REVIEW ARTICLE

Annals of Agricultural and Environmental Medicine 2018, Vol 25, No 3, 517–526
www.aaem.pl

High-density lipoprotein (HDL) cholesterol – more complicated than we think?

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

Nessler K, Windak A, Grzybczak R, Nessler MB, Siniarski A, Gajos G. High-density lipoprotein (HDL) cholesterol – more complicated than we think? Ann Agric Environ Med. 2018; 25(3): 517–526. doi: 10.26444/aaem/92350

Abstract

Introduction and objective. There are some clinical situations where a high level of HDL cholesterol (HDL-C) may be unfavourable. In these situations, HDL-C may undergo some changes, and even if its quantity is within the reference range, its quality is no longer the same.

Brief description of state of knowledge. Diabetes is the state of elevated oxidative stress. Studies conducted to-date have revealed an increased production of the reactive forms of oxygen as the result of tissue damage in diabetes patients. The expression 'dysfunctional HDL' has been coined in the literature to describe high-density lipoproteins that lose their antioxidative and anti-inflammatory properties, that is, HDL-C that loses its basic functions. Recent observational studies have confirmed that the atheroprotective activity of properly functioning HDL-C is frequently impaired in clinical situations associated with oxidative stress. The presented review lays the foundation for a new approach to understanding how the functional properties of HDL help reduce cardiovascular risk.

Conclusions. In the light of presented findings it seems that there is a need to seek a better diagnostic marker than HDL-C level. This study presents some possible directions for future research to bring us closer to the full understanding of the HDL particle and its role in patients with ischemic heart disease and type 2 diabetes.

Key words

cardiovascular disease, diabetes mellitus, dysfunctional HDL

INTRODUCTION

The incidence of diabetes continues to rise worldwide, with the number of patients exceeding 425 million adults and expected to rise to 642 million people by 2040 [1]. This growing incidence has been related to urbanization and dramatic lifestyle changes, particularly in developed countries. As a result, there has been an increase in the incidence of risk factors for numerous diseases, including type 2 diabetes [2]. So far, several modifiable risk factors have been associated with type 2 diabetes, including overweight, unhealthy diet, and lack of physical activity [2]. The most recent evidence shows that the growing incidence of diabetes constitutes a huge health burden for global society [2].

The major cause of mortality and morbidity in diabetic patients is cardiovascular disease (CVD) [3]. Moreover, in patients with diabetes and concomitant CVD, the risk of major adverse cardiac events is increased, compared with patients without diabetes [3]. On average, it is estimated that patients with type 2 diabetes die prematurely, about 5–10 years earlier than those without type 2 diabetes, mostly due to coronary heart disease (CHD) [4]. In Europe, the treatment of CVD accounts for a significant proportion of health care costs attributed to type 2 diabetes (10%–12%) [1].

Dyslipidaemia is the major risk factor for atherosclerosis, although to-date the mechanism of this association has not been fully elucidated. Low-density lipoprotein cholesterol (LDL-C) has been determined as the major atherogenic lipoprotein, and its central role in atherosclerosis has been confirmed in numerous studies [5–7]. On the contrary, epidemiological, pathological, and experimental studies have demonstrated that high-density lipoprotein cholesterol (HDL-C) may protect against coronary artery disease [8, 9]. Moreover, HDL-C has been shown to reduce the risk of atherosclerosis by multiple pathophysiological mechanisms.

Despite the atheroprotective properties of HDL-C, some most recent clinical studies have identified individuals with a significant atherosclerotic burden despite normal or elevated levels of HDL cholesterol [8]. Nascent discoidal HDL-C is composed of cholesterol, apolipoprotein A-I (apoA-I) and phospholipids. Its particles undergo lipidation and remodeling by a series of reactions mediated by ATP-binding cassette sub-family G member 1 (ABCG1), membrane-associated ATP-binding cassette transporter A1 (ABCA1), hepatic lipase, endothelial lipase, cholesteryl ester transfer protein (CETP), and phospholipid transfer protein [10, 11]. This complex structure and involvement

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Received: 24.03.2018; accepted: 17.06.2018; *first published: 28.06.2018*

in various metabolic pathways are the potential causes of qualitative and quantitative modifications of HDL particles, which may result in the loss of at least a few pleiotropic properties of HDL-C and the development of new potentially proatherogenic activities. Therefore, the HDL-C level itself is not always a good indicator of its atheroprotective features.

Since it has been established that a significant number of CHD events in patients with type 2 diabetes occur in individuals with normal or even elevated HDL-C level, it is necessary to identify biomarkers with a better predictive value in this group of patients. In addition, these patients have atherogenic dyslipidemia and therefore may develop atherosclerosis.

The mechanisms that deprive HDL-C of its cardioprotective properties are poorly understood. Therefore, the presented review aimed to discuss some of the possible directions for future research to bring us closer to a full understanding of the HDL particle and its role in patients with ischemic heart disease and type 2 diabetes.

Biocharacteristics of HDL-C. The HDL particle consists of lipids and proteins (apolipoproteins) with different biochemical activities. So far, over 100 proteins bound to HDLs have been identified, with apoA-I as the main surface protein. Immunoseparation is used to separate HDL particles containing apoA-I from those containing both apoA-I and apolipoprotein A-II (apoA-II) (Fig. 1 and 2).

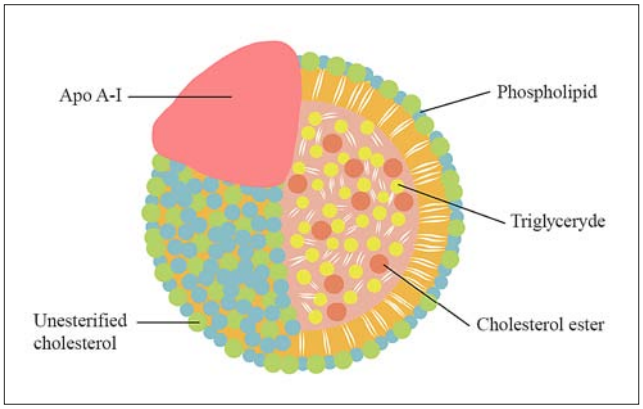

Figure 1. HDL particle containing apoA-I

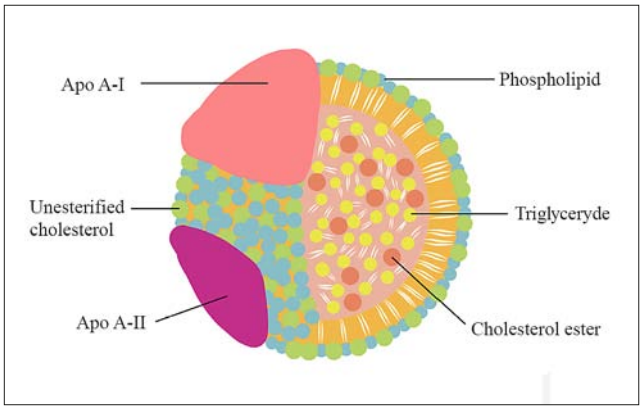

Figure 2. HDL particle containing ApoA-I-A-II

It has been suggested that these apolipoproteins have different metabolic properties and thus may have a different atheroprotective potential [12]. This cited experimental study revealed reduced anti-inflammatory activity in transgenic mice with the over-expression of apoA-II in HDL particles. The authors also hypothesized that patients with ischemic heart disease and type 2 diabetes may show differences in HDL protein profiles.

Interestingly, little is known about proteins other than apoA-I contained in normal and in dysfunctional HDL-C, and data on the potential role of different HDL-C subpopulations in the inflammatory process are still limited [13]. Meanwhile, a growing body of evidence indicates that the determination of HDL subpopulations might significantly improve our knowledge on cardiovascular risk [14]. It is believed that such data would be particularly valuable for diabetic patients.

HDL-C as a protective factor. HDL-C is currently being widely studied in experimental and clinical research. It has been recognized as an independent protective factor in CHD. This was first shown in the Framingham Heart Study, which confirmed an inverse correlation between HDL-C and the incidence of CHD [15]. HDL-C exerts anti-inflammatory and antioxidant effects and protects against atherosclerosis, as shown by a considerable amount of experimental data [16]. There are many recognized pathways that have been proposed to account for the involvement of HDL-C in protective mechanisms against CHD.

HDL-C and its major protein, apoA-I, are essential for mediating reverse cholesterol transport, which is a multi-step process involving cholesterol transfer from peripheral tissues, such as arterial walls, back to the liver via plasma for excretion. The HDL transformation cycle is shown in Figure 3.

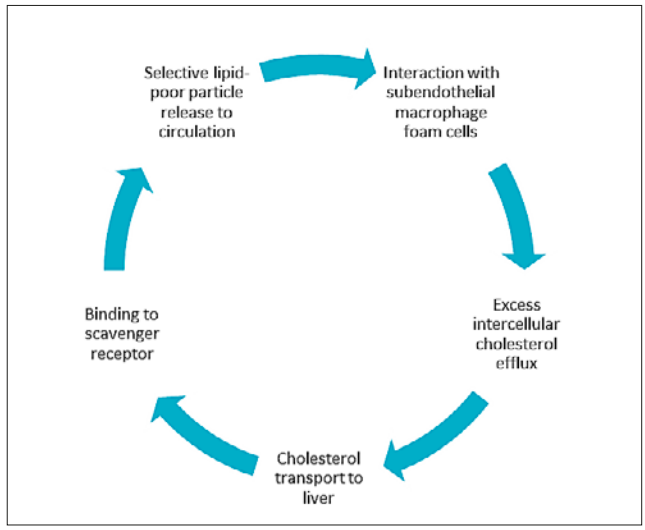

Figure 3. HDL-C transformation cycle

This function likely plays an important role in the atheroprotective mechanism of HDL-C. Other protective activities of HDL-C include the removal or detoxication of oxidized sterols and phospholipids. It also exerts antithrombotic actions and has a beneficial effect on endothelial cells [17, 18] (Tab. 1).

Effects of a pharmacological increase in HDL levels. A meta-analysis of randomized controlled trials has not confirmed the hypothesis that any agent raising HDL level should decrease the number of cardiovascular events [19].

Table 1. Main features of HDL cholesterol

Features of HDL cholesterol	Description
Anti-inflammatory and antioxidant (detoxification of oxidized sterols and phospholipids)	Protective role against atherosclerosis. Main antioxidant protein of HDL is Apo A-I. Its role strongly depends on myeloperoxidase, which promotes endothelial dysfunction and plaque rupture. Excessive production of malondialdehyde and phospholipid aldehyde resulted from the fact that oxidative stress deprives the ability of Apo A-I to promote atheroprotective features. On the other hand, paraoxanase-1 in HDLs limits lipid oxidation and provides additional atheroprotective effects.
Reverse cholesterol transport	Protective role against atherosclerosis by transporting the cholesterol from arterial walls and peripheral tissues to the liver and activating nitric oxide synthase.
Antithrombotic activity	The effect of HDL-C on platelet function remains unclear. Some studies showed that HDL particles changed platelet signaling pathways by limiting intraplatelet cholesterol overload and inhibiting nitric oxide and prostacyclin production. Decreased HDL-C level was associated with high platelet reactivity both in patients with ST-elevation myocardial infarction and stable coronary artery disease.
Healing the endothelium	HDL particles inhibit the VCAM-1 expression. The inhibition of this process was observed in diabetes and cardiovascular diseases and led to increased inflammatory activity by macrophage adhesion to activated endothelial cells.

LDL cholesterol (LDL-C)-lowering agents. The finding that elevated LDL-C and low HDL-C level is associated with increased cardiovascular mortality encouraged the search for targeted drug treatments. The main assumption for new therapies was either to increase HDL-C level or lower LDL-C level, or to achieve both. Since then, lowering of LDL-C level by using statins has repeatedly been found to reduce the risk of cardiac events and all-cause mortality in the setting of secondary and primary prevention [19].

Multiple strategies targeting the inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) have emerged as effective modalities for LDL-C lowering. PCSK-9 monoclonal antibodies are the most advanced to-date in clinical development, and in 2015 alirocumab and evolocumab were approved for clinical use by regulatory agencies. Adverse events associated with these medications are minimal. Importantly, most studies confirmed that PCSK9 improve clinical CVD outcomes, although the results of a long-term study are yet to be reported [20].

Contrary to the above findings, the authors of the most recent study published in the *European Heart Journal* have found no associations between PCSK9 and apoA-I, HDL-C, lipoprotein(a) and high-sensitivity C-reactive protein. Furthermore, the baseline levels of PCSK9 did not predict the first cardiovascular events [21]. In addition, it should be noted that the more general use of PCSK-9 monoclonal antibodies has thus far been limited by the high cost [20].

Nowadays, with the generic availability of statins and their widespread use, the aim of reducing LDL level has been fulfilled. However, the achievement of the second goal, namely, elevating HDL level, seems to be more complicated.

HDL-C-elevating agents. The three main substances proposed to increase HDL level with the aim of reducing cardiovascular morbidity and mortality are niacin, fibrates, and the recently developed CETP inhibitors. Different classes of lipid-modifying agents are presented in Table 2.

A recent study, HPS2-Thrive, has reported that the addition of niacin to statin-based LDL-C-lowering therapy did not significantly reduce the risk of major vascular events, but it did increase the risk of serious adverse events (such as gastrointestinal complications, bleeding, musculoskeletal side effects, or increased incidence of diabetes) [22, 23].

Fibrates have been shown to consistently reduce some cardiovascular outcomes but only in patients with high serum triglyceride levels and low HDL-C level. Fibrates, unlike CETP, increase HDL-C level mostly through the stimulation of apoA-I production [24].

In the class of CETP inhibitors, three agents have been studied: anacetrapib, dalcetrapib, and torcetrapib. Two studies involving the promising torcetrapib were stopped prematurely because of adverse events in the treatment arms, and one study involving dalcetrapib was also discontinued because of futility [25–27]. Although the above CETP

Table 2. Lipid-modifying agents

Pharmacological targets	**Description**
Statins	Reduced cardiac events and all-cause mortality, mostly by lowering LDL cholesterol. The effect on HDL-C is more complicated and less well-investigated.
Niacin	Adding niacin to statin did not significantly reduce the risk of cardiovascular disease and increased the risk of major side-effects (e.g. gastrointestinal, bleeding, musculoskeletal)
Fibrates	Fibrates increase HDL-C level mostly through the stimulation of apolipoprotein A-I production.
CETP inhibitors (anacetrapib, dalcetrapib, and torcetrapib, TA-8995)	Beneficial effects of TA-8995 on lipid profiles in patients with dyslipidaemia, well-tolerated by patients. No evidence of the effectiveness of other agents, or trials discontinued due to adverse events.
PCSK-9 monoclonal antibodies	The FOURNIER study proved that it significantly reduces major vascular events in patients with stable atherosclerotic cardiovascular disease, also patients with prior MI. Patients closer to their most recent MI, with multiple prior MIs or residual multivessel CAD benefit from substantial risk reductions with **evolocumab**.
Evolocumab	**Evolocumab** significantly reduces cardiovascular risk in patients with and without diabetes.
Alirocumab	ODYSSEY OUTCOMES study showed that **alirocumab** reduces the risk of MI and ischemic stroke. Also, it significantly reduces LDL-C and other atherogenic lipid parameters and is generally well tolerated in persons with diabetes and atherosclerotic cardiovascular disease. Both agents are safe and well-tolerated, but high cost and lack of cost-effectiveness limit their routine use.

inhibitors have not been able to prevent clinically important events, a number of clinical trials (such as ACCELERATE and REVEAL) with other CETP inhibitors are still ongoing, and the results are anticipated in the next few years.

The authors of a recent study published in *The Lancet*, TULIP, presented the results for a novel CETP inhibitor called TA-8995. This agent has been shown to have beneficial effects on lipid profile in patients with dyslipidemia and to be well-tolerated by patients. Moreover, it did not cause any serious adverse events [28]. In this randomized, double-blind, placebo-controlled study, HDL-C levels were increased in patients receiving TA-8995, with larger increases correlating with higher doses. Although the authors underlined that further studies were needed to determine the effect of TA-8995 on cardiovascular outcomes, the results are promising.

Although the results of the TULIP study are encouraging, most of the attempts to reduce cardiovascular events or mortality by increasing HDL-C level using those three different classes of drugs on top of statins have been unsuccessful so far [29].

Insight from genetic studies. A large-scale meta-analysis of genome-wide association studies revealed that plasma lipid levels are affected by common genetic variants, which explains from 10%–12% of the total variance and from 25%–30% of genetic variability in plasma lipid phenotypes [30]. This means that although a portion of the genetic contribution to variation in plasma lipids and lipoproteins has been characterized, there is still variance that remains without known assignment [31].

The evidence from a cumulative meta-analysis and replication studies suggests that a more careful examination of the common variants is required, considering the available genetic data. This might help explain the portions of missing heritability, as well as clarify the pathways and mechanisms involved in lipid metabolism and CVD. The authors of a recent article published in the *American Journal of Human Genetics* suspect the possibility of identification of potential loci in which rare single nucleotide polymorphisms (SNPs) with large effects on the phenotype can be discovered [32]. To investigate the causal role of HDL-C and triglycerides in CVD using multiple instrumental variables for Mendelian randomization, Holmes et al. developed weighted allele scores based on SNPs with established associations with HDL-C, LDL-C, and triglycerides. The findings from this analysis (which included over 62,000 participants with 12,000 CVD events) support the causal effect of triglycerides on the risk of CVD, while the involvement of HDL-C has not been confirmed [33].

Should we aim at increasing HDL-C and apoA-I levels? It is still unclear whether an increase in HDL-C and apoA-I level is associated with a reduced risk of cardiovascular events. A recent study by Boekholdt et al. showed that an increase in HDL-C level was not associated with a lower risk of major cardiovascular events, independently of established risk factors. However, the authors reported an association between increased apoA-I level and a reduced risk of major cardiovascular events [34]. These results were consistent with the data reported by the EPIC-Norfolk and Rotterdam Studies, which suggested that the association between changes in HDL-C level caused by lipid-modifying therapy and risk of CHD was mostly explained by established risk factors [35]. Based on combined data from those studies, the change in HDL-C level caused by lipid-modifying therapy was associated with a reduced cardiovascular risk when adjusted for age, gender, and baseline HDL-C level. However, this association was attenuated and was not significant when further adjusted for non-HDL-C (calculated as total cholesterol level minus HDL-C level, as LDL-C and triglyceride level were not measured for all participants during all examination rounds), as well as for smoking history, prevalent diabetes, systolic blood pressure, body mass index, use of antihypertensive medications, previous myocardial infarction, prevalent angina, and previous stroke. These studies provided no evidence to support a significant benefit of increasing HDL-C level, independently of the effect of lowering non-HDL-C.

A systematic review and meta-regression analysis of randomized controlled trials testing lipid-modifying interventions showed that an increase in HDL-C level was not associated with cardiovascular outcomes [36]. The analysis included 108 randomized trials involving 299310 participants at risk of cardiovascular events. There was no association between treatment-induced rise in HDL-C level and risk ratios for CHD-related or total mortality and CHD events. A study performed by Grover et al. showed that the change in HDL-C level was a strong independent risk factor for CV events [37]. In contrast, a recent published meta-analysis showed that a rise in HDL-C level was not associated with a lower risk of major cardiovascular events independent of established risk factors [34]. However, an increase in apoA-I level was associated with cardiovascular risk such that patients with the largest increases had the lowest cardiovascular risk [34]. The authors argued that although these results did not provide evidence for the potential causality of the association between increased apoA-I level and reduced cardiovascular risk, they supported further research into apoA-I-modifying therapies.

In summary, most recent studies have questioned the hypothesis that lipid-modifying therapy should be aimed at increasing HDL-C level. On the other hand, there have been studies showing that an increase in apoA-I level is associated with a reduced cardiovascular risk, independently of established risk factors, which reinforces the rationale for using apoA-I as a target for the treatment of atherosclerosis.

Selected indices of HDL and their superiority over chemical measurement of HDL-C level. Recent studies of drugs that increase HDL-C level, but without reducing the rate of cardiovascular events or progression of atherosclerosis, revealed the limitations of the specific agents tested [38–40]. HDL particles (HDL-P) are quite heterogeneous and because their activity cannot be inferred from the chemically measured plasma HDL-C level, some recent studies have focused on measuring other indices of HDL, such as the function, size, or concentration (number) of HDL-P. It is hypothesized that these indices may be better clinical markers of atheroprotective effects of HDL [41].

A review published in 2011 by Asztalos et al. confirmed that HDL subclasses differ in physical and chemical properties, protein and lipid composition, metabolism, and physiological functions, and, consequently, they have different pathophysiological significance [41]. The results from the large, randomized, double-blind JUPITER trial showed that among patients who did not receive lipid-lowering therapy, HDL-C, apoA-I, and HDL-P level showed

similar inverse associations with CVD [42]. However, among individuals who were treated with rosuvastatin, HDL-P had a stronger and statistically significant inverse association with CVD in comparison with HDL-C or apoA-I level. The authors suggested that HDL-P may be a better marker of residual risk than HDL-C or apoA-I among individuals receiving potent statin therapy to achieve very low LDL-C level. It has also been shown that the association of HDL-C level with CVD is influenced by insulin resistance, abdominal obesity, and inflammation [43]. In contrast, HDL-P appeared to be much less influenced by these factors [44].

So far, only HDL-C has been the standard parameter of HDL measured in clinical practice. However, it may be important to assess also other parameters in clinical trials of HDL-elevating therapies. Considering the results of the recent studies, it seems that HDL-P may be an alternative to HDL-C as a marker of HDL-related cardiovascular risk.

HDL-C efflux capacity. HDL-C exerts numerous antiatherosclerotic effects that are not readily reflected by HDL-C level [45]. The key function of HDL is to promote reverse cholesterol transport from peripheral tissues to the liver, and the critical initial step in this transport is cholesterol efflux from macrophages to HDL [46]. Cholesterol efflux by HDL is also required for lipoprotein signaling in endothelial cells, which underlies the ability of HDL to activate endothelial nitric oxide synthase, promote endothelial repair, and induce angiogenesis [47]. Impaired cholesterol efflux capacity has also been shown to correlate with increased platelet reactivity *in vitro* [48].

Macrophage-specific cholesterol efflux capacity has been directly and causally linked to the prevention of atherosclerosis in animal models [46]; therefore, it has become the focus of recent research as a promising indicator of HDL function with possible antiatherosclerotic effects [49]. Khera et al hypothesized that cholesterol efflux capacity is a determinant of atherosclerotic burden that was independent of HDL-C level [50]. The authors examined the relationship of efflux capacity with HDL-C level and two measures of atherosclerosis, namely, carotid intima-media thickness and angiographically confirmed CHD. They showed that cholesterol efflux was inversely correlated with both measures, independently of HDL-C level. In addition, cholesterol efflux was associated with a higher level of apoA-I, also independently of HDL-C level. Moreover, a recent population-based cohort study involving individuals without CVD at baseline showed that cholesterol efflux capacity was inversely correlated with incident atherosclerotic CVD [51]. This association was also observed after adjustment for traditional cardiovascular risk factors, HDL-C level, and number of HDL-P. Rohatgi et al. suggested that the association of HDL function with cardiovascular risk is explained by processes other than those shown by the HDL-C level, HDL-P concentration, or traditional cardiovascular risk factors [51]. Finally, Hutchins et al. recently reviewed evidence that cholesterol efflux capacity is a strong inverse predictor of incident and prevalent CVD. The authors suggested that impaired macrophage cholesterol efflux to HDL contributes to the risk of CVD [52].

It should be noted that cholesterol efflux from macrophages represents only a small fraction of the overall flux through the reverse-cholesterol-transport pathway. However, this might be the most relevant component in atheroprotection [53].

HDL and type 2 diabetes. In glucose-resistant tissue observed in such conditions as metabolic syndrome, nonenzymatic glycosylation of HDL particles was shown to occur, which was considered as one of the main mechanisms of dysfunctional HDL. This modification significantly impairs the reverse cholesterol transport from peripheral tissues via ABCA1 and ABCG1 transporters. Glycated substrate molecules are also susceptible to oxidation and lose antioxidant properties themselves. In addition, they show a dramatically lower potential to inhibit the release of proinflammatory cytokines (tumour necrosis factor alpha and interleukin 1b) from activated macrophages. Also, the glycosylation process reduces the HDL-mediated activation of lecithin-cholesterol acyltransferase, an enzyme that catalyzes the conversion of cholesterol to cholesteryl ester. It has been shown that without this conversion, mature spherical HDL particles are not formed and excess peripheral tissue cholesterol is less efficiently transported to the liver for excretion from the body [54].

The usual HDL-induced inhibition of endothelial expression of vascular cell adhesion molecule 1 is impaired in patients with type 2 diabetes and CVD [55]. This anti-inflammatory activity of HDL is lost due to favoring the adhesion of macrophages to activated endothelial cells in patients with diabetes [56]. Moreover, it has been shown that the HDL paricle in this group of patients loses its vasorelaxant effects. It has also been confirmed that in this group of patients, HDL has a reduced ability to stimulate endothelial nitric oxide production and endothelial-dependent vasodilation [57].

Interestingly, Riwanto et al showed that HDL in patients with type 2 diabetes with CHD does not inhibit endothelial apoptosis because it fails to activate antiapoptotic proteins, while simultaneously stimulating proapoptotic pathways [58]. Furthermore, a study of diabetic patients showed that cholesterol efflux was positively associated with the total number of HDL-P but not with HDL-C or apoA-I level [59].

HDL and oxidative stress. In some clinical situations, high HDL-C level might be unfavourable. For example, in acute phase response, as seen after surgery, or in inflammation or diabetes, HDL may undergo some changes that affect its quality even though its level remains within the normal range [60–62].

Recent studies have focused on so-called dysfunctional HDL, which is HDL deprived of its primary function as well as atheroprotective and anti-inflammatory actions [63]. The latest observational studies have shown that the antiatherosclerotic effect of normally functioning HDL is frequently impaired in clinical states associated with systemic inflammation [63]. It is hypothesized that common atherosclerotic risk factors, such as dyslipidaemia, diabetes, hypertension, sedentary life style, obesity, cigarette smoking, or unhealthy diet, are all characterized by the presence of systemic inflammation and oxidative stress and may explain why HDL loses its protective features [64]. It has been also suggested that both systemic inflammation and oxidative stress involve the conversion of HDL to a dysfunctional form, which is no longer cardioprotective [50, 65, 66].

The conversion of antiatherogenic HDL molecules to proatherogenic dysfunctional HDL is caused by the loss of activity of antioxidant enzymes, such as paraoxonase-1 (PON-1), and also by chemical modifications of apoproteins and enhancement of acute phase protein response [67].

It has been shown that in such conditions, acute phase proteins are the major protein component of HDL particles, constituting 27% of the whole composition. However, the mechanism underlying this transformation is still unclear, and there are no widely accepted methods for determining HDL function in selected groups of patients. It has been suggested that these transformed HDL particles with reduced antioxidative activity may become a more useful biomarker of cardiovascular risk than the 'old' HDL. The effects of HDL's conversion to its dysfunctional form are presented in Table 3.

Table 3. Effects of HDL-C conversion to its dysfunctional form

Loss of antioxidant activity
Chemical modifications of apoproteins
Enhancement of acute phase proteins

It is believed that antiatherogenic effects of the higher numbers of HDL-P may be related to protein or other cargo (e.g. apoA-I, PON-1, myeloperoxidase [MPO]), rather than to cholesterol cargo of HDL [45]. The main antioxidant protein in HDL is apoA-I, whose role strictly depends on MPO. Recent studies have revealed that deficiency in apoA-I plays a major role in the development of atherosclerotic lesions, and that there is a close relationship between high MPO level and the development of atherosclerotic plaque. High apoA-I level was shown to be associated with a reduced risk of atherosclerotic plaque and inhibition of atherosclerosis [68]. MPO is found in neutrophils and monocytes and plays an important role in killing microorganisms. MPO catalytically consumes nitric oxide *in vitro* and *in vivo* and promotes lipid peroxidation and activation of protease cascades involved in plaque fissuring or rupture. This enzyme also induces the expression of endothelial cell tissue factor, oxidative conversion of LDL, and modification of apoA-I, impairing its ability to promote cholesterol efflux [69]. Finally, circulating MPO level strongly correlates with the degree of endothelial dysfunction [70].

Recent studies have revealed the unfavourable effect of MPO in numerous clinical conditions associated with systemic inflammation and oxidative stress, such as type 2 diabetes [71]. It has been shown that the expression of MPO is markedly enhanced in human atherosclerotic lesions. It binds with apoA-I and modifies HDL-C. When apoA-I is oxidized by MPO, its ability to promote cellular cholesterol efflux by ABCA1 pathway is diminished [66]. In addition, biochemical studies have revealed that oxidation of specific tyrosine and methionine residues in apoA-I contributes to the loss of ABCA1 activity. Therefore, one potential pathway involves oxidative damage of HDL proteins by MPO. A mass spectrometric analysis demonstrated that the levels of 3-chlorotyrosine and 3-nitrotyrosine, two characteristic products of MPO, are elevated in HDL isolated from patients with established CVD. In summary, it may be hypothesize that plasma levels of MPO and its activity are higher in type 2 diabetes patients with CVD than in non-diabetic patients.

There are also other enzymes that can potentially modify HDL proteins. A number of studies have shown that the antioxidant activity of HDL is associated with the levels of PON-1 protein. PON-1 is an enzyme that is synthesized in the liver and is present in HDL particles consisting of apoA-I. PON-1 slows down lipid oxidation and contributes to antioxidant and atheroprotective effects of HDL. Its protective properties result not only from the ability to eliminate potential oxidants but also from the ability to neutralize their final products to nontoxic particles. Recent studies have shown a low level of PON-1 in patients with type 2 diabetes [72]. Rani et al. reported a significant reduction in PON1 activity along with a decrease in HDL-C level in diabetic patients in comparison with non-diabetic individuals. Moreover, the authors stated that the progression of diabetes over the years resulted in a much higher reduction in PON-1 activity, as confirmed by Pearsons' correlation analysis. Thus, they concluded that diabetes, as a condition associated with oxidative stress, leads to a reduction in the antioxidant activity of PON-1. Also, lower serum level of PON-1 has been associated with higher morbidity and mortality related to cardiovascular complications in patients with type 2 diabetes. Taken together, the above findings suggest that PON-1 may be a better predictor of atherosclerotic risk in type 2 diabetes than HDL.

Some recent studies have demonstrated that plasma MPO level has a significant inverse correlation with PON-1 level in patients with stable and unstable angina pectoris, and suggested that the imbalance between pro-oxidants and antioxidants may contribute to the progression of coronary plaque instability [73]. Based on current knowledge, the authors of the current study believe that there may be such a correlation in patients with stable ischemic disease and type 2 diabetes, but this issue requires further studies.

HDL and malondialdehyde. Diabetes mellitus is a condition associated with oxidative stress. Extensive research has shown that an increased production of reactive oxygen species results in tissue injury in such pathological conditions as diabetes or chronic degenerative diseases [74]. Some recent studies have demonstrated that malondialdehyde (MDA) and phospholipid aldehydes can be produced under the condition of oxidative stress and contribute to tissue injury and dysfunction by depleting glutathione, leading to the modification of proteins, lipids, and DNA [74]. Recently, Shao et al. have shown that the exposure to increased concentrations of MDA progressively and dramatically deprived ApoA-I of its ability to promote cholesterol efflux [75, 76]. Moreover, it has been reported that MDA levels are elevated in diseases associated with an increased risk of CVD, such as diabetes [77]. Importantly, immunochemical analyses demonstrated that HDL isolated from atherosclerotic tissue contained higher levels of MDA-modified proteins than HDL originating from the plasma of apparently healthy humans [76]. This suggests that MDA modifies HDL in human atherosclerotic tissue.

HDL and coagulation. Several studies have confirmed the anticoagulant properties of HDL-C, although there have also been studies suggesting that it has pro-coagulant effects [78–80]. This is due to the fact that HDL-C is a very heterogeneous group of particles. ApoA-I, the predominant protein of HDL-C, was shown to have antiatherogenic properties mostly associated with reverse cholesterol transport [81–83]. However apoA-I oxidation could modify its atheroprotective features [78, 84, 85]. On the other hand, apoA-II, the second major HDL particle, has been found to be associated with pro-coagulant effects and progression of atherosclerosis [86–88]. Of note, the EPIC-Norfolk study demonstrated that apoA-II was not associated with coronary

artery disease and its major complication––myocardial infarction. Coagulant properties of HDL-C, and particularly their effects on platelet function, still remain unknown. A few studies showed that HDL particles change platelet signaling pathways by limiting intraplatelet cholesterol overload and inhibiting the production of nitric oxide and prostacyclin [89, 90]. It is still not known whether HDL particles influence the tissue expression on the endothelial surface [78, 91, 92]. Nevertheless, decreased HDL-C level was associated with high platelet reactivity, both in patients with ST-segment elevation myocardial infarction and in those with stable coronary artery disease [93, 94].

Association of HDL with diet and physical activity. The effect of lifestyle interventions, such as the use of diet, on HDL function in patients with type 2 diabetes remains unclear [95]. However, for example, the traditional Mediterranean diet is now widely recommended in the prevention of CVD.

A recent meta-analysis reported that a lifestyle intervention resulted in a significant improvement of risk factors associated with CVD, such as body mass index, haemoglobin A_{1c}, systolic blood pressure, and diastolic blood pressure, in patients with type 2 diabetes. However, HDL-C was not significantly changed by the intervention [96–98]. The described lifestyle intervention included an exercise and diet component and at least one other component such as smoking cessation, behavior modification, or counseling. A further analysis of the data revealed an improvement in HDL and haemoglobin A_{1c} levels only for interventions that included pharmacotherapy [93].

In contrast, a recent multicentre randomized clinical trial, Look AHEAD (Action for Health in Diabetes), showed a significant effect of an intensive lifestyle intervention on HDL-C in comparison with the control group [99]. This association was not shown for other risk factors. The intervention included diet modification and physical activity. In order to increase dietary compliance, a portion-controlled diet was used, with liquid meal replacements provided free of charge and recommendations to use other portion-controlled items. In addition, the authors aimed to encourage the participants to achieve at least 175 minutes of physical activity per week, using activities similar in intensity to brisk walking. Behavioural strategies included self-monitoring. During each of the four years of this study, HDL-C level in the group of patients receiving the lifestyle intervention was approximately 8%–9% higher, compared with baseline levels. The results of another recent study confirmed that encouraging adults with newly diagnosed type 2 diabetes to interrupt prolonged periods of sedentary time with physical activity may be an effective strategy to maintain metabolic health [100]. The study showed that reallocation of 30 minutes of long-bout sedentary time with light physical activity was associated with higher HDL-C level.

To the knowledge of the authors of the presented study, there are only a few studies that analyzed the correlation between diet and apoA-I and apoA-II profiles in patients suffering from CHD and type 2 diabetes. Also, only a few studies have investigated gender-related differences in HDL-C level or apoA-I and apoA-II level in response to diet. Nevertheless, some evidence suggests that women could respond differently to diet compared with men, partly due to sex hormones [101, 102]. In fact, the response of HDL-C to alterations in dietary fats and carbohydrates appears to be greater in women than in men [101]. Another recent study has revealed a more pronounced decrease in apoA-II level in men than in women after introducing an experimental Mediterranean diet [103]. Moreover, the LDL-C to HDL-C ratio was also significantly decreased in men; therefore, the authors suggested that the decrease in apoA-II level in men in response to the Mediterranean diet did not affect the metabolism of plasma lipids and lipoproteins.

The above-results show that further studies are needed to improve our knowledge on the effect of diet and physical activity on HDL-C, apoA-I, and apoA-II level in patients with type 2 diabetes. This might allow the development of more specific nutritional strategies for the prevention of CVD.

CONCLUSIONS

Type 2 diabetes is currently considered a worldwide epidemic; therefore, it is crucial to find an effective therapeutic strategy for this disease. The progress in our knowledge about lipid disorders and their influence on the prognosis of patients with CHD and type 2 diabetes may soon require the development of a new and more specific lipid panel, as the one used in current medical practice may prove insufficient. The standard measurement of HDL-C level may not be enough to reflect its antiatherogenic potential because cardiovascular events have been widely observed in type 2 diabetes patients with normal or even increased HDL-C level. Therefore, the search for new markers with a better prognostic value is needed in this patient group.

The association between dysfunctional HDL and type 2 diabetes is important, both for physicians and for clinical researchers, but to-date the issue has not been fully elucidated. Currently, several studies investigating these relationships are being conducted. The entire March 2015 issue of the *European Heart Journal* focused on lipoproteins and diabetes [104]. The journal's Editor-in-Chief, Thomas Luscher, underlined that despite all the progress that had been made, there were still some unanswered questions concerning the involvement of lipids in CVD. In particular, he mentioned such issues as the management of homozygous autosomal dominant hypercholesterolaemia, the role of HDL-C, and the problem of obesity [105–107]. He also underlined that all attempts to modify HDL-C pharmacologically have failed so far [104].

All the data reviewed above lay the foundation for a new approach to understanding how the functional properties of HDL help reduce the risk of CVD. Therefore, in the light of those findings, there is a need to find a better diagnostic marker than HDL-C level. It is hoped that the elucidation of the mechanisms of oxidative stress and its effects on HDL in type 2 diabetes may take us a step further in the ongoing search for new lipid markers.

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