Review Article

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PREPARATION CHOLESTEROL AND EFFECTS OF CHOLESTEROL PARADOX: A REVIEW

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ABSTRACT

Cholesterol is the most significant sterol in mammals, which contributes to preserving plasma membrane fluidity and serves as a precursor of oxysterols, bile acids, and steroid hormones. Plasma membranes contain large amounts of cholesterol, which interacts with other molecules in the membrane in various ways. Cholesterol, one of the most significant structural elements, is regarded as a lipid-type molecule. It plays a crucial role in life, primarily in cell membranes and as a precursor to the biosynthesis of numerous steroid hormones in cell membranes. Cholesterol absorption is linked to recurrent cardiovascular events, and patients with higher cholesterol absorption experienced less of a statin's favourable effects. One of the essential and prevalent conditions that affect people's health worldwide is coronary artery disease (CAD), and its incidence has grown over time. The best predictor and moderator of coronary artery disease is the low-density lipoprotein cholesterol plasma level. Higher than lower HDL cholesterol levels were associated with a lower risk of major cardiovascular events. Contrarily in cholesterol paradox states, individuals with advanced HF often have low cholesterol, associated with a poor prognosis and hypercholesterolemia, a key risk factor for CAD. On average, patients with a total cholesterol level of 232 mg/dl had a 25% higher survival rate than those with a total cholesterol level of 193 mg/dl who were suffering from heart failure. A total cholesterol level under 200 mg/dl is generally preferred.

Keywords: Cholesterol, Cholesterol paradox, Coronary artery disease, High-density lipoprotein.

INTRODUCTION

Cholesterol (or other higher sterols like ergosterol and phytosterols) is universally present in substantial concentrations (20-40 mol percent) in eukaryotic plasma membranes, whereas it is missing in prokaryote membranes. Cholesterol has the distinctive capability to maintain diffusion rates and fluidity while increasing lipid order in fluid membranes. Cholesterol provides lipid membranes with low permeability barriers and high mechanical coherence[1]. Also found in modest levels in the endoplasmic reticulum (ER) membrane, where it is required for metabolic control[2]. Cholesterol is widespread in plasma membranes and interacts with other membrane molecules in various methods[3]. Cholesterol is crucial for life, especially in cell membranes, and is a precursor to numerous steroid hormones' production[4]. "Endogenous" cholesterol governs cholesterol homeostasis, mainly made in the liver, and "exogenous" cholesterol comes from food and is absorbed in the small intestine. The liver primarily manages the circulating cholesterol level, with dietary or external cholesterol accounting for around 30% of total cholesterol and the remaining 70% generated in the body. Cholesterol is discharged in the bile, reabsorbed in the gut or expelled in the faeces during catabolism[5]. Cholesterol is derived from food or can be synthesized by de novo. In immune cells, cholesterol levels play a role in monocyte priming, neutrophil activation, hematopoietic stem cell mobilization, and increased T cell generation[6].

Cholesterol helps the body make steroid hormones, vitamin d, bile acid, and substrates that help digest food[3].

Cholesterol is a 27-carbon molecule with a unique structure that includes a hydrocarbon tail, a four-ringed sterol nucleus, and a hydroxyl group. All steroid hormones have a sterol nucleus or ring in the centre. Because the hydrocarbon tail and centre ring are non-polar, they do not dissolve in water. As a result, cholesterol (lipid) is packed with apoproteins (protein) and transported as a lipoprotein through the bloodstream[3].

Biosynthesis of cholesterol

1. Synthesis of HMG CoA
2. Formation of mevalonate (6C)
3. Production of isoprenoid units (5C)
4. Synthesis of squalene (30C)
5. Conversion of squalene to cholesterol (27C)

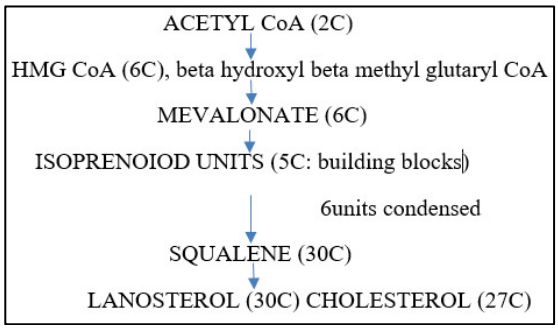

Figure 1: Biosynthesis of Cholesterol

The degradation of cholesterol (50%) helps produce steroid hormones, vitamin d, coprostanol, bile acid, and cholestanol. The major organs indulged in cholesterol biosynthesis are the liver (50%), intestine (15%), skin, adrenal cortex, and reproductive tissues. Adults produce 1g of cholesterol per day[7].

Endogenic Synthesis of cholesterol

Fasting rates are much lower than feeding rates, which can be due to nutritional substrate. Furthermore, chronically excessive calorie intake is connected to cholesterol overproduction, whereas calorie restriction lowers synthesis[8]. The exchange of polyunsaturated fats for saturated fats was already reported to increase production rates in specific investigations, although no variations in cholesterol synthesis have been detected in others[9].

Types of cholesterol

Lipoproteins are a combination of fat and protein and thus can travel in the blood.

HDL (high-density lipoprotein)

- It is also known as good cholesterol because it carries cholesterol to the liver; hence liver helps in removing it from the body.
- In the Framingham heart study, HDL levels are a more powerful risk factor for coronary artery diseases, whereas LDL was more harmful to heart health than HDL[10].
- In statin-treated patients, HDL cholesterol levels were predictive of major cardiovascular events. This link was also discovered in people whose LDL cholesterol levels were less than 70 mg per decilitre[10].

LCAT in HDL metabolism

RCT pathway facilitates the clearance of excess cellular cholesterol from peripheral tissues and its transport to the liver for bile excretion[11].

The gradient of free cholesterol concentration between cell membranes and HDL is increased by the esterification of cholesterol on HDL[7]. Without continuous cholesterol esterification, HDL's ability to remove and bind more cholesterol would deteriorate over time. CETP may improve this process by moving cholesteryl esters generated by LCAT, allowing HDL to bind cholesterol more effectively. Because cholesteryl esters are substantially more hydrophobic than cholesterol, LCAT also limits the spontaneous back exchange of cholesterol from HDL to cells, promoting net cellular elimination of cholesterol. Cholesteryl esters on HDL and LDL are effectively retained on these lipoproteins until the liver can remove them from circulation[11].

Bile acids are important micelle detergents; they are required for cholesterol absorption, and when they are diverted from the gut, such as in total biliary obstruction, no cholesterol is absorbed.

LDL (Low-density lipoprotein)

- LDL cholesterol is also known as bad cholesterol because high levels of VDL form plaque in the body, which leads to severe cardiac complications. It mainly carries cholesterol[10].
- LDL distributes cholesterol to most tissues via an endocytic mechanism conciliated by the LDL receptor (LDLr).
- LDL, which is otherwise called bad cholesterol and always heard that it should be kept at low levels[12].
- LDL can build up on the insides of your arteries, narrowing them. The fatty deposits harden into plaque, which lines your arteries and can block them. Atherosclerosis is the name for this build-up.
- Arteries are the blood veins that transport oxygen-rich blood from your heart to your other organs[12].
- Saturated and trans fats are the fats that are associated with high LDL cholesterol levels and should be avoided in your diet. When saturated fats are at room temperature, they are solid or waxy. Saturated fats are typically found in animal products such as meat, milk, cheese, and butter.
- Trans fats are formed when liquid fats are solidified during the hydrogenation process. Fast meals and fried foods include trans fats, which are utilized to extend the shelf life of processed foods such as cookies, crackers, and baked goods[10].
- VLDL, also known as bad cholesterol, mainly carries triglycerides[12].
- VLDL cholesterol belongs to the VDL receptor protein family, which binds to triglyceride-rich protein, not VDL and works as a peripheral recombinant lipoprotein receptor. VLDL receptors are found in fatty acid-active tissues heart, skeletal muscle, fat, brain, and macrophages.
- The major functions of VLDL- are lipoprotein metabolism, metabolic syndrome, cardiac fatty acid metabolism, atherosclerosis, neuronal immigration, angiogenesis, cancer, and signal transduction[4].
- Meat from domestic animals is the utmost fat source in the human diet, while seafood has a lot of cholesterol. Raw and cooked beef and poultry items have cholesterol levels ranging from 40-90 mg/100 g[13].

Table 1: Cholesterol content from various meat and poultry species

Source	Cholesterol content (mg/100g)
Beef, brisket	52
Pork, belly	70 – 120
Pork cuts	43 – 60
Chicken, breast meat	47 – 56
Turkey, breast meat	53
Lamb	60 – 70
Goat	55 – 60[13]

Cholesterol is a firm, nearly planar molecule with a steroid skeleton of four fused rings, three six-membered and one five-membered, lettered A to D (1,2 cyclopentanoperhydrophenanthrene ring system). There are four critical domains in the cholesterol molecule. The 3-hydroxy group's polarity is an active site for hydrogen bond interactions with the heterogeneity of biological components in domain I. (e.g., phospholipids in membranes). The absence of methyl groups at C-4 and C-14 controls the molecule's planarity in domain II, whilst the natural (R) configuration at C-20 defines the side chain's "right-handed" conformation in domain III. Finally, intermolecular interactions in domain IV are heavily influenced by the shape and length of the side chain. The amphiphilic property of the molecule is due to a hydrophilic 3-hydroxy headgroup on the A-ring, additionally to a hydrophobic hydrocarbon body, which makes cholesterol the most well-known sterol4. Conversion in the stereochemistry and oxidation states of the fused rings, the side chain, and the functional groups of sterol results in a broad range of biologically significant compounds, including bile acids, vitamin D, and many steroid hormones[4].

Biological synthesis and metabolism of cholesterol

In the mid-1930, after many years of exertion, the underlying clarification of cholesterol had arrived at the phase of fruition, and with this accomplishment, perhaps the most splendid part of natural science came to a nearby[14]. A mutant of Neurospora crassa, which E. L. Tatum had separated, filled the necessity for cholesterol creation admirably because the mutant's development was exposed to exogenous acetic acid derivation due to scarcity of pyruvate digestion[10]. Mutant strain cells become on named acetic acid derivation delivered ergosterol essentially without

weakening of the isotope, and this demonstrated that no other carbon source contributed altogether for the production of the sterol skeleton cholesterol, in the same way as other normal substances, was derived from a polyisoprenoid intermediate For this view to grab hold, the ground was, Robinson's hypothesis, as indicated by which the cyclization of squalene, a polyisoprenoid hydrocarbon shaped cholesterol. At this stage, a blueprint of the general cycle arose: acetate -> isoprenoid intermediate -> squalene --> cyclization product --> cholesterol[15].

Metabolism and immersion of cholesterol

Intestinal mucosa secretion is a third probable source[9]. Although the cholesterol in bile is not esterified, a tiny percentage of cholesterol consumed in the diet may be in the form of esters, in which cholesterol and fatty acids are linked; however, pancreatic cholesterol esterase rapidly hydrolyzes the cholesterol, which enters into the intestine[9]. Sterol regulatory element-binding protein 2 (SREBP2) transcription factor and ubiquitin and lysosomal–proteasome degradation is useful for regulating NPC1L1 during cholesterol insufficiency. Inside the enterocytes, a cholesteryl ester-rich core, lipoprotein rich in triglyceride type, and a surface containing a single molecule of apolipoprotein B (ApoB)48 protein, chylomicrons are assembled by re-esterifying cholesterol by using enzymes such as acetyl-CoA (Ac-CoA) acetyltransferase 2 (ACAT2). VLDL and triglycerides are present in chylomicron by using lipoprotein lipase (LPL)[8]. The hepatic lipase (HL) enzyme catabolizes the LDL particles and chylomicron[9].

Cholesterol absorption

- Complete cholesterol intake is impossible because, unlike AA and glucose, cholesterol is never completely dissolved in the intestinal contents[16].
- Mixed micelles, including conjugated bile acids, hydrolytic products of triglycerides and lecithin fatty acids, monoglycerides, and lysolecithin, must first solubilize cholesterol before it can be absorbed.
- Micelles increase cholesterol immersion in inclusion to solubilizing it by aiding transport over the unstirred layer of water next to the luminal cell's surface." Diffusion is accountable for this transfer[16]. The rate-limiting factor for cholesterol absorption appears to be moved across the unstirred layer rather than penetrating the microvillus membrane. The micelle as a whole does not enter the cell membrane, and cholesterol passes through the membrane's structural lipid by monomolecular passive diffusion[17].
- The upper gut absorbs the most cholesterol because fats and monoglycerides swell micelles; the lower intestine absorbs less cholesterol, presumably because fat absorption disrupts micelles.
- Plant sterols are another dietary component that affects cholesterol absorption. They inhibit cholesterol absorption but, for unknown reasons, are themselves harmful. Only a minimal amount is absorbed. Competing for its absorption by mixed micelles, the mucosal cell membrane and/or prevent it from doing so, esterification occurs in the mucosa, preventing incorporation of the substance into chylomicrons[18].
- Plant sterols are in modest amounts in the diet (200 to 300 mg per day), and in these amounts, they are unfavourable to slow cholesterol absorption significantly. However, when given in large doses (5 to 15 grams per day), these sterols block cholesterol absorption, lowering cholesterol levels[17].

Hepatic metabolism

- Cholesterol comes from three places in the liver: newly absorbed cholesterol (provided by chylomicrons), peripheral tissues (supplied by plasma lipoproteins), and cholesterol produced within the liver cell[18].
- Total body synthesis in healthy people ranges from 9 to 13 mg per kg of body mass per day or from 650 to 900 mg per day for a normal 70-kg man[7].
- Acetyl coenzyme A (CoA) is an antecedent for sterol secretion, and the synthetic cholesterol route has at least 21 stages.' The initial steps in cholesterol synthesis are the construction of acetoacetyl CoA, /3-hydroxyl/3-methyl glutarate (HMG CoA), and mevalonic acid. Condensation reactions convert mevalonic acid to squalene, a long-chain hydrocarbon. Squalene is then cyclized and turned into cholesterol by a sequence of reactions[17].
- The enzyme HMG CoA reductase mediates the conversion of HMG-CoA to mevalonic acid, which is where feedback inhibition occurs[14].
- Also, the complexion of active feedback agent is in dispute; While it has long been assumed that cholesterol is the primary inhibitor, oxygenated cholesterol derivatives (such as 25-hydroxy-cholesterol and 7-keto-cholesterol) have been found to inhibit HMG CoA reductase actively.
- Several factors may influence the Hepatic cholesterogenesis rates, including cholesterol's feedback regulation. However, the bile acids which regulate hepatic cholesterol production are debatable and likely complex[18].
- Bile acids can affect cholesterol production in three ways. First, because bile acids influence cholesterol absorption, an elevation in the intestine should boost absorption, limiting cholesterol synthesis; conversely, a lack of bile acids causes more remarkable synthesis. Second, bile acids block cholesterol synthesis, which should increase liver cholesterol concentrations; this process should decrease synthesis via feedback inhibition by cholesterol[19]. Third, bile acids may interact directly with a step in the manufacture of cholesterol; however, some researchers question this process.
- Hepatic cholesterol can take one of three paths: it is partially converted into acids in bile, released into bile as cholesterol, or secreted into plasma with lipoproteins[20].
- About a third of daily cholesterol production—roughly 200 to 300 mg daily—is converted to bile acids[21].

Metabolism

Bile acids are reabsorbed in the small intestine. In contrast, bile acid reabsorption is often assumed to occur mainly in the ileum[22].

Bile acids return to the liver via the portal vein after reabsorption, where they are quickly removed and resecreted into bile to complete the enterohepatic circulation (EHC). The EHC builds a pool of bile acids, usually 2 to 3 grams in normal persons, due to the excellent reabsorption efficiency (approximately 98 percent)[19]. When a small fraction of bile acids travel through the EHC and comes into touch with colonic bacteria, the hydroxy-groups on their steroid nucleus change, resulting in "secondary" bile acids.

Biliary cholesterol comprises newly generated cholesterol and cholesterol recycled from the gut in a steady state when extrahepatic cholesterol pools remain constant. The daily hepatic production of cholesterol in adults of normal body weight ranges from 800 to 1,200 mg.'

Hepatic cholesterol destined for bile is first dissolved by phospholipids, which occur naturally in many biological membranes, and then these cholesterol-phospholipid complexes are dissolved by bile acids to create mixed micelles.

Cholesterol secretion in humans is a two-step process: first, phospholipids pre-solubilize a portion of biliary cholesterol before bile acids dissolve it, and then extra cholesterol is taken by mixed micelles[20].

Most people can handle the average loads of newly synthesized sterol and absorbed cholesterol, but their secretory processes are ineffective, and any slight deviation, whether due to more remarkable cholesterol synthesis or decreased bile acid pools, leads to supersaturation and in a multitude of cases, cholesterol gallstones[23].

Detection of cholesterol and its derivatives

FID or MS is a tool to detect and quantify cholesterol derivatives. Higher sensitivity and linearity range was established in FID. It is commonly used to determine fat levels in meals such as meat and poultry. Other methods of cholesterol detection have been reported, including ultraviolet (UV), fluorescence detection (FD), evaporative light-scattering detection (ELSD), infrared detection, nuclear magnetic resonance, and electrochemical detection (ECD). Point to analysis in cholesterol, these detection methods are subsequently used in conjunction with HPLC to estimate additional unsaponifiable substances like tocopherols, tocotrienols, and plant sterols[13].

Several factors influence blood plasma lipid concentration, including genetics, lifestyle, environment, and medication[24].

Table 2: Cholesterol level by Age and Sex

Age and sex	Total cholesterol	Non-HDL cholesterol	HDL cholesterol	LDL cholesterol
People aged 19 years and youngers	<170mg/dl	<120mg/dl	>45mg/dl	<110mg/dl
Men aged 20 years and older	125-200mg/dl	<130mg/dl	40mg/dl OR higher	<100mg/dl
Women aged 20 years and older	125-200mg/dl	<130mg/dl	50mg/dl OR higher	<100mg/dl

LDL cholesterol levels

- The optimal (or best) score is less than 100 mg/dl if you do not have heart disease or blood vessel disease and are not at high risk of developing heart disease.
- Your healthcare professional may want your LDL level to be less than 70 mg/dl if you have heart or blood vessel disease or several risk factors. If you have diabetes, your LDL level should be less than 100 mg/dl, preferably less than 70 mg/dl, according to your healthcare practitioner.

Triglycerides

- Triglycerides are crucial since they make up the majority of the fat in your body. These levels are frequently more significant in people with diabetes and obese people. The following are the values you need to know about triglycerides:
- If they are less than 150, they are considered normal.
- They're on the high side if they're between 150 and 199.
- They're in the upper echelon if they're between 200 and 499.
- If they're 500 or greater, they're high.

HDL cholesterol levels

- The value for HDL (remember, it's the good cholesterol) is the one you want to be higher.
- HDL levels below 40 are considered low and are linked to an increased risk of heart disease in both men and women.
- For men, the HDL objective is 40 or greater, which is desirable.
- Women's HDL objective is 50 or greater, which is good.
- HDL levels of 60 or higher are optimal and protective against heart disease.
- According to the mendelian randomization approach, 1 mmol/l(39mg/dl) elevated triglyceride is associated with a 2.8-fold causal risk for ischemic heart disease independent of low HDL cholesterol[25].
- Moreover, the incidence of Major adverse cardiovascular events is significantly increased in cardiovascular patients with high non-HDL-C/HDL-C, irrespective of Stable angina or Acute coronary syndrome[12].
- Atherosclerosis is combined with dyslipidemia, which has been researched extensively. Several epidemiologic studies and randomized clinical trials have revealed that high LDL-C is the leading cause of atherosclerotic CVD and should be managed to lower the risk of ASCVD[28].
- Small dense LDL-C (sdLDL-C) appears more atherogenic than sizeable buoyant LDL-C, according to growing research [18]. LDL-C subfraction 3 (LDLC-3) to LDLC-7 make up SdLDL-C, while LDLC-1 and LDLC-2 make up large buoyant LDL-C (lbLDL-C)[26].

Cholesterol level calculation

- The LDL-C is a risk factor for CVD, a primary laboratory parameter used to find cardiovascular risk, and a primary therapeutic target; consequently, it is difficult to prove that LDL-C levels are accurately measured.
- In some situations (high triglycerides [TG], very low LDL-C), current LDL-C estimate models have poor accuracy.
- The main laboratory parameter utilized for the control of HDL-C is LDL-C. Regarding TG, LDL-C, and nonhigh-density lipoprotein cholesterol (non-HDL-C)/TG ratios, Friedewald, Martin/Hopkins, Vujovic, and Sampson formulas were used.

LDL-C determination (VLDL)

Friedewald formula (FF)- The fundamental mathematical formula for calculating LDL-which a fixed factor of 2.2 (or 5 for mg/dL) describes the link between very-low-density lipoprotein and triglyceride[27].

Limitations

It should not be used with high TG levels (above 4.5 mmol/L) if chylomicrons or intermediate-density lipoprotein (IDL) are seen in a sample. It has been demonstrated to be ineffective in populations with high cholesterol and diabetic and renal patients.

1. The Friedewald formula's (FF) validity in populations with serum triglycerides (TGs) less than 400 mg/dl is debatable. Not valid for a patient with type 3 dyslipoproteinemia[28] compared to the Friedewald formula calculation was less

accurate than the Martin/Hopkins, Vujovic, and Sampson formulas[27].

2. Martin/Hopkins formula-
   Samples with TG levels up to 9.0 mmol/L can be used. It provides a more accurate conclusion than the Friedewald equation[27].
   Adjustable factors are the rata-specific median. Traditional linear regression analysis is used for this formula, and this unique method has assisted in the reclassification of patients who had formerly undertreated, and it is the method utilized for LDL-C measurement in numerous clinical laboratories[29].
3. Sampson formula[30]
   It can use samples with TG levels up to 9.0 mmol/L.
   SF's C-LDL estimates and the equivalent D-LDL had the highest concordance rate. This is essential since a misclassification of the grade of hypercholesterolemia could result in treatment delays and potentially cause the development or progression of CVD. LDL-C lowering medication should be started in adults with D-LDL 100 mg/dl and moderate cardiovascular (CV) risk and in people with D-LDL > 115 mg/dl and low CV risk, according to the most recent ESC/EAS guidelines.
   The factor of 0.026 is essential to convert LDL-C from mg/dL into mmol/L if necessary[30].
4. Vujovic formula
   To determine which formulas can provide the most reliable LDL-C results for the general population, their external validation uses samples from fasted and non-fasted states, with various fat levels obtained from multiple patient populations, using different laboratory techniques.
5. The total error (percent) between the mathematically estimated LDL-C and the measured LDL-C was calculated for each sample using the formula [(LDL-C calculated – LDL-C measured)/LDL-C measured] 100. The discrepancy of 12% is defined by total error as per National Cholesterol Education Program (NCEP) standards[27].

The beta-quantification (BQ) method is the established reference method for lipoprotein fraction measurement. It is possible in a limited setting but not ideal for mass screening due to its high cost and labour-intensive nature. For the building of inferential and predictive models, machine learning (ML) employs complex mathematical representation. In various disciplines of cardiovascular medicine, machine learning has been proven to improve modelling and outcome prediction development of the unique method for estimating LDL-C from a typical lipid profile using an ML method based on the random forests algorithm to improve LDL-C estimation in this era of precision medicine[29].

Cholesterol paradox

In what is known as the "cholesterol paradox," "reverse epidemiology," or "risk factor paradox or reversal," patients with low TC and LDL-C plasma concentrations had a worse prognosis. The "LDL cholesterol paradox" is explained as a drop in CVE threat with a fall in LDL-C blood concentration that is not escorted by a decline in total death[31]. The backtracking of a risk element could be because of various factors. In one sense, an improved prognosis in people with hypercholesterolemia could be due to (a) the "obesity paradox's" beneficial effects: adipokine protection against tumour necrosis factor-, lipoprotein protection against endotoxins, adipokine sequestration of lipophilic toxins by adipose tissue, and inflammatory process modulation (b) the previously mentioned evidenced pleiotropic effect of hypolipidemic drugs recommended for patients with prior diagnosed hypercholesterolemia who are treated without meeting the recommended goals; and (c) the previously mentioned evidenced pleiotropic effect of hypolipidemic drugs recommended for patients with prior diagnosed hypercholesterolemia who are treated without meeting the recommended goals. On the other hand, the "cholesterol paradox" may be a result of "reverse causality," in which poor prognosis in patients with low cholesterol blood concentrations is caused by (d) unfavourable effects of comorbidities such as systemic inflammation, malabsorption syndrome, malnutrition, neoplasm, COPD[32].

AF is the utmost avoidable arrhythmia, with an incidence that nearly doubles every decade of life, accounting for 25% of the average lifetime risk. According to several reports, the AF population will skyrocket in life due to the ageing of civilization[33].

Hypertension, T2DM, cardiovascular illnesses, metabolic syndrome, obesity, and chronic renal disease is recognized as risk elements for AF. 4,5 Dyslipidemia, also a major CVS risk factor, should raise the fate of AF in this scenario[33]. Several prior investigations have found a link between lessened levels of HDL-C and the prevalence or incidence of AF. However, it's perplexing that conflicting findings were stated concerning different lipid profiles: Numerous studies have exhibited an inverse dating among TC and AF, and a go-sectional study found no courting between lipoprotein (a) and AF and triglycerides have yielded blended results. Although the findings are contradictory, there's an opposite epidemiology (i.e., the "LDL cholesterol incongruity") among lipid profiles and AF, wherein low tiers of HDL-C and LDL-C or TC are related to increasing AF[33].

Watanabe *et al.* 10 reports in this issue of the Journal that (1) low HDL-C levels were highly related to a greater chance of developing AF, and (2) at the same time, LDL-C and TC levels were inversely associated with AF, confirming the cholesterol paradox in AF[31].

Watanabe *et al.* discuss sex differences in lipid profiles and AF, pointing to electrical aspects of the atrial in addition to hormonal characteristics, such as menopause. As an outcome, the link between lipid profiles and AF has a complex pathophysiology in the background, allegedly leading to contradictory findings in prior small or cross-sectional studies[29].

Although the TC level rises with age in younger groups, it falls in those over 60–70. In addition, the male sex is combined to a lower TC level[30]. Because AF is highly affected by age and male sex, these interactions could explain the reverse correlation between TC and rising AF. However, this correlation will not explain the inverse relationship because LDL-C on AF was still independent after adjusting cofactors such as age and gender in a study by Watanabe *et al.* [10].

Many clinical trials have explained that LDL-C-lowering medication with statins (hydrophilic or lipophilic) can dramatically lessen the incidence of CAD in both primary and secondary prevention. Although statins have anti-inflammatory and anti-oxidant multiple phenotypic effects, their positive effects are primarily proportional to the magnitude of LDL-C level reduction. The "cholesterol paradox" is the term for this situation[34].

The efficacy of early intensive cholesterol-reducing therapy was not confirmed on the short-term mortality of ACS patients. It's uncertain whether lowering LDL-C levels sooner will help improve ACS patients' short-term mortality[34].

In the recent observation, the standard threat factors for CAD and other medical variables, the mixture of statin medicinal drug with

LDL-C 100mg/dl, was discovered to be an individualistic predictor of decreased in-medical institution mortality. A low LDL-C level is probably linked to illness and more significant all-cause mortality, whereas higher LDL-C levels are linked to better nutrition and health status, likely linked to better tolerance of acute medical stress.

Tsai *et al.* assessed the consequences of statin medication in patients with ACS with serum LDL-C levels of less than 80 mg/dl. The statin-treated group had a 9.5 percent incident rate, much lower than the 29 percent rate in the untreated group.
The premise of "the lower, the better" was founded on these earlier studies, and the American College of Cardiology/American Heart Association (ACC/ AHA) recommendations set a treatment target for LDL-C of 70 mg/dl for high-prone patients with ACS.

Administered the findings of this trial, which suggest that statin treatment during hospitalization improves short-term in-hospital outcomes in a population with AMI regardless of LDL-C levels on admission, statins should be given to all patients with AMI, whether or not their LDL-C levels are elevated. In the end, this huge-scale observational look provides the body of proof helping statin medication in AMI patients at some point in the less severe segment. However, this investigation did not discover the processes behind why statin medication reduces short-term mortality, the stretch of statin therapy initiation after starting AMI, or the kind or dose of statin.
LDL-C levels beyond a certain threshold are merged with an increased risk of CVD. LDL-C reduction has been associated with depletion in cardiovascular endpoints such as coronary events and strokes. As a result, the consensus in cardiology is that the lower the LDL-C, the better. As documented in multiple investigations, low LDL-C was also linked with a significantly greater in-hospital death in AMI patients as an apparent paradox in that perspective ("the lipid paradox"). These confusing findings may imply that, in certain circumstances, both low and high LDL-C levels may be disease risk factors[35].

Recent research suggests high blood TG levels and low HDL-C levels in acute pancreatitis are linked to persistent organ failure (POF). LDL-C levels tested within one day of admission were considerably lower in patients with POF than those without POF, according to a study conducted on 66 patients with acute pancreatitis[35].

Chronic elevations in serum LDL-C cause oxidative stress is a key contributor to endothelial dysfunction and associated consequences in cardiovascular disorders. Pancreatitis is exacerbated by oxidative stress. Evidence from clinical and fundamental studies tells that the reactive oxygen and nitrogen species (ROS and RNS) may have a main part in the aetiology of acute pancreatitis (RNS). ROS/RNS may cause protein misfolding by disrupting the mitochondrial membrane directly. Furthermore, ROS/RNS might increase inflammation by activating proinflammatory signalling pathways.

It's possible that neutrophils having oxidative stress triggered while it is responding to the inflammation that causes acinar injury is to blame for the spread of systemic and local inflammation in acute pancreatitis. It was concluded that high LDL-C levels are merged with a high chance of developing SAP.

CAD is defined as a stenosis of 50% or more, not less than one primary vessel or one of its major branches. Non-obstructive CAD was explained as seen plaque with luminal stenosis of < 50%[26].

LDL-C subfractions have proven important enough to be included in clinical screening tests for people with dyslipidemia or high-risk CAD[26].

Heart failure (HF) is a prevalent ailment in the Western world, with an estimated frequency of 1% to 2%. It controls roughly 5% of medical admissions and complicates another 10% to 15%. More than 50% of these instances are attributable to the inappropriate function of LV systole, which is most commonly caused by coronary artery disease (CAD) or dilated cardiomyopathy. Hypercholesterolemia is a peril for CAD[36].

Metabolic syndrome, Obesity, and T2DM can all be managed with a ketogenic diet. Athletes in the ultra-endurance world are increasingly adopting lower-carbohydrate/higher-fat diets. While carbohydrate restriction and nutritional ketosis improve dyslipidemia (high triglycerides, lesser HDL-C, and a predominance of tiny LDL particles), the effects on total and LDL-C are less predictable[37].

Regular aerobic exercise raises HDL-C levels, particularly the more considerable HDL2-C percentage, with greater effects shown at greater levels of training.

Aerobic exercise also causes lesser LDL-C, tiny small LDL particles, and triglycerides, albeit the benefits are inconsistent and more consistent with increasing activity volumes. According to studies, ultra-endurance athletes have lower total and LDL-C and greater HDL-C concentrations corresponding to inactive people.

Finding advice that high exercise differences have a minute impact on blood lipoprotein relies on carbohydrate and fat-rich diets[38].

The 'strokes' observed in epidemiological research may differ from those seen in large statin interventional studies. The epidemiological data regarding the stroke category that may be merged with fat may be inaccurate. Coronary atheroma, or large-vessel disease, is well-established to be linked to fats and CHD. Furthermore, persons with stroke develop the disease considerably younger than those with CHD. As a conclusion of the mortality connected with CHD, the total number of people who could have acquired a cholesterol-related stroke by the time they are old is reduced.

Patients that have already had an MI run not only a risk of a second MI but also a subsequent stroke.

The multiple phenotypic effects of statins and their capacity to decrease cholesterol may provide a whole alternative expansion for the stroke-cholesterol conundrum.

Although there are signs that a rise in cholesterol is connected to the risk of non-haemorrhagic stroke, statins lessen the stroke problem in the population who have had a prior MI, according to new research. This impact could be arbitrated by variation in fat metabolism, but it could be arbitrated by non-lipid-related plaque stabilization and improvements in endothelial dysfunction. Possible pathways include neuroprotection actions. Several extensive secondary trials are underway to assess the recurrence problem in people with a previous stroke. The conclusion of the Medical Research has only recently been released[38].

Cardiovascular risk caused by ultra-processed food

Growing exposure to ultra-processed food products gives up to the world’s noncommunicable illnesses (UPPs). These extensively promoted UPPs are inexpensive, handy for

customers, and profitable for manufacturers, yet they are more in salt, fat, and sugar. All procedures and techniques that can be used by the food, beverage, and related industries to turn whole fresh ingredients into food products are known as food processing. Ultra-processed products (UPP) are a conglomeration of industrial components made from raw food constituents' extraction, refining, and transfer, with little or no complete food present. Unlike most fresh foods, they are frequently sold as ready-to-eat or ready-to-heat items. They're long-lasting, easy to transport, and meant to be convenient and tasty. Ultra-processed foods and culinary components are often less expensive in the UK than fresh, lightly processed foods and culinary ingredients. UPPs usually have a high glycaemic load and are calorie-rich. Freshly prepared meals and dishes from unprocessed or minimally processed food and culinary components are often more sweet, salty, fatty, and energy-rich than processed and ultra-processed foods. Obesity and other chronic non-communicable diseases are due to the low nourishment value of these meals combined with excessive consumption habits (NCDs)[39].

Given the growing epidemiological research examining its relationship with the beginning of chronic diseases, diet is a significant modifiable risk element in the aetiology of diseases. The methodology for identifying a specific population's eating pattern has been widely employed in observational research and has proved beneficial in determining the link between diet and cardiometabolic risk. Because they consider the entire dietary intake, the interrelationships between many foods and nutrients, and their synergistic effects, dietary patterns can provide more information regarding diet-disease associations than an isolated food product. They've become popular due to the realization that nutrients are rarely ingested in isolation and that nutrient-only studies undervalue the potential interactions between nutrients or foods and other diet components. Commute in body composition, biochemistry, and inflammatory markers in kids and adolescents may be linked to the detection of poor dietary patterns[40].

CVD is giving the highest mortality rate in the world, accounting for one-third of all deaths. Diet has a crucial play in the buildout and avoidance of CVD among modifiable risk and preventative factors. At the population level in Europe, dietary factors contribute to CVD mortality: In 2015, dietary variables were responsible for 56 percent of men's CVD fatalities and 48 percent of women's CVD deaths. The global consumption of ultra-processed foods has risen dramatically in the recent decennary. Ultra-processed foods account for between 25% and 60% of total daily energy consumption, according to nationwide food surveys examining intakes, household expenses, or supermarket sales in European countries, the United States, Canada, New Zealand, and Latin American countries. Microbiologically safe, convenient, and extremely tasty, these foods are regarded to be. It's also possible that these foods have an impression on satiety and glycaemic responses. Acrylamide, a contaminant produced by the Maillard reaction in heat-treated processed foods (whether industrially or not), may be related to the risk of CVD. Acrolein, a chemical generated when fat is heated and caught in caramel candies, may correlate to an elevated CVD threat. According to a meta-analysis of observational studies, the packaging of ultra-processed foods may contain food-contact substances like bisphenol A, which may increase the risk of cardiometabolic diseases[41].

Although traditional risk factors for CVD, such as a positive ancestry history, diabetes mellitus, hypertension, dyslipidemia, and obesity, have been recognized as key contributors to an elevated threat of CVD, over 20% of people with CVD have none of this established threats[42]. The new risk elements, such as exposure to environmental pollutants, may also play a role in the augmentation or onset of CVD[43]. AA is used in plastics, residues, cosmetics, and water treatment products and is produced industrially worldwide. In 2002, when it was frequently detected in carbohydrate-rich meals typically served at temperatures above 120 °C and low moisture, such as French fries, potato chips, bread, biscuits, and coffee, an international health alert about AA was elicited as a Group 2A likely carcinogen. Glycidamide (GA) (HbGA) are well-established indicators of internal AA exposure following long-term exposure throughout the usual lifespan of erythrocytes and are widely used to examine the internal dose from workplace exposure and in the standard population. Aside from oxidative stress, cancer prevalence and inflammatory states are markers of different chronic diseases, including CVD[44].

NOVA classifies foods based on the scope and goal of industrial operations utilized to conserve, remove, change, or manufacture them rather than by nutrient content. The ultra-processed food (UPF) category represents the last of the 4 primary classifications of food products and beverages created by the NOVA classification. This category includes products (such as snacks, drinks, and ready-to-eat meals) that are "made entirely derived from dietary ingredients or derived from food constituents with little if any intact food, and which frequently contain flavourings, colours and other additives that mimic or enhance the sensory aspects of foods or culinary preparations created with foods "[45]. These food products are convenient (ready-to-eat), appealing (hyper-palatable), economical, have a long shelf life and compete with naturally ready-to-eat foods and freshly prepared dishes and meals[46].

In the U S, ultra-processed foods like sugary snacks and cakes add to over half of all caloric intake. Heterocyclic amines, acrylamide, polychromatic hydrocarbons, and furans present in ultra-processed foodstuff may affect endocrine systems and the microbiome[47,48].

NCDs were responsible for 63 percent of the 57 million deaths worldwide in 2008. Cardiovascular disease (CVD) is the major death cause, which accounted for 48 percent of NCD deaths. NCDs and CVDs are correlated to four behavioural problem factors: poor diet, cigarette use, scarcity of muscle activity, and problematic alcohol use. Most people consume far more sodium, hydrogenated fat, and trans-fatty acids than the diet recommends. All of these factors play a significant role in hypertension and cardiovascular risk[39].

Many dietary parameters have been projected for CHD risk, including total and saturated fat consumption, fruit and vegetable intake, and dietary fibre. Fruits, legumes, vegetables, and whole grain cereals, which are high in dietary fibre, are also high in vitamins, minerals, antioxidants, phytochemicals, and other micronutrients[49,50].

CONCLUSION

Cholesterol is a lipid molecule that is present abundantly in cell membranes. Numerous studies suggest that increased cholesterol levels are associated with increased cardiovascular morbidity in patients. Ultra-processed food products are also intended to increase cholesterol levels. However, it is also noted in the cholesterol paradox that in some cases, patient morbidity is also seen in patients with low cholesterol level indicators, contrary to the other theory. Therefore, we lack significant data explaining this, requiring additional studies to establish a linkage between cholesterol paradox and cardiovascular morbidity.

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