REVIEW

Is a high concentration of high-density lipoprotein cholesterol still relevant?

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ABSTRACT

The importance of cholesterol management, particularly high-density lipoprotein (HDL) cholesterol, has always been believed to be essential in preventing and managing cardiovascular disease (CVD). While HDL has long been accepted as the 'good' cholesterol, various studies have started to challenge this paradigm. Most of these studies found that HDL cholesterol concentrations did not linearly translate into a reduction in CVD risk. There is a suspicion of dysfunctional HDL particles leading to the loss of HDL's cardioprotective function. Some of these dysfunctions were caused by changes in the structure of HDL particles due to an underlying disease or genetic mutations, causing defects in the reverse cholesterol transport (RCT) mechanism and vascular inflammation inhibition. Therefore, therapies that focus on these two mechanisms are expected to be one of the new cornerstones in reducing CVD. Simultaneously, cholesterol efflux capacity (CEC) assay could become the new therapeutic target as it has an inverse correlation with CVD risk regardless of HDL cholesterol concentration, increasing the accuracy in stratifying CVD risk in patients. However, standardization and a more thorough study on CEC assay and various subcellular cholesterol metabolism should be conducted before stepping further.

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INTRODUCTION

Cardiovascular disease (CVD) is the world's leading cause of death, which is estimated to cause 17.8 million deaths in 2017, representing 31% of total deaths in the world. Not only in developed countries, but this estimate also tends to increase in developing countries such as ASEAN, slowly causing the pattern of mortality from communicable to non-communicable diseases.[1] Given that most risk factors for CVD can be modified (diet, obesity, activity, alcohol consumption, high cholesterol), preventive efforts should be sought first, both in screening and management.[2] In addition, several screening instruments that have been used extensively to determine the risk of CVD in a person such as SCORE (Systematic Coronary Risk Evaluation), PCE (ASCVD Risk Estimator), RRS (Reynolds Risk Score), QRISK / JB13 and Framingham CVD Risk Score uses a component of HDL cholesterol concentration in its analysis.[2–4]

Up until now, high-density lipoprotein (HDL) cholesterol has long been labelled as "good" cholesterol in the eye of both health practitioners and the general public. This leads to people thinking that higher HDL cholesterol concentration equals better health. The majority of guidelines focus solely on lowering low-density lipoprotein (LDL) cholesterol concentrations.[2–4] For example, the 2019 European Society of Cardiology/ European Atherosclerosis Society (ESC/ EAS) dyslipidemia guidelines recommend lowering LDL concentrations to at least 50% of baseline and target LDL cholesterol to be <55 mg / dL for patients at very high risk for CVD. These targets vary depending on the stratification of the risk level of each patient. However, there has been no specific target for optimal HDL cholesterol and triglyceride concentrations, although so far, an increase in HDL cholesterol concentrations is thought to reduce the incidence of atherosclerosis.[3] This knowledge departs from preliminary research, which consistently shows a linear relationship between HDL cholesterol levels with the reduction of CVD.[5]

However, several recent studies have shown the opposite correlation. HDL cholesterol concentration that is too high will cause dire implications to the cardiovascular (CV) system.[6–9] These findings certainly raise critical questions about the role of HDL cholesterol as a cardio-protector, which will have implications for the medical community, especially in how healthcare providers assess and manage their patients, particularly those who already have a CVD. Furthermore, this phenomenon will also urge us to reconsider the current screening instruments, given that it is true. This paper aims to present the latest knowledge and developments regarding the association of HDL concentrations with CVD risk and its implications for the future.

CORRELATION OF HDL CHOLESTEROL WITH CVD

Cholesterol is a lipophilic molecule that has various vital roles in the physiology of the human body. Some of these include precursors for the synthesis of vitamin D and steroid hormones as well as absorption of vitamins in the digestive tract. Due to their lipophilic nature, cholesterol particles require suitable particles to be transported in the blood, namely LDL and HDL. In general, LDL and HDL are particles that have the most prominent role in cholesterol transport. LDL plays a role in transporting cholesterol to peripheral tissues, whereas HDL does the opposite transporting excess cholesterol back to the liver for excretion. This vital mechanism is called reverse cholesterol transport (RCT).[10] Moreover, HDL in healthy individuals has several protective effects for the vascular system, specifically endothelial cells. HDL stimulates the release of nitric oxide (NO) from endothelial cells, suppresses molecular adhesion, reduce thrombotic activity, repair endothelial cells, and reduces the level of endothelial cell apoptosis.[11] The most commonly used cholesterol test in the clinical setting is the plasma concentration of HDL cholesterol which is thought to reflect the cholesterol level being transported by HDL particles. Therefore, HDL cholesterol is often referred to as "good" cholesterol, where the higher the concentration, the lower the risk of atherosclerosis.

Nevertheless, Madsen et al. showed a contradictory relationship to our current knowledge concerning the relationship between HDL cholesterol concentration and CVD risk. The study involved 52,268 men and 64,240 women from two cohorts (Copenhagen City Heart Study and Copenhagen General Population Study) and discovered that the association between HDL cholesterol concentration and mortality from all causes had a 'U' shape curve for both sexes. Hence, suggesting an increased mortality rate in patients with low and very high HDL concentrations. Similar results were also seen in the CANHEART (Cardiovascular Health in Ambulatory Care Research Team) study, an observational cohort involving 631,762 individuals without prior CVD or severe comorbidities. It was observed that individuals with low (<50 mg / dL for women and <40 mg / dL for men) and very high (> 80 - 90 mg / dL) HDL cholesterol had a higher risk of mortality than individuals with moderate HDL cholesterol concentrations (50 - 79 mg / dL). However, what differentiates this from the previous study is that the mortality rate in individuals with very high HDL cholesterol concentrations is not correlated with CVD mortality.[6] EPOCH-JAPAN reported a similar finding (2018), where individuals with very high HDL cholesterol (> 90 mg / dL) did not experience increased mortality due to CVD. On the other hand, there was an increase in mortality due to CV atherosclerosis (HR, 2.37; 95% CI, 1.37-4.09), chronic heart disease (HR, 2.46, 95% CI, 1.13 - 5.32), and ischemic stroke (HR, 2.30, 95% CI, 1.06 – 4.98).[8]

Doubts regarding HDL cholesterol's role as "good" cholesterol are heightened by the results of several clinical trials of drugs aimed at increasing HDL cholesterol. Several studies have tried using cholesteryl ester transfer protein (CETP) inhibitor / anti-CETP. CETP facilitates cholesterol transport from HDL particles to particles containing apolipoprotein B (apo B), such as LDL.[12,13] Therefore, in theory, inhibition of CETP would increase HDL cholesterol concentration while lowering LDL cholesterol concentrations, which will reduce the risk of atherosclerosis. Thus, using anti-CETP can help to clarify the effect of HDL cholesterol on the risk of CVD.

The first clinical study was ILLUMINATE, a randomized, double-blind study involving 15,067 patients at high risk of CVD. In this study, patients were divided into the torcetrapib plus atorvastatin group and atorvastatin group. There was an increase in HDL cholesterol concentration up to 72.1% and a decrease in LDL cholesterol by 24.9% in the torcetrapib group compared to the placebo group (P <0.001). Unfortunately, the study was terminated prematurely because of increased morbidity and mortality (95% CI, 1.14 - 2.19; P = 0.006), which was thought to result from missed therapeutic targets.[14] Further investigations showed that torcetrapib caused increased blood pressure and aldosterone production.[15]

The subsequent study is dal-OUTCOMES, which was published in 2012. This randomized, double-blind clinical trial involved 15,871 patients who had recently developed the acute coronary syndrome. Participants were divided into two groups, the dalcetrapib (anti-CETP) group and the placebo group. The study was terminated due to an insignificant outcome after 31 months of observation. Although there was an increase in HDL cholesterol (31–40%) in the dalcetrapib group compared to the placebo group, the primary outcome and total mortality in the study did not produce any significant differences (HR, 1.04; 95% CI, 0.93-1.16; P = 0.52). This study's failure is presumed to be due to the insignificant increase in HDL cholesterol; therefore, a more potent anti-CETP is needed.[16]

The third study was ACCELERATE (2017), a randomized, double-blind clinical trial involving 12,092 patients who had experienced CVD 30-365 days earlier. Similar to previous studies, patients will be divided into the evacetrapib (anti-CETP) and placebo groups. There was a significant increase in HDL cholesterol concentrations in the evacetrapib group compared to the placebo group (difference of 131.6%; 95% CI, 130.0 - 133.1; P <0.001). In addition, there was also a decrease in LDL cholesterol concentrations in the evacetrapib group compared to the placebo group (difference -37.1%; 95% CI,-38 - 36.1; P <0.001). However, interim analysis results of the available data in 2015 (82% final data estimate) did not show any significant difference in key outcomes between the two groups (HR, 1.03; 95% CI, 0.93 - 1.15; P = 0.58). On this basis, the study was agreed to be terminated early because of the low efficacy. One plausible hypothesis for the low efficacy was the dysfunction of HDL particles in the study patients, which caused a disturbance in HDL's anti-atherogenic effect.[11]

The most recent study of the use of CETP inhibitors is REVEAL (2017). The randomized, double-blind clinical trial involved 30,449 patients, which is twice as large as previous studies. Patients were divided into the anacetrapib plus statin group and statin plus placebo group. Observation for 4.1 years showed that there was a significant reduction in the

incidence of coronary disorders (combined coronary death, myocardial infarction, and coronary revascularization) in the anacetrapib group versus the placebo group (1640 of 15,225 patients [10.8%] vs 1803 of 15,224 patients [11.8%]; rate ratio, 0.91; 95% CI, 0.85 - 0.97; P = 0.004). This difference was even more apparent when assessed in terms of morbidity, risk of myocardial infarction (rate ratio, 0.87; 95% CI, 0.78 - 0.96; P = 0.007) and coronary revascularization (rate ratio, 0.90; 95% CI, 0.83 - 0.97; P = 0.01). However, in terms of the death rate from CV events (3.4% in the anacetrapib group vs. 3.7% in the placebo group, P = 0.17), death other than CV events (4.0% vs. 3.9%, P = 0.77), or death from all events (7.4% vs. 7.6%, P = 0.46) were not seen to be significantly different. Although there was a significant increase in HDL cholesterol in the anacetrapib group (104% / 43 mg / dL) compared to the placebo group, the relative reduction in risk of coronary death or myocardial infarction was only 11%, similar to the results of a similar previous study (10%).[17] Moreover, based on previous studies, this risk reduction mechanism is speculated to be the impact of reducing non-HDL cholesterol rather than the increasing HDL cholesterol.[18] Thus, It can be concluded that an increase in HDL concentration does not have an impact on reducing mortality due to coronary disorders but on reducing the risk of coronary disorders.

Broadly speaking, the failure of these four studies poses big questions to the role of HDL as a cardioprotector. Perhaps it suggests that the high concentration of HDL cholesterol does not necessarily imply a reduction in CVD incidence but solely as a marker of CVD or a person's wellbeing.[6] Furthermore, this may indicate a dysfunction of HDL cholesterol that causes disturbance in HDL cholesterol's cardioprotective mechanism, or even worse, to become dangerous.[19,20]

GENETIC MUTATION IN HDL

Apart from various external factors that cause an increase in HDL cholesterol, it might be wiser to start investigating from the internal factors. Up to now, at least three HDL metabolism components are considered to play a pivotal role in this phenomenon, mainly the scavenger receptor class BI (SR-BI), CETP, and the endothelial lipase gene (LIPG). The discovery of the SR-BI encoded by the SCARB1 gene has become one of the pioneers of fundamental knowledge on HDL metabolism. SR-B1 bridges the selective transfer of HDL cholesteryl ester (HDL-CE) to enter liver cells to metabolize the cholesterol in HDL particles.[21] Further studies have shown that overexpression of SR-BI reduces the risk of atherosclerosis despite low HDL cholesterol concentrations; moreover, deletion of the gene increases the risk of atherosclerosis despite high HDL cholesterol concentrations. One possible explanation is the flow of cholesterol from macrophages through the RCT mechanism, where overexpression of SR-B1 will increase macrophages' RCT and vice versa.[22,23]

P376L is a variant of the SCARB1 gene that mutates and results in the loss of the main function of SR-BI in transporting HDL cholesterol selectively. The implication of this mutation is an increased risk of coronary heart disease for heterozygous carriers of the P376L variant. (OR, 1.79; P = 0.018). Moreover, there is a shift in the composition of HDL to large HDL particles, while it is known that large HDL particles have weaker antioxidant and anti-inflammatory properties than small HDL particles.[23,24]

The second component is the LIPG gene which encodes endothelial lipase. Endothelial lipase acts as a negative regulator of HDL cholesterol concentration, which means an increase in this enzyme will lower HDL cholesterol and vice versa. A Mendelian study showed that individuals with the LIPG Asn396Ser allele polymorphism had higher concentrations of HDL cholesterol without a reduced risk of myocardial infarction (OR: 0.99, 95% CI, 0.88 - 1.11, P = 0.85).[25] A similar outcome was seen in a recent meta-analysis by Zhao et al. (2020), who found a higher suspicion of coronary artery disease in the carrier of 584C / T, a mutation of the LIPG gene.[26]

CETP rs708272 (C>T) and rs1800775 (C>A), are CETP polymorphisms which are crucial components in HDL metabolism. Individuals with these polymorphisms have a higher risk of myocardial infarction.

However, this phenomenon is only found in Caucasians whose mechanisms are still not fully understood.[27] Despite various failures in CETP inhibitors' clinical trials, it is possible that these polymorphisms can be a marker for the early diagnosis of myocardial infarction. Nonetheless, studies with larger sample sizes and involving multiple ethnicities are needed.

In conclusion, there is strong evidence that these genetic variants have implications for HDL dysfunction. Nevertheless, some of these variants are classified as rare, and their frequency is low. Therefore, it might be too immature to attribute this to the high mortality rate in previous studies. Furthermore, some of these studies are limited by their small sample sizes, less variety of ethnicity, and numerous unstudied HDL genes, demanding a further investigation to strengthen the concept.

STRUCTURAL CHANGES IN HDL

This new development demands a change in the focus of investigation from merely HDL cholesterol concentration to the function of HDL particles. These functional changes are mainly observed in patients with cardiovascular, kidney, and metabolic diseases.[28–31] To date, there are still numerous HDL related molecules that are not fully understood regarding their role and its implication if it is dysfunction. However, in general, there are changes in HDL's protein and lipid structure due to various mechanisms such as oxidation or glycation that eventually bring forth the same consequence, a decrease in the cardioprotective function of HDL.

As mentioned previously, the majority of diseases cause a reduction in the amount of sphingosine 1-phosphate (S1P) in blood plasma.[32] S1P is a lipid mediator that activates the sphingosine 1-phosphate 1 (S1P1) receptor located on endothelial cells. S1P1 activation will later provide a cardioprotective function through suppression of vascular inflammation and atherosclerosis.[33] This mechanism may be the basis for the study outcomes by Yuji et al. (2019), who found endothelial dysfunction in male patients with very high HDL cholesterol concentrations (≥80 mg / dL).[34] This dysfunction is indicated by a decrease in flow-mediated vasodilation

(FMD), which is known to have a strong correlation with CVD risk factors. Besides, S1P needs to bond with Apolipoprotein M (ApoM) on HDL in order to work. In patients with metabolic disorders such as uremia, the ApoM concentration is reduced and results in the inactivation of S1P.[35]

Another HDL particle structure that is often become the target of modification is Apolipoprotein AI (ApoAI). ApoAI is the most abundant apolipoprotein in HDL and plays an essential role in RCT and cellular cholesterol homeostasis.[36] Modifications to apoAI can occur due to glycation and oxidation processes. The oxidation process is mediated by myeloperoxidase (MPO), a component of the human immune system that functions to kill microbes through the formation of reactive oxidants and free radicals. When MPO circulates in the blood vessels, it can bind to apoAI in HDL, which cause damage and resulting in apoAI dysfunction.[37] Likewise, this mechanism also happened in glycation. Glycation is the process of adding sugars covalent to proteins or lipids. Aside from apoAI dysfunction, glycation also reduces the S1P concentration in HDL, leading to increased cardiomyocyte cell death due to ineffective activation of the intracellular survival pathway.[29,37]

A study by Vaisar et al. (2015) shows that acute inflammation affects the efflux capacity of HDL cholesterol regardless of HDL cholesterol concentration. The proteomic analysis demonstrated that this cholesterol efflux capacity is closely related to serum amyloid A (SAA) 1 and SAA2 in HDL particles. Acute inflammation will cause changes in the HDL structure mediated by SAA, resulting in a decrease in HDL cholesterol's efflux capacity.[38] This finding is supported by Tölle et al. (2012), in which patients with chronic inflammation showed an increase in SAA concentration, which resulted in the stimulation of monocyte chemoattractant protein-1 (MCP-1) production. MCP-1 is a pro-inflammatory molecule that contributes to the initiation and progression of atherosclerosis.[31]

Based on the various mechanisms described above, it can be concluded that HDL's reduced cardioprotective function occurs due to decreased RCTs and failure of inhibition of vascular inflammation. Therapy that focuses on both of these may lower CVD risk and preferably be sought rather than merely focusing on HDL cholesterol concentrations. Although there are still various other factors that contribute indirectly, and until further research, a definite conclusion still cannot be drawn.

HDL AS A THERAPY TARGET

In the future, the examination of HDL cholesterol concentration may become less relevant in determining an individual's CV risk. A more sensitive and specific test is needed, and by far, the cholesterol efflux capacity (CEC) test is probably one of the most likely candidates. The cholesterol efflux capacity test is used to check the capacity of HDL particles to remove cholesterol from cells in vitro without modifying or eliminating the subpopulation of HDL to simulate the body's HDL metabolism closely.[39] The CEC test principally requires two components: donor cells that will excrete the labelled cholesterol and cholesterol acceptor cells (serum HDL from the patient).

A meta-analysis showed that a high CEC test result was associated with a reduced CV risk than the lowest CEC (RR, 0.56%; 95% CI, 0.37-0.85; I², 89%). Furthermore, compared with the lowest CEC, the prevalence of CVD was significantly reduced in the participants with the highest CEC (OR, 0.30; 95% CI, 0.17 - 0.51; I² = 71%). Nevertheless, there was no significant difference in the highest CEC and lowest CEC groups regarding all-cause mortality. This finding indicates that CEC is more closely associated with CV risk and not with other risks. It should be noted that the type of CVD in this study is not specific. Thus a larger clinical trial is needed to validate this concept. Moreover, there is no primary benchmark for the CEC test, so differences in donor cell type (J774 or THP-1) and labelled cholesterol (fluorescent or radiolabel) can produce varying results.[40]

A more recent study by Ritsch et al. (2020) showed that cholesterol efflux could predict mortality due to CVD regardless of HDL cholesterol level. Moreover, CEC is also associated with various HDL parameters (varying HDL size and HDL composition) and various inflammatory markers (CRP, Fibrinogen, Il-6 and SAA). A high level of CEC indicates a low level of inflammation and vice versa. In other words, inflammatory conditions cause HDL dysfunction, which translates into decreased RCTs. These findings support the study of Vaiser et al. on the concept of inflammation and HDL dysfunction.[38] However, it should be noted that this study was conducted in vitro, as was the case with other CEC studies, which means that there are still some subcellular mechanisms of cholesterol metabolism in the body that were not involved.[41]

CEC is an essential key in the RCT system to the liver. Hence, adding a CEC assay to the traditional risk factors is expected to increase the accuracy in stratifying CVD risk.[42] However, before the CEC assay can be widely applied in the clinical setting, it is necessary to standardize the CEC assay so that each examination result produces similar accurate results. Moreover, the CEC assay is principally done in vitro; therefore, it requires a comprehensive understanding of the various subcellular mechanisms of cholesterol metabolism in the body, which must then be applied to the analysis. This is vital so that the CEC assay can provide an accurate representation of our body HDL function.

CONCLUSION

The current paradigm of HDL cholesterol as the "good cholesterol" might need to be reconsidered. An increasing number of studies challenged this paradigm and indicate that the relationship between HDL cholesterol and CVD risk factors is "U" shaped. This relationship curve explains that very high HDL concentrations also increased mortality rate, which then questions the role of HDL cholesterol in stratifying the risk of CVD. Moreover, studies on drugs aimed to increase HDL cholesterol concentration failed to reduce mortality raise a suspicion that HDL particles might be dysfunctional, leading to the loss of HDL's cardioprotective function caused by changes in the structure of HDL particles due to an underlying disease or genetic mutations. Additionally, the CEC assay measure of HDL RCT function showed

an inverse correlation with CVD risk and the level of inflammation regardless of HDL cholesterol concentration. Therefore, the CEC assay could improve the accuracy of CVD risk stratification. Nevertheless, standardization and a more thorough study on CEC assay and various subcellular cholesterol metabolism should be conducted before stepping further.

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