

The Hypercholesterolemia Paradox in Relation To Mortality in Acute Coronary Syndrome: A Meta-Analysis Review

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Abstract: ***Background:** For numerous decades it has been known that individuals with high cholesterol levels in their body are at increased risk of developing Acute Coronary Syndrome (ACS). However a number of researches in the recent past have been composed, scrutinizing the relevance of such a notion. **Objective:** The general objective was to search, analyze and compile relevant studies done to show an inverse relationship between high levels of cholesterol in relation to acute coronary syndrome. **Methodology:** We sought relevant articles from Cochrane Database of Systemic Reviews (2014), PubMed, BMJ, Clinical Cardiology journal, Journal of American College of Cardiology, journal of Critical Care Medicine, Journal of Lipid research, New England journal of Medicine and several circulations. **Results:** More than 167685 patients were involved in the chosen studies and they have shown significant inverse association between high cholesterol and ACS while a few of the studies displayed no association. **Conclusion:** There is a well-founded paradox of hypercholesterolemia in relation to ACS. Our study can be used as a set point for more researches to explore on this concept and review the various guidelines on the treatment of elevated cholesterol. It can as well be used to open doors for studies to be performed in African countries so as to test the validity of the concept.*

1. Introduction

For numerous decades it has been known that individuals with high cholesterol levels in their body are at increased risk of developing Acute Coronary Syndrome (ACS).

There are several contradictions against this view so far; no proper randomized studies done from the general population that have revealed an association between total cholesterol (TC) and degree of atherosclerosis. Moreover, in most of the Japanese epidemiological studies, high TC is not a risk factor for stroke and furthermore, there is an inverse association between TC and all- cause mortality irrespective of age and sex. [1]

Several studies done in the past have shown that oxidized low density lipoprotein (ox-LDL) is thought to play a key role in the genesis of the inflammatory process in atherosclerotic lesions which is the initial point of ACS development.

The question arises whether an increase in the blood levels of ox-LDL could be involved.[2]

Many studies have been done to investigate the validity of this concept, but they have not conveyed such impression to be given much weight. It is mostly due to this that we took the initiative to review and compile the findings of such studies so as to create more awareness and probably reevaluate what is already known among the medical fraternity and the public in general. Results in the reviewed studies have shown a

substantial paradox between high levels of cholesterol and existence of ACS.

2. Overview

Hypercholesterolemia is generally a well-known risk factor for the development of coronary artery disease. However, in observational analyses of either ACS clinical trials or registry databases, hypercholesterolemia has repeatedly been shown to be associated with a lower risk of adverse outcomes. [3]

Dyslipidemia is often referred to as an elevation of total cholesterol and/or LDL-cholesterol or non-HDL-cholesterol in the blood >200mg/dl.

Uptake of dietary lipid in the intestine and delivery of fatty acids;

After fat has been ingested from the diet, the emulsification process by bile salts in the small intestine follows to form mixed micelles. Intestinal lipases then degrade the triacylglycerols to glycerol and fatty acids which are then taken up by the intestinal mucosa then converted again to triacylglycerol. Triacylglycerols are combined with cholesterol and apoprotein C type 2 (ApoC II) into chylomicrons. The later moves into the tissues through the lymphatic system and bloodstream. Lipoprotein lipase in the capillary beds is activated by ApoC II, to release fatty acids and glycerol, which then enter the cells. Fatty acids in the cells are oxidized for fuel or re-esterified for storage.

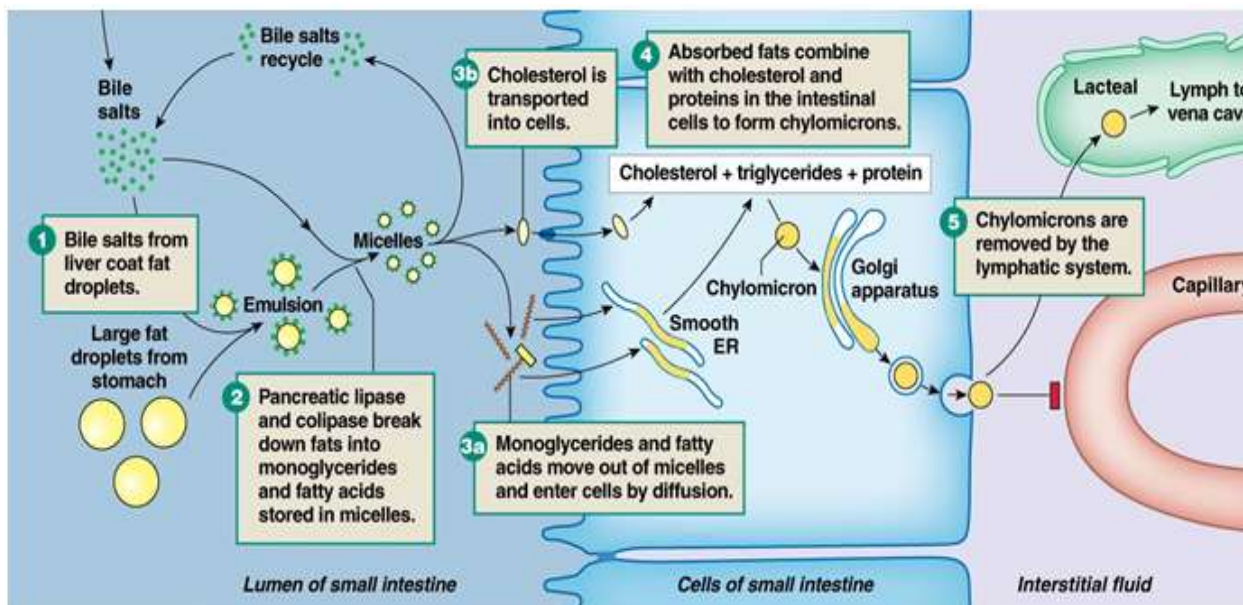


Figure 1: Lipid uptake and metabolism. [4]

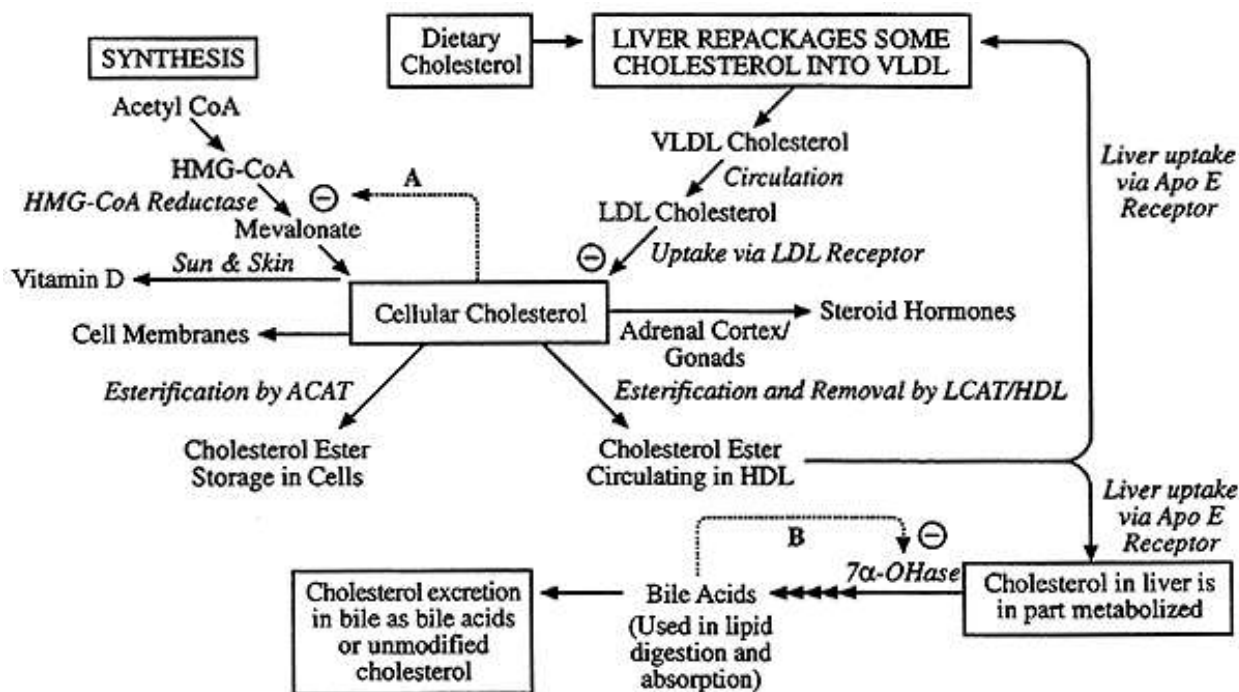


Figure 2: Lipid synthesis [5]

Acute Coronary Syndrome (ACS)

ACS encompasses a spectrum of unstable coronary artery disease from unstable angina to transmural myocardial infarction.

The spectrum of acute ischemia related syndromes range from Unstable Angina (UA) to Myocardial Infarction (MI) with or without ST elevation that are secondary to acute plaque rupture or plaque erosion. It accounts for 1.57 million hospital admissions per year.[6]

Types of angina

Stable angina: There is a stable pattern of onset, duration and intensity of symptoms. Pain is triggered by a predictable degree of exertion or emotion.

Variant Angina (Prinzmetal's): Usually cyclical and may occur at rest. Ventricular arrhythmia, brady-arrhythmia and conduction disturbances occur. Syncope associated with arrhythmia may occur.

Nocturnal Angina: Occurs only at night, possibly associated with rapid eyes movements during sleep.

Unstable Angina (Pre-infarction angina): Pain is more intense, lasts longer. [6]

Pathophysiology of ACS

This is clearly summarized in figure 2 below.

It is important to note that once MI has set in, it becomes an irreversible process which explains the significance of early diagnosis and hence intervention in pre-MI stage. [6]

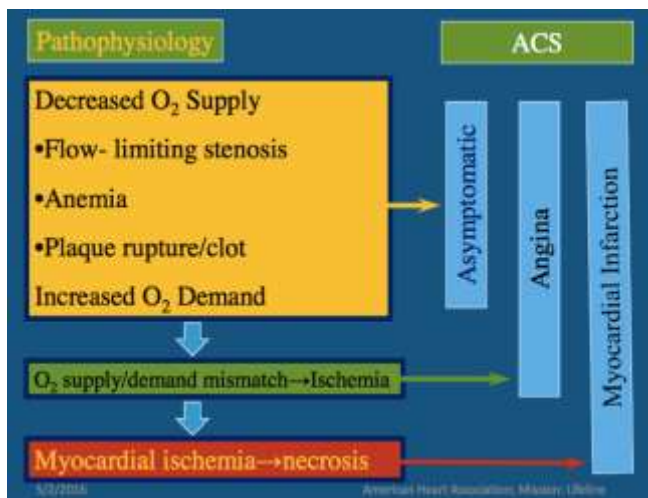


Figure 3: Pathophysiology of ACS. [6]

3. Diagnosis of ACS

There should be at least 2 of the following;

- History (angina or angina equivalent).
- Acute ischemic ECG changes.
- Typical rise and fall of cardiac markers.
- Absence of another identifiable etiology.[6]

Pathogenesis of atheromatous plaque

There is increasing evidence that acute coronary syndromes relate to recent activation of the immune-mediated inflammatory process associated with atherosclerotic plaques.[2] Moreover, atherectomy specimens obtained from patients with unstable angina pectoris (UAP) and acute myocardial infarction (AMI) have revealed a distinct and significant increase of interleukin-2 receptor-positive lymphocytes, which is indicative of recent activation of atherosclerotic plaques.[2]

Hence, an increased number of inflammatory cells in coronary atherosclerotic plaques are related to an increase in the severity of the acute coronary syndrome. Oxidized Low Density Lipoprotein (oxLDL) moves rapidly into arterial walls and engorges them with cholesterol. Cholesterol ultimately converts into plaque, blocking the arteries or, in a worst-case scenario, rupturing and sending clots into the bloodstream, causing heart attacks and/or strokes. [7]

Today atherosclerosis is considered an inflammatory process that occurs as a response to the accumulating lipid within the arterial wall. It begins with elevation of plasma cholesterol levels which result in changes in the arterial endothelial cell permeability that allow the insudation of lipids, especially “cholesterol-containing low-density lipoproteins (LDL)” into

the arterial wall where they bind to the extracellular proteoglycan rich matrix and aggregate (Fig. 4). [8].

Also, circulating monocytes now begin to adhere to the endothelial cells that express adhesion molecules, like vascular adhesion molecule-1 (VCAM-1) and selectins, which result in the migration of monocytes via diapedesis between endothelial junctions and reside in the subendothelial space. The monocytes then acquire characteristics of macrophages and convert to foamy macrophages.[8].

The prolonged residence of LDL particles in the subendothelial space results in their oxidation and other chemical modification. LDL oxidation is promoted in vitro by monocytes, endothelial cells, and smooth muscle cells. Oxidized LDL is a potent chemo-attractant and induces the secretion of macrophage-chemotactic protein 1 (MCP-1) by endothelial cells. Further- more, macrophages express several scavenger receptors (SR) [SR A and B1, CD36, CD68 and scavenger receptor for phosphatidylserine, and oxidized LDL] which can bind a broad spectrum of ligands, including modified lipoproteins, native lipoproteins, and anionic phospholipids, many of which facilitate the massive accumulation of intracellular cholesterol.[8]

It has been shown that macrophage infiltration is the first step towards the eventual formation of atherosclerotic plaque. In vitro studies have shown that LDL uptake by macrophages is facilitated by a two-step oxidation process. The first step begins with mild oxidation of lipid followed by apolipoprotein B oxidation, a modification required for its recognition by the scavenger receptor, which is unaffected by the cholesterol content of the cell. Oxidized cholesterol is delivered to the lysosomes where the oxidized-LDL is hydrolyzed to free cholesterol and free fatty acids, the excess cholesterol undergoes re-esterification by acyl coenzyme A: acyl cholesterol transferase (SOAT; also known as ACAT). The excess free cholesterol produced by the macrophage is exported out of the cell most likely via the SR-B1 receptor or other mechanism to HDL particles. Esterified cholesterol accumulates in the cytosol of the macrophage to form intracellular lipid droplets seen in foam cells As the plaque progresses, the free cholesterol content of lesion increases while cholesterol esters decrease.[8]

The early atherosclerotic plaque progression from pathologic intimal thickening (PIT) to a fibroatheroma is thought to be the result of macrophage infiltration. PIT is characterized by the presence of lipid pools, which consist of proteoglycan with lipid insudation. The conversion of the lipid pool to a necrotic core is poorly understood but is thought to occur as a result of macrophage infiltration, which releases matrix metalloproteinase (MMPs) along with macrophage apoptosis that leads to the formation of an acellular necrotic core. The fibroatheroma has a thick fibrous cap that begins to thin over time through macrophage MMP release and apoptotic death of smooth muscle cells converting the fibroatheroma into a thin cap fibroatheroma (TCFA).

Atherosclerotic plaque rupture with luminal thrombosis is the most common mechanism responsible for the majority of acute coronary syndromes and sudden coronary death.[8]

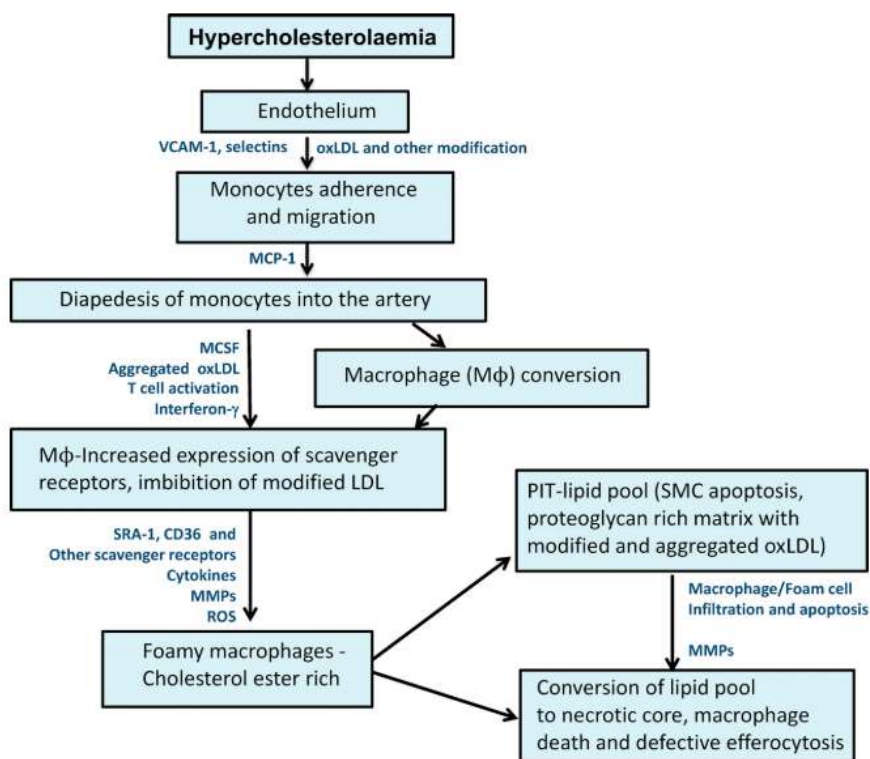


Figure 4: Sequence of events that lead to the atherosclerotic change and its progression [8]

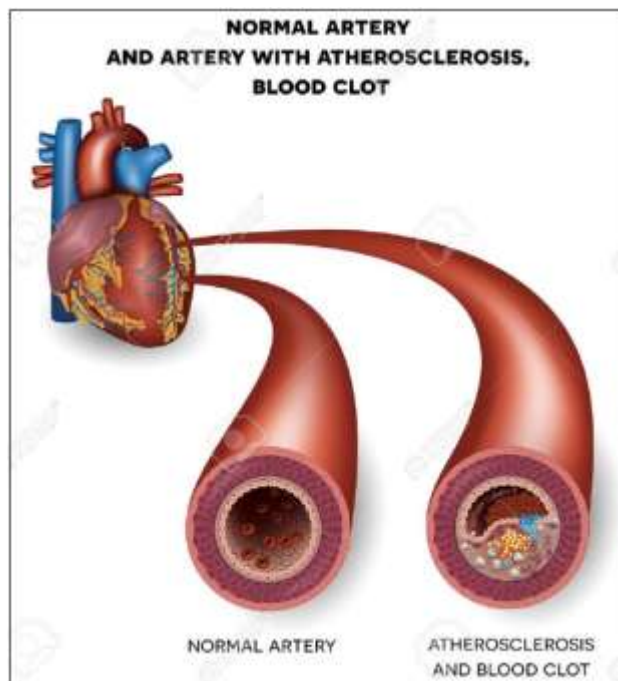


Figure 5: Atherosclerosis and blood clot [9]

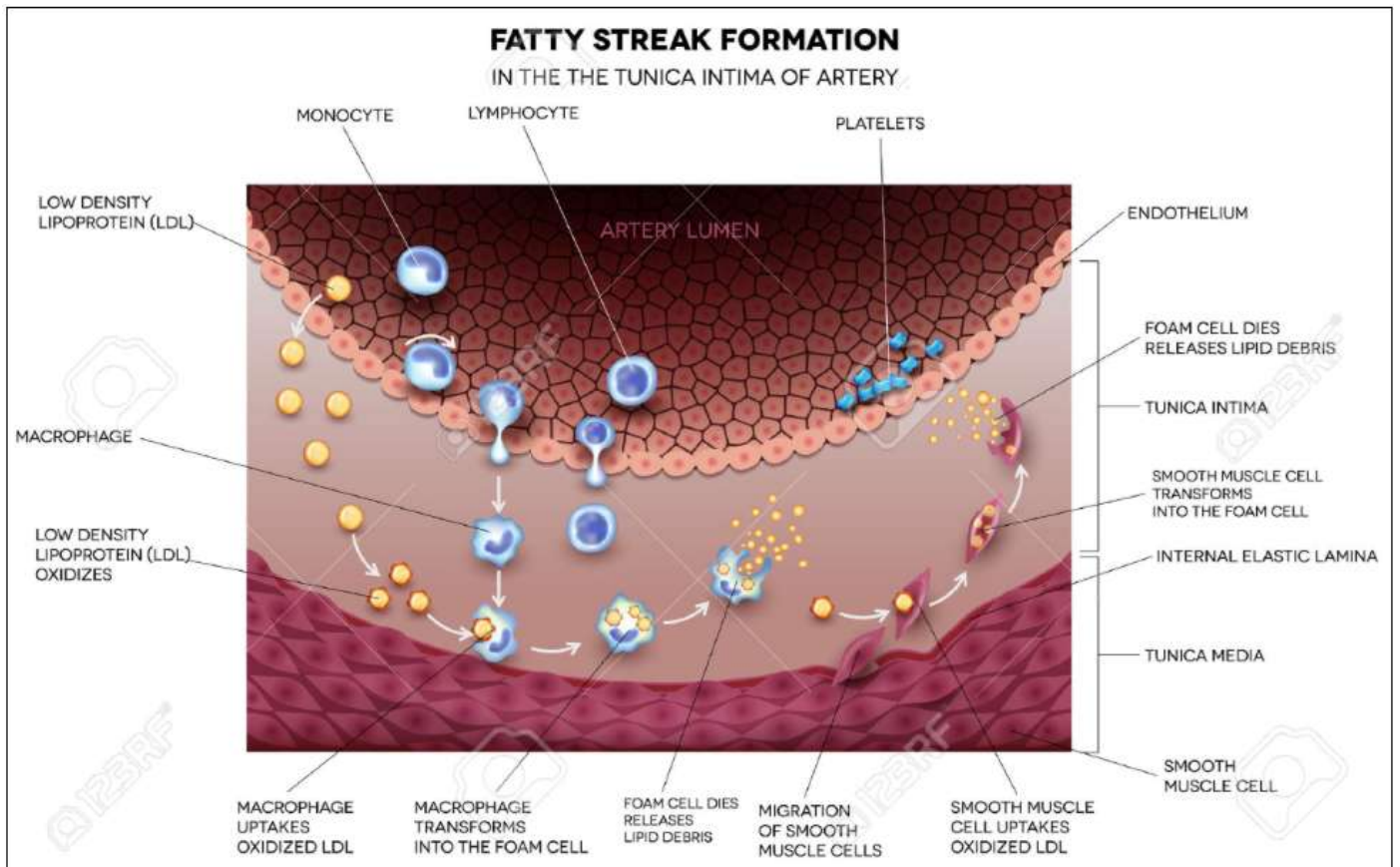


Figure 6: Fatty streak formation. [10]

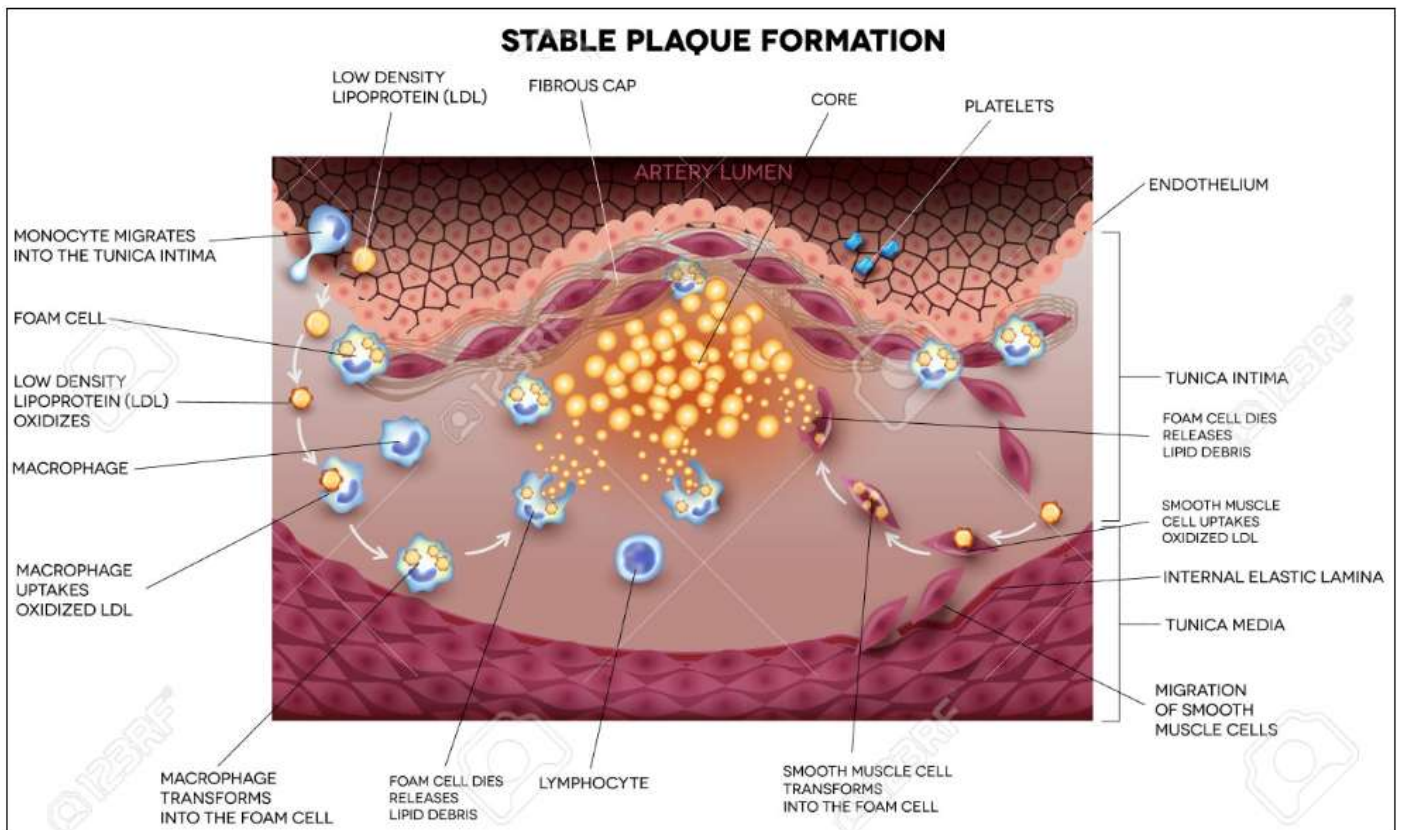


Figure 7: Stable plaque formation. [11]

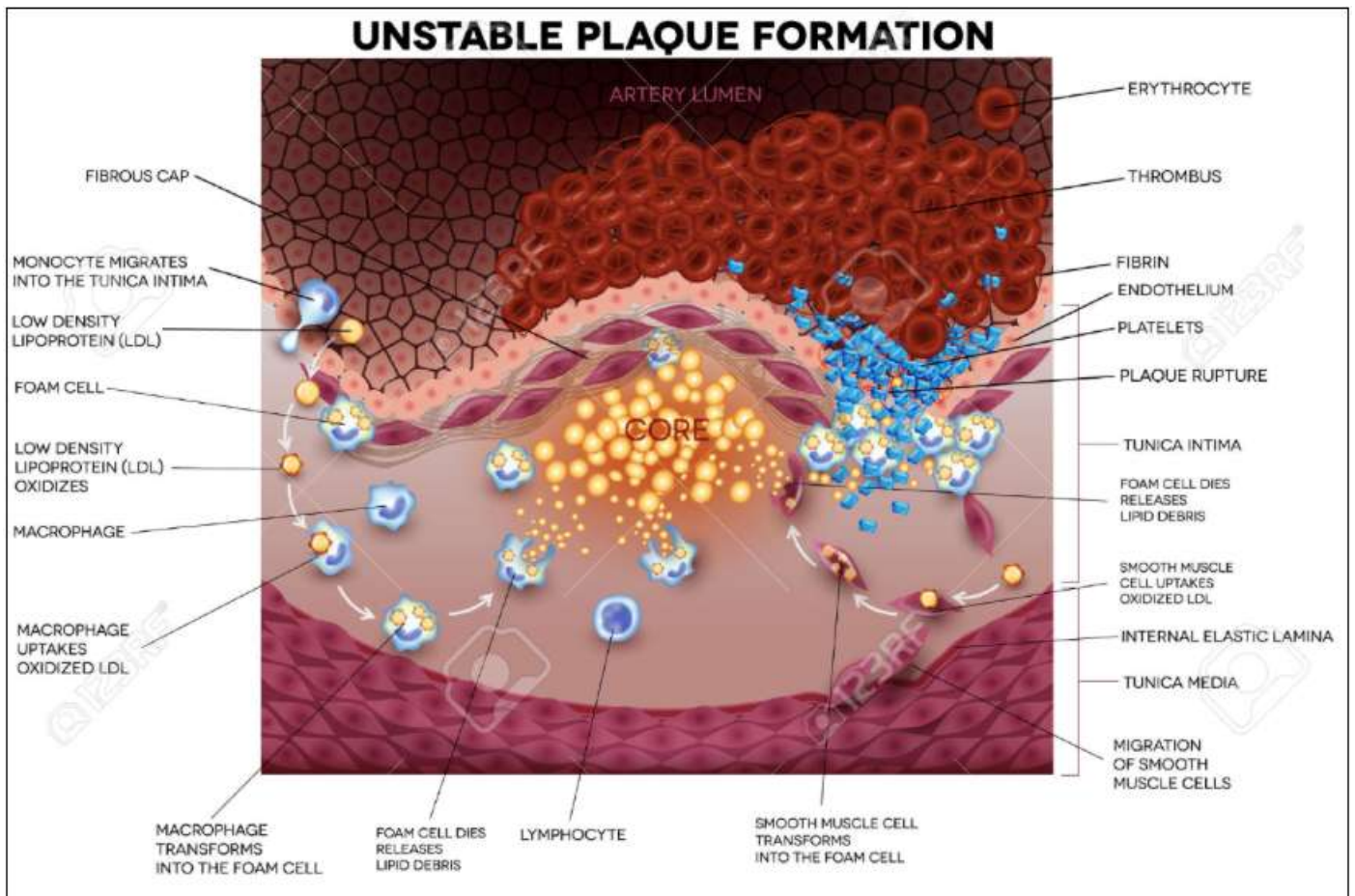


Figure 8: Unstable plaque formation. [12]

4. Discussion

Hypercholesterolemia has been implicated as a risk factor for atherosclerosis by numerous observational studies in the general population. Studies in patients suffering from various chronic illnesses and in individuals with advanced age have indicated an inverse association between cholesterol level and mortality suggesting that the classical Framingham paradigm may not apply to these groups. It is yet unclear what the reasons for these paradoxically inverse associations are but following are some interesting studies that have been done so far.

It is important to measure serum lipids and lipoprotein levels as well as to know their varying characteristics. For example, to measure the level of High Density Lipoprotein (HDL) does not exactly show the composition, functionality and anti-inflammatory characteristics of HDL. It was seen that there were phasic changes in serum lipid and lipoprotein levels following an ACS. Therefore, it is difficult to find the patient's baseline lipid profile correctly. However, if we consider that the changes are minimal in the first 24 hours, it seems reasonable to evaluate the lipid profile in that period. On the other hand, it is expected that Triglyceride Cholesterol (TC), Low Density Lipoprotein (LDL) and HDL levels that are measured following ACS are lower than the basal values. [13].

This modification change may explain the variation in the levels of cholesterol when done later in the course of disease, which is not a true reflection of the actual baseline cholesterol levels.

In another study it was demonstrated that high-capacity selective Cholesteryl Ester (CE) uptake is a major pathway of cholesterol delivery to macrophages during native LDL-induced foam cell formation. The results showed that LDL oxidation results in progressive inhibition of this pathway, in contrast to the well-known enhancement of LDL particle uptake that occurs with LDL oxidation due to recognition by macrophage scavenger receptors. The mechanism is unknown, but the studies suggest that this occurs via inhibition of macrophage up- take activity, resulting in reduced selective uptake from both oxLDL as well as native LDL. The impact of altered CE uptake at each stage of LDL oxidation was reflected by significant differences in macrophage foam cell formation. Instead of increasing the amount of cholesterol uptake and accumulation in the macrophage foam cells, mildly oxidized LDL almost completely prevents increases in cholesterol. [7]

It is also important to note that fatty acids from triglycerides are a major energy source, low-density lipoprotein cholesterol is critical for cell membrane synthesis, and both are critical for cell survival. Significantly higher prevalence rates of ST

Elevated Myocardial Infarction (STEMI) and higher Killip (fig. 7) were noted in both low LDL and low triglyceride groups, and significantly higher prevalence rates of diabetes, End Stage Renal Disease (ESRD) and higher ratios of TC/HDL were found in patients with high-Killip class. Similar differences were also found between those who expired compared with those who survived over 30 days. Interestingly, there was a lipid paradox with significantly lower TC, LDL, triglyceride and BMI in the high-Killip patients and in those who died. This study supports a lipid paradox in patients presenting with AMI with significantly lower TC, LDL and triglyceride in patients with severe Killip classification and in those who died in the hospital within 30 days. Cumulative survival showed significantly higher mortality rates in patients with LDL less than 62.5mg/dL and triglyceride less than 110mg/dL (optimal cutoff points by each lipid) groups. The synergistic effects of both low LDL and low triglyceride in addition to Killip classification on AMI patients were demonstrated. The high-Killip group had a 2.5-fold higher risk of mortality than the low severity group, whereas the group with both low LDL and low triglyceride had a 10.9-fold higher risk than the group with both high LDL and high triglyceride. [14]

Killip classification.

- Stage I— **No heart failure.** No clinical signs of cardiac decompensation;
- Stage II— **Heart failure.** Diagnostic criteria include **rales, S3 gallop and pulmonary venous hypertension.** Pulmonary congestion with wet rales in the lower half of the lung fields;
- Stage III— **Severe heart failure.** Frank pulmonary oedema with rales throughout the lung fields;
- Stage IV— **Cardiogenic shock.** Signs include hypotension (SBP 90mmHg), and evidence of peripheral vasoconstriction such as oliguria, cyanosis and diaphoresis.

Figure 7: Killip classification.[14]

In another study, PubMed for cohort studies, where LDL had been investigated as a risk factor for all-cause and/ or cardiovascular (CV) mortality in individual ≥ 60 years from the general population. They identified 19 cohort studies including 30 cohorts with a total of 68 094 elderly people, where all-cause mortality was recorded in 28 cohorts and CV mortality in 9 cohorts. Inverse association between all- cause mortality and LDL was seen in 16 cohorts (in 14 with statistical significance) representing 92% of the number of participants, where this association was recorded. In the rest, no association was found. In two cohorts, CV mortality was highest in the lowest LDL quartile and with statistical significance in seven cohorts, no association found. High LDL is inversely associated with mortality in most people over 60 years. This finding is inconsistent with the cholesterol hypothesis (i.e. that cholesterol particularly LDL is inherently atherogenic). Since elderly people with high LDL live as long as or longer than those with low LDL, the analysis provides reason to question the validity of the cholesterol hypothesis.

Moreover, the study provided the rationale for a re-evaluation of guidelines recommending pharmacological reduction of LDL in the elderly as a component of cardiovascular disease prevention strategies. [1]

In another review from Cochrane database of 2014 showed that statins decrease morbidity and mortality in patients with atherosclerosis, thus supporting their use for the primary and secondary prevention of ischemic heart disease. Different pathological pathways that are triggered in the setting of ACS, such as endothelial dysfunction, activation of inflammatory and coagulation cascades, and thrombus formation, are known to be inhibited by statins, thereby justifying the use of these agents in patients with ACS. The early period following the onset of ACS represents a critical stage of coronary heart disease, with a high risk of recurrent events and deaths. Based on moderate quality evidence, due to concerns about risk of bias and imprecision, initiation of statin therapy within 14 days following ACS does not reduce death, myocardial infarction, or stroke up to four months, but reduces the occurrence of unstable angina at four months following ACS. [15]

5. Conclusion

The traditional medical thinking is that LDL particles that have reacted with oxLDL are highly inclined to dump their cholesterol stores onto artery walls, using white blood cells to transfer the cargo. Eventually, they claim, this process leads to plaques—the main cause of heart attacks and strokes, “This theory is based on evidence showing LDL in the wrong place at the wrong time”—circumstantial, even after decades of research. The dogma that LDL cholesterol is nothing but bad news—and the multi-billion-dollar statin drug industry that rests on it—is beginning to erode. As Meyer et al stated, oxidized LDL actually has a possibility to create a medicine from oxidized LDL to help prevent or treat this killer disease.

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