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Review Article

The Facts About High Density Lipoprotein Cholesterol (HDL-C). I'm Pretty Good Within Limits

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Abstract

Cardiovascular disease (CVD) is one the leading causes of mortality and morbidity in the world. High density lipoproteins (HDL) cholesterol is considered as good cholesterol, as it is inversely associated with the atherosclerotic cardiovascular disease (ASCVD) through the reverse transport cholesterol system. Lifestyle modifications, novel therapeutic and pharmacological therapy towards raising the levels of HDL-C is still under trials. The short review had explained the positive role of high HDL-C in CVD and non CVD cases, but would also like to emphasize the negative effects of high HDL-C. Many guideline state the prominent role of HDL-C in preventing and reducing the risks of CVD but it is suggestive that one should not assume that high levels of HDL-C is a good prognosis instead clinicians should caution the patients with extremely high HDL-C levels and should be evaluated with at-most care by reducing the possibility of other possible associated risk factors. The present review also shortly highlighted the role of HDL-C levels in various non-cardiovascular diseases helping to understand their pathogenesis. The review states that both diet and drugs can increase the levels of HDL-C but could not support that extremely high HDL would prevent CVD and related mortality. HDL-C is good cholesterol within the limits. Further innovative research studies are recommended to establish the exact cut-off ranges of HDL-C levels based upon the cultures, weather and eating habits of the human population across the world.

Keywords: High Density; Lipoprotein; Cholesterol; HDL-C

Introduction

Cardiovascular disease (CVD) is one the leading causes of mortality and morbidity in the world. Lipoproteins play a very crucial role individually where in, LDL is learnt to be the reason for causing atherosclerosis leading to CVD and on contrary HDL lowers the risk of CVD. Abnormal lipid homeostasis causing hyper lipidemia is the risk factor for the advancement of CVD. High density lipoproteins (HDL) cholesterol is considered as good cholesterol, as it is inversely associated with the atherosclerotic cardiovascular disease (ASCVD)through the reverse transport cholesterol system. In reverse transport cholesterol system HDL helps in transportation of free cholesterol from peripheral tissue to liver for further catabolism to bile acids. There is a myth regarding serum HDL levels, stating good cholesterol is really very good to maintain healthy heart. But, one should understand the extent of range to be maintained in respect to the HDL levels too. As it is always said that "less is less (leads to deficiency) and a more is more (leads to complications)." HDL cholesterol (HDL-C) is considered as cardio protective upto 60mg/dl. The normal HDL level is < 40 mg/dl, High or ≥ 60mg/dl [1,2]. It is assumed that HDL cholesterol levels lower

than 40mg/dl, considered having higher risk of cardiovascular diseases. Need of the time we should know to what extent HDL cholesterol is good, complications of high HDL-C and how to maintain the required levels of HDL-C to lead a healthy life. Though literature states benefits of HDL, it should be known whether high HDL levels are harmful and the role it has in CVD and non-cardiovascular diseases. The present review focuses on the serum levels of HDL-C within the given range and complications of low and high HDL-C levels and its impact on health.

Mechanism

The frame gets rid of the extra LDL cholesterol from the peripheral tissues through the mechanism of delivery LDL cholesterol delivery machine. During the opposite delivery LDL cholesterol machine the HDL consists of extra LDL cholesterol from peripheral tissues to the liver. From the liver, the extra LDL cholesterol is excreted via bile. HDL synthesized in the liver incorporates unfastened LDL cholesterol and phospholipids and apolipoprotein-A (synthesized and secreted from the liver), C II, E.

- **LCAT (lecithin LDL cholesterol acyl transferase) mechanism:** LCAT is synthesized and launched from the liver, while LCAT bind to the nascent HDL Apo A-I turned on the LCAT. LCAT begins the off evolved gentrification of unfastened LDL cholesterol inside the peripheral tissues and esterified LDL cholesterol taken up through the HDL lipoprotein.

- **Reverse delivery LDL cholesterol machine:** The mechanism of removing excess cholesterol from theperipheral tissues, further delivering it to the liver, metabolized and removed from the body through gallbladder refers to reverse cholesterol transport mechanism. Lipoprotein HDL-c is involved in this mechanism. A constituent of HDL-c is Apo A-1 protein goes to peripheral tissues via blood stream; it interacts with receptors (ATP- binding cassette) of different cell types like macrophages, enterocytes and hepatocytes in arteries and veins [3]. This reverse cholesterol process is catalysed by an enzyme Lecithin- cholesterol acyltransferase (LCAT).

- HDL-c has anti-inflammatory functions, exerting positive effects on Cholesterol reverse transport, thus plays a crucial role in treating and preventing atherosclerotic diseases. Many studies had stated that the functionality of HDL cholesterol exhibit a greater potentiality in few diseases like chronic renal disease (CKD), coronary artery disease (CAD), diabetes, cardiomyopathy and dyslipidemia. Lipooxygenases, myeloperoxidase affects HDL causing reduction in the availability of endothelial nitrate. This leads in increase in pro-inflammatory activation, inhibition of endothelial repair, leads to endothelial efflux. Further research to understand the implication or role of abnormal HDL in pathogenesis and its clinical applications in atherosclerotic cardiovascular diseases is recommended [4].

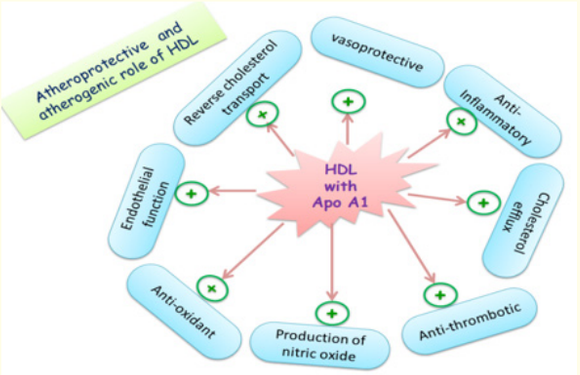

Figure 1: Functions of HDL.

- **Reduced HDL Cholesterol related disorders:** Reduced HDL-C level is the indictor that should be examined for inflammatory pathology and in metabolic disorders. Low HDL-C is observed in diabetes mellitus or in metabolic syndromes. Low HDL-C levels are directly associated with few systematic inflammations like chronic kidney disease, chronic inflammatory disease or cigarette smoking [5,6].

- **Therapeutic measures to increase HDL-C:** Lifestyle modifications, novel therapeutic and pharmacological therapy towards raising the levels of HDL-C are still under trials. Lifestyle modifications include physical activity, smoking cessation, alcohol consumption and Mediterranean diet i.e., consumption of unsaturated fatty acids. Lifestyle modifications those are in wide practice are dietary changes and physical activity, learnt to contribute for the increase of HDL-C levels and are positively associated with decreasing the risks of CVD [7]. It is studied that regular physical activity not only contributes to improve HDL-C levels but also influences HDL functionality [8] with simultaneous improvement in triglyceride-rich lipoprotein metabolism and insulin sensitivity [9,10].

- **Statins, Fibrates and Niacin:** It is a well-known competitively inhibitor of the enzyme HMG-CoA reductase, a regulatory enzyme of cholesterol metabolism. Studies state that, although statins contribute to lower TG and cause slight increase in HDL-C but, statins have substantial contribution towards lowering the events of CVD [11-13]. Fibrates on other hand were noticed to reduce the risk of cardiovascular events by about 10%bbut was not effective on patients with diabetes mellitus

[14,15]. The administration of niacin and its derivatives are learnt to reduce the adverse coronary events and cardiovascular events by about 25% and 34% respectively [16]. But, as of now, neither fibrates nor niacin can be considered as drug-based therapy as till date there is no literature is available in proving the reduction of clinical events on the administration of niacin and fibrates in combination with statins.

- **Beneficial effects of HDL Cholesterol through Mediterranean diet**: It is an accepted fact that healthy diet and regular physical exercise improves serum lipid profile contributing to low total cholesterol and LDL and rise in HDL-C. Diet low in trans-fatty acids, saturated fatty acids and reduce intake of dietary cholesterol and consuming good amount of fresh vegetables, fruits, fish, legumes, cereals, nuts, etc; may contribute to the increase in HDL-C. Eggs and ethanol had learnt to have modulating contribution in increasing serum HDL-c in humans. Studies conducted in rat modules had given favourable changes in risk factors of CVD and in HDL-c on regular and moderate administration of ethanol. But, the clinical implication of this practice is ethically incorrect due to the well-known potential hazards of alcohol consumption [17]. Meta-analysis and multiple research data had extracted different conclusions of the effects of consumption of eggs on the levels of serum cholesterol and cardiovascular health. Increase in serum HDL-C on consumption of eggs was found in patients with metabolic syndrome but not shown any insignificance in healthy subjects [18,19]. Systematic review conducted to learn the effects of consumption of bergamot, red yeast rice, virgin olive oil and artichoke, the components of MediterrAsian diet. The review stated promising effects of these four components in contributing to the increase of serum levels of HDL-C.

- **Red Yeast rice:** A systematic review was conducted by including 7 clinical trials having a total number of samples of about 5444 (females-4224 and males 1620). Administration of red yeast was given for 8 to 216 weeks and the range of the dosage was from 1200- 4800mg/die. The participants considered for the study possess a history of or previous myocardial infarction. Among the studies considered only one study showed a positive outcome of red yeast rice on HDL-C. The studies suggested that components such as plant sterols, lovastatin hydroxylate, isoflavones and glycosides had contributed to the results [20-26].

- **Virgin Olive Oil:** A systemic review considered 15 clinical trials with 1053 adult participants, to study the effect of virgin Olive oil on HDL-C. Dietary intervention of extra virgin oil was given for a period of 2- 52 weeks with a dose between 2.28-54g/day or administrated 75g/day of virgin oil or high polyphenol olive oil (HPOO) was given ranging dose was of 22- 6g/day. In conclusion the results were positive with the study that had administered poly-phenol rich olive oil. This contributed to the increase in HDL-C with a slight decrease in LDL, justified by the presence of omega- 9 mono-unsaturated fatty acid i.e., oleic acid (18:1; n-9). The constituents being hydroxytyrosol phenolic acid facilitates increase in HDL-C and decreases LDL-C, total cholesterol (TC) and triacylglycerol (TG) levels. These results were observed in hyperlipidemic rats and rabbits [27-30]. The responsive mechanism for this not yet available but it is believed that the cholesterol efflux capacity which is the main anti-atherogenic function of HDL is promoted by polyphenols of olive oil. Polyphenols also increases the oxidative stability of HDL, its size and stability [31]. A study conducted by Covas., *et al*., in 2006 showed an increase in the levels of HDL-C and oxidative damage in addition to the contents of monounsaturated fatty acids on the administration of 2.2g of polyphenol containing olive oil regularly for about 15 weeks. This study recommends consumption of virgin olive oil as a fat source as it is capable of increasing HDL-c levels and can promote the reduction of cardiovascular risk factors [32].

- **Bergamot:** Bergamot extract contains natural polyphenols, helps in modulating vascular peripheral biomarkers related to cardiometabolic risk. This was learnt to have two benefits one being contributing to raise the HDL-C levels and second is to decrease fasting serum glycaemia. Bergamot extract (BPF) inhibits the activity of HMG-CoA reductase enzyme, increases reactive vasodilation [33]. Acting as efficient phytotherapeutic component BPF is actively working against lipidemic and glycemic disorders. In addition to this it is also learnt that polyphenols extracts from bergamot juice helps in enhancing the rosuvastatin effect. It helps in reduction of daily dosage of rosuvastatin by normalizing the serum lipemic levels. Limited studies recommend further research in this area.

- **Artichoke:** Artichoke leaf extract (ALE) was administrated as a dietary intervention for about 6-12 weeks with varying dosage depending upon the parts of the plant extract for instance artichoke dry leaf extract is given as a dosage of 1.8g/day, fresh leaf extract is of 0.5-6g/day and leaf extract of flowering bud is about 0.6g/day. ALE also has positive effect on increasing HDL-C levels and is well tolerated, safe dietary source to be administrated to the patients with mild hypercholesterolaemia with low HDL levels. This positive effect is also stated to be contributed by polyphenolic sources present in ALE [34-38].

The review explained the observations done on virgin olive oil and leaf extract of artichoke and stated that the increase in HDL-C content is well noted on administration of both artichoke and virgin olive oil. Wherein, non-virgin olive oil had no promising role towards increasing the levels of HDL-C. On the other hand admin-

istration of red yeast rice had shown positive increase in HDL-C levels in patients with prior myocardial infarction, but, the results were noticed only after long term administration. Administration of red yeast rice in subjects with asymptomatic dyslipidaemia showed negative effects on the levels of HDL-C. Even though the Mediterr Asian diet shows promising results in increasing HDL-C levels, requires structured randomized controlled studies in larger population, in both the genders with low HDL-C levels. Correlation between the effects of an increase in non-functional HDL particles and HDL-C should also be evaluated.

Effect of HDL on non-cardiovascular diseases

Studies had stated an inversely proportional relationship between HDL-C and infectious diseases like it was observed that low HDL-C levels are associated with increased risk for infectious diseases [39] and the effect is vice versa. Similar to the results of association of infectious diseases with levels of HDL-C are the results of HDL-C with autoimmune diseases. It was observed from the cross-sectional studies that low HDL-C is associated with increase in the risk of about 42 different autoimmune diseases a few among those are listed here. Diabetes type-I, Graves disease, Hashimoto's thyroiditis, Multiple sclerosis, Sarcoidosis, Ankylosing spondylitis, etc;. Studies to know the association of HDL-C levels with various cancers were conducted. The reviews in this context showed that low levels of HDL-C and (Apolipoprotein A1) Apo A1are associated with high risks of nervous and haematological related cancers and are also associated with respiratory and breast cancers to the minimum extent [40]. Many studies are available in proving the positive association of low HDL-C levels with increased risk of type-2 diabetes. However, the genetical studies in this subject area had failed to explain the underlined mechanism behind this scenario. Genetical data and the observational studies had shown association of low HDL-C with reduced kidney function [41]. The impact of HDL-C levels on lung diseases had also shown inversely proportional relationship i.e., low HDL-C had positive association with lung diseases, showing decreased lung functioning [42]. All this findings retrieved from various systematic and meta-analysis of huge studies concludes with the same statement that detailed mechanism of the association of HDL-C levels in various non-cardiovascular diseases had to be still learnt.

Interesting facts about high HDL-C

The short review had explained the positive role of high HDL-C in CVD and non CVD cases, but would also like to emphasize the negative effects of high HDL-C. It is very important to know the cut off levels of HDL-C and to what extent these high levels of HDL-C are healthy and contributing to lead a normal life. In the recent decade many randomized clinical trials and genetic studies were taken up to understand role and impact of high HDL-C on CVD and non-CVD cases. The observational cohort studies in about 3 million populations had ended up with a conclusion that extremely high HDL-C is positively associated with high mortality rate [43-53]. This outcome recommends huge studies to explore the facts behind the association of High HDL-C with high mortality rates. Possible hypothesis to explain the mechanism of high levels of HDL and its complication is made by Madsen et.al; carrying different genetic variants could be one of the reasons for extremely increased HDL-C levels in some individuals. These variants not only have potentiality to increase HDL-C but also have an impact on changing the human physiology leading to the detrimental effects on health thereby increasing the risk of diseases and may even lead to death [54]. At present no such data stating genetically elevated HDL-C leading to increase in mortality rate is available. The available information states that HDL-C has capability to protect against atherosclerosis by clearing accumulated or excess cholesterol from macrophages in the walls of arteries, which can be considered as a narrow interpretation. Because mechanism studied till date explain only the capability of HDL in cholesterol efflux from macrophages [55,56]. but had not documented the HDL functionality in border aspect by studying biological and change in size and composition of HDL particles [57-59]. One of the dietary cofounder found was alcohol intake that could be having positive association with increased HDL-C with increase rate of mortality. This was observed in a study of about 2464 men wherein the association was established between high HDL-C with elevated liver enzymes thereby leading to all-cause mortality [60,61]. Further research must be taken up to study other such cofounder like hormone replacement therapy or menopause in female population to understand this association.

Many guideline state the prominent role of HDL-C in preventing and reducing the risks of CVD but it is suggestive that one should not assume that high levels of HDL-C is a good prognosis instead clinicians should caution the patients with extremely high HDL-C levels and should be evaluated with at-most care by reducing the possibility of other possible associated risk factors. The present review also shortly highlighted the role of HDL-C levels in various non-cardiovascular diseases helping to understand their pathogenesis. The review states that both diet and drugs can increase the levels of HDL-C but could not support that extremely high HDL would prevent CVD and related mortality. Extremely high HDL-C should be evaluated in terms of its positive impact on health and risk leading to prognosis of other CVD's and mortality rate, should consider the available data by possible explanations of genetic variants of HDL, dysfunctional HDL and confounders of HDL. It is highly recommended to know the role of extremely high HDL-C in non-cardiovascular diseases. It is the need of the time to take up animal experimental and genetic studies in humans to understand the role of HDL in the development of major other non-cardiovascular diseases.

Conclusion

Diet and lifestyle modification would contribute to increase the levels of HDL-C but could not suggestively decrease the mortality rate. As HDL-C levels correlates healthy individuals with cardiovascular risks. Low HDL-C should be a prompt examination in understanding inflammatory pathogenesis and additional metabolic pathogenesis. Extremely high HDL-C levels are equally dangerous as the low HDL-C. HDL-C is good cholesterol within the limits. Further innovative research studies are recommended to establish the exact cut-off ranges of HDL-C levels based upon the cultures, weather and eating habits of the human population across the world.

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