Journal of Advances in Medicine and Medical Research

32(2): 11-21, 2020; Article no.JAMMR.54072
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Dietary and Blood Lipids in Cardiovascular Disease

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JAMMR/2020/v32i230362
Editor(s):
(1) Dr. Pietro Scicchitano, Department of Cardiology, Hospital "F. Perinei" Altamura (Ba), Italy.
Reviewers:
(1) Arunima Chaudhuri, Affiliated to West Bengal University of Health Sciences, India.
(2) Franco Cervellati, University of Ferrara, Ferrara, Italy.
(3) Muhammad Muizz Uddin, Dow University of Health Sciences, Pakistan.
Complete Peer review History: http://www.sdiarticle4.com/review-history/54072

Review Article

Received 20 November 2019
Accepted 25 January 2020
Published 21 February 2020

ABSTRACT

Blood lipids are essential for life; at the same time, elevated or reduced levels of some of the components of lipid are related to risk of atherosclerotic cardiovascular disease (ASCVD). This article provides a review on dietary and blood lipids with their impact on cardiovascular health. The role of apolipoprotein B (ApoB), Lipoprotein(a) ((Lp(a)) and other lipoprotein particles in the development of ASCVD has been reviewed. There are new evidences that ApoB the structural protein of most of the lipoprotein particles (carrier of blood lipids), in addition to low density lipoprotein-cholesterol (LDL-C), plays a central role in the pathogenesis of atherosclerosis with increased risk for ASCVD. Elevated levels of Lp(a) concentrations are associated with an increased risk of ASCVD, but it appears to be a weaker risk factor than ApoB or LDL-C.

Keywords: LDC-cholesterol; Non-HDL-cholesterol; lipoprotein(a); apolipoprotein B; atherosclerotic cardiovascular disease.

1. INTRODUCTION

Lipids are a broad group of macronutrients which play a significant role as a source of energy and a structural molecule of human body. However certain components of lipid, when excess or low, are associated with atherosclerosis leading to adverse cardiovascular events (CVE). The risk of developing coronary artery disease (CAD) in relation to the increased blood levels of low

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density lipoprotein cholesterol (LDL-C) and decreased blood levels of high density lipoprotein cholesterol (HDL-C) is well documented [1,2,3]. Atherosclerotic cardiovascular disease (ASCVD) like heart attack, stroke, and peripheral vascular disease is the leading cause of mortality and morbidity globally [4]. Atherosclerosis is a chronic inflammatory process [5] where endothelial cell dysfunction is the initial step occurring at arteries that are subjected to low shear stress and disturbed blood flow (atherosclerosis prone areas) [6]. The local hemodynamic factors and flow characteristics of arteries are linked to endothelial dysfunction, inflammation and the subsequent development of atherosclerosis [7]. In atherosclerosis there is deposition of cholesterol in the intimal layer of artery walls which forms a plaque known as atheroma. The atheroma will narrow or occlude the lumen of the artery to compromise blood supply of the affected organ and is at a substantial risk of rupture with thrombus formation that acutely obstructs blood flow resulting in acute CVE or death. For many years, blood total cholesterol (TC) was considered to be an important marker for predicting the risk of cardiovascular disease (CVD) ('cholesterol hypothesis') [8]; the focus later shifted to LDL-C that the latter is directly responsible for the pathogenesis of atherosclerosis ('LDL-C hypothesis') [1]. However, the majority of subjects presenting to the hospital with acute CVE do not have elevated levels of LDL-C, but tend to have low levels of HDL-C [9]. Interests have grown to find out whether other components of lipids or lipoproteins, including apolipoprotein B (ApoB), lipoprotein(a) ((Lp(a)) and very low density lipoprotein (VLDL), might serve as an important predictors of CVE rather than quantifying LDL-C content alone.

The goal of this review article is to focus on the dietary and blood lipids, their impacts on cardiovascular (CV) health, and finally to detect the role of lipids and lipoproteins in the pathogenesis of atherosclerosis.

2. DIETARY LIPIDS

Important dietary lipids include (a) triglyceride (TG) (b) saturated fat (c) unsaturated fat (d) trans fat (e) cholesterol and (f) phospholipid. Animal fats are complex mixtures of TGs, saturated fats, cholesterols and phospholipids. Vegetable fats contain unsaturated and saturated fats. Marine oils and fatty fishes are good source of polyunsaturated fats.

2.1 Triglycerides (or Triacylglycerol)

The dietary lipid is predominantly found in TG form. In the United States (US), 30–40% of the calories in a typical Western diet come from lipid, and >90% of the ingested lipid is in the form of TG [10]. Excessive intake of carbohydrate, fat or alcohol contribute to increased plasma TG by different mechanisms. Fats are the common name given to TG. Each TG contains a glycerol molecule bound to 3 fatty acids chains. Fatty acid chains are made up of carbon and hydrogen atoms (hydrocarbons) having an alkyl group at one end and a carboxylic acid group at the other end. Dietary fatty acids are usually long-chain fatty acids with >12 carbon atoms [10,11]. Medium-chain fatty acids (C8–C12) are rarely found in food (except for coconuts) and are thus less important for digestion and absorption in humans [12]. Short-chain fatty acids (<C8) are not found in food; they result from the digestion of fats by the bacteria in the colon; they are the major anions found in the stool, and often contribute to diarrhea by providing an osmotic gradient [12]. Based on the presence or absence of double bonds between the carbon atoms, fatty acids are categorized as (i) saturated fatty acids (SFA)- no double bonds (ii) unsaturated fatty acids (UFA)- having double bonds.

2.2 Saturated Fats

The saturated fat contains fatty acids that are saturated meaning that they don't have any double bonds between the carbons in their chain. Thus they are "saturated" with hydrogen. Animal fats usually consist of a higher quantity of saturated fats. Animal sources include beef, lamb, pork, poultry skin, lard and dairy products (milk, yogurt, butter, ghee). Cream, chocolate, pastry and cake are rich in saturated fat. Plant sources include several types of oil (coconut oil and red palm oil). Natural oil if it exists in solid form at room temperature indicates a higher saturated fat content. Foods containing saturated fats are rich in cholesterol. Saturated fat plays an important role in blood LDL-C formation.

2.3 Unsaturated Fats

The unsaturated fat contains fatty acids that are unsaturated meaning that they have a minimum of one double bonds between the carbons in their chain. Thus they are "unsaturated" with hydrogen. Most of the plant oils and fish oils are the source of unsaturated fats. Natural oil, if it exists in liquid form at room temperature

indicates a higher unsaturated fat content. UFAs are classified as monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). MUFAs are distinguished from the other fatty acid classes on the basis of having only one double bond between each carbon atoms. In contrast, PUFAs have 2 or more double bonds, and SFAs have none. The position of the hydrogen atoms around the double bond determines the geometric configuration of the MUFA and hence whether it is a cis or trans isomer. In a cis MUFA, the hydrogen atoms are present on the same side of the double bond, whereas in the trans configuration, they are on opposite sides [13]. In animals and plants, UFA usually occurs in cis configuration. The most common MUFA is oleic acid. Dietary sources of MUFA include—olive oil, sunflower oil, peanut oil, palm oil, canola oil, almond, cashew-nut, and hazelnut. PUFA contains "essential fatty acids" since the body requires them, but cannot be synthesized. Important essential fatty acids include α- linoleic acid, α-linolenic acid, eicosapentaenoic acid & docosahexaenoic acid. PUFA exists in food as either omega–6 or omega–3 fatty acids, which are named for the position of the first double bond (from the methyl end) in their carbon chains. Omega-6 fatty acids consist of α- linoleic acid, which is found in vegetable oils (soybean, corn oil, canola oils and sunflower oils), as well as nuts and seeds (grapeseed, peanut). The important omega-3 FAs are α-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid. Alpha-linolenic acid, is found in vegetable oils (soybean, canola oil, flaxseed oil), nuts, seeds and leafy green vegetables. Eicosapentaenoic acid and docosahexaenoic acid are found in marine oils or oily fish (salmon, sardine, cod liver oil). Omega-3 PUFAs, that contains eicosapentaenoic acid and docosahexaenoic acid, have been widely regarded as cardioprotective [14]. Researches indicate that omega-6 fatty acids also reduce the risk of CVD [15,16]. It has been recently observed that the high consumption of omega-6 PUFA results in significant attenuation of the beneficial effect of omega-3 PUFA on CAD [15].

2.4 Trans Fats/Fatty Acids (TFAs)

Artificial trans fats are typically created commercially by a process of partial hydrogenation of unsaturated fats. Trans fatty acids are UFAs containing double bonds in trans configuration. Repeated/ prolonged heating of UFAs in high temperature may convert them to trans-fat. The presence of TFAs make oils more solid and extend their shelf life. Major sources of TFA are fast foods, fried foods, margarines, commercially baked cookies, cakes, crackers, French fries, potato chips, donuts and some breads. Trans fat plays an important role in blood LDL-C formation. A high intake of TFAs decreases HDL-C and increases LDL-C, the ratio of TC to HDL-C, inflammation, diabetes, cancer, and mortality from CVD [13]. Higher trans fat intake is associated with an increased risk of all-cause mortality. TFAs appear to increase the risk of CVD more than any other macronutrient on a per calorie basis. All artificial trans-fat should be avoided. Natural TFAs which are trans-isomers, do not occur in significant amounts; found in milk, dairy products, and meat, in small quantities; may actually be beneficial.

2.5 Dietary Cholesterol

Cholesterol is found exclusively in animals; it is often called as animal sterol. All foods with animal fat contain cholesterol to varying extents. Major dietary sources of cholesterol, include egg yolks and some of the shellfish (shrimp, prawn, lobster, crabs). Human breast milk also contains significant quantities of cholesterol. Research has shown that that the dietary cholesterol intake has a less impact on blood lipid profile in most people [17]. Some people may show elevation of LDL-C and HDL-C, typically with a maintenance of the LDL-C/HDL-C ratio resulting weak associations between the intake of eggs and CV risk [17]. Research also shows that, dietary cholesterol taken in access amount, can influence blood cholesterol and CV risk in a people with dyslipidemia [18]. People who have diabetes, or dyslipidemia should limit their egg consumption to a maximum of 7 eggs per week. All saturated fats (beef, pork, dairy products) and trans fats are source of cholesterol; blood cholesterol levels are more influenced by the dietary saturated fats and trans fats that needs to be avoided. Eggs, specially the yolk, are richest source of dietary cholesterol; a large egg (≈50 gm) contains approximately 186 mg of cholesterol [19]. The average intake of dietary cholesterol in US adults is typically between 200–350 mg/day, depending on gender and age [19]. A recent research has shown that among US adults, higher consumption of dietary cholesterols or eggs was significantly associated with higher risk of CVD and all-cause mortality in a dose-dependent manner [18].

2.6 Phospholipids

Phospholipids are also present in diet; these are the major constituents of biologic cell membranes. Phospholipids contain mainly glycerol, fatty acids, phosphate and lecithin. Phospholipids are important structural components of brain and nervous tissue, of membranes throughout body tissues, and of lipoproteins. Phospholipids and their constituents can be synthesized in the body and are thus not necessary in the diet.

3. FUNCTIONS OF LIPID

Lipids are essential for all animal life. Phospholipids are present in cell membranes and forms important structure. Myelin sheaths derived from Schwann cell in many neurons, which are rich in cholesterol, provide insulation for more efficient conduction of impulses. In the liver, cholesterol is converted to bile, which is then stored in the gallbladder. Bile contains bile salts, which help in intestinal absorption of fat molecules as well as the fat-soluble vitamins, A, D, E and K. Cholesterol is an important precursor molecule for the synthesis of vitamin D and steroid hormones (cortisol, aldosterone and sex hormones e.g. progesterone, estrogens, and testosterone). Steroid hormones are secreted by three glands—the adrenal cortex, testes and ovaries. Steroid sex hormones are also secreted by the placenta during pregnancy. Fat acts as a reservoir of energy; adds taste and texture to the food.

4. DIGESTION, ABSORPTION AND DELIVERY OF DIETARY LIPIDS

Dietary fat is exclusively composed of long-chain TGs (LCTGs)—i.e., glycerol is bound to three long chain fatty acids. LCTGs, saturated and unsaturated fatty acids are handled identically by three integrated processes: (a) an intraluminal, or digestive, phase (b) a mucosal, or absorptive, phase and (c) a delivery, or post absorptive, phase. The digestive phase has two components, lipolysis by pancreatic enzymes and micelle formation. In the intestinal lumen, dietary TGs and cholesterols are emulsified by bile salts which enhance their digestion and uptake. After emulsification, TGs are generally digested by pancreatic lipase in the upper intestine [20]. The breakdown products of TG hydrolysis are fatty acids and monoglycerides. In the absorptive phase bile acids form water soluble micelles in the intestine, which help in carrying the digested lipids for absorption. Micelles are molecular aggregates composed of fatty acids, monoglycerides, phospholipids, cholesterol and bile acids. In the post absorptive phase, fatty acids and monoglycerides are re-esterified to form TGs in the intestinal epithelial cells. Cholesterol is esterified by the addition of a fatty acid in the enterocyte to form cholesteryl esters. The TGs and cholesteryl esters exit from the intestinal epithelial cells into the lymphatics after forming chylomicrons in the endoplasmic reticulum of enterocytes. Chylomicron particles are composed of lipoprotein containing TG, cholesterol, cholesterol esters and phospholipids. Chylomicrons play a central role in the transport of TG and fat-soluble vitamins to the rest of the body. The chylomicrons enter the lymphatics, not the portal vein, ultimately reach the blood stream and deliver the fatty acids (again after lipolysis of TG by tissue lipoprotein lipase) to skeletal muscle, cardiac muscle, adipose tissue for utilization of fatty acids for energy or fat production. Fat particles which are not used, remains in more cholesterol-rich chylomicron remnants, and are cleared up from the bloodstream by the liver.

Dietary cholesterol in the intestinal lumen and that derived from biliary sources, is taken into the enterocyte via a specific intestinal membrane transporter termed Niemann-Pick C1-like protein 1 (NPC1L1). Enterocyte cholesterol and cholesteryl esters are incorporated into chylomicrons and transported with TG. In addition, enterocyte cholesterol can be directly excreted into the intestinal lumen.

Medium-chain TGs (MCTGs) do not require pancreatic lipolysis as they can be absorbed intact by the intestinal epithelial cell [12]. Micelle formation is not necessary for the absorption of MCTGs (or MCFAs, if hydrolyzed by pancreatic lipase). Enterocytes do not re-esterify the MCFAs. MCTGs/ MCFAs do not require chylomicron formation to exit intestinal epithelial cells. The route of MCTG exit is not via lymphatics; they are delivered directly into the portal blood to be transported to the liver bound to serum albumin. Short-chain fatty acids are not found in food and thus appear in the digestive tract only after the bacterial break-down of undigested fats in the colon, leading to their synthesis and absorption almost exclusively in the colon. Short-chain fatty acids are the major anions found in the stool; they are both water and lipid soluble [12].

5. TRANSPORT OF LIPIDS IN BLOOD WITHIN LIPOPROTEINS

Since lipids are insoluble in blood, they are transported in the circulatory system within lipoprotein particles. Lipoproteins are essential for transport of lipids and fat-soluble vitamins in the blood. Lipids are carried to tissues for energy utilization, fat deposition and steroid hormone production. Lipoproteins also transport cholesterols to liver for bile acid synthesis. Lipoproteins contain a core of hydrophobic lipids (TGs, cholesterols which may be esterified and unesterified) surrounded by a shell of phospholipids, free cholesterol and proteins called apolipoproteins [21]. The lipoproteins play a key role in the transport of dietary lipids from the small intestine, in the transport of lipids from the liver to peripheral tissues, and the transport of lipids from peripheral tissues to the liver and intestine.

There are seven classes of lipoproteins in blood that vary mainly in density, size, lipid content and apolipoprotein [21]. The lipoproteins are chylomicrons, chylomicron remnants, VLDL, intermediate-density lipoprotein (IDL), low density lipoprotein (LDL), Lp(a) and high density lipoprotein (HDL) [21]. The balances are mostly genetically determined, but can be changed by life style, medications, food choices, and other factors. Chylomicrons are the most lipid-rich and therefore least dense lipoprotein particles; they carry TGs (predominantly), cholesterols and cholesterol esters from the intestine to muscle and other tissues that need fatty acids for energy or fat production. The removal of TG from chylomicrons by peripheral tissues results in formation of chylomicron remnants. Chylomicron remnants are cleared by the liver. Cholesterol that is synthesized in the liver, is packed together with TG to form VLDL [22,23]. VLDL is very rich in TGs, the latter is derived after esterification of long chain fatty acids in the liver. After secretion into the blood, the TGs of VLDL are hydrolyzed by lipoprotein lipase, especially in muscle, heart, and adipose tissue; the remnant particles referred to as IDL, contain roughly similar amounts of cholesterol and TG. The IDL can be taken up by the liver for remodeling (after removing TG), but most are progressively hydrolyzed to become LDL particles [22,23]. The LDL particles are the major blood cholesterol carriers. They act as a source of cholesterol for tissues and are taken up by the LDL receptor in tissues including the liver, the latter being the predominant site of uptake. LDL particles transport cholesterol to peripheral tissues and thus if the LDL-C is elevated, lipids can deposit in the arterial lumen leading to plaque formation, and thickening or narrowing of the blood vessel, the hallmark of atherosclerosis. Most of the LDL particles are taken up by the hepatocytes for further metabolism. The native HDL particle is produced mainly by the liver and it contains apolipoprotein A1 (ApoA1). ApoA1-containing HDL particles transport excess cholesterol from the peripheral cells back to the liver in a process referred to as reverse cholesterol transport. This is one potential mechanism by which HDL may be anti-atherogenic. In addition, HDL particles have anti-oxidant, anti-inflammatory and anti-thrombotic properties, which may also contribute to their ability to inhibit atherosclerosis [21]. The cholesterol from HDL may be utilized for bile acid synthesis or disposed as cholesterol via bile or carried either by TG rich lipoproteins (VLDL) or by LDL particles [22]. Lp(a) is a lipoprotein similar to LDL in lipid and protein composition. It is synthesized in the liver and attached to apoB-100 by a di-sulphide linkage. The major site of clearance of Lp(a) is the liver.

The apolipoproteins (ApoA, ApoB, ApoC, ApoE), are synthesized mainly in the liver and act as structural components, ligands for cellular receptor binding, and enzyme activators or inhibitors [21,22]. ApoA1 is the important structural protein of HDL particle. ApoB exists in two forms ApoB48 and ApoB100 [24]. ApoB48 is synthetized by intestine and is the major structural protein of chylomicrons and their remnants. ApoB100 is synthetized by the liver and is present in VLDL, IDL, LDL and Lp(a). ApoB100 assembles cholesterol and TG that is synthesized in the liver to form VLDL [22,23,24]. ApoB100 is in fact cholesterol rich ApoB and plays a central role in the development of atherosclerosis.

6. CHOLESTEROL METABOLISM

Blood cholesterol is derived from two sources, exogenous dietary cholesterol and endogenous de novo synthesized cholesterol. Humans can produce cholesterol endogenously and in fact, most of the cholesterol in the body comes from biosynthesis [25,26]. Only about 25% of blood cholesterol in humans is derived from the diet while the rest is derived from biosynthesis [17]. Total fat intake, especially saturated fat and trans fat, plays a larger role in blood LDL-C than intake of dietary cholesterol itself. β-hydroxy β- methyl glutaryl CoA (HMG CoA) reductase, the rate-limiting enzyme regulates the biosynthesis of

endogenous cholesterol. HMG CoA reductase is present in endoplasmic reticulum of all the nucleated cells in the body. The LDL receptor is present in the liver and most other tissues. It recognizes ApoB containing lipoproteins and hence mediates the uptake of chylomicron remnants, VLDL, IDL and LDL. After internalization, the lipoprotein particle is degraded in lysosomes and the cholesterol is released. The delivery of cholesterol to the cell decreases the activity of HMG CoA reductase and the expression of LDL receptors. The hepatic LDL-receptor number plays a major role in determining plasma LDL level (a low number of receptors is associated with high plasma LDL levels while a high number of hepatic LDL receptors is associated with low plasma LDL levels) [21].

Cholesterol balance is achieved both by synthesis in the body and by absorption in the gastrointestinal tract. A higher intake from food leads to a net decrease in endogenous synthesis of cholesterol, whereas lower intake from food has the opposite effect. The intestine regulates the amount of dietary cholesterol that enters the body. As the dietary intake of cholesterol increases, there is a corresponding decrease in absorption from the intestine and an increase in the excretion of cholesterol via bile. There is a feedback inhibition of cholesterol biosynthesis and increased excretion of bile with high cholesterol diets [27]. When cellular cholesterol is increased, both cholesterol biosynthesis and uptake are reduced via feedback inhibition [27].

All nucleated cells can synthesize cholesterol, including arterial wall, but the major sites of cholesterol biosynthesis are liver, adrenal cortex, testes, ovaries and intestine. Normally cholesterol regulates the expression of HMG CoA reductase gene and LDL-receptor gene. If sufficient cholesterol is present in the cell, transcription of the gene for HMG CoA reductase is suppressed & cellular synthesis of cholesterol is decreased. The free cholesterol released within the cell has following fates: (i) incorporated into cell membranes (ii) metabolized to steroid hormones, especially in adrenal cortex & gonads or (iii) esterified with saturated fatty acids and stored in cells. Only hepatocytes and enterocytes can effectively excrete cholesterol from the body, into either the bile or the gut lumen. In the liver, cholesterol is secreted into the bile directly, as well as after conversion to bile acids. The main dietary source of plasma cholesterol is the intake of saturated fat and TFA, which reduce LDL-receptor activity in the liver. Plant sterols inhibit intestinal cholesterol absorption and are effective, because they also reduce the re-utilization of biliary cholesterol.

7. BLOOD LIPIDS

Major components of lipid in the blood are measured for assessing ASCVD risk. A standard blood lipid profile includes: (a) Total cholesterol, (b) HDL-C, (c) TG and (d) LDL-C. Total cholesterol and TG values reflect cholesterol and TGs in all circulating lipoproteins (chylomicrons, chylomicron remnants, VLDL, IDL, LDL, Lp(a) and HDL). LDL-C are traditionally termed "bad cholesterols" because they have been linked to atheroma formation in the walls of arteries and increase the risk of CVD. LDL-C is considered a better measure of risk than TC. HDL-C, on the other hand, in high concentrations, remove cholesterol from cells and atheroma, offer protection and are traditionally referred to as "good cholesterols". Low levels of blood HDL-C is associated with increased CV risk. TGs are fat carried in the blood mainly from the food we eat. Excess calories, alcohol, or sugar are converted into TG in the body and stored in fat cells (adipocytes) throughout the body.

8. MEASUREMENT OF BLOOD LIPIDS

Lipid measurements are usually performed for the following reasons: (a) screening for primary or secondary prevention of CVD, (b) investigation of patients with clinical features of lipid disorders and their relatives and (c) monitoring of response to pharmacological and non-pharmacological therapy for dyslipidemia. Cholesterol in humans is distributed primarily among three major lipoprotein classes: VLDL, LDL, and HDL. Smaller amounts of cholesterol are also contained in other minor lipoprotein classes like IDL and Lp(a) [22]. For cost reasons only the TC, HDL-C and TGs are measured directly. With these values, the LDL-C concentration is calculated. TC is conventionally defined as the sum of HDL-C, LDL-C, and VLDL. The VLDL is estimated by dividing total blood TGs by five (if measured in mg/dL) or by 2.2 (if measured in mmol/L), and LDL-C concentration can be calculated using the Friedewald equation [28]:

LDL-C = Total Cholesterol – (HDL-C) − (Triglyceride/5) (all values in mg/dL)

The Friedewald formula is reasonably accurate if test results are obtained on fasting blood (fasting for 12 hours) and if the TG level does not exceed

200 mg/dL; with high TG values (>400 mg/dL or >4.5 mmol/L) the formula cannot be used because of inaccurate results. In that case, the LDL-C is measured by direct assay using plasma ultracentrifugation.

Traditionally, blood sampling for lipid analysis has been recommended in the fasting state for maximum accuracy and consistency. Recent systematic studies suggest that the difference in the values between a fasting and non-fasting sample is small and has been shown to have no impact on CV risk estimation [22,29]. Therefore, both fasting and non-fasting samples can be used for lipid screening; non-fasting lipid testing is acceptable. Indeed, a number of guidelines recommend non-fasting sampling [22,29,30]. In most individuals, direct measurement of LDL cholesterol does not provide additional CVD risk information beyond calculated LDL cholesterol. However, even if non-fasting sampling is used, in patients with metabolic syndrome, DM, or hypertriglyceridemia, calculated LDL-C should be interpreted with caution [22,30]. Testing should be postponed until after resolution of acute illness because TG and Lp(a) levels increase and cholesterol levels decrease in inflammatory states.

Other risk markers, such as Non-HDL-C or ApoB, may assess risk of CVD more accurately than LDL-C when TG levels are increased [31]. Non-HDL-C can be calculated as TC – HDL-C; non-HDL-C is a measure of total cholesterol present in all atherogenic lipoproteins (VLDL, IDL, LDL-C and Lp(a)) [22]. Non-HDL-C has been considered as a better predictor of CV risk than LDL-C. Non-HDL-C can be used to evaluate CV risk when TG is >4.5 mmol/L [31].

ApoB provides an estimate of the total concentration of atherogenic lipoprotein particles (VLDL IDL, LDL-C and Lp(a)) [22]. It is thus a better measure of the total atherogenic burden of an individual [32]. The 2019 European Society of Cardiology guideline recommends measurement of ApoB as part of routine lipid analysis among patients with DM or high TG levels and in patients with very low LDL-C levels considering the potential inaccuracy of LDL-C in dyslipidemia [22]. LDL-C, non-HDL-C and ApoB concentrations are very highly correlated and comparable in magnitude to each other; they provide very similar information about ASCVD risk [22].

Lp(a) levels are genetically determined and when elevated are recognized to be independent risk factor for ASCVD, including heart attack, stroke and peripheral vascular disease [33,34]. The 2018 American Heart Association/American College of Cardiology guideline on the management of blood cholesterol lists elevated Lp(a) as one of the risk-enhancing factors for developing ASCVD [35]. The 2019 European Society of Cardiology guideline recommends to consider measurement of Lp(a) at least once in each person's lifetime, if available, to identify people who have inherited an extremely elevated levels of Lp(a) and have a very high lifetime risk of ASCVD [22].

One study has suggested that TC/ HDL-C ratio is a better marker of the risk of CVD than either TC or LDL cholesterol levels alone [36]. However, a prospective study concluded that the levels of components of the TC/ HDL-C ratio have little influence on its prediction of CAD [37]. A combination of a high ratio accompanied by high LDL-C may warrant more aggressive therapy [37].

9. IMPACTS OF DYSLIPIDEMIA AND DIETARY LIPIDS ON CARDIO-VASCULAR DISEASE

Dyslipidemia is an established risk factor for CVD. The risk of developing CAD in relation to the elevated LDL-C and reduced HDL-C is well known; LDL-C levels are found to be directly associated with CVE; whereas HDL-C levels are found to be inversely related to risk of CVE [1,2,3]. New evidences reveal that the key initiating event in atherogenesis is the retention of LDL-C and cholesterol rich ApoB-containing lipoproteins within the subendothelial space of the arterial wall, and there is no longer an 'LDL-C hypothesis' [22,23,38]. Infiltration and retention of ApoB containing lipoproteins in the artery wall is a critical initiating event that trigger an inflammatory response and promotes the development of atherosclerosis [23]. Arterial injury causes endothelial dysfunction promoting modification of ApoB containing lipoproteins, and infiltration of monocytes into the subendothelial space. The macrophages internalize the retained ApoB containing lipoproteins to become foam cells forming the fatty streak which is the hallmark initial phase of atherosclerosis. Fatty streaks may not result in clinical complications and can even undergo regression. People with higher concentrations of plasma ApoB-containing lipoproteins will retain more particles and accumulate lipids faster, resulting in more rapid growth and the progression of atherosclerotic

plaques. Continued macrophage inflammation results in cytokine secretion, more LDL/remnant oxidation, endothelial cell activation, monocyte recruitment, and foam cell formation. Macrophage inflammatory cytokines stimulate infiltration and proliferation of smooth muscle cells. Once smooth muscle cells infiltrate, and the lesions become more advanced with formation of atheroma and fibrous cap, regression is less likely to occur. The advanced atherosclerotic lesion is essentially a non-resolving inflammatory condition leading to formation of the vulnerable plaque characterized by two fundamental morphological changes: (a) formation of a necrotic core and (b) thinning of the fibrous cap [23]. Rupture of the thin fibrous cap promotes thrombus formation resulting in acute ischemic CVE. The total atherosclerotic plaque burden is likely to be determined by both the concentration of circulating LDL-C and ApoB containing lipoproteins, and by the total duration of exposure to these lipoproteins [22,23,38].

High concentrations of HDL-C are associated with greater protection from CAD and other CVD [39]. HDL removes cholesterol from the tissues to the liver where it is metabolized and excreted in bile. HDL, ApoAI and endogenous ApoE reduce atheroma formation by preventing endothelial cell activation, inflammation, and oxidative stress and also by promoting cholesterol efflux from foam cells. The majority of ApoE in plasma is produced by the liver; ApoE serves as the ligand for clearance of all of the ApoB containing lipoproteins from the blood by the liver except for LDL [23]. Consequently, low HDL-C levels, are associated with increased risk of CAD [40]. There is no evidence from randomized trials that therapeutically increasing plasma HDL-C or directly infused HDL mimetic that increase plasma HDL-C concentrations, reduces the risk of CVE [41,42]. Higher plasma Lp(a) concentrations are associated with an increased risk of ASCVD, but it appears to be a weaker risk factor for most people than LDL-C [43].

The role of TG as a CV risk factor is controversial and not as robust as is with LDL-C. It is believed that TG is not directly atherogenic but remains a biomarker of CV risk via its association with remnant lipoproteins [44]. The risk of acute pancreatitis is known to increase when blood triglyceride level exceeds 500 mg/dL [45].

High dietary intake of SFAs and TFAs are associated with increased CVD mortality. Dietary intake of marine omega-3 PUFAs and replacing SFAs with plant MUFAs are associated with lower total CVD mortality [46]. TFAs affect serum lipid levels, fatty acid metabolism, and endothelial function; high TFA intake is linked to increased all-cause mortality [47]. A high intake of TFAs decreases HDL-C and increases LDL-C, the ratio of TC to HDL-C, inflammation, diabetes, cancer and mortality from CVD [13]. A reduction of dietary saturated fat intake, in addition to equivalent calorie replacement of saturated by unsaturated fat, has been found significantly to be associated with reduced TC and LDL-C concentration [48]. There are controversies regarding the impact of dietary cholesterol (egg) intake on adverse CVE. Based on the findings from observational studies that do not support an association between dietary cholesterol and CVD risk, the most recent Dietary Guidelines for Americans from the US Department of Health and Human Services set no specific recommended limits for the amount of dietary cholesterol intake [49]. However, another recent research revealed that higher consumption of dietary cholesterols is significantly associated with higher risk of CVD in a dose-dependent manner [18].

10. CONCLUSION

Plasma lipid and lipoprotein levels are important modifiable risk factors for ASCVD. ApoB is an atherogenic lipoprotein present in LDL, IDL, VLDL and Lp(a). Increased levels of ApoB is currently held responsible to play the causative and central role in the development of atherosclerosis. ApoB or Non-HDL-C may assess risk of CVD more accurately than LDL-C when TG levels are increased. Lipid-related ASCVD risk can be assessed in most peoples from standard lipid profile, however the overall effect of the lipoprotein and blood lipid profile must be interpreted carefully when assessing CV risk.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/54072