid profile and inflammatory markers with coronary plaque characteristics as assessed by multi slice coronary CT angiography in patients with coronary artery disease

Imaging modalities for assessment of coronary artery plaques

The concept of the "vulnerable plaque" being responsible for most of acute coronary syndromes (ACS) has become widely accepted. Coincidentally, there has been rapid development of coronary imaging techniques, both noninvasive and invasive, seeking the ability to detect high-risk plaques before their disruption and formation of occlusive thrombus *(William et al., 2011).*

It has been established that the majority of acute coronary events (>70%) are caused by plaque rupture followed by thrombus formation. The most common substrate for superimposed thrombus formation is thought to be the thin-capped fibroatheroma (TCFA); a plaque with a large necrotic core and thin fibrous cap ,infiltrated by macrophages and lymphocytes. The thin fibrous cap contains less smooth muscle content, which in certain circumstances can rupture causing the thrombogenic parts of the plaque to be exposed to the circulating blood into the lumen. This will lead to the activation of the clotting cascade and the formation of a thrombus that can occlude the lumen, resulting in an ACS. *(Virmani et al., 2000).*

Traditionally, imaging of the coronary arteries by means of invasive coronary angiography has focused on the assessment of luminal dimensions and the presence of luminal stenosis. However, invasive coronary angiography can only assess the degree of stenosis and is less able to evaluate the presence of atherosclerosis, including the presence of vulnerable plaques. As a result, there is an emerging need for imaging modalities that can detect atherosclerotic plaques with high-risk features

indicating increased vulnerability for acute coronary events. *(Joella et al., 2009).*

In this chapter we will focus on the role of current and future techniques of cardiovascular imaging in the diagnosis of coronary heart disease, by detecting the vulnerable plaques and significant lesions. These modalities may help to decrease ACS mortality and reduce the individual, social and economic burden of coronary heart disease.

1--Intravascular ultrasound (IVUS):

IVUS is a catheter-based imaging technique, that allows the detection of atherosclerotic plaque in clinical practice and research. It is considered as the ''gold standard'' for detection, assessment and quantification of coronary plaques *(Mintz et al., 2001).*

IVUS is performed at the time of coronary angiography and involves a tiny ultrasound probe that emits high frequency signals (20–40 mHz). This wire-based probe can be placed over a guidewire into the coronary artery and withdrawn at a set rate (0.5 mm/sec) to provide segmental tomographic images of the vessel. IVUS has demonstrated great discrepancy between the extent of atherosclerosis detected by coronary angiography and the actual extent of atherosclerotic disease *(Nissen and Yock 2001).*

Quantitative assessment of the coronary vessel and plaques was made possible by the introduction of greyscale IVUS analysis and the further analysis of individual plaque components has been made possible with virtual histology (VH) IVUS*(Nissen and Yock2001).*

Grayscale IVUS:

Conventional grayscale IVUS imaging allows accurate determination of vessel and lumen dimensions and the distribution, morphology, and severity of the atherosclerotic plaques.**(Murray et al 2010)**

The classic trilaminar appearance of IVUS include three layers : the intima, media, and adventitia (figure 1). The innermost layer, the intima, is in direct contact with the intraluminal space and is typically one to two cell layers thick in healthy arteries. Therefore, in normal coronaries, as seen in young individuals, the intima will not be detcted by IVUS because of the limits of the axial resolution. However, due to age as well as remodeling and deposition of atherosclerotic plaques, the majority of adults evaluated in the catheterization lab have a much thicker intima allowing its detection by IVUS, which appears echogenic. The intima is separated from the media by the internal elastic membrane that is composed mainly of homogenous layers of smooth muscle cells. As the smooth muscle cells do not reflect sound waves well and there is less elastin and collagen as compared to the intima and adventitia, the media appears as a thin echo lucent strip surrounding the vessel and separating the intima from the adventitia. The media is separated from the adventitia by the external elastic membrane. It is composed of fibrous connective tissue with a high amount of elastin and collagen and therefore appears echogenic. The imaged vessel wall therefore has a classic trilaminar appearance (bright-dark- bright) providing important land marks for assessment and measurement. **(Nair et al,2002)**

However , Conventional IVUS has limited ability to characterize the plaque components that determine vulnerability. Automatic processing

uses the amplitude of the backscattered echo signal to differentiate echolucent components (lipid ,necrotic core) from highly echogenic ones (calcium, dense fibrous tissue) ,but is unable to accurately diffrentiate fatty from fibrous plaques. (figure 2). *(Low et al., 2009).*

Grayscale IVUS features of high vulnerable plaques have been evaluated prospectively by Yamagishi et al. The investigators evaluated 114 coronary plaques without significant luminal obstruction and assessed which plaques were related to an acute coronary event during a follow-up period of about 21 months. Surprisingly, The results reported that large, eccentric, positive remodeled plaques with an echolucent zone were at higher risk of unstability (Figure 2) *(Yamagishi et al., 2000).*
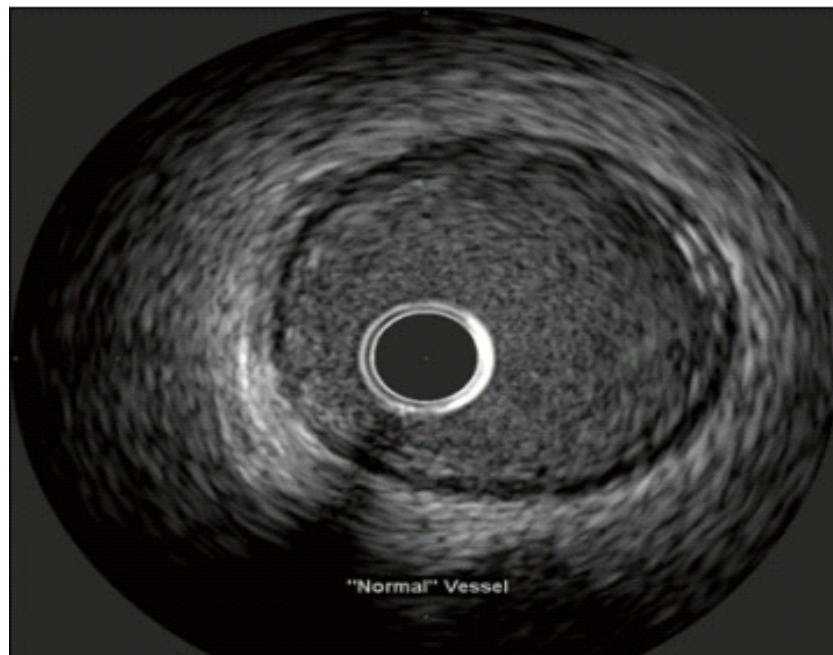
Figure (1): Healthy vessel. the trilaminar appearance with a thin echogenic intima, echo lucent media bounded by the internal and external elastic lamina, and echogenic adventitia.*(Graning R, 2015).*
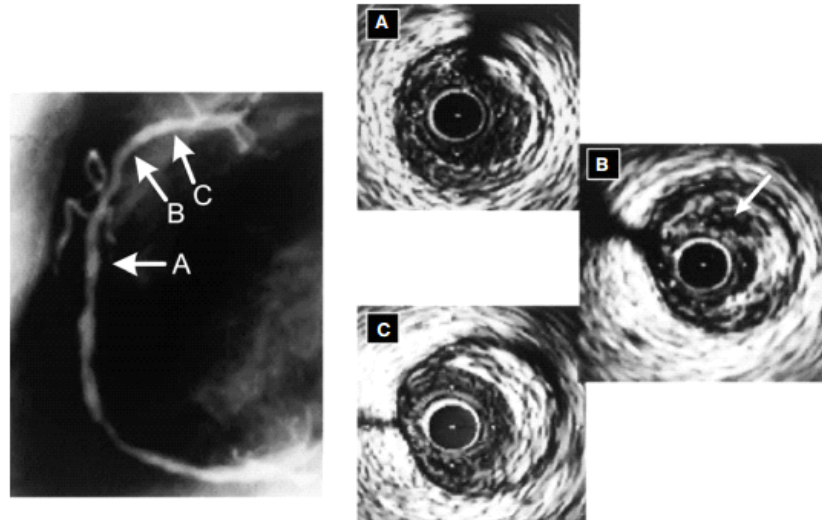
Figure (2): Coronary plaque in the right coronary artery (RCA) of a patient presenting with an acute coronary syndrome as evaluated by coronary angiography (left) and intravascular ultrasound (right). A: A mild concentric lesion in the distal part of the RCA. B: In the proximal portion, a significant eccentric lesion with an echolucent area (arrow) and high plaque burden of 67%. C: More proximally, an eccentric lesion with high echo density *(Yamagishi et al., 2000).*

Virtual Histology IVUS (VH- IVUS):

VH-IVUS uses an auto regression model to generate multiple spectral parameters of the backscattered ultrasound signal (maximum power and corresponding frequency, minimum power and corresponding frequency, y intercept, slope, mid band fit, and integrated backscatter) *(Nair et al., 2002).*

These parameters are used in classification trees to generate a tissue map of the plaque components: dense calcium (White) , necrotic core(red) ,fibrous (dark green), fibrofatty (yellow-green) *(Okubo et al., 2008).*

Tissue types:

1. Fibrous

Fibrous tissue is represented by dark-green pixels (Figure 3). Histologically, it is formed of collagen tissue with no lipid .On grey scale IVUS, this tissue tends to be medium-bright regions *(Burke et al., 2002)*.

2. Fibrofatty

Fibrofatty tissue is denoted in VH IVUS by light-green pixels (**Figure 3**). This tissue is loosely packed collagen, but it can have a cellular element with potential for foam cells to start invading *(Nair et al., 2002)*.

There is usually no necrotic core and even cholesterol products are rare. If thrombus or plaque rupture are considered as plaque during analysis, then they are displayed as fibrofatty plaques *(Murray and Palmer, 2009)*.
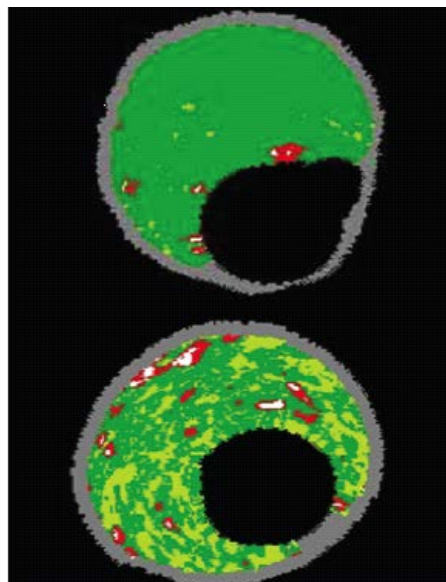
Figure (3): Fibrous plaque appearing as dark green (top) and fibrofatty plaque appearing as light green (bottom) *(Murray et al., 2010)*.

3. Necrotic core:

In VH the necrotic core is seen as red (**Figure 4**). This tissue is a mixture of soft lipid-like dead cells, trapped blood cells and foam cells .

The majority of any real structure is lost and with some areas producing micro-calcification as a by-product from the dead cells, this leads to a recipe for gross instability and rupture with friable areas next to sharp calcification *(Burke et al., 2002)*.

4. Dense calcium

White pixels represent dense calcium (**Figure 4**). These calcified regions can be lost during histological analysis but on grey scale IVUS, they act as very strong reflectors of signal and appear as bright white.

Figure (4): Necrotic core in a thin-cap fibroatheroma (TCFA) lesion appearing as red (top) and dense calcium in fibrocalcific disease appearing as white (bottom) *(Murray et al., 2010)*.

The accuracy and ability of VH IVUS to evaluate the presence of vulnerable plaques were first demonstrated by Rodriguez-Granillo et al. The investigators observed that vulnerable plaques as determined on VH IVUS were more prevalent in patients presenting with ACS than in those with stable coronary artery disease. *(Rodriguez-Granillo et al., 2006).*

Similar results were recently reported by Pundziute et al., who detected that in culprit lesions of patients with ACS, the thin-capped fibro atheroma was more prevalent than in plaques of patients presenting with stable anginal symptoms. *(Pundziute et al., 2008).*

Thin-cap fibroatheroma (TCFA) have a confluent necrotic core (>10%) in direct contact with the lumen (no evidence of a cap is detected by IVUS) and a minor amount of calcium (<10%). If this is present on three consecutive VH -IVUS cross-sectional frames, this indicates an increase in vulnerability. It is currently thought that the higher the extent of surface contact the necrotic core has with the lumen, and the presence of increased amounts of calcium, produces the highest risk of plaque rupture. This appears to be different from the common thought theory that non-significant plaques are the ones with higher risk of rupture *(Kolodgie et al., 2003).*

Interestingly, the presence of positive remodeling detected by VH IVUS was found to be similarly linked to the presence of vulnerable plaques. A retrospective study using VH IVUS demonstrated that plaques with positive remodeling contained significantly more necrotic core and features of high-risk plaque, while negative remodeled plaques showed a more stable phenotype *(Rodriguez-Granillo et al., 2006).*

Notably, in addition to remodeling, it was demonstrated that plaque composition on VH IVUS was influenced by the location of the plaque in

the coronary artery tree. As shown by VH IVUS, proximal segments of coronary arteries had a larger necrotic core area when compared to distal coronary segments, whereas the other plaque components (fibrofatty, fibrous and dense calcium) were distributed almost equally along the coronary artery tree. Accordingly, the distance from the coronary ostium was shown to be inversely associated with plaque vulnerability, which may explain the higher incidence of culprit lesions in proximal parts of the coronary vessels. *(Valgimigli et al., 2006).*

Therefore, exact coronary dimensions and elements of plaque composition, such as the presence of necrotic core, degree of calcification, plaque burden, and coronary remodeling, are all anatomic features detected by IVUS and IVUS-VH, but not by traditional coronary angiography. However, the limited resolution of IVUS-VH (approximately 150 µm) makes it unable to visualize and assess thin fibrous caps (<65 µm). In order to improve visualization of the coronary lumen we need to improve resolution, and this is best obtained with a newer invasive tool called optical coherence tomography (OCT) *(Murray et al., 2010)*.

2--Optical Coherence Tomography (OCT)

Optical coherence tomography (OCT) provides high resolution imaging of tissue microstructure by recording backscatter and light reflections from a fiber optic wire while being simultaneously pulled back and rotated. It has an excellent spatial resolution of 10-20 µm, which is ten times higher than that of IVUS. Furthermore, using histological controls, it has been demonstrated that OCT is superior to IVUS in detecting important features of plaque vulnerability including thickness of fibrous cap, thrombus and density of macrophages *(Jang et al., 2002).*

Plaque composition assessment with OCT

OCT can detect a variety of vascular morphologies either before or after PCI based on the following criteria:

• *Backscatter (high or low) and signal intensity (rich or poor):* Backscattering refers to the signal intensity and the higher the backscattering, the more rich the signal is , and the brighter the image will appear. While Lesion characteristics with low backscattering will have poor signal and will appear dark .

• *Attenuation (high or low):* Attenuation refers to penetration beyond the lumen. In the catheterization laboratory, when there is a a lesion with low attenuation, one can evaluate more easily the lumen and the wall beyond the lesion; while if the lesion had characteristics of high attenuation, luminal and wall assessment would be more difficult.

• Shape (focal, linear, layered).

• Borders (sharply or poorly delineated).

• Consistency (homogenous or heterogeneous).

• Location. *(Tearney GJ, 2008).*

Each lesion is characterized by a specific set of features (figure 5):

▪ Fibrous plaques have high backscatter with low attenuation So appear diffusely and homogenously bright with the ability to see clearly beyond the lumen.

▪ Lipid plaques have low backscatter with low attenuation and appear as if there is a pool of darkness, which is confined within a higher superficial cap.

- Calcified plaques or nodules within the vessel wall have low backscatter with low attenuation therefore appearing dark. Due to the nature of calcific nodules , the borders of calcium are sharp and well defined.

- Thin-capped fibrous atheromas and thicker capped fibrous atheroma can be differentiated by the thickness of the bright superficial layer, which may have implications in assessing plaque vulnerability. *(Tanaka et al., 2009).*

- Inflammation of the intimal lining may produce strong optical signals as the densely infiltrating macrophages on the surface of plaque may scatter light signal and appear as dark shadow and can be misinterpreted as a thin-cap fibroathermona creating a superficial optical artifact.
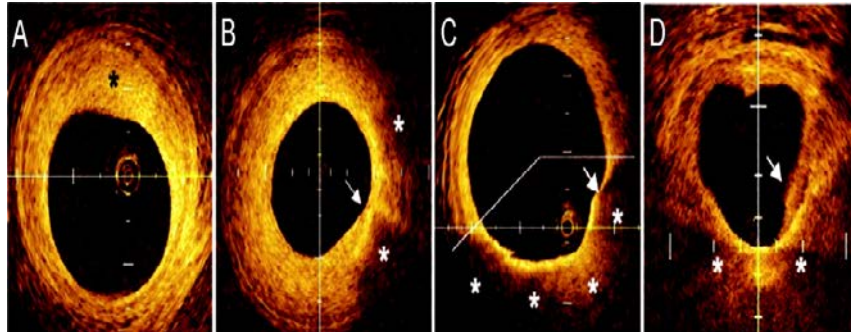
Figure (5): A, Fibrous plaque (*). B, Lipid tissue (*) under fibrous cap. The fibrous plaque thickness at the thinnest part (arrow) is 130 μm. C, Lipid plaque (*) with very thin fibrous cap (arrow). Minimal thickness of the fibrous cap is 20 μm. Arch of the lipid was measured as an angle between the 2 straight lines that joined the center of lumen to both ends of lipid area. D, Protruding thrombus (arrow) overlying thin-cap lipid plaque (*) *(Takano et al., 2008).*

• Thrombi are defined as protruding masses into the vessel lumen that are discontinuous from the surface of the vessel wall, with a variable degree of OCT signal attenuation behind the mass (Figure 6) *(Tearney et al., 2003).*
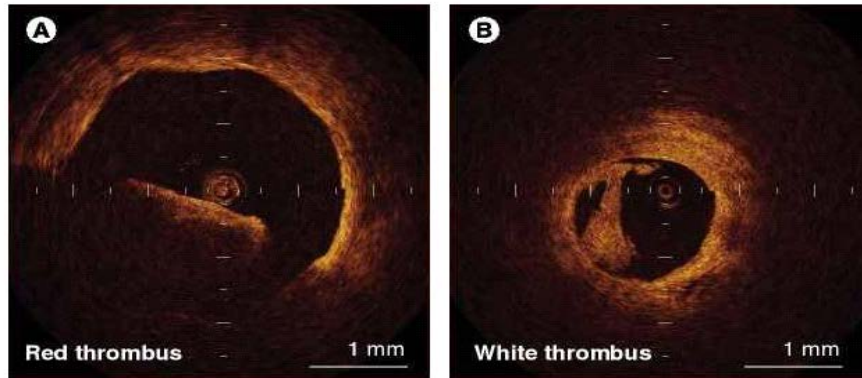
Figure (6): Optical coherence tomography examples of red and white thrombus. (A) Red thrombus shows signal attenuation due to the red blood cell component, while (B) white thrombus is platelet-rich and exhibits low signal attenuation *(Shinke and shite, 2010).*

- OCT images for red thrombi, which mainly consist of red blood cells, are characterized by high backscattering protrusions with strong signal attenuation. A large amount of red thrombus may interrupt the visualization underneath plaque morphologies owing to signal attenuation

- White thrombi, which consist mainly of platelets and white blood cells, are characterized by a signal-rich protruding mass *(Kume et al., 2006).*

- Thrombi are frequently found in the culprit lesion of patients with acute coronary syndrome (ACS).So, OCT has the potential to detect high-risk coronary plaques for early intervention strategies in acute coronary syndrome patients. *(Tanaka et al., 2009).*

Vessel sizing with OCT

Optical coherence tomography can obtain cross-sectional images with clear delineation between the vessel wall and coronary lumen, although the shallow penetration of OCT may limit the visualization of whole-vessel structure when compared to IVUS .Yamaguchi *et al.* reported that the minimal lumen area and diameter measured on OCT images correlated well with those measured on IVUS images *(Yamaguchi et al., 2008).*

Kawamori *et al.* reported that lumen diameter at the proximal site of culprit lesions measured on Time domain OCT (TD-OCT) images was almost identical to that measured with IVUS. However, the lumen diameter at the distal site of the culprit lesions on OCT images was smaller than that measured on IVUS images. This may be due to decrease in intracoronary pressure during OCT imaging resulting from proximal vessel occlusion with a balloon *(Kawamori et al., 2009).*

Image acquisition without vessel occlusion by Frequency domain OCT (FD-OCT) systems may be more accurate and effective for measurement of vessel size and estimation of the suitable size of the coronary stent *(Takarada et al., 2010).*

Limitations of TD-OCT:

Major limitation of endovascular OCT is its signal attenuation by blood and its limited penetration depth in tissue. Hemoglobin and red blood cells (RBCs) attenuate light from the OCT catheter through absorption and scattering of light, respectively. Several techniques have been developed to overcome this limitation focusing on displacing the blood medium with saline flushes or balloon occlusion. A previously

published technique employed brief proximal vessel occlusion and saline flush to remove blood from the imaging window. Although feasibility and safety have been documented using this technique, there are always possible risk of fluid overload with saline flushes and potential ischemic complications with balloon occlusion *(Yamaguchi et al., 2008).*

A possible alternative approach is isovolemic replacement of blood with an optically transparent, hemoglobin-based blood substitute, which has been tested in mouse myocardium. Because of its oxygen-carrying capacity and immiscibility (i.e., not capable of being mixed), the use of a blood substitute has the potential to improve OCT imaging applications *(Villard et al., 2002).*

Later, OCT technology has been developing over time, moving from Time domain to Frequency domain OCT systems. Currently available Frequency domain OCT (FD-OCT) systems have much higher frame rates and scanning speeds, enabling the acquisition of long coronary segments very rapidly. With FD-OCT, 100 frames\sec can be obtained, with an automatic pullback of 20 mm/sec and a resolution of 500.000 pixel /frame during a single injection of contrast bolus. *(Geraci et al., 2010).*

3--Angioscopy

Angioscopy applies fiber-optic technology to visualize directly the luminal surface and is able to characterize plaque composition and to distinguish between white and red thrombus. Endoluminal irregularities such as tears , fissures and ulceration can also be seen *(__William et al., 2011__).*

Angioscopy describes the appearance of the luminal surface based on color (Figure 7)
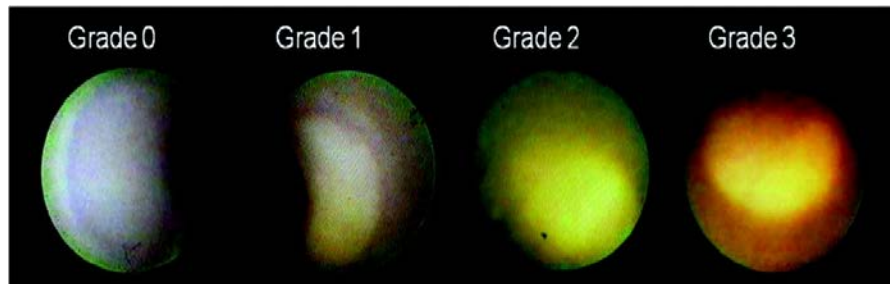
Figure (7): Classification of plaques according to the yellow color intensity: grade 1, light yellow; grade 2, yellow; and grade 3, intensive yellow *(Ueda et al., 2010).*

A normal coronary artery appears as glistening white, while atherosclerotic plaques can be categorized as yellow or white. Data from histopathological analysis supports the association of yellow color with high concentrations of cholesterol-laden crystals with or without plaque degeneration *(Thieme et al., 1996).*

The intensity of yellow color is also an indicator of fibrous cap thickness, with high yellow intensity associated with thin fibrous caps overlying a lipid core. In a study using angioscopy and OCT, the specificity and sensitivity of the angioscopy-identified yellow plaques for having a fibrous cap measuring <110 μm by OCT was 96% and 98%, respectively *(Takano et al., 2008).*

Furthermore, yellow plaques are seen most commonly at the site of culprit lesions, increasing the risk of a subsequent coronary event, and indicate increased susceptibility to rupture and thrombosis with increased intensity of yellow color. All that data support the concept that yellow lesions mostly represent a Vulnerable Plaque *(Ueda et al., 2004).*

Further, Hirayama et al. showed that statin therapy for 28 weeks was effective in decreasing yellow intensity by angioscopy and reducing atheroma volume by IVUS, suggesting stabilization of the plaque *(Hirayama et al., 2009).*

Although their findings are promising, angioscopy only assess the plaque surface, and that atherosclerotic surface changes may not be sufficiently sensitive to detect subtle significant changes in plaque composition, *(William et al., 2011).*

4--Spectroscopy

Spectroscopy, the study of energy wavelengths, is used routinely in physical science to determine the chemical composition of substances. A spectrum of a given molecule is unique, enabling these techniques to identify the chemical composition of a subject. Spectra are created by processing the collected light scattered from an artery that is emitted during laser or infrared light illumination. Plaque components such as cholesterol and calcium have unique absorption and reflectance patterns of light, also referred to as diffuse reflectance spectroscopy. To date, the most validated spectroscopy methods are Raman Spectroscopy (RS) and Near-Infrared Spectroscopy (NIRS) *(Moreno et al., 2002).*

RS is based on the unique laser light wavelength shifts reflected off a substance, also referred to as Raman shift. The molecular characteristics of lipid and calcium and their unique Raman shift patterns make RS highly sensitive for plaque detection *(Brennan et al., 1997).*

A major limitation of RS is that only a small number of photons are recruited into the Raman shift, resulting in poor tissue penetration and low signal-to-noise ratio. Additionally, background noise from

backscattered light within the optical fibers of the catheter-based system also degrades signal quality. *(Nazemi and Brennan, 2009).*

However, combining RS with other intravascular imaging modalities such as IVUS provides synergism between the structural definitions of vulnerable plaque (VP) by IVUS and the chemical quantification by RS *(Romer et al., 2000).*

NIRS measures diffuse reflectance signals by using NIR light (wavelengths from 800nm to 2500 nm) as an energy source. An NIRS emits light onto a substance and measures the light that is reflected back over a wide range of optical wavelengths; this information is then processed to produce a spectrum. Spectra obtained from a scan are applied to an algorithm that predicts the probability of VP and are displayed on a chemogram, with lipid pools colored yellow in a background of red *(Waxman et al., 2009).*

The major advantage of NIRS is that imaging can be performed without replacing the blood in the vessel, which is required for OCT. However, the major limitations of NIRS are that it only detects one characteristic of VP and is unable to determine depth, superficial versus deep, of the lipid core *(William et al., 2011).*

5--Fractional flow reserve (FFR)

FFR is invasive physiological index that can be measured during intracoronary administration of acetylcholine to assess the functional significance of coronary artery stenosis *(Pijls and De Bruyne 1998).*

Technological innovation allows calculating coronary flow and pressure based on anatomic MDCT image data ,therfore allowing measurment of FFR noninvasively *(Koo et al., 2011).*

Recent multicenter international study investigated the ability of FFRCT for diagnosis of ischemia compared to an invasive FFR measurement in 252stable patients with suspected or known CAD. In this study, diagnostic accuracy, sensitivity, specificity, positive and negative predictive values of FFRCT plus MDCT were 73% , 90% , 54% , 67% , and 84% , respectively.

In addition, FFRCT was associated with better evaluation of ischemia compared to CT alone as meta-analyses from 5 studies including 706 patients and 1,165 vessels showed that sensitivity and specificity were 83% and 78% by per-segment analysis; 90% and 72% by per-patient analysis, respectively. The area under the curve was 0.94 at the per-patient level and 0.91 at the per-vessel level *(Deng et al.,2015).*

These observations indicate FFRCT as a potential noninvasive tool to assess the presence of ischemia. However, several potential limitations should be considered. The diagnostic performance of FFRCT is impaired by CT imaging artifacts including misalignment, motion, and beam hardening from coronary calcification, and increased image noise. Physiologic conditions may affect assumed parameters such as fluid density and viscosity on FFRCT. *(Renker et al., 2014).*

6--Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA)

<u>Assessment of Coronary artery stenosis</u>

Coronary MRA assesses the proximal and mid portion of coronary arteries, especially left anterior descending and right coronary artery. By contrast, the image quality of left circumflex is diminished due to an increased distance from the cardiac coil.

Previous studies showed an excellent agreement between the proximal segments of coronary on MRA and invasive angiography **(Figure 8)** *(Bogaert et al., 2003)*
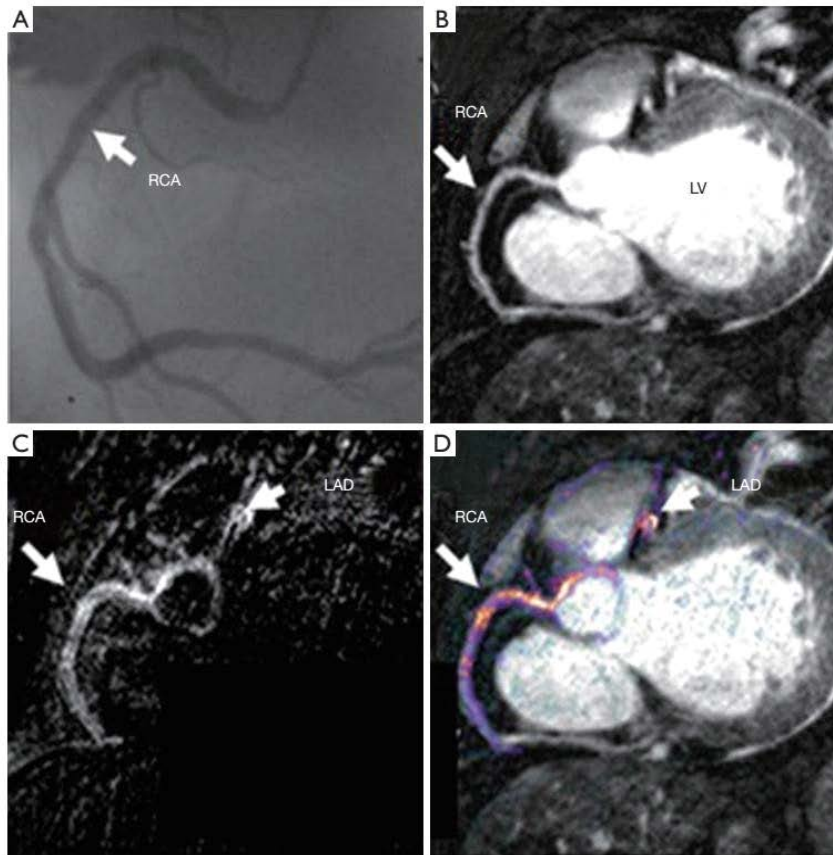
Figure 8 Contrast-enhanced cardiac MRI of coronary artery. (A) Invasive coronary angiography shows the presence of mild stenosis in the right coronary artery; (B) MRA visualizes the right coronary artery; (C, D) contrast-enhanced cardiac MRI revealed diffuse contrast enhancement (white arrow) in the right coronary artery. MRI, magnetic resonance imaging; MRA, magnetic resonance angiography *(Ibrahim et al., 2009)*.

It should be noted that MRA imaging takes more time compared to MDCT and some patients cannot tolerate, while the advantage of MRA is to visualize coronary arteries without any contrast medium. Therefore, MDCT seems to be more applicable non-invasive imaging tool in the

clinical settings and MRA is good for patients with kidney disease *(Hamdan et al., 2011)*.

Assessment of plaque compositon

MRI is able to differentiate plaque components on the basis of biochemical and biophysical parameters, such as water content , chemical composition, physical state, molecular motion, or diffusion *(Fayad, 2003).*

Specifically, recent improvements in MR techniques such as multi contrast MR, generated by T1- and T2-weighted, proton-density-weighted, have been shown to help to characterize lipid rich , fibrocellular, and calcified regions of atherosclerotic coronary plaques *(Cai et al., 2002).*

There were studies about plaque instability which demonstrated that coronary high- intensity plaques detected by non-contrast T1-weighted MRI are associated with positive coronary remodeling and low density on MDCT. *(Kawasaki et al., 2009).*

Multi slice CT angiography and coronary artery disease

MSCT angiography is a rapidly developing imaging tool that permits noninvasive visualization of coronary atherosclerosis. Following the introduction of 4-slice scanners, the technique has developed rapidly and 64-slice , 128 –slice and even 320-slice systems are currently available. Accordigly temporal and spatial resolution have improved , leading to superior image quality and diagnostic accuracy for the detection of CAD. Although the resolution of invasive coronary angiography remains superior to that of MSCT angiography, MSCT has proved high diagnostic accuracies for the detection of significant CAD *(Budoff et al., 2008).*

1- Coronary calcium

In the coronary arteries, calcifications occur almost exclusively in the context of atherosclerosis. The only exception are patients with advanced chronic kidney disease, in whom medial (non atherosclerotic) calcification of the coronary artery wall may occur in addition to atherosclerotic calcification. Not every atherosclerotic coronary plaque is calcified, but within a coronary artery, the amount of coronary calcium roughly correlates to the extent of atherosclerotic plaque burden *(Burke et al., 2003).*

Calcification is neither a sign of vulnerability nor stability of an atherosclerotic plaque, and its presence or absence is not closely associated with the risk of an individual lesion to rupture and cause an acute coronary event. *(Pham et al., 2006).*

However , Plaques with healed ruptures usually contain calcium, while plaques with erosions (a less frequent mechanism of acute coronary syndromes) are often non calcific plaques *(Taylor et al., 2000)*.

It is important to consider that in spite of the relationship between coronary calcification and coronary plaque burden, there is only a weak relationship between the amount of coronary calcium and the angiographic severity of luminal obstruction. Even large amounts of coronary calcification is not necessarily associated with significant coronary artery stenosis. Although the absence of coronary calcium makes the presence of significant luminal obstruction relatively unlikely, it is not absolutely impossible and a 'zero' calcium score cannot be used to rule out coronary artery stenosis especially in young symptomatic patients when they present with acute symptoms. *(Marwan et al., 2009)*.

A- Detection of coronary calcium

MDCT and Electron beam computed tomography with electrocardiogram gating nearly have the same accuracy for detection and quantification of coronary artery calcium (CAC) *(Stanford et al., 2004)*.

Images are obtained without injection of contrast and at a relatively low dose of radiation. (About 0.7 –3.0 mSv) *(Gerber et al., 2005)*.

The amount of calcium is quantified using the (Agatston score.)

Several reference data are available that describe the significance and distribution of 'Agatston score' stratified by gender and age

(McClelland et al., 2006).

In addition to Agatston score, alternative methods of quantification of coronary artery calcification include calcium volume score and calcium mass score has been used in other studies *(Becker et al.,2001).*

However, the accuracy of each Ca score is still on debate. Currently, Ca scoring by score remains the most widely used measure to evaluate the extent of coronary artery calcification in both clinical settings and research. *(Alluri et al., 2015).*

Interscan variability for calcium scores can be high, especially in patients with small calcium amounts. A study of 3355 individuals had found an average variability of 18% for calcified plaque volume and 20% for Agatston score.*(Detrano et al., 2005).*

B- Clinical significance of coronary calcium

Several cohort studies have shown that the presence of coronary calcification detected by MSCT in asymptomatic individuals is a prognostic parameter with high predictive power concerning the development of acute cardiac events during the following 3–5 years *(Budoff et al., 2006).*

Several meta-analyses showed that a calcium score of 0 is associated with an extremely low mid-term risk of acute myocardial infarction or death due to coronary artey disease (0.03% per year) *(Arad et al., 2005).*

However, even relatively small amounts of coronary calcium indicate an elevated risk. Recently large population-based trial showed a three-fold increased risk for acute cardiovascular events in patients with an 'Agatston score' between 1 and 10 when compared with patients with the absence of detectable calcification *(Budoff et al., 2009).*

While the absence of Coronary calcification was associated with a very low risk of cardiovascular events (0.5%),, in case of intermediate coronary calcification (Ca score 100–400) and high levels of coronary calcification(Ca score >400), the relative risk of cardiovascular events rise to 4.3% and 7.2% respectively. *(O'Rourke et al., 2000)*.

Furthermore, many studies showed that coronary calcium allows better risk stratification than other markers of risk such as intima to media thickness *(Folsom et al., 2008)*.

So According to these findings, the use of Coronary artery calcium quantification in intermediate risk patients is a Class IIb recommendation by the American Heart Association to improve assessment and risk stratification. *(O'Rourke et al., 2000)*.

It was also shown that progression of CAC was associated with multiple risk factors and increased risk for future cardiovascular events ,and shows a genetic association *(Schmermund et al., 2001)*.

A number of trials suggested the potential use of serial evaluation of CAC scores to assess the efficacy of anti-atherosclerotic therapies for the reduction of cardiovascular events. However, they have reported conflicting results, currently no sufficiently strong data are available to support the use of serial calcium scans for assessing the efficacy of risk factor modification . For instance, statins did not slow the progression of CAC in any randomized trials *(Schmermund et al.,2006)*.

Coronary plaque burden:

Coronary plaques are defined as structures > 1 mm2 within or adjacent to the coronary artery lumen, which can be clearly diffrentiated from the vessel lumen and the surrounding tissue in two perpendicular image planes. **(Pundziute et al, 2008).**

Plaque burden can be assessed by various methods such as segment involvement score SIS, degree of segment stenosis and total plaque volume and area.

1. Segment Involvement Score (SIS). (*Khazai et al, 2015*).

Using a 17-segment model according to the modified American Heart Association reporting system of the coronary arteries. The presence of coronary plaques(either obstructive or non-obstructive) is evaluated visually then the (SIS) is determined by summing number of coronary segments with plaques (maximum scoring=17) figure 9.
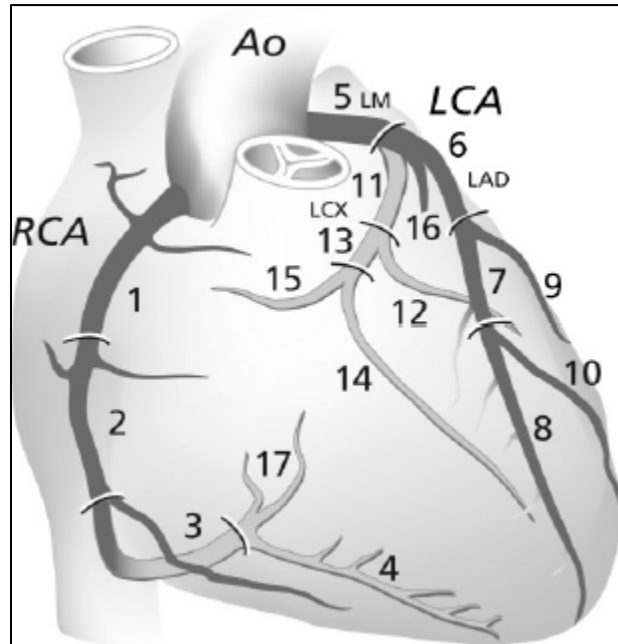
Figure (9): Modified 17-segment of the AHA reporting system of the coronary arteries used in calculation of (SIS) by summing number of coronary segments containing plaques.*(Jesse Habets, et al., 2012).*

2- Detection of degree of segment stenosis*:*

Because of its speed and convenience, visual assessment of luminal stenosis is the most commonly performed assessment method in clinical practice, both for coronary CT angiography as well as for invasive coronary angiography. The observer interrogates the lesion in different views and identifies the minimum lumen diameter (MLD). The observer then compares the MLD to an arterial diameter at an appropriate reference site, (i.e., a non-diseased arterial segment close to the lesion, with no branch vessels in between.) Maximum diameter stenosis severity can be graded using either a qualitative or semi quantitative stenosis grading system. Table (1) and Table (2) provide the stenosis grading systems recommended by the Society of Cardiovascular Computed Tomography *(Raff et al., 2009)*

Table (1): Recommended Qualitative Stenosis Grading *(Raff et al., 2009)*.

Descriptive Lumen Obstruction	Qualitative Stenosis Grading
Normal	Absence of plaque/no luminal stenosis
Minimal	Plaque with negligible impact on lumen
Mild	Plaque with no flow-limiting stenosis
Moderate	Plaque with possible flow-limiting disease
Severe	Plaque with probable flow-limiting disease
Occluded	

Table (2): Recommended Quantitative Stenosis Grading *(Raff et al., 2009)*.

Descriptive Lumen Obstruction	Quantitative Stenosis Grading
Normal	Absence of plaque/no luminal stenosis
Minimal	Plaque with <25% stenosis
Mild	25%–49% stenosis
Moderate	50%–69% stenosis
Severe	70%–99% stenosis
Occluded	

3- Quantification of coronary plaque volume and area.

Because of the 3-dimensional nature of CT data and its ability to reconstruct multiplanar images in both cross-sectional and perpendicular planes, MDCT may be able to assess plaque compositon and morphology as well as total plaque burden similar to IVUS *(Nissen et al., 2001).*

The most widely used MDCT metrics for plaque size are based on area and volume measurements. Plaque area is calculated as the difference between outer vessel area and lumen area, while plaque volume is calculated as the sum of plaque areas of individual cross-sections multiplied by cross-section thickness *(Achenbach et al., 2004).*

several studies that used 16-slice MDCT showed a moderate to-good correlation between plaque area and volume measurements obtained by MDCT compared with measurments obtained by IVUS scanning (r = 0.55– 0.8, P < 0.001). The agreement is higher for plaque located in proximal and middle segments than in distal segments. *(Hur et al., 2009).*

However, the reported accuracy of MDCT to measure plaque volume and size varies from underestimation of plaque volume to overestimation of plaque dimensions even if advanced 64-MDCT technology is used *(Leber et al., 2006).*

Overall, the accuracy and aggrement vary with plaque composition, because the dimensions of calcified plaques are usually underestimated, while the volume of noncalcified and mixed plaques is mostly underestimated *(Hur et al., 2009).*

This can be explained mainly by calcium blooming and partial volume effects caused by the contrast-enhanced vessel lumen *(Sarwar et al., 2008).*

The main challenge for plaque quantification is the exact identification and separation of lumen, plaque, and vessel wall. Despite the improved temporal and spatial resolutions of the 64-slice scanners, the definition of the outer vessel border, especially for noncalcified plaques, remains difficult, leading to high interscan and interobserver variability (20%–38%) *(Achenbach et al., 2004)*.

More recently, automated segmentation tools for plaque quantification have been introduced by most manufacturers, with improved interobserver variability between 12%–17% *(Blackmon et al., 2009)*.

The most important advantage of these tools is that they are not affected by display settings. However, these tools are not currently suitable for clinical practice or research because they use relatively simple techniques for plaque detection and often need extended manual adjustment, especially if image calcification, noise, or other artifacts are present. *(Hoffmann et al., 2009)*.

As a result, published studies evaluate the presence and extent of atherosclerotic plaques on a per segment basis This method has been shown to be highly reproducible. The overall plaque burden is calculated simply by summarizing the number of coronary segments with atherosclerotic plaques *(Hoffmann et al., 2009)*.

To summarize, although there is overall good agreement between IVUS and MDCT scanning for assesment of plaque area and volume per patient, assessment of individual plaques significantly varies with plaque size,morphology and composition.

Assessment of coronary plaque composition

There is great morphologic heterogeneity of coronary atherosclerotic plaques (Figure 10). Typically, investigators use **Hounsfield unit (HU)** measurements to differentiate between calcified and noncalcified plaques and furthermore between fibrous and lipid-rich plaques compared with IVUS scanning . Kopp et al. showed the feasibility of such plaque differentiation with the use of MDCT by measuring CT attenuation values *(Kopp et al., 2001)*.
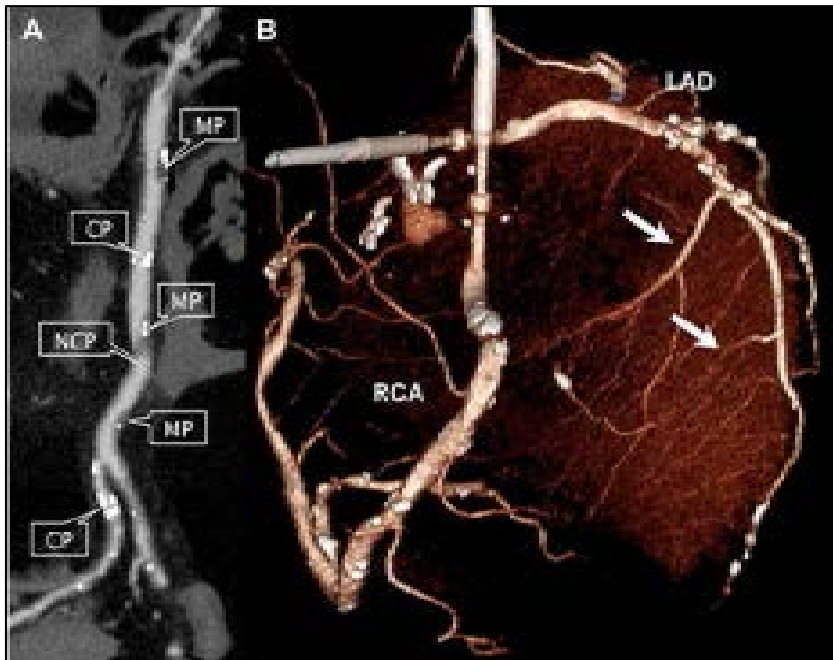
Figure (10): Ex vivo MDCT coronary angiography shows different atherosclerotic lesions in the RCA (A). Volume-rendered image shows the LAD and RCA, arrows point at the septal branches (B). RCA, right coronary artery; LAD, left anterior descending artery; CP, calcified plaque; MP, mixed plaque; NCP, noncalcified plaque *(Maurovich-horvat et al., 2010)*.

Overall, the subsequent studies showed a significant difference in HU values between calcified and noncalcified plaques (mean values across studies, 490 HU for calcific plaques and 75 HU for noncalcific plaques) However, the main focus of most studies was the differentiation between lipid-rich and fibrous plaque. The results of early ex vivo studies were promising and showed that differentiation may indeed be possible *(Schroeder et al., 2004).*

Schroeder et al. in their study suggested the following MDCT attenuation values for differentiation of plaques: (< 60 HU» mostly lipid-rich plaques,,, 61–119 HU» intermediate plaques; and ≥ 120 HU» calcified plaques.) However, in vivo studies have showed that CT values vary widely for non-calcified plaque components. Although mean values were significantly different between lipid-rich and fibrous plaques, a substantial overlap of Hounsfield units was observed. (Table 3) *(Achenbach and Raggi, 2010).*

Table (3): Computed tomography attenuation values found in lipid-rich and fibrous plaques in various studies (HU, Hounsfield units) *(Achenbach and Raggi, 2010)*

Author	*Reference*	*Mean CT attenuation values in lipid rich plaque (HU)*	*Mean CT attenuation values in fibrous plaque (HU)*
Becker et al	*Histology*	*47±9*	*104±28*
Carrascosa et al	*IVUS*	*71±32*	*116±36*
Schroeder et al	*IVUS*	*14±26*	*91±21*
Sun et al	*IVUS*	*79±34*	*90±27*
Motoyama et al	*IVUS*	*11±12*	*78±21*

This can be explained by the similar chemical composition of fibrous and lipid-rich plaques and the limited spatial and low-contrast resolutions of MSCT as well as factors such as image noise, motion artifacts and partial volume effects .Furthermore, contrast enhancement affects

attenuation measurements within plaque, resulting in variations of attenuation values of plaque according to luminal enhancement. *(Cademartiri et al., 2005)*.

Plaque morphology and thickness of the Fibrous Cap

Histological investigations had revealed three different features of plaques associated with acute coronary syndrome : rupture; erosion; and calcified nodule. Two thirds of luminal thrombi in acute events result from ruptured atherosclerotic plaques characterized by a necrotic core covered by a thin layer of fibrous cap **.** Plaques vulnerable to rupture may have the same morphological features as ruptured plaques, but with an intact thin fibrous cap. These lesions termed thin cap fibro-atheroma (TCFA), with a cap thickness of <65 μm are considered to be the precursor lesions of plaque rupture**.** *(Achenbach, 2004).*

Histopathological investigations show that plaques prone to rupture are enlarged in all three spatial dimensions**.** In TCFAs the necrotic core length is ~2–17 mm (mean 8 mm) and the area of the necrotic core is >1.0 mm2**.** These dimensions are over the plaque detection threshold (>1 mm plaque thickness) for CTA. Moreover, most of TCFAs occur in the proximal portion of the main coronary arteries, where vessel diameter is largest, and CTA has the highest image quality and accuracy for plaque detection **(Hoffmann et al., 2006)**.

Inflammatory markers in cardiovascular disease

Inflammation has been detected as an important mechanism for different subsets of Coronary artery disease. Also, current evidence supports a major role for inflammation in all phases of the atherosclerotic process. Indeed, large number of recent studies in anaimals and humans have confirmed that early and advanced atherosclerotic lesions are significantly paralleled by signs of local and systemic inflammation *(Mavrogeni, 2010)*.

The science of biomarkers is a highly promising aspect of medicine that will redefine the whole process of disease management in the near future. Biomarkers are being utilized in diagnosing various diseases and they can also have a great role in the follow up and detecting both long- and short-term outcomes. They will soon help us in identifying the high risk populations early, leading to primary prevention of many of these disorders. The role of the available new biomarkers in our clinical practice is expected to grow tremendously in the next few years. *(Bhat et al., 2013).*

Systemic inflammation can be measured by using a variety of hematological and biochemical markers. Although novel disease specific biomarkers have been identified, most of which are expensive and time consuming . several Observational studies have thoroughly investigated the role of CRP , total leukocyte count , NLR and lipid profile in different chronic conditions. *(Imtiaz et al., 2012)*

HS-CRP as a predictor of CAD

Large number of studies indicate that hsCRP , a sensitive marker of underlying systemic inflammation, is elevated among men and women at high risk for future cardiovascular events, and that addition of CRP testing to standard lipid screening seems to provide more accurate method to determine vascular risk. These accumulating data suggested that CRP might have direct inflammatory effects at different cellular and organic levels *(Collaboration, 2012)*.

The CRP molecule has characteristics that make it a particularly attractive subject of study: as a positive acute phase protein it is a marker of systemic inflammation that increases in response to various types of injury that function as inflammatory stimuli. Its production in the liver is induced mainly by interleukin 6 and, unlike other acute phase markers, its levels are relatively stable, with no significant diurnal variation, and so it can be accurately measured.

It has been proven that CRP levels, which is an indicator of inflammation, correlates with coronary artery disease activity, and endothelial dysfunction. Another study stated that, systemic inflammation determined by CRP may contribute to impaired vasomotor function in the microvessels . *(Bitigen et al., 2007)*.

CRP and primary prevention

- Several prospective trials in healthy individuals have shown that elevated hs-CRP is positively correlated with cardiovascular morbidity and mortality. The Physician's Health Study (PHS), a controlled prospective study of individuals without cardiovascular disease, showed that those with higher baseline hs-CRP had double

the risk of stroke, three times higher risk of myocardial infarction (MI), and four times higher risk of severe peripheral arterial disease. Cardiovascular risk was not affected by smoking or lipid levels**. (Ridker et al 1997)**

In the prospective PREVEND study (Prevention of REnal and Vascular End stage Disease study) of 8139 individuals without previous documented CAD, followed for the incidence of coronary angiography and coronary events from 1997 to 2003, hs-CRP levels were associated with angiographic characteristics and clinical consequences of plaque instability during follow-up. **(Geluk et al 2008)**

However, there is not complete consensus regarding these findings. Other studies have concluded that the predictive power of hs-CRP alone and in association with conventional risk factors is relatively low. **(Wang et al 2006)**

In a 2010 study of the contribution of 30 biomarkers to cardiovascular risk estimation, Blankenberg et al. concluded that none of the biomarkers under study, including hs-CRP, provided additional prognostic value compared to traditional risk scores. However, adding a score based on three biomarkers (hs-CRP, troponin I and BNP) to a conventional risk model improved estimation of 10-year risk for cardiovascular events in two middle-aged European populations (***Blankenberg et al2010) .***

To summarize, as measurement of hs-CRP in primary prevention is not consensual and it is not clear whether its superior predictive ability is clinically relevant by helping reduce cardiovascular morbidity and mortality, large-scale validation trials are required before it should be used in routine clinical practice**.*(Libby *et al 2010).***

CRP and secondary prevention

Stable coronary artery disease

It has been consistently demonstrated that hs-CRP is a marker of adverse events in patients with stable CAD.. It has been shown that hs-CRP levels correlate inversely with degree of coronary collateral circulation. **(Kadi et al 2011)**

A substudy of the placebo-controlled randomized Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial of 3771 patients for a mean of 4.8 years, showed that hs-CRP >1mg/l was associated with significantly higher risk of cardiovascular death, MI and stroke, even after adjustment for patients' baseline characteristics and current treatment**.(Sabatine et al 2007**)

Other studies have shown that hs-CRP is inversely correlated with left ventricular ejection fraction and is an independent predictor of worsening New York Heart Association (NYHA) functional class in patients with CAD referred for elective coronary angiography, irrespective of CAD severity. These authors concluded that hs-CRP was an independent predictor of adverse cardiac events (ACS and cardiovascular death) in patients with stable CAD irrespective of the presence of significant atherosclerotic lesions. **(Espliguero et al 2009).**

This may be explained by arterial wall remodeling, which is known to be associated with the development of CAD; positive correlations have been demonstrated between hs-CRP and degree of coronary remodeling, and between hs-CRP and plaque composition, particularly the proportion of central necrotic tissue, as assessed by intravascular

ultrasound in patients with CAD referred for elective coronary angiography**.(Kubo et al2009)**

Unstable coronary artery disease

It is now known that hs-CRP levels correlate with the presence of unstable plaque documented by carotid Doppler study and with increased temperature in such plaques as measured by a thermography catheter. However, their relation with extent of MI as assessed by elevated cardiac enzymes or ejection fraction is the subject of debate. **(Smit, et al 2008)**

In the context of ACS, hs-CRP has consistently proved a marker of adverse cardiac events including MI, urgent revascularization, restenosis after percutaneous coronary intervention (PCI) and cardiovascular death. In the randomized Thrombolysis in Myocardial Infarction (TIMI 11A) trial, Morrow et al. showed that hs-CRP levels after ACS were significantly higher in patients who died during follow-up than in survivors (p<0.001)**. (Morrow et al 1998)**

In 2005, Foussas et al. concluded that hs-CRP levels had prognostic usefulness when added to the well-validated TIMI risk score for ST- and non-ST elevation MI and that both should be used to stratify risk in MI patients. **(Foussas et al 2005).**

Hs-CRP has been found to be an independent predictor of mortality in patients with ACS even after early coronary revascularization. In a prospective study in 2002 of patients undergoing PCI following non-ST elevation MI, hs-CRP of >10mg/l at admission was associated with increased mortality in a 20-month follow-up. Reperfusion was more often unsuccessful in patients with elevated hs-CRP (>5mg/l). **(Mueller et al 2002).**

HsCRP in clinical guidelines

In 2003, the American Heart Association published guidelines on the use of markers of inflammation in cardiovascular risk assessment. According to these guidelines, hs-CRP should not be measured in the general population to determine cardiovascular risk, but can be used in risk stratification of adults at intermediate risk for CAD (10–20% risk at 10 years), to help decide whether to begin primary prevention with statins. hs-CRP levels should be expressed in mg/l and patients should be classified as low risk (<1.0mg/l), intermediate risk (1.0–3.0mg/l), or high risk (>3.0mg/l). If the concentration is <3mg/l, measurement does not need to be repeated. If the value is >3mg/l, it should be repeated at least two weeks later when there is no evidence of active systemic inflammation; the lower of the two results should be used. Values of >10mg/l suggest a very strong acute phase response and, if not of cardiovascular cause, require further etiological investigation.

Therapy (statins or aspirin) based on hs-CRP levels should be at the discretion of the clinician, since its benefit is still uncertain, and little evidence supports the use of serial testing for hs-CRP as a means to monitor therapy in primary prevention. Individuals with persistently high levels should improve their lifestyles irrespective of their LDL cholesterol levels. (**Myers et al 2009**)

In 2009, the Canadian Cardiovascular Society also published new guidelines on primary cardiovascular prevention, which recommend that in individuals with intermediate cardiovascular risk according to conventional risk scores, hs-CRP should be assessed as well as LDL and HDL cholesterol in order to improve risk stratification. **(Genest et al 2009)**

Both European and American guidelines consider that in patients with documented CAD hs-CRP measurement may be useful as an independent marker for assessing likelihood of death, MI or restenosis after PCI**. (Messerli et al 2006)**

White blood cell count and Neutropil to lymphocyte raio(NLR) as predictor of cardiovascular diseases.

Despite all these studies, total WBC count has not been explored for its utility in predicting cardiovascular risk. It has been proposed as one of the potential biomarkers for risk assessment in cardiovascular disease *(Pearson et al., 2003).*

However ,there has been a recent focus on differential white cell count, and identification of a particular cell type (neutrophil [N], lymphocyte [L] and monocyte [M]) as a stronger predictor of cardiovascular risk than the total WBC count. Significant evidence has suggested a possible role of N count as an independent prognostic factor in both acute as well as chronic cardiovascular diseases, which is also supported by some laboratory studies explaining different mechanism of this association *(Guasti et al., 2011)*.

The recent remarkable observation has been that a ratio of N to L count (NLR) has a greater predictability than total WBC count or N count as a marker in cardiovascular diseases and is slowly emerging as an independent useful prognostic parameter in cardiovascular diseases *(Horne et al., 2005).*

The predictive superiority of NLR may be due to many reasons including the fact that it is less likely to be influenced by various physiological conditions such as dehydration and exercise, even though

these conditions may affect absolute number of individual cell types. Second and most importantly, NLR is a ratio of two different yet complementary immune pathways, thus integrating the deleterious effects of Ns, which are responsible for active nonspecific inflammation and lymphopenia, which is a marker of poor general heath and physiological stress *.(Bhat et al., 2013).*

Average Value of NLR

In analysis of a large US data set including over 9000 subjects for the average value for NLR in the general population, Azab et al, found that such normal value significantly varies with race; NLR is particularly low in Non-Hispanic Black subjects, from 2.24 observed in Whites to 1.76 in Blacks. This finding has important clinical implications *(Azab et al., 2014).*

Another result of this analysis is that NLR is associated with several self-reported chronic conditions, such as diabetes and heart disease, with being a smoker, with high body max index (BMI), and with increasing age, all conditions that are known to increase the body inflammatory milieu *(Azab et al., 2014).*

In addition this study shows that an index of socioeconomic status, the income to poverty ratio, is inversely associated with NLR. A low socio economic status may be a proxy for poor dietary habits, low in nutrients and antioxidants, or lack of physical exercise, or occupational exposures to chemicals and carcinogens *(Azab et al., 2014).*

This analysis also shows that the association between personal and behavioral factors and NLR differs with race. For example, among black patients only BMI was significantly associated with elevated NLR, while

among white patients several expected factors, such as age and smoking habits were associated with higher NLR. *(Azab et al., 2014).*

Cardiovascular uses of NLR

1- NLR & stable coronary artery disease:

Elevated NLR, independently and in correlation with other risk factors, is a significant predictor of mortality in stable coronary artery disease, as well as its progression and development . *(Kalay et al., 2012).*

Horne *et al.* were among the first who observed the significance of NLR in stable CAD. In their prospective study, more than 3000 patients and with angiographically assessed CAD and without acute coronary syndrome event were followed for more than 6 years . Total WBC count was confirmed to be an independent predictor of MI or death in patients at high risk for CAD, but greater predictive ability is provided by low L or high N counts. The greatest risk prediction is given by the N/L ratio, increasing the hazard by 2.2-fold. They reported that the significant improvement in risk prediction achieved with WBC differential was similar to or greater than that reported for hs-CRP *(Horne et al., 2005).*

Another prospective study analyzed the predictive ability for cardiac events of differential WBC against established risk factors in angiographically proven CAD patients. They evaluated various biomarkers of inflammation: (C-Reactive Protien and serum iron), fasting glucose, total, HDL and LDL cholesterol) and established risk factors in 422 patients. High NLR (5.19 ± 3.81), together with C-Reactive Protein, left ventricular ejection fraction,HDL , serum iron and fasting blood glucose were associated with significantly ($p = 0.02$) increased cardiac

death and nonfatal MI in patients with stable CAD on a 3-year follow-up. *(Papa et al., 2008).*

Association between NLR and other established indirect markers of cardiovascular disease like coronary calcium score (CCS) was studied in more than 800 Korean adult patients. The degree of arterial stiffness or atherosclerosis , measured by brachial–ankle pulse-wave velocity and Coronary calcium score, was associated to NLR as higher scores among the patients with high NLR ≥ 2.5 ($p < 0.001$ for brachial–ankle pulse-wave velocity and $p = 0.032$ for CCS) *(Park et al., 2011).*

2- NLR & acute coronary syndrome (ACS):

The question of whether NLR on admission has any diagnostic utility in patients admitted with chest pain was studied by Zazula *et al.* Patients diagnosed with non cardiac chest pain reported lowest admission level of NLR (3 ± 1.6), followed by unstable angina (3.6 ± 2.9) , then non-ST-elevation MI (4.8 ± 3.7) and ST-elevation MI (STEMI) (6.9 ± 5.7) ($p < 0.0001$) . NLR above 5.7 reported 91% specificity for the final diagnosis of ACS when compared with the groups with NLR <3.0 ($p < 0.001$) *(Zazula et al., 2008).*

Being a reproducible and inexpensive predictive marker, NLR can be of relevance while evaluating chest pain. Elevated CRP and NLR, markers of underlying acute-phase inflammation, serve as indicator for thrombus formation in patients with acute MI. Compared with the patients with acute MI and no thrombus formation, the levels of hs -CRP, total N count and NLR were significally higher ($p < 0.05$) in the patients with acute MI and thrombus formation *(Licata et al., 2009).*

Risk stratification and prediction of outcome is of great importance in management of CAD. There are multiple scoring systems in clinical practice utilized for risk stratification of patients with ACS. NLR itself is not part of any risk stratification scoring system ,however high NLR has been associated with poor outcomes ,higher inhospital mortality($p=0.013$) and higher 6 month mortality($p< 0.001$) in patients with ACS *(Muhmmed MA et al., 2010).*

Patients with non-STEMI and NLR >4.7 had significantly higher in-patient and 4-year mortality rate (29.8 vs 8.4%) compared with those with NLR <3 ($p < 0.0001$) *(Azab et al., 2010).*

Also, among patients with STEMI, long-term mortality was significantly higher (47.9% vs 6.4%, $p< 0.001$)in the group with maximum NLR compared with those with lowest NLR *(Nunez et al., 2008).*

In summary, NLR has been consistently shown to be an independent risk marker for ACS both in the short term as well as long term but similar association was not found by Kruk *et al.* who showed that only high-sensitivity CRP and WBC count independent of each other have predicted early outcome in STEMI patients treated with primary PCI *(Kurk et al., 2008).*

3- NLR & cardiac arrhythmias:

The association between inflammation and AF is well known and has been studied extensively. *(Aviles et al., 2003).*

Although various inflammatory markers have been associated with incidence, recurrence and outcome in AF, association of NLR has not been much detected into in this group of patients. Also , Association of

inflammation and inflammatory markers in other arrhythmias, especially ventricular arrhythmia, is not well established or understood.*(Wu et al., 2013).*

However, Chatterjee *et al.* in a retrospective study in patients undergoing PCI, reported that preprocedural elevated WBC count, neutrophilia and elevated NLR were significant predictors of ventricular arrhythmias *(Chatterjee et al., 2011).*

Thus, it is evident that the evidence is not enough to make any conclusion on association of NLR or other inflammatory markers and various cardiac arrhythmias.

4- NLR & coronary artery bypass surgery:

NLR, by integrating information on inflammatory and physiologic stress, can serve as a prognostic marker for postoperative AF and outcome from coronary artery bypass grafting (CABG) surgery. Elevated preoperative NLR has been associated with worse outcome after CABG. During 3.6-year followup in patients undergoing CABG, mortality was significantly high in the group who had preoperative NLR >3.36 (p < 0.001) *(Gibson et al., 2010)*

5-NLR & heart failure:

Previous studies have shown that relative neutrophilia has been associated with increased incidence of acute decompensated heart failure (ADHF) in patients admitted with acute MIs *(Arruda-Olson et al., 2009).*

In addition, relative lymphocytopenia has shown to be an independent predictor of mortality in heart failure *(Rudiger et al., 2006).*

Similarly, ADHF patients with high NLR (≥7.6) had significantly higher 30-day readmission rate (p < 0.001) compared with those with lower NLR *(Uthamalingam et al., 2011).*

Patients and Methods

Study population:

This cross sectional study included 265 patients who presented with exertional chest pain and referred for MSCT angiography at kobry elkoba hospital in the period from May 2018 to March 2019.

Inclusion criteria & Patient selection:

All adult patients presented with recurrent exertional chest pain (symptoms suggestive of coronary artery disease) are eligible for inclusion in the study and fulfilling these criteria:

1. Sinus rhythm.
2. Their heart rate less than 70 bpm spontaneously or Beta blocker induced.
3. They can hold breath for more than 20 seconds.
4. Weight less than 150 kg.

Exclusion criteria:

1. Respiratory failure.

2. Decompensated heart failure.

3. Presence of arrhythmias.

4. Previous history of coronary invasive maneuvers(PCI or CABG)

5. Hypersensitivity to dye.

6. Treatment with statin.

7. Renal impairment (serum creatinine $\geq$ 1.5 mg/dl).

8. Patients presented with acute coronary syndrome event.

9. Morbid obesity.

10. Difficulties in performing CT like inadequate breath holding

Ethical consideration:

Study protocol was explained to all subjects participated in this study and an informed written consent was obtained prior to participation to the study.

Methodology:

All the patients were subjected to the following:

- *Personal data* and risk factors assay such as age, gender, presence or absence of hypertension, diabetes, smoking, dyslipidemia and family history of premature CAD.

- *Clinical examination* including vital signs with general, chest, and cardiac examination.

- *12- Lead ECG:* detect ischemic changes and ensure sinus rhythm.

- *Echocardiography:* was done for all patients, using an echocardiograph equipped with a broad band transducer m4s Iside, with the left arm widely abducted, parasternal long and short axis views were taken, also apical four chamber, apical five chamber and apical three chamber views were taken to assess

a)Ejection fraction (by modified Simpson method: this method requires the measurement of LVEF by tracing endocardial border in both apical four-chamber and two-chamber views in end-systole and end-diastole.)

b) Segmental regional wall motion abnormality.

c) Degree of mitral regurge (using venae contracta width:

<3mm→mild,   3-6mm→moderate,   >6mm→severe)

d) Assessment of diastolic dysfunction (using mitral inflow signal: gradeI→ E/A <0.9,   gradeII→ 0.9<E/A<1.5, grade III→ E/A>2 and reversed during valsalva, gradeIV→ E/A>2 and fixed during valsalva.) **(Feigenbaum 1972).**

- *Routine lab investigations:*

  - Serum creatinine.
  - Lipid Profile (including Total cholesterol, LDL, HDL, TG, VLDL).
  - Complete blood picture, Neutrophil lymphocyte Ratio was calculated.
  - High sensitive C reactive Protein (hs-CRP) was measured in plasma samples by an immunoturbidimetric assay
  - Cardiac enzymes to exclude patients with acute coronary syndrome.

- *Coronary CT angiography:*

  The CT angiography was performed to all patients utilizing a dual source scanner (Somatom Definition Flash, Siemens) with slice configuration of 128×0.625 mm and gantry rotation time of 330 ms.

- *Patient preparation:*

  - *Patients were instructed to avoid* Caffeine and smoking 12 hours prior to the procedure to avoid cardiac stimulation, *And to avoid* eating solid food 4 hours before the study and to increase fluid intake prior to the exam.

- *Patients were instructed to* take Beta blocker (oral bisoprolol 5 mg 1 hour before scan) to achieve heart rate control below 70 bpm. Avoided if HR below 60 bpm, ABP< 100 mm Hg.

- A second dose of oral bisoprolol 5 mg was given one hour after the initial one if the heart rate was not satisfactory (above 70 bpm). Some patients needed an additional bolus of intravenous propranolol (1-2 mg).

- *Patients were instructed* how to hold breath, it is crucial for the exam, told and reassured about the side effects of the contrast as warm sensation in the body after injection.

- The patients were given a tablet of 5 mg isosorbide dinitrate sublingually before the test which dilates the coronary arteries and increases side branch visualization.

➤ *Assessment of coronary calcium score: (Raff et al., 2009).*

- All patients undergone coronary artery calcium scoring which is a non-contrast study done by average about 50–60 non overlapping thick tomographic slices with 3 mm thickness, starting scan from coronary artery ostia to inferior wall of heart using ECG gated prospective sequential scans to evaluate the coronary calcification. The sequential scans were acquired at the diastolic intervals of the patient's ECG while the patient was holding a deep inspiration.

- If coronary calcification was present, the total coronary calcium score and calcium score of every calcification in each coronary artery for all of tomographic slices was calculated on a second workstation.

- The summed score for each vessel is generated by a scoring program based on an area-density (Agatston calcium score).

- The calculation is based on measuring the area of each calcified coronary lesion and multiplying it by a coefficient of 1 to 4 representing the density factor given to the highest attenuation value within the lesion.

Density factor

- 130-199 HU→ 1 , 200-299 HU→ 2 , 300-399 HU→ 3, > 400HU→ 4

The score of every calcified speck is summed up to give the total calcium score. Based on total calcium score the coronary artery disease is graded

- No evidence of CAD→ 0 calcium score ,Minimal→ 1-10 , Mild→ 11-100 ,Moderate→ 101-400 ,Severe→ >400 **(van der Bijl et al 2010).**

  ➢ Using a double head automatic injector (85) mL of contrast agent (Ultravist 370) was injected in the antecubital vein at a rate of (5.0) ml/s, directly followed by (60) ml IV saline. Bolus tracking in the ascending aorta with an additional scan delay of 5 s was used for timing. The patient was asked to hold his or her breath at mid inspiration with mean scan time 11 s *(Raff et al., 2009).*

Plaque assessment:

Coronary plaques were defined as structures > 1 mm^2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding tissue in two perpendicular image planes. *(Pundziute et al , 2008).*

Coronary plaques were assessed according to the following parameters:

➢ **Degree of stenosis:** *(Kim et al, 2015).*

Plaques are classified as obstructive and non-obstructive according to the quantitative stenosis grading recommended by the Society of Cardiovascular Computed Tomography. Obstructive plaques are those plaques showing 50% stenosis of the arterial lumen or more.

- **Coronary plaque type and composition:** *(Maiken Glud Dalager et al., 2011)* Coronary plaque composition was determined by calculating the mean density of the plaque which was calculated using a dedicated software program. Region of interest (ROI) was placed within the plaque and the MSCT attenuation of the measured ROI was represented in Hounsfield units (HU)**.** A Hounsfield unit (HU) is a normal index of X-ray attenuation based on a scale of -1000 of air to +1000 of bone, with water being 0. **Using Hounsfield unit three types of plaques will be identified:**

  ✓ Non-calcified lipid-rich plaques had a density of ≤ 60 HU.

  ✓ Mixed fibrous plaques had a density of (61 ± 119) HU.

  ✓ Calcified plaques had a density of ≥ 120 HU.

Signs of vulnerable plaque:

*Positive Remodeling: Positive remodeling (outward expansion) is defined as 5% increase in the luminal cross-section at the site of plaque compared with the normal proximal segment of the vessel. Positive remodeling indicates plaque instability and is common in plaques with large necrotic cores,. *(Hong et al,2009).*

*<u>Napkin Ring sign:</u> The napkin ring sign is defined by inhomogeneous plaque containing a core of lower attenuation material and an outer rim with higher attenuation material. *(Otsuka et al 2013).*

Data management and statistical analysis

The clinical data were recorded on a report form. These data were tabulated and analysed using the computer program SPSS (Statistical package for social science) version 20 to obtain:

Descriptive data:*(Winters, et al 2010).*

Descriptive statistics were calculated for the data in the form of:

1. Mean and standard deviation $(\pm SD)$. Median and inter-quartile range (IQR) for quantitative data.

2. Frequency and distribution for qualitative data.

Statistical analysis:

In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests after establishing their non -normality by K-S test (**One-Sample Kolmogorov-Smirnov Test**) of normality.

1- Student's *t*-test and Mann-Whitney test:- Used to compare mean of two groups of quantitative data of parametric and non-parametric respectively.

2- Inter-group comparison of categorical data was performed by using chi square test (X^2-value) and fisher exact test (FET).

$$x^2 = \frac{\sum(observed - \exp ected)^2}{Expected}$$

$$Expected = \frac{col.total \; x \; row \; total}{Grand \; total}$$

3- Correlation coefficient:- to find relationships between variables.

A *P* value <0.05 was considered statistically significant (*) while >0.05 statistically insignificant P value <0.01 was considered highly significant (**) in all analyses.

Results

The current study is a single center cross sectional observational study conducted over 265 patients presented with chest pain and referred for MSCT angiography at kobry elkoba hospital in the period from May 2018 to March 2019.

Demographic data , risk factors and echocardiographic findings of the studied group:

In our study, the median age of the patients was 57 years, 83.8% of the studied patients were males compared to 16.2% females .Concerning the risk factors, 46.8% of the patients were hypertensive, 27.9% were diabetic , 43.8% were current smokers and 41.9% had positive family history of coronary artery disease. As regarding echocardiographic data, 33.6% of the patients had diastolic dysfunction (ranging from grade I to grade III), 18.1% had mitral regurge (ranging from mild to severe) and their median EF was 65.0%.

Table (4) Demographic data , risk factors and echocardiographic findings of the studied group:

Number of the studied group = 265		Value
Age (y)	Median(IQR)	57.0(49.0-65.0)
Gender	N(%)	
Male		222(83.8)
Female		43(16.2)
Hypertension	N(%)	124(46.8)
DM	N(%)	74(27.9)
Current smoking	N(%)	116(43.8)
Family HX of CAD	N(%)	111(41.9)
EF%	Median(IQR)	65.0(61.0-68.0)
Diastolic dysfunction	N(%)	89(33.6)
Mitral regurge	N(%)	48(18.1)

Laboratory findings of the studied group;

   Regarding the lipid profile and inflammatory markers, the mean of total cholesterol was 197.51±43.6 mg/dl, the median of LDL was 118.0 mg/dl, the median of HDL was 40 mg/dl , the median of VLDL was 28 mg/dl, the median of TG was 143 mg/dl and the median of NLR was 2. HsCRP was positive in 59.2% of the studied group (median of hsCRP was 9.32 mg/l) .

Table (5):Laboratory findings of the studied group :

No of the studied group = 256		Value
TC (mg\dl)	mean ±SD (range)	197.51±43.6 (100-401)
LDL (mg\dl)	Median(IQR)	118.0(99.0-144.0)
HDL (mg\dl)	Median(IQR)	40.0(36.0-46.0)
VLDL (mg\dl)	Median(IQR)	28.0(21.0-33.0)
TG (mg\dl)	Median(IQR)	143.0(115.0-184.5)
HsCRP (mg\l)	Median(IQR)	9.32(4.0-23.15)
CRP : Positive	N(%)	157(59.2)
NLR	Median(IQR)	2.0(1.63-2.65)

MSCT findings of the studied group

Among the 265 patients included in our study, 145 patients were found to have Coronary plaques, 47 patients have atherosclerotic vessels without any identifiable plaques, 50 patients have normal coronaries, 15 patients have high Ca score and did not complete the examination, 5 patients have intra myocardial bridge and finally 4 patients have ectatic coronaries.
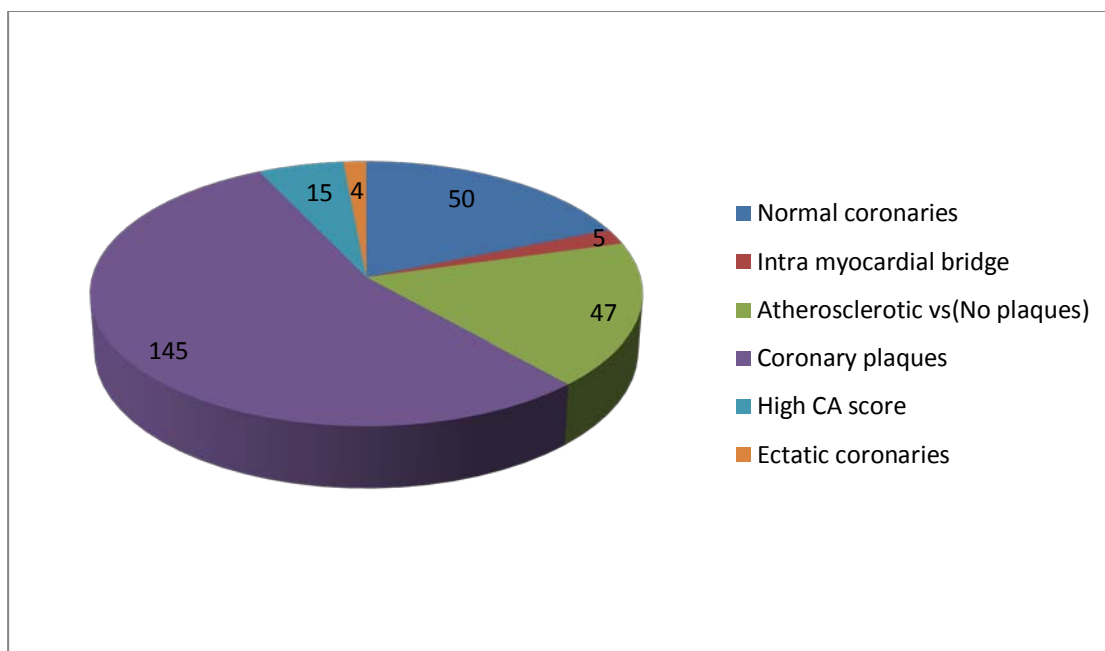
Figure(11): distribution (number) of the patients according to MSCT findings.
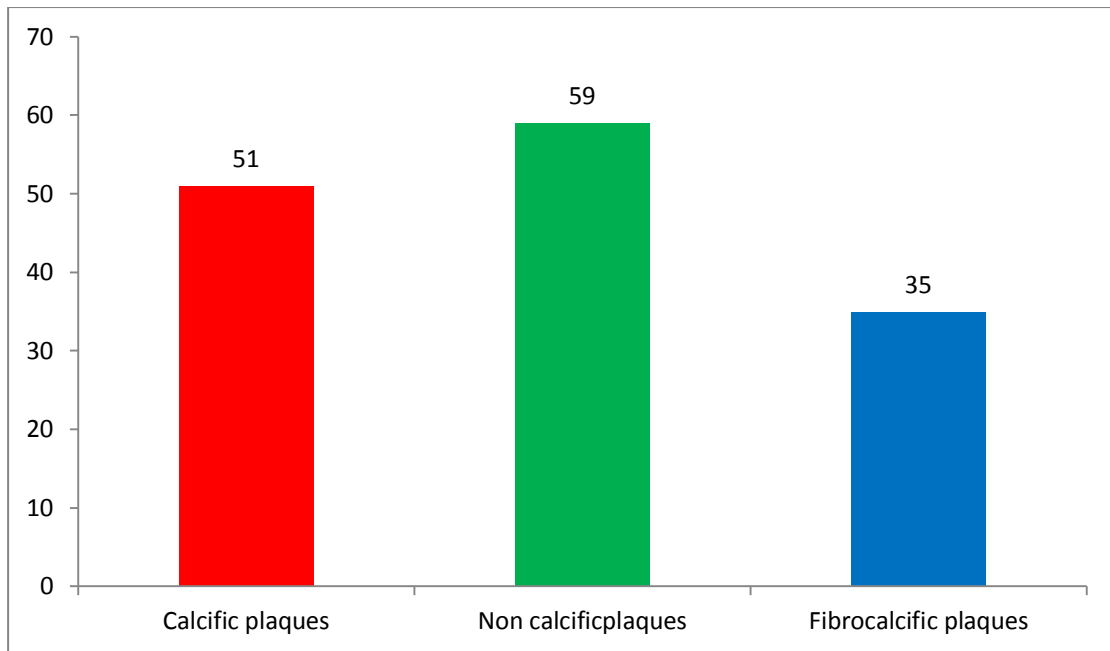
So Final number of patients with coronary plaques that will undergo statistical analysis in our study is 145 patients.

N.B:In patients with more than one plaque, the plaque causing the highest degree of coronary stenosis is the only one considered during statistical analysis

Fifty one caclcific plaques(19.2%) were detected in the studied group , compared to 59 (22.3%) non-calcific plaques and 35(13.2%) fibrocalcific plaques. The median degree of coronary stenosis among different types of plaques was 70%.

Table(6): MSCT findings of the studied group

Ca score	Median(IQR)	23.2(0.0-116.15)
Calcified plaques	N(%)	51(19.2)
Degree of obstruction of calcified plaques (80)	Median(IQR)	70.0%(50.0%-80.0%)
Non-Calcified plaques Yes	N(%)	59(22.3)
Degree of obstruction of non-calcified plaques (87)	Median(IQR)	70.0%(50.0%-75.0%)
Fibro-Calcified plaques Yes	N(%)	35(13.2)
Degree of obstruction of fibro-calcified plaques(63)	Median(IQR)	70.0%(50.0%-80.0%)
LM	N(%)	26/145(17.9)
LAD	N(%)	124/145(85.5)
LCX	N(%)	45/145(31.0)
RCA	N(%)	65/145(44.8)
No of vs affected : **Multi-vessels disease** **Two vessels disease** **Single vessel disease**	N	44 37 64
Remodeling **Positive** **Negative**	N(%)	2(1.4) 143(98.6)
Napkin ring sign **Positive** **Negative**	N(%)	2(1.4) 143(98.6)
Fissure in plaque **Positive** **Negative**	N(%)	2(1.4) 143(98.6)

Figure(12): Number of different types of plaques among the studied patients.
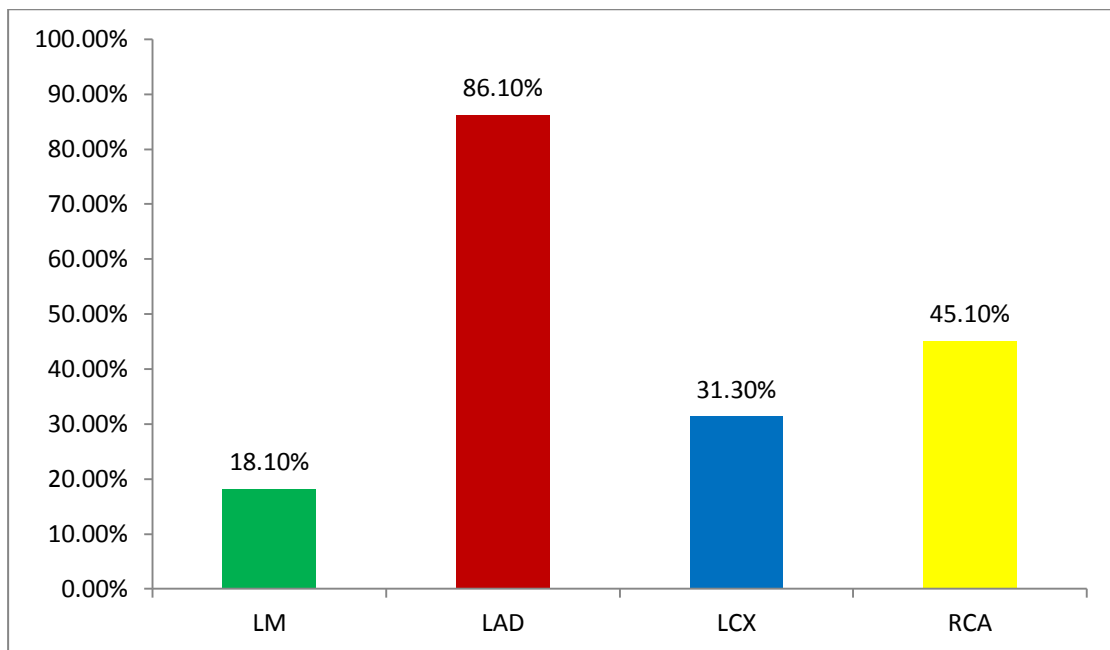
Figure(13): Percentage of affected vessels among the studied patients.

Correlation of Lipid profile and inflammatory markers with degree of coronary stenosis:

Among the inflammatory markers and lipid profile, hsCRP was found to be significantly higher and HDL was found to be significantly lower in patients with obstructive plaques (P< 0.001) .TC , LDL , VLDL , TG and NLR were found to be higher in patients with obstructive plaques but the relation was statistically insignificant.

Table (7): Correlation of Lipid profile and inflammatory markers with degree of coronary stenosis:

| Degree of stenosis		≤50 (41) Non obstructive	>50 (104) Obstructive	Statistical test	P value
HsCRP	Median(IQR)	13.21(8.75-18.81)	26.0(20.0-34.08)	Z=6.49	<0.001**
Total cholesterol	mean ±SD (range)	200.02±43.34 (139-401)	211.13±48.15 (100-399)	St t=1.29	0.20
LDL	Median(IQR)	124(102-147)	136.5(104-164.75)	Z=1.68	0.093
HDL	Median(IQR)	40.0(37.0-45.5)	36.0(32.0-41.0)	Z=3.57	<0.001**
VLDL	Median(IQR)	27.0(21.5-32.5)	29.0(23.0-35.0)	Z=1.64	0.102
TG	Median(IQR)	135.0(109.5-183.0)	149.5(125-203.5)	Z=1.82	0.069
NLR	mean ±SD (range)	1.99±0.63 (1.07-3.43)	2.1±0.79 (0.32-4.45)	St t=0.80	0.43
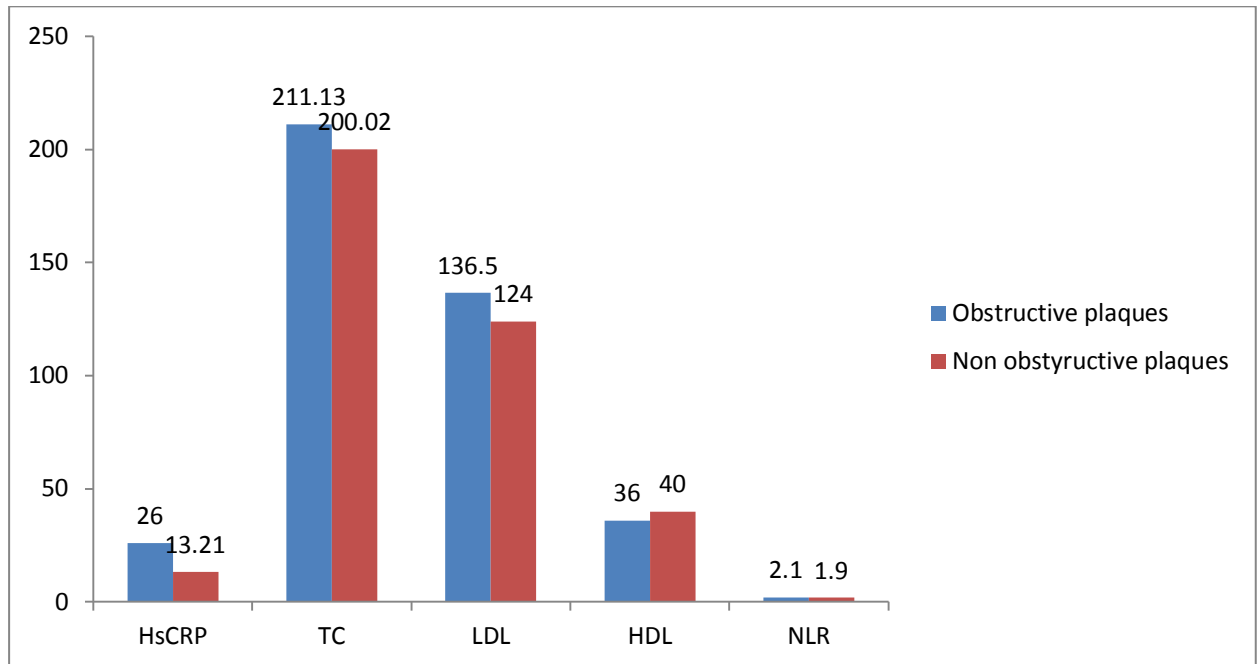
Figure (14) : Correlation of Lipid profile and inflammatory markers with degree of coronary stenosis

Correlation between inflammatory markers and lipid profile against plaque characters and burden:

HsCRP has positive correlation with Ca score (p<0.001), calcific plaque burden(p<0.001) and non-calcific plaque burden(p<0.001). As regard to lipid profile, Total cholesterol, LDL have positive correlation while HDL has negative correlation with Ca score(p<0.001) and non-calcific plaque burden (p<0.001).

Table(8): Correlation between inflammatory markers and lipid profile against plaque characters and burden

	hsCRP		Total Cholesterol		LDL		HDL		VLDL		TG	
	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p
Neutrophil/lymphocyte	-0.099	0.11	-0.14	0.025*	-0.154	0.012*	0.076	0.218	-0.11	0.073	-0.013	0.828
Ca score	0.485	<0.001**	0.23	<0.001**	0.266	<0.001**	-0.28	<0.001**	0.17	0.006**	0.17	0.006**
Calcific plaque burden	0.55	<0.001**	0.081	0.478	0.075	0.51	-0.17	0.14	0.13	0.24	0.17	0.14
Non-calcified plaque burden	0.641	<0.001**	0.351	0.001**	0.381	<0.001**	-0.37	<0.001**	0.081	0.458	0.164	0.129
Fibro-calcific plaque burden	0.21	0.11	0.076	0.55	0.102	0.43	-0.08	0.533	-0.05	0.70	-0.009	0.95

Differentiation of lipid profile and inflammatory markers among patients with coronary plaques:

Among patients with coronary atherosclerotic plaques, hsCRP , TC and LDL were significantly higher while HDL was significantly lower than patients without any atherosclerotic plaques (p<0.001) .

Table(9):Differentiation of lipid profile and inflammatory markers among patients with coronary plaques:

|		Patients with coronary plaques (145)	Patients without coronary plaques (120)	Statistical test	P value
CRP	Median(IQR)	22.3(14.3-30.0)	4.0(3.0-5.0)	Z= 12.61	<0.001**
Total cholesterol	mean ±SD (range)	207.99±46.96 (100-401)	184.84±35.41 (100-321)	St t= 4.45	<0.001**
LDL	Median(IQR)	132(103-161)	103.5(92.25-127.75)	Z= 5.85	<0.001**
HDL	Median(IQR)	37.0(33.5-42.0)	44(40-49)	Z= 7.4	<0.001**
VLDL	Median(IQR)	28(22-34)	27(19-32)	Z=2.31	0.021*
TG	Median(IQR)	144(119.5-194.5	143(103-176.75)	Z=1.77	0.077
N/L ratio	mean ±SD (range)	2.07±0.75 (0.32-4.45)	2.21±0.68 (0.47-3.53)	St t= 1.63	0.103
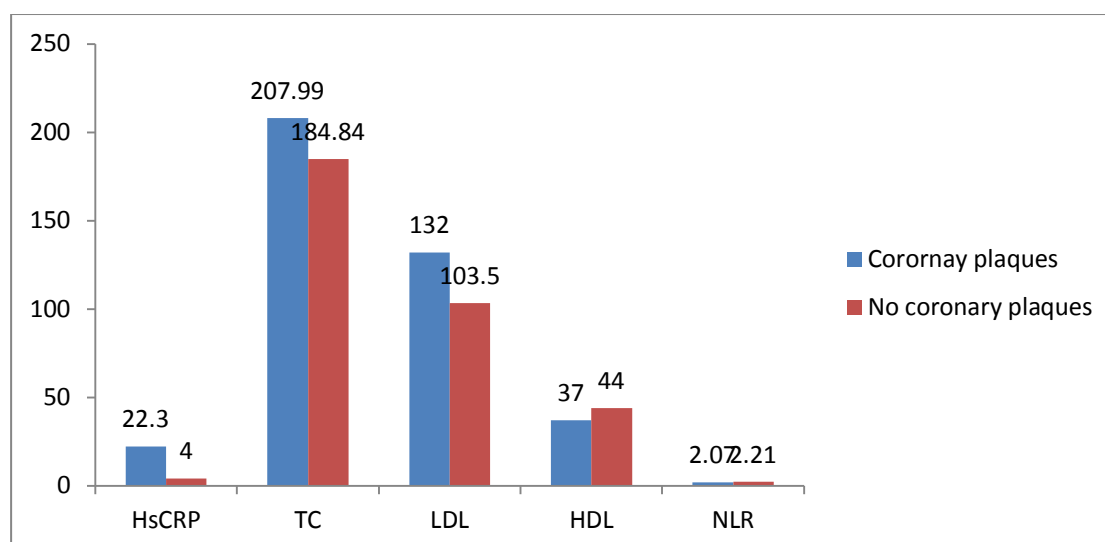
Figure(15): Differentiation of lipid profile and inflammatory markers among patients with coronary plaques

Differentiation of lipid profile and inflammatory markers among different types of plaques:

Among the 145 patients with identified coronary plaques, hs-CRP was found to be significantly higher with calcific plaques than non-calcific and fibro-calcific plaques.It was also found that hs-CRP is significantly higher among non-calcific plaques than fibro-calcific plaques (P<0.001). However TC, LDL, HDL , VLDL ,TG and NLR failed to show significant difference among different types of plaques.

Table (10) Differentiation of lipid profile and inflammatory markers among different types of plaques:

		Calcified plaque (51)	Non calcified plaque (59)	Fibro calcified plaque (35)	Statistical test (KW)	P value
No		51	59	35		
Hs-CRP	Median(IQR)	26.3 (20.0-34.6)	22.3 (16.0-28.75)	13.2 (9.2-27.0)	16.72	<0.001**
TC	mean ±SD (range)	204.31±46.19	211.24±48.35	207.86±46.65	F= 0.30	0.75
LDL	Median(IQR)	130.0 (101.0-151.0)	134.0 (104.0-165.0)	128.0 (101.0-164.0)	1.12	0.57
HDL	Median(IQR)	38.0 (32.0-45.0)	38.0 (34.0-42.0)	37.0 (34.0-40.0)	0.28	0.87
VLDL	Median(IQR)	29.0 (23.0-35.0)	28.0 (21.0-34.0)	29.0 (21.0-32.0)	1.35	0.51
TG	Median(IQR)	146.0 (119.0-210.0)	143.0 (121.0-176.0)	145.0 (115.0-220.0)	0.48	0.79
NLR	mean ±SD (range)	1.97±0.69	2.14±0.77	2.09±0.80	F= 0.74	0.48
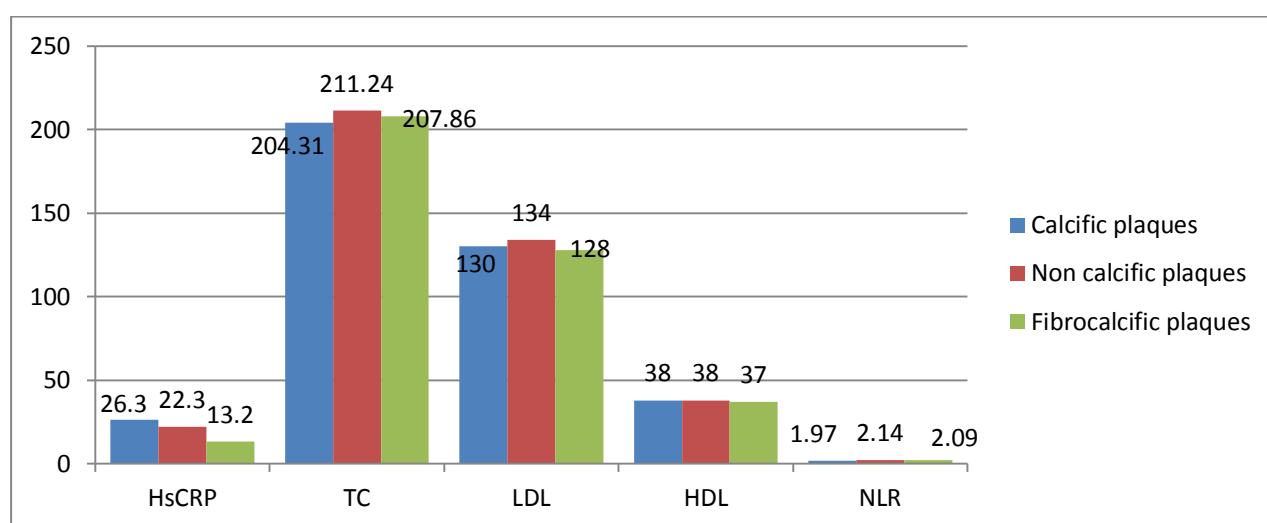
Figure(16):Differentiation of lipid profile and inflammatory markers among different types of plaques

Case presentations

Case no(10)

*Male patient,33 years old, not hypertensive, diabetic(NIDDM) for 3 years on oral hypoglycemic drugs , Smoker(smokes about 10 cigarettes per day for 9 years) with positive family history of coronary artery disease.

*The patient complained with dyspnea on exertion for 2 months duration.

***ECG** showed T wave inversion in v1 – v6.

***Echo** showed anterior wall hypokinesia, Diastolic dysfunction grade I, EF= 60%.

***Laboratory findings** were:

 TC=348, LDL=278, HDL=30, VLDL=21, TG=200, CRP= +ve(40.54), NLR=2.43.

***MSCT** showed Multi vessel disease with Ca score=406.6:

LM →Atherosclerotic vs with no significant lesions.

LAD→Atherosclerotic vs showing proximal significant calcific lesion followed by midsegment subtotal occlusion by fibro calcific lesion showing fissure.

LCX→Atherosclerotic vs showing totally occluded OMB by noncalcific plaque.

RCA→Atherosclerotic vs showing midsegment significant noncalcific lesion.

Case no (18):

*Male patient,61 years old, diabetic(NIDDM) for 14 years on oral hypoglycemic drugs, hypertensive for 10 years,non smoker with no family history of coronary artery disease.

*The patient complained of attacks of typical chest pain on exertion of 1 month duration.

* **ECG** showed mild ST segment depression in v1,v2,v3.

***Echo** showed Apical and lateral wall hypokinesia , Diastolic dysfunction grade I , EF=57%.

***Laboratory findings** were:

TC=207, LDL=127, HDL=40, VLDL=46, TG=200, CRP=+ve(35.76), NLR=1.82
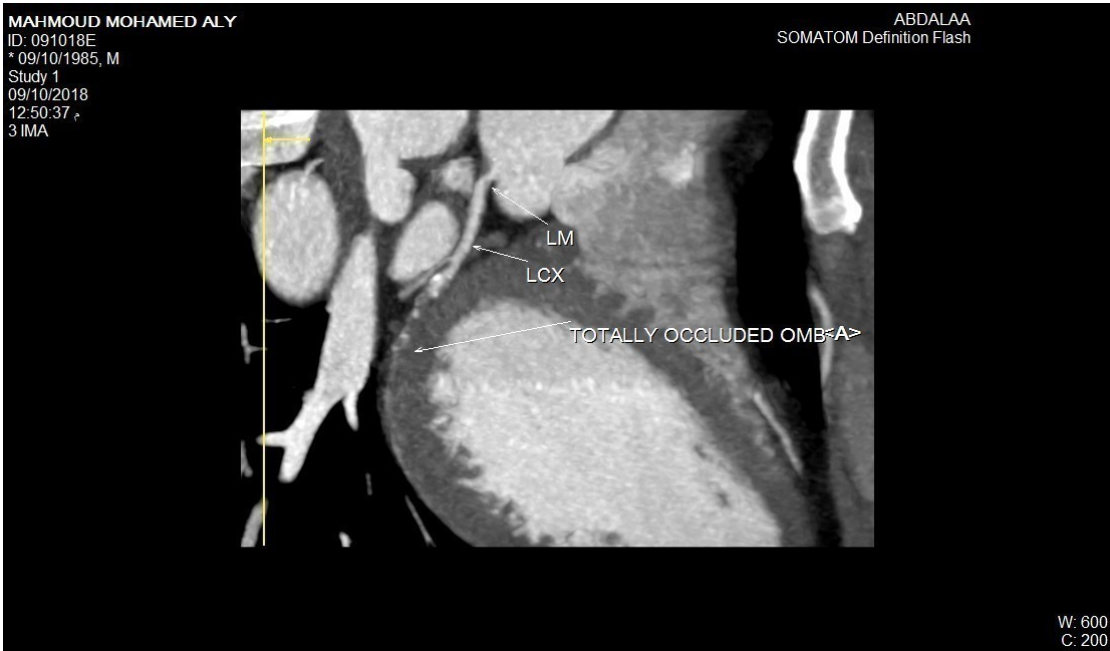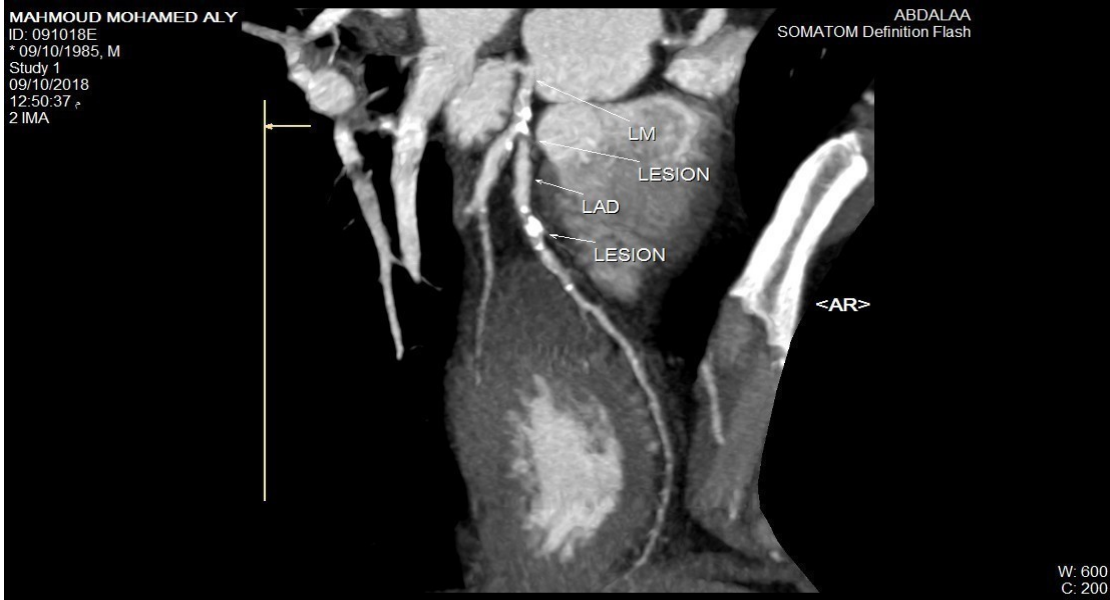
***MSCT** showed multi vessel disease with Ca score= 320.6

LM→Atherosclerotic vessel showing distal 30% calcific lesion.

LAD→Atherosclerotic vessel showing proximal significant calcific lesion.

LCX→Atherosclerotic vessel showing midsegment signigficant calcific lesion.

RCA→Atherosclerotic vessel showing midsegment significant noncalcific lesion with napkin ring sign denoting vulnerability.

Case no (111):

*Male patient, 64 years old, not hypertensive, diabetic (NIDDM) for 15 years on oral hypoglycemic drugs, smoker(smokes about 20 cigarettes per day for 25 years)with positive family history of coronary artery disease.

*The patient presented by attacks of typical chest pain on exertion for about 2 months.

***ECG** showed T wave inversion in LIII (Non specific).

***Echo** showed Mild MR,Mild AR ,Diastolic dysfunction grade I ,EF=65%.

***Laboratory findings** were:

TC=185, LDL=135, HDL=25,VLDL=42, TG=125, CRP= +ve(38.1), NLR=2.13.

***MSCT** showed Multi vessel disease with Ca score= 157.2:

LM→Atherosclerotic vs with no significant lesions.

LAD→Atherosclerotic vs showing proximal 55% calcific lesion with positive remodeling.

LCX→Atherosclerotic vs showing midsegment non calcific 70% lesion.

RCA→Atherosclerotic vs showing ostial 50% non calcific lesion followed by mid segment fibrocalcific 75% lesion then distal segment isnot clearly evaluable due to breathing and motion artifacts.

MOHAMED ABDELMONIM ABDELLATIF
ID: 240219l
* 24/02/1955, M
Study 1
24/02/2019
01:22:02 م
137 IMA

R

SL 0.75/ p0.27/ FpR 10.3
mAs 209
kV 120
SP -1224.9
Comment: 78 bpm, 38 % S, 75 ms

A

ABDALAA
SOMATOM Definition Flash

5cm

W: 600
C: 200

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W: 600
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155 IMA

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kV 120
SP -1232.1
Comment: 78 bpm, 38 % S, 75 ms

A

ABDALAA
SOMATOM Definition Flash

5cm

W: 600
C: 200

Case no(247):

   *Male patient, 74 years old, hypertensive for 10 years, diabetic (NIDDM) for 20 years on oral hypoglycemic drugs , non smoker with positive family history of coronary artery disease.

   *The patient presented by dyspnea on exertion and Epigastric pain not responding to proton pump inhibitors for about 2months duration.
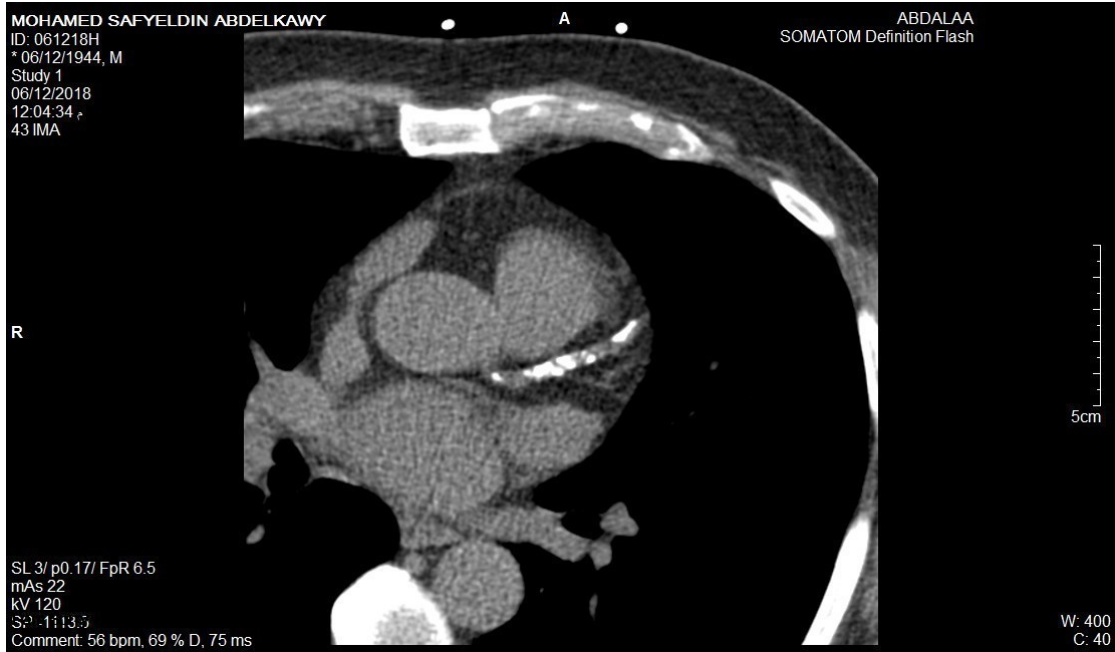
   ***ECG** showed T wave inversion in LI, avL.

   ***Echo** showed Moderate MR(Mostly Rheumatic), Mild AR, diastolic dysfunction grade I, EF=59%.

   ***Laboratory findings** were:

   TC=233, LDL=162, HDL=41, VLDL=28, TG=152, CRP=negative(4), NLR=2.01.

   ***MSCT** showed **high Ca score >1000** making the evaluation not possible.

Case no(248):

*Male patient,64years old, not hypertensive, diabetic(NIDDM) for 15 years on oral hypoglycemic drugs, non smoker with no family history of coronary artery disease.

*The patient presented with attack of typical chest pain and palpitation 1 week ago.

***Ecg** showed ST depression in LI, avL, v5, v6.

***Echo** showed Septal and lateral wall hypokinesia, diastolic dysfunction grade I, EF=60%.

***Laboratory findings** were:

TC=339, LDL=255, HDL=60, VLDL=23, TG=119, CRP= +ve(40.2), NLR=2.6.

***MSCT** showed Multivessel disease with Ca score= 234.9:

LM→Atherosclerotic vessel with no significant lesions.

LAD→Atherosclerotic vessel showing ostial 40% calcific lesion followed by proximal 80% fibro calcific lesion.

LCX→Atherosclerotic vs showing proximal focal 50% fibrocalcific eccentric lesion.It give OM2 that show ostial total occlusion by fibrocalcific plaque.

RCA→Atherosclerotic vessel showing distal focal 70% noncalcific lesion.
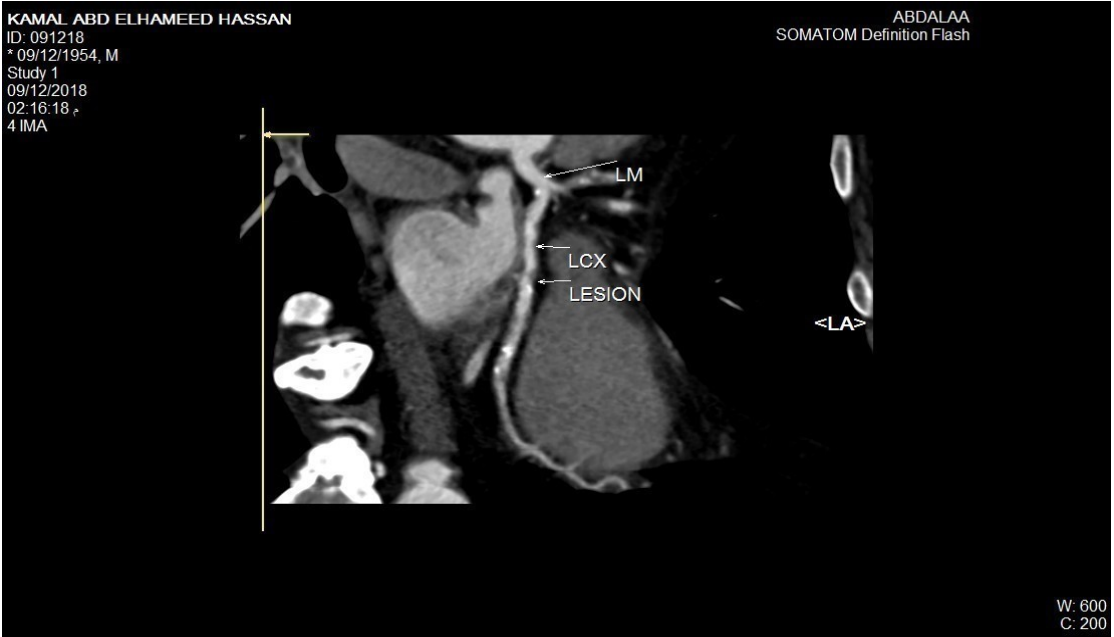
Discussion

Inflammation has been detected as an important mechanism for different subsets of CAD. Also, current evidence supports a major role for inflammation in all phases of the atherosclerotic process **(Mavrogeni, 2010).**

Systemic inflammation can be measured by using a variety of inflammatory markers. several Observational studies have thoroughly investigated the role of hsCRP, total leukocyte count , NLR and lipid profile in different chronic conditions. **(Imtiaz et al., 2012)**

Traditionally, imaging of the coronary arteries by means of invasive coronary angiography has focused on the assessment of luminal stenosis. However, invasive coronary imaging is less able to evaluate the presence of vulnerable plaques. As a result, there is an emerging need for imaging modalities as MSCT that can detect atherosclerotic plaques with high-risk features indicating increased vulnerability for acute coronary events. *(Joella et al., 2009).*

In our study, we evaluated 265 patients to detect the relationship between inflammatory markers(hsCRP , NLR) and Lipid profile with characters of atherosclerotic plaques detected by MSCT.

Patients included in our study have median age of 57 years, 83.8% of the patients were males compared to 16.2% females , 46.8% of the patients were hypertensive, 27.9% were diabetic , 43.8% were current smokers and 41.9% had positive family history of coronary artery of these patients, which makes this population appropriate for the analysis of the association between lipid profile and inflammatory markers of patients and the atherosclerotic coronary artery plaques.

Regarding hsCRP, it was positive in 59.2% and negative in 40.8% of the studied group, with median value = 9.32 mg/l . There is significantly higher values of hsCRP in patients with any type of atherosclerotic plaque as compared to patients without any detected plaques (p<0.001).

We observed positive correlation between level of hsCRP and value of Ca score, calcific plaque burden and non-calcific plaque burden (p<0.001). Also, higher degree of fibro calcific plaque burden was associated with higher values of hsCRP but the difference was statistically insignificant (p=0.11).

Furthermore, hs-CRP is significantly higher with calcific plaques than non-calcific and fibro-calcific plaques . Also hs-CRP is significantly higher among non-calcific plaques than fibro-calcific plaques (P<0.001).

In agreement with our results, **Chun-Lin et al** in 2011 examined 256 patients with suspected acute coronary syndrome and found that mean hsCRP in patients with any type of atherosclerotic plaque (hard , soft , mixed) was statistically higher than those without any detected atherosclerotic plaque(p<0.01).

Also, **Jonathan Rubin et al** in 2011 examined 1004 south Korean patients who underwent MSCT angiography and found that high level of hsCRP was associated with increased prevalence of different types of atherosclerotic plaques , but in contrast to our study he observed that hsCRP has positive correlation with mixed plaque burden more than any other type of plaques.

Elevated CRP, a marker of inflammation, has been clearly related to poor cardiovascular outcomes. CRP has been shown to participate in the whole atherosclerotic process, including damage of blood vessel endothelium and the formation, maturation, instability and final disruption of atheromatous plaque. **(Chun-lin et al , 2011).**

In an effort to directly establish the relationship between hsCRP and plaque vulnerability, **Ishikawa et al** in 2003 demonstrated greater amounts of CRP-stained cells in samples from culprit lesions of unstable angina patients as compared with lesions from patients with stable angina. They also found an increased rate of restenosis on follow-up angiography in the elevated CRP group, suggesting that CRP might be related to plaque vulnerability. Providing further support for this hypothesis, in a postmortem study in 2003, **Burke and his colleagues** demonstrated that elevated serum CRP correlated with an increased number of thin-cap fibro atheromas (TCFA), a key component of vulnerable plaque.**(Burke et al 2003)**

As regard to lipid profile, the mean value for total cholesterol in our study was 197.51 mg/dl, median values of LDL was 118 mg/dl , HDL was 40 mg/dl and TG was 143 mg/dl.

We found that TC, LDL was significantly higher and HDL was significantly lower in patients with any type of atherosclerotic plaque as compared to patients without any detected plaques (p<0.001).

Also, we observed positive correlation between level of TC, LDL and non-calcific plaque burden (p<0.001). Furthermore, negative correlation was noticed between level of HDL and non-calcific plaque burden (p<0.001)

.Also ,higher degree of calcific plaque burden and fibro calcific plaque burden was associated with higher values of TC, LDL and lower values of HDL but the difference was statistically insignificant.

Isolated hypertriglyceridemia failed to show any significant relation with any type of plaque burden.

In agreement with our study, **Rafaela Andrade and his colleagues** in their retrospective study among 107 patients in 2008 showed that TC , TC/HDL were markers of severity of coronary artery disease and number of vessels affected**.(Penalva et al 2008**)

Also, **Nakazato et al**, in 2013 observed a correlation between serum levels of TC, HDL, LDL with coronary artery plaque composition, as detected by cCTA in amulticenter study. Their study showed a significant correlation between high LDL, low HDL, high TC, and high non-HDL,and an increased prevalence of noncalcified plaques, partially calcified plaques, and calcified plaques (all P<0.05).

Furthermore, Allison and Wright in their study of 6093 participants in 2004, showed that the individuals with an HDL-c level < 40 mg/dl had significantly higher calcium scores while increases in HDL-c were associated with a significant reduction in risk for the presence of atherosclerotic plaques mostly calcified ones.

Also, **Paramsothy et al** in 2010 showed that isolated hypertriglyceridemia was not significantly related to coronary artery disease and calcification. However in contrast to our study, he showed that there is no significant association between low HDL level and CAD.

Dyslipidemia is a well-established risk factor for the development of CAD, and this has been demonstrated in several clinical and epidemiological studies. **(Smith, et al 2004).**

High plasma low-density lipoprotein (LDL-C) concentrations are directly correlated with the development of coronary artery disease, and low high-density lipoprotein (HDL-C) concentrations have been pointed out as one of the strongest independent risk factors for coronary atherosclerotic disease. *(Tsao and Donnell 2013).*

The negative effects of high low-density LDL-C and low HDL-C levels on the cardiac outcome of patients were previously reported in the Framingham study. **(Syed, et al 2014)**

More studies showed a reduction in plaque volume and decreased serum LDL levels after initiating lipid-lowering therapy, a treatment that uses the pleiotropic effects of statins**.(Kazankov, et al 2017).**

As regard NLR, the median value in our study is 2. Higher neutrophil to lymphocyte ratio was significantly correlated with level of total cholesterol and LDL (p=0.025, p=0.012 respectively).

However in our study, NLR failed to show significant relation with plaque vulnerability or degree of coronary obstruction.

That was disconcordant with **Horne** *and his colleagues* who observed the significance of NLR in stable CAD in their prospective study in 2005. Among more than 3000 patients with angiographically assessed CAD and without acute coronary syndrome events,total WBC count was confirmed to be an independent predictor of MI or death in patients at high risk for CAD, but greater predictive ability is provided by

low L or high N   counts. The greatest risk prediction is given by the N/L ratio, increasing the hazard by 2.2-fold. They reported that the significant improvement in risk prediction achieved with WBC differential was similar to or greater than that reported for hs-CRP *(Horne et al., 2005).*

Summary

Coronary artery disease (CAD), the leading cause of mortality worldwide, places a serious economic burden on health care systems. CAD is mainly due to atherosclerosis, an inflammatory process that is based on the interaction between immune mechanisms and metabolic risk factors. Abnormal lipid levels, particularly elevated low-density lipoprotein (LDL-C) and decreased high-density lipoprotein (HDL-C), as well as higher level of inflammatory markers especially high sensitive CRP (hsCRP) are well-established risk factors for atherosclerosis and CAD. **(Tsao et al 2013).**

Major advances in CAD prevention require early detection of the vulnerable plaques. A noninvasive assay to detect coronary atherosclerosis directly would therefore be beneficial. MSCT coronary angiography provides comprehensive information noninvasively regarding the location, severity, and characteristics of coronary atherosclerotic plaques. **(Chu et al 2010).**

Our study included 265 patients who presented with recurrent exertional chest pain (symptoms suggestive of CAD) and referred for MSCT angiography at kobry elkoba hospital.

The aim of our work was to study the relation between lipid profile and   different inflammatory markers (hsCRP, NLR) with coronary plaque characteristics as assessed by multi slice coronary CT angiography.

The study excluded patients presenting with acute coronary syndrome and patients with Previous history of coronary intervention (PCI or CABG).

We used MSCT coronary angiography to assess the coronary plaques as regard their number ,distribution, type , composition , degree of stenosis and presence of signs indicating vulnerability.

The study showed that there is significantly higher values of hsCRP, TC, LDL and significantly lower values of HDL in patients with any type of coronary atherosclerotic plaque as compared to patients without any detected plaques.

We also observed positive correlation between level of hsCRP and value of Ca score, calcific plaque burden and non-calcific plaque burden.

Furthermore, we observed positive correlation between level of TC, LDL and non-calcific plaque burden, and negative correlation between level of HDL and non-calcific plaque burden.

Isolated hypertriglyceridemia failed to show any significant relation with any type of plaque burden.

As regard Neutrophil to lymphocyte ratio, higher neutrophil to lymphocyte ratio was significantly correlated with level of TC and LDL.

So our study recommends the Use of hsCRP and lipid profile for risk stratification of patients to detect coronary plaque burden and predict vulnerable coronary plaques.

Conclusion

HsCRP is significantly higher in patients with coronary atherosclerotic plaques than patients without any coronary plaques. Moreover,HsCRP has positive correlation with Ca score, calcific plaque burden and non-calcific plaque burden.

TC, LDL is significantly higher while HDL is significantly lower in patients with coronary atherosclerotic plaques than patients without any coronary plaques. Furthermore, TC, LDL have positive correlation while HDL has negative correlation with Ca score and non-calcific plaque burden.

HsCRP is significantly higher while HDL is significantly lower in patients with obstructive plaques than in patients with non-obstructive plaques.

Hs-CRP is significantly higher with calcific plaques than non-calcific and fibro-calcific plaques . Also hs-CRP is significantly higher among non-calcific plaques than fibro-calcific plaques.

Recommendations

1- Use of hsCRP and lipid profile for risk stratification of patients to detect plaque burden and predict vulnerable coronary plaques.

2- Large scale studies involving more patients and conducted in multiple centers are needed.

3- Further studies to assess the impact of inflammatory markers and lipid profile on the decision and results of interventions.

4- Further studies to assess the role of inflammatory makers and lipid profile during the follow up of ischemic patients.

Study limitations

1- It is a single medical center study.

2- No follow up.

3- No data about intervention result if done.

4- In patients with more than one plaque, the plaque causing the highest degree of coronary stenosis is the only one considered during statistical analysis .

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