Would Janus’ view on HDL be useful?

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ABSTRACT

Low-density lipoprotein cholesterol (LDL-C) is generally considered to be pro-atherogenic and high-density lipoprotein cholesterol (HDL-C) to be anti-atherogenic. The clinical approach to the diagnostics and treatment of clinical manifestations of atherosclerosis is the examination of the lipid spectrum. In routine clinical practice, the effects of the HDL class are measured only by determining the concentration of HDL cholesterol. It is questionable whether this clinical approach provides sufficient information to evaluate both the overall cardiovascular risk and the effect of hypolipidemic therapy. Recent studies revealed a shift from large to small HDL particles within the HDL family in the state of atherosclerotic cardiovascular diseases (CVD). This trend of lipoprotein constellation seems to be pathognomonic for dysfunctional lipoprotein profile under pathological state of the cardiovascular system. Thus, the diagnostic and therapeutic approach based on “good” cholesterol concept needs remediing (Fig. 1, Ref. 28). Text in PDF www.elis.sk.

KEY WORDS: HDL, cholesterol, lipoproteins, atherosclerosis.

Introduction

Cardiovascular (CV) system homeostasis is substantially dependent on lipid transport to the tissues provided by lipoproteins. The disturbed interaction between lipoproteins and the vascular wall – especially endothelium, induces atherosclerotic changes. Atherosclerosis as the leading cause of CVD is the crucial cause of mortality in Europe, with 45% of all deaths (accounting for 4 million) and with 1.4 million of these deaths being premature. Coronary heart disease (CHD) represents the major cause of CVD death, with 20% of all deaths (1). Based on clinical and epidemiological studies, it is well known that levels of blood lipids/lipoproteins are closely and independently associated with CVD; low-density lipoprotein (LDL) cholesterol directly and high-density lipoprotein (HDL) cholesterol inversely (2). After long-standing substantial body of evidence HDL cholesterol has started to be labelled as the “good” cholesterol, especially for its ability to dispose cholesterol from blood vessels. Practically the sole surrogate used in clinical praxis for examination of the whole HDL fraction (which encompasses wide lipoprotein spectrum in blood) is the concentration of HDL-C. Most recent evidence reveals controversy in the traditional concept of the “good” HDL cholesterol in the meaning of its ambivalence (3, 4, 5). Even the more distant studies pointed out the importance of HDL subpopulation analysis and have begun to dispute the proclaimed holistic HDL protectiveness (6).

Moreover, the latest US Dietary guidelines – Scientific Report of the 2015 Dietary Guidelines Advisory Committee (7) – bring lightening outcome in relationship with dietary cholesterol. There is no more restriction in cholesterol intake and dietary cholesterol is no more “risk”. Guideline authorities stressed that it is the quality (composition) which plays the key role in the fat/cholesterol intake. Thus, a novel marker for more effective estimation of atherosclerotic CV risk is needed.

HDL cholesterol versus HDL particles

HDL is composed of heterogeneous circulating complexes of (apo)proteins and lipids. These high-density particles contain cholesterol, which represents the main component of the particle and can be chemically measured. On the other hand, HDL-C comprises heterogeneous lipoprotein particles with different size and compositions.

Given that under pathological condition – atherosclerosis, there is observed a shift from larger to smaller HDL particles in the HDL profile (8, 9, 3, 5), this finding supports a hypothesis that the existence of higher amount of smaller HDL particles in atherosclerotic CVD patients is due to the disturbed constellation of the HDL spectrum as a consequence of impaired function of small HDL particles. As an example can be described one mechanism under proinflammatory state when serum amyloid A (SAA), an acute phase protein, interacts with the HDL subpopulation of small particles; circulating SAA substitutes Apo A-I, the main protein component of HDL-mediated reverse cholesterol transport, and incorporated into the lipoprotein membrane produces dysfunctional SAA-rich HDL, with diminished cholesterol efflux capacity. HDL has an anti-inflammatory capability, but under chronic proinflammatory state (obesity, smoking or diabetes) HDL particles are...
trapping and inactivating the constantly generated free radicals in blood circulation (10). By overaccumulation of these substances the whole HDL population is probably becoming dysfunctional what is mirroring in the growth of small HDL levels.

Moreover, there is observed a novel mechanism of interaction between HDL particles and inflammation which involves circulating microparticles (MPs) and microRNAs (miRNAs). A schematic model „HDL on the background of influence of MPs and miRNAs“ is represented by Figure 1 (11–14). As a result of these processes the (dys)functionality of HDL projected into the size of HDL particles can be crucial for the pathophysiological basis of atherogenic dyslipidaemia and cholesterol homeostasis.

**HDL cholesterol and CV risk**

Current guidelines of the European Society of Cardiology/European Association of Cardiovascular Prevention and Rehabilitation (ESC/EACPR) concerning CVD prevention, recommend improvement of blood cholesterol by targeting LDL-C, but not HDL-C. However, achieving the goals for LDL-C even with intensive statin therapy could not prevent many of CV events (15). Measuring the concentration of HDL-C is in daily clinical praxis usually used to evaluate the effect of HDL family/spectrum.

The main roles of high-density lipoprotein fraction are:

- reverse cholesterol transport – CETP (cholesterol ester transfer protein) – from the periphery back to the liver,
- a source of cholesterol for biostructures,
- the esterification of free cholesterol by LCAT (lecithin-cholesterol acyltransferase).

HDL exhibits a variety of properties that act against atherogenesis (16):

- endothelial function enhancement,
- inhibition of formation/effect and incorporation of the oxidized LDL,
- suppression of proinflammatory processes,
- immunomodulatory effects,
- thrombomodulatory function,

and is an important modifier when total CV risk (SCORE system) is calculated. Extended view on these relationship leads to step-by-step uncovering of residual risk as a serious obstacle in the way to further reduction of atherosclerotic impairment in the adult population. Even more, awareness of pre-existence of pro-atherogenic state in clinically healthy subjects (atherogenic dyslipidaemia and cholesterol homeostasis).

The relationship between the HDL family and atherosclerotic disease seems to be more complex as usually is accepted in clinical praxis. The Framingham study disputed already in 1977 the predictive value of the relationship between HDL cholesterol and the risk of CHD. It was for the first time when a large study identified a wide diversity of lipoprotein populations (20). It may be assumed that low HDL is a part of residual risk. On the other hand, the latest evidence showed that the current HDL-C modifying approaches (concentration increase) did not reduce CVD mortality despite observational studies suggested they did. A finding that HDL-C is not always associated with CV events is emerging, and even, under type 2 diabetes condition a higher HDL cholesterol level at baseline was associated with a higher risk of CV events and all-cause mortality (21, 22). The impaired HDL population on the background of atherosclerosis seems to play an important role in residual risk. The role of HDL in the pathogenesis of CVD arises when it comes to disturbance in the complex of structural-functional relationship inside the HDL fraction; potentiating endothelial dysfunction and consecutive residual risk.

**Clinical approach to HDL cholesterol**

The latest evidence did not confirm decrease in CVD risk by HDL cholesterol level-improving interventions in spite of existence of the independent negative correlation between HDL-C level and prevalence of CVD (23). Thus, the CVD causality for HDL-C was not proven. On the other hand, there are already available data, that inhibition of inflammation, without affecting cholesterol levels, improve CV outcome by atheroprotection (24). Anti-inflammatory therapy with canakinumab showed similar effect to monoclonal antibodies targeting proprotein convertase subtilisin-kexin type 9 on prevention of cardiovascular events.

Recent studies with high-density lipoproteins and their subfractions in relation to atherosclerotic CVD aiming the shift of understanding the “good” cholesterol as HDL cholesterol concentration to HDL properties and another component than contained cholesterol (25, 3, 5, 8, 9). The subfraction-analysis diagnostic method allows examination of the CV risk beyond the common blood cholesterol testing. Separation of HDL subpopulations under pathological state has revealed a characteristic shift toward small HDL particles (5, 9, 25). Significantly higher amount of
small HDL particles and their disturbed correlation within HDL fraction supports the concept of dysfunctional lipoproteins and their subfractions.

The analysis of HDL subpopulations provides more comprehensive insight into the conventional measuring and interpretation of HDL cholesterol as an independent risk variable. In the last few years, much more information on the role of HDL has become available and an increasing number of studies have found direct association between small HDL and atherosclerotic impairment. Nowadays we are on a crossroad where it is inevitable to reconsider the traditional role of lipoproteins in the concept of atherosclerosis. It is becoming known that not just the amount of the lipid fraction, but its composition is what matters.

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The estimation of HDL subfractions can give the clinician further information about CVD risk state and thus better calculate global CV risk. Future studies on the current topic are therefore required in order to elucidate ways how to influence the high-density lipoprotein composition rather than to raise the HDL-C spectrum en block. Whether the small HDL particles are markers of atherogenesis or play a direct role in atherogenic process a further research will clarify.

The lipoprotein subpopulation-testing provides advantageous HDL analysis in the setting of (sub)clinical atherosclerotic impairment and thus can bring actual contribution to routine clinical praxis. The clinical use of advanced lipoprotein subfraction capabilities carries additional benefits in blood cholesterol analysis and subsequent atherosclerotic CVD risk prediction with tailored primary and secondary interventions.

Reduced levels of HDL-C are usually of secondary origin, caused by smoking, abdominal obesity (as a consequence of energy dysbalance), hypertriglyceridemia and insulin resistance. Smoking cessation, regular exercise, body weight control and healthy diet improve both HDL cholesterol levels and HDL constellation with positive effect on CV outcomes (26 – 28, 7). HDL-C-neutral diet contains ω-3 polyunsaturated fatty acids, monounsaturated fatty acids, saturated fatty acids. HDL-C is lowered by trans-forms of fatty acids (partially hydrogenated vegetable oils), refined carbohydrates and by ω-6 polyunsaturated fatty acids.

Conclusion

The concept of dysfunctional HDL, which is linked with lipoprotein particle size underlines the importance of a new approach in dyslipidaemia diagnosis and treatment: the analysis of HDL subfractions appear to be a better predictor of atherosclerotic burden and CVD. Non-pharmacological intervention to improve the HDL population, such as life style and risk factor modification, is a reasonable strategy in the paradigm of a CVD continuum. The direction of lipoprotein constellation (increasing of the concentration of small HDL particles) seems to be pathognomonic for dysfunctional lipoprotein profile under pathological state, when HDL cholesterol is generated by the number of HDL particles instead of the HDL particles size and cholesterol mass.

References


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