Epidemiology: Disease Associations and Modulators of HDL-Related Biomarkers

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Contents

Abstract

Epidemiological studies have shown an inverse association between high-density lipoprotein cholesterol (HDL-C) levels and risk of ischemic heart disease. In addition, a low level of HDL-C has been shown to be a risk factor for other diseases not related to atherosclerosis. However, recent studies have not

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supported a causal effect of HDL-C in the development of atherosclerosis. Furthermore, new drugs markedly elevating HDL-C levels have been disappointing with respect to clinical endpoints. Earlier, most studies have focused almost exclusively on the total HDL-C without regard to the chemical composition or multiple subclasses of HDL particles. Recently, there have been efforts to dissect the HDL fraction into as many well-defined subfractions and individual molecules of HDL particles as possible. On the other hand, the focus is shifting from the structure and composition to the function of HDL particles. Biomarkers and mechanisms that could potentially explain the beneficial characteristics of HDL particles unrelated to their cholesterol content have been sought with sophisticated methods such as proteomics, lipidomics, metabonomics, and function studies including efflux capacity. These new approaches have been used in order to resolve the complex effects of diseases, conditions, environmental factors, and genes in relation to the protective role of HDL but high-throughput methods are still needed for large-scale epidemiological studies.

Keywords
High-density lipoproteins • Cholesterol • Atherosclerosis • Coronary heart disease • Apolipoproteins • Cholesterol efflux • Diabetes • Obesity • Cancer • Proteomics • Lipidomics • Metabonomics

Abbreviations

ApoA-I	Apolipoprotein A-I
ApoA-II	Apolipoprotein A-II
ApoC-III	Apolipoprotein C-III
CHD	Coronary heart disease
CETP	Cholesteryl ester transfer protein
CVD	Cardiovascular disease
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
GI	Glycemic index
GL	Glycemic load
HDL	High-density lipoproteins
HDL-C	High-density lipoprotein cholesterol
HDL2	High-density lipoprotein fraction 2
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
NMR	Nuclear magnetic resonance
PON1	Paraoxonase 1
S1P	Sphingosine-1-phosphate
T2DM	Type 2 diabetes mellitus

Low levels of high-density lipoprotein (HDL) particles in the plasma of patients with coronary heart disease (CHD) were observed already in the early 1950s (Barr et al. 1951; Nikkilä 1953). At that time the lipoprotein fraction was called alpha lipoprotein as electrophoresis methods were used. Twenty years later the same relationship was confirmed in large epidemiological studies using ultracentrifugation or precipitation methods. The new interest for HDL research was then stimulated by the reverse cholesterol transport hypothesis (Glomset et al. 1966) and a Lancet review written by Miller and Miller (1975). These authors proposed that low plasma HDL concentration accelerates the development of atherosclerosis by impairing the clearance of cholesterol from the arterial wall.

1 Protective Role of HDL: Evidence from Epidemiological Studies

The protective role of HDL has been well established in several epidemiological studies. An increment of 2.5 % corresponding to 1 mg/dl or 0.04 mmol/l is associated with a 2 and 3 % reduction in CHD risk in men and women, respectively (Gordon et al. 1989; Jacobs et al. 1990). So far, it is mainly the total cholesterol concentration in HDL particles that has been determined using standardized methods applicable also to routine clinical work. However, cholesterol represents only a small fraction, approximately 15 %, of the HDL particle mass. Furthermore, the proportion of free cholesterol to esterified cholesterol varies between lipoprotein particles.

The relationship between HDL-C and CHD is complex and HDL-C may not be an appropriate indicator of the impact of this lipoprotein fraction on cardiovascular risk. This has been demonstrated, e.g., by the fact that carotid intima media thickness is not increased in apoA-I(Milano) mutation carriers with very low levels of HDL-C (Sirtori et al. 2001). Moreover, recently, drugs that increase HDL cholesterol (HDL-C) level have failed to reduce cardiovascular risk, and Mendelian randomization studies have failed to show a causal relationship between HDL-C and cardiovascular diseases (van Capelleveen et al. 2013).

Despite this controversy, the hard evidence for low HDL-C level as a risk factor of atherosclerosis will be described in the first part of this presentation. It is noteworthy that the cholesterol concentration in HDL fraction is not necessarily associated with the antiatherogenic properties of HDL. Therefore, later in this chapter, other potential HDL-related biomarkers for the prevention of atherosclerosis by HDL will be presented. These include not only the other major lipid and apolipoprotein components of HDL but also minor bioactive lipid molecules residing in the HDL particles. Furthermore, the physicochemical characteristics of various subfractions of HDL as well as the large number of molecules circulating more or less firmly bound to HDL particles may contribute to the antiatherogenic potential of HDL via antioxidative and anti-inflammatory effects or cholesterol transport capacity.

2 HDL Cholesterol as a Risk Factor for Atherosclerosis and Its Complications

Until recently, the clinical evaluation of HDL as a risk factor has focused almost exclusively on the total HDL-C without regard to the chemical composition or multiple subclasses of HDL particles. A large body of epidemiological research has shown a solid inverse and independent relationship between HDL-C and the risk of cardiovascular disease (Toth et al. 2013).

Gofman et al. first reported an inverse association between HDL-C levels and the risk of ischemic heart disease (Gofman et al. 1966). This was shown in case–control studies from Framingham and Livermore cohorts with 10–12 years of follow-up. Later, the inverse relationship has been observed also in several larger studies in the USA (the Honolulu Heart Program, Rhoads et al. 1976, and the Framingham Heart Study, Gordon et al. 1977), in Norway (the Tromsø Heart Study, Miller et al. 1977), in Germany (the Prospective Cardiovascular Münster Study, Assmann et al. 1996), and in Israel (the Israeli Ischemic Heart Disease Study, Goldbourt et al. 1997). Recent meta-analyses have corroborated the relationship between HDL-C and atherosclerosis and its complications (Chirovsky et al. 2009; Boekholdt et al. 2013; Touboul et al. 2014). The association is independent of triglyceride levels and other risk factors (Goldbourt et al. 1997). Many CHD risk algorithms have included HDL-C as a factor to improve the prediction of CHD events (Cooper et al. 2005; Halcox et al. 2013; Hippisley-Cox et al. 2013; Tehrani et al. 2013).

Recently, the picture has become less clear. Mendelian randomization studies have not supported a causal effect of HDL-C in the atherosclerotic disease process (Voight et al. 2012; Holmes et al. 2014). Moreover, statin trials have shown that HDL-C is predictive among patients treated with statin even at low LDL levels (Barter et al. 2007), whereas it is not predictive among patients taking placebo (Ridker et al. 2010; Mora et al. 2012). Further research is needed to clarify the role of HDL-C as a risk factor. It is possible that other characteristics of HDL particles may be more important in this respect than the total cholesterol concentration.

In patients with CHD, the protective role of HDL-C is controversial (Silbernagel et al. 2013). Some studies have shown that low HDL-C is associated with atherosclerotic progression in myocardial infarction survivors (Johansson et al. 1991; Duffy et al. 2012; Liosis et al. 2013), provides additional prognostic value also in patients with acute coronary syndrome (Correia et al. 2009), and reduces the risk after coronary interventions (Sattler et al. 2009), whereas some studies have shown that HDL-C has no protective role in the secondary prevention of CHD after bypass operation (Angeloni et al. 2013).

3 HDL Cholesterol as a Risk Factor for Other Diseases

The low level of HDL-C has been shown to be a risk factor for other diseases not related to atherosclerosis. Recent reports have shown that HDL-C may be a biomarker for diseases like psoriasis (Holzer et al. 2012), rheumatoid arthritis

(Raterman et al. 2013), and liver fibrosis in hepatitis C patients (Gangadharan et al. 2012). Alterations in HDL composition have been observed also in hemodialysis patients (Mangé et al. 2012).

Special interest has been recently focused on HDL in cancer patients. Several epidemiological studies have shown that low HDL-C level may be a risk and/or prognostic factor of biliary tract cancers (Andreotti et al. 2008), prostate cancer (Mondul et al. 2011; Kotani et al. 2013), colon cancer (van Duijnhoven et al. 2011), breast cancer (Furberg et al. 2005, Melvin et al. 2012) and gastric cancer (Tamura et al. 2012), but not that of endometrial cancer (Cust et al. 2007; Esposito et al. 2014) or rectal cancer (van Duijnhoven et al. 2011). Confounding factors related to obesity and metabolic syndrome may be more strongly associated with the latter cancer types (Kotani et al. 2013).

The association with low HDL-C levels is shared among many types of cancer, and it is mainly linked to obesity and inflammation, suggesting a common pathway (Melvin et al. 2013; Vílchez et al. 2014). The mechanism of cancer protection is not known. Lipoprotein particles may carry cancerogenic molecules but at least one small study has shown that persistent organogenic pollutants in HDL particles are more associated with CVD than cancer (Ljunggren et al. 2014).

The potential importance of HDL particles in cancer protection has recently led to attempts to develop cancer treatments by HDL-mimetic synthetic nanoparticles (Zheng et al. 2013; Yang et al. 2013). These interesting approaches need to be followed closely in the future.

4 Total HDL-C in Various Populations

Racial differences. Several studies have shown differences in HDL-C between various ethnic groups (Thelle et al. 1982; Heiss et al. 1984; Haffner et al. 1986; Saha 1987). The differences may in part be due to genetic factors but the role of behavioral and anthropometric variables seem to affect the HDL-C (Thelle et al. 1982; Haffner et al. 1986). Environmental factors such as diet, smoking, and alcohol use may confound the differences observed between ethnic groups.

In the USA, the African-American population has higher HDL-C than Caucasians after adjustment for weight, smoking, and alcohol consumption than Caucasians (Heiss et al. 1984), while people originating from India have lower HDL-C than Europeans or many other populations (Saha 1987; de Munter et al. 2011). Differences in HDL-C and other lipoproteins between various ethnic groups can be observed already in children (van Vliet et al. 2011). Even at an early age, the HDL-C levels are confounded by other cardiovascular risk factors including blood pressure, overweight, and obesity.

Gender differences. Women have higher HDL-C levels than men (Heiss et al. 1980; Seidell et al. 1991), and significantly increased CHD risk is defined at levels below 50 mg/dl (1.29 mmol/l) and 40 mg/dl (1.03 mmol/l), respectively. The reason for the gender difference may mainly be sex hormones but the fat distribution seems to play a central role since adjustment for waist/thigh ratio almost totally removed the gender difference in HDL cholesterol (Seidell et al. 1991). In women HDL-C levels decline after menopause (Heiss et al. 1980) but the sex difference remains significant even in the seventh decade of life (Ostlund et al. 1990).

Age-related differences. Lipoprotein levels are very low at birth and then increase during childhood. HDL-C levels decrease in males during puberty and early adulthood and thereafter remain lower than those in women (Kreisberg and Kasim 1987; Walter 2009). HDL-C levels decline with age and low HDL cholesterol remains a powerful risk predictor into old age (Kreisberg and Kasim 1987; Walter 2009). A selection bias by HDL-lowering genetic variation may explain why HDL deficiency is rare among very old people (Kervinen et al. 1994; Baggio et al. 1998).

5 Total HDL-C Modulated by Environmental Factors

Alcohol consumption in moderation is associated with a reduced risk for cardiovascular diseases. Alcohol consumption increases the concentration of HDL-C, possibly secondary to an inhibition of CETP (cholesteryl ester transfer protein) (Savolainen et al. 1990; Hannuksela et al. 1992). A common polymorphism in the CETP gene (TaqIB2) modifies the relationship of alcohol intake with HDL-C suggesting a gene-environment interaction on the risk of CHD (Jensen et al. 2008). However, it has not been definitely shown whether the HDL-C elevation associated with alcohol consumption is cardioprotective.

The quantity of alcohol needed to increase HDL-C by 0.1 mmol/l (3.87 mg/dl) is about 30 g/d (Brien et al. 2011). Therefore, alcohol drinking cannot be recommended as a method to raise low HDL-C levels. The alcohol-induced increase in HDL-C occurs commonly without significant changes in other lipids although alcohol may increase triglyceride levels especially in subjects with elevated triglyceride concentration.

The death rate from CHD among moderate alcohol users is lower than in total abstainers or heavy drinkers (Rimm et al. 1999; Brien et al. 2011; Bergmann et al. 2013). Even very low alcohol consumption, e.g., a couple of drinks per week, seems to protect from CHD even though it does not have any significant effect on HDL-C. To explain this fact, it has been suggested that ethanol metabolism may produce specific bioactive lipids, e.g., phosphatidylethanol, that could serve as a memory molecule in the body (Liisanantti et al. 2004). If HDL particles of alcohol drinkers contain this bioactive lipid, it could circulate for several days even without daily alcohol drinking, and when HDL enters into the endothelial cell, it could then exert its positive effects on the vascular endothelium (Liisanantti and Savolainen 2005). However, the concentration of phosphatidylethanol in HDL may be in the low nanomolar range which makes the analysis challenging and may hamper its determination of epidemiological studies.

Smoking reduces HDL-C level and smoking cessation is associated with an increase in the plasma concentration of HDL-C (Maeda et al. 2003). The mechanism by which smoking reduces HDL-C is not known. It is noteworthy that in many cases smoking is associated with alcohol drinking and therefore smoking could attenuate the alcohol-induced increase in HDL-C.

Physical activity is associated with high HDL-C (Marti 1991). Low level of physical activity is very common in the developed countries, and therefore, increasing the level of exercise might be more beneficial for HDL-C than any other preventive measure.

Education and socioeconomic status. HDL-C levels increase with income and educational attainment after controlling diet, exercise, and other risk factors for elevated cholesterol (Muennig et al. 2007). The mechanisms are not clear. It has been suggested that stress differences by social class may play a role (Muennig et al. 2007). However, several lifestyle factors including leisure-time physical activity, smoking, alcohol drinking, and dietary habits correlate with the socioeconomic status, classified as the degree of educational level (Schröder et al. 2004).

Dietary carbohydrates affect the lipoprotein profile. The epidemiological studies can be divided into three categories. First, the type of carbohydrate modulates the impact of carbohydrates on plasma lipoproteins. The intake of refined carbohydrates has increased in Western societies, and they have more deleterious effects on abdominal obesity and consequently on insulin resistance and hepatic lipogenesis in comparison with complex carbohydrates or starches (Ma et al. 2012; Stanhope et al. 2009). The end result of high intake of refined carbohydrates is a low HDL-C level (Heiss et al. 1980; Sonestedt et al. 2012).

Second, trials focusing on dietary carbohydrate restriction have shown modulation of atherogenic dyslipidemia. The effect on HDL-C is modest but commonly greater than that on total cholesterol, and thus, the atherogenic burden is improved. Results from epidemiological studies are difficult to interpret due to differences in diets.

The third type of studies involves the replacement of carbohydrate with different fats in order to maintain isocaloric intake of macronutrients. A classic meta-analysis of 60 trials (Mensink et al. 2003) showed that replacement of 10 % of energy from carbohydrate with saturated fat, monounsaturated fat, and polyunsaturated fat increased HDL-C by 4.7, 3.4, and 2.8 mg/dl (0.12, 0.09, and 0.07 mmol/l), respectively. However, LDL cholesterol increased by 13 mg/dl (0.34 mmol/l) with saturated fat substitution and decreased by 3.3 mg/dl (0.09 mmol/l) with polyunsaturated fat substitution while the substitution with monounsaturated fat had no effect on LDL-C. Thus, the atherogenicity of the plasma lipoprotein profile improved with the unsaturated fat substitution of carbohydrate.

The effects of dietary carbohydrates on HDL-C and CHD risk have been analyzed also on the basis of their glycemic index (GI, the effect on blood glucose level) or glycemic load (GL, including carbohydrate content and intake of foods in addition to GI). High GL and GI were associated with significant increased risk of CVDs, specifically for women. Several cross-sectional studies have reported inverse associations of low GI and GL diets with HDL-C, but meta-analyses (Kelly et al. 2004; Goff et al. 2013) have not found any effect on HDL-C.

Fatty acids and especially omega-3 fatty acids have been the focus of many epidemiological studies. The most important omega-3 fatty acids in this respect are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that increase HDL-C by 1–3 % (Balk et al. 2006).

6 HDL-C in Diseases and Conditions

Type 2 diabetes. Patients with type 2 diabetes may have various types of dyslipidemias that usually are accompanied with a low concentration of HDL-C (Chehade et al. 2013; Morgantini et al. 2014). Low HDL-C contributes to diabetes-related CHD risk more in women than in men, the diabetes-related hazard ratio for a major CHD event being 3 times higher in women after adjustment for other cardiovascular risk factors (Juutilainen et al. 2004). On the other hand, lipid composition of HDL particles is associated with the development of metabolic syndrome (Abbasi et al. 2013; Onat et al. 2013).

Dyslipidemias. Traditionally, dyslipidemia has been characterized by an elevation in plasma triglycerides and total or LDL cholesterol and reduction in HDL-C. This is commonly referred to as the atherogenic triad. LDL particles are small and dense (Mooradian 2009). Genetic studies have indicated linkage of apoB gene to peak LDL size and plasma triglycerides, HDL-C, and apoB levels.

Obesity. Overweight and obese subjects usually have low HDL-C concentrations (Seidell et al. 1991). The underlying cause may be insulin resistance that promotes free fatty acid flux to the liver, stimulates hepatic lipogenesis, and finally enhances the secretion of triglyceride-rich apoB-containing lipoproteins from the liver. The excess triglyceride-rich particles also enhance the CETP-mediated exchange of cholesteryl esters from HDL to apoB-containing lipoprotein particles and simultaneous transfer of triglycerides into HDL (Mann et al. 1991; Liinamaa et al. 1997). This may further reduce HDL-C levels.

Weight reduction is an important modulator of the lipoprotein profile and long-term weight reduction increases HDL-C levels especially in subjects with type 2 diabetes. It is noteworthy that the effect of weight reduction on HDL-C is different in the initial weight loss period compared with the weight maintenance phase. A meta-analysis has shown that HDL-C is increased by 0.35 mg/dl (0.009 mmol/l) per kilogram weight lost during the stable weight reduction. During active weight loss, however, HDL-C is reduced by 0.27 mg/dl (0.007 mmol/l) for every kilogram of weight lost (Browning et al. 2011). Theoretically, an increase in HDL-C of 2.45 mg/dl (0.06 mmol/l) could be expected during the stable weight maintenance stage after a weight reduction of 7 % in an individual with an initial weight of 100 kg. Furthermore, this would translate into 7.4 % reduction in CHD risk in women.

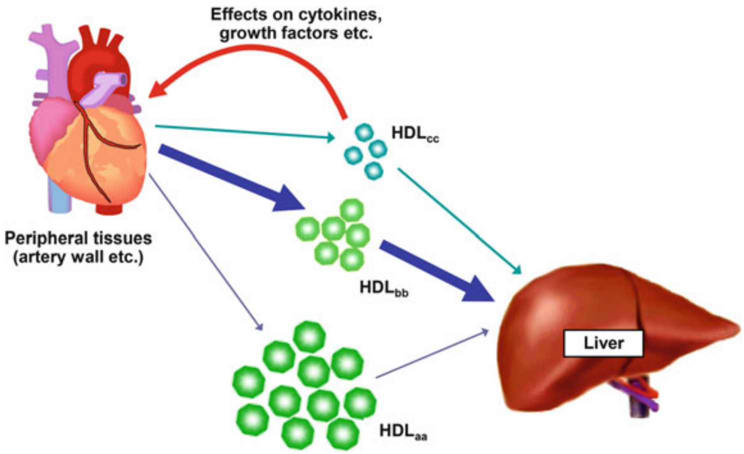

Fig. 1 Potential differences in the functions of HDL particles. HDL_{aa} depicts a theoretical subclass of particles comprising the bulk of plasma HDL-C concentration but without any significant role in reverse cholesterol transport or pleiotropic effects of HDL, whereas HDL_{bb} may be a smaller fraction but more active in reverse cholesterol transport. HDL_{cc} could be a small subclass without any significant contribution to the HDL-C quantity. These particles may, however, have many pleiotropic effects on cytokines, growth factors, etc. [Modified from Hannuksela et al. (2004)]

7 High HDL Levels Do Not Add to the Protection

While low levels of HDL-C are associated with increased CHD risk, high HDL-C levels are not uniformly atheroprotective. At higher concentrations the curve of CHD risk gradually tapers off as depicted in Fig. 1 which is based on the results from the Framingham Heart Study (Gordon et al. 1977), and there is no additional effect of higher HDL-C levels compared with average HDL-C concentrations.

8 Effect of HDL on Stroke

In contrast to the role of HDL-C as a major risk factor of CHD, the role of HDL-C in the pathogenesis of ischemic stroke is less clear. Epidemiological studies of carotid intima media thickness and stroke protection have provided conflicting results. Even in the studies reporting positive results, the effect of HDL-C on protection of stroke is modest (a 10 mg/dl or 0.38 mmol/l increase in HDL-C reduces stroke risk by 11–15 %) compared with its protective effect on CHD. The discordant results in prospective cohort studies as well as in case-control studies may be due to the heterogeneity of stroke, since dyslipidemia including low HDL-C levels may not be involved in the pathogenesis of some subtypes such as lacunar and cardioembolic strokes (Amarenco et al. 2008).

9 Time Trends in Total HDL-C

During the last decades, favorable trends in HDL-C levels have occurred in US adults and youths aged 6–19 years despite changes in physical activity, obesity, and diabetes (Carroll et al. 2012; Kit et al. 2012). Similar trends have been observed also in Europe and India (Muntoni et al. 2009; Gupta et al. 2012).

10 Are There Other Biomarkers than the Total HDL-C?

The cholesterol in HDL (i.e., HDL-C) may reflect the rate of reverse cholesterol transport from the peripheral tissues to liver. However, it may be that the bulk of HDL cholesterol does not necessarily represent the particles that are involved in the reverse cholesterol transport or any other potentially antiatherogenic activity of HDL (Fig. 1).

HDL particles comprise a heterogeneous fraction of lipoprotein which vary by the apolipoprotein and lipid content and consequently also in density, shape, size, and charge. Various subfractions can be analyzed, e.g., by ultracentrifugation (density), electron microscopy (shape), nondenaturing gel electrophoresis, gel filtration or nuclear magnetic resonance (NMR) spectroscopy (size), NMR or immunoaffinity (composition), and 2-dimensional electrophoresis (charge).

11 HDL Fractions

Analytic ultracentrifugation was first used to separate subclasses of HDL (DeLalla et al. 1954). Later, the sequential ultracentrifugation and various precipitation methods enabled the analysis of larger series in epidemiological studies.

Sequential ultracentrifugation methods have enabled separation of two major HDL subfractions, namely, HDL2 and HDL3, while the isolation of further subclasses has required more tedious methods such as gradient ultracentrifugation. Nuclear magnetic resonance (NMR) spectroscopy has simplified the differentiation into five subclasses. However, the nomenclature has varied and it is generally quite difficult to compare HDL subclasses separated by different methods. Recently, a unified nomenclature for a simplified differentiation into 5 subclasses according to particle size (very small, small, medium, large, and very large HDL) has been proposed (Rosenson et al. 2011).

Controversial results have been obtained in studies aimed at distinguishing cardiovascular differences between HDL subclasses separated by density (Superko et al. 2012; Pirillo et al. 2013). A majority of the studies, however, have found HDL2-C to be more predictive of CHD risk than total HDL-C or HDL3-C (Johansson et al. 1991; Drexel et al. 1992; Lamarche et al. 1997). A recent study with 29-year follow-up of the Gofman’s Livermore cohort showed that HDL2 and HDL3 are independently related to CHD risk (Williams and Feldman 2011).

12 HDL Particle Size

Further characterization of HDL subfractions by nondenaturing polyacrylamide gels has identified three HDL3 and two HDL2 subclasses. Very large HDL particles (HDL2b subfraction with diameter between 9.7 and 12.9 nm) are strongly correlated with the total HDL-C concentration and most strongly inversely related to CHD risk in normotriglyceridemic subjects (Johansson et al. 1991). On the other hand, an increased concentration small HDL particles (HDL3b subfraction, 7.8–8.2 nm) is associated with an atherogenic lipoprotein profile characterized by low HDL2b levels, high plasma triglyceride concentration, and increased level of small, dense LDL particles (Berneis and Krauss 2002). Low concentration of HDL2b subclass has also been shown in patients with T2DM (Xian et al. 2009).

13 HDL Particle Number

The complexity of HDL metabolism leads to the formation of multiple HDL subpopulations with varying density, size, charge, and chemical composition. Two individuals with the same HDL-C concentration may have HDL particles of different size distribution, and consequently, the particle number is different. Recently, NMR methods have enabled high-throughput determination of HDL particle concentration. Plasma levels of large particles and low particle number are consistently associated with low CHD prevalence (Mora et al. 2012).

14 HDL Lipids

Some of the effects of HDL on cellular functions are mediated by sphingomyelin-1-phosphate (S1P) that is a bioactive lipid in HDL. Alterations in S1P content in HDL particles could explain the dysfunction of HDL since the HDL-associated S1P seems to be responsible for many of the pleiotropic effects of HDL by activating special S1P receptors. In epidemiological studies low levels of S1P in HDL has been associated with coronary heart disease (Argraves et al. 2011). Sphingomyelin content in HDL particles has been associated with coronary heart disease in postmenopausal women (Horter et al. 2002). Sphingomyelin has also been associated with kidney disease in patients with type 1 diabetes (Mäkinen et al. 2012).

15 HDL Apolipoproteins

The structure of HDL particles is very complex, apoA-I and apoA-II being the major protein components. ApoA-I accounts for about two-thirds of the protein content of HDL and is also functionally important since it is the acceptor in the efflux of phospholipids and free cholesterol from peripheral cells. The measurement of apolipoprotein levels is more expensive and time-consuming than that of lipid concentrations. To circumvent this, data from large epidemiological cohorts was recently used for the development of computer software that enables accurate estimation of apolipoprotein levels on the basis of lipid measurements (Raitakari et al. 2013).

High plasma levels of apoA-I are protective against atherosclerosis in some studies (Arsenault et al. 2011; Emerging Risk Factor Collaboration 2012). It has been proposed that apoA-I concentration could even be a better predictor of atherosclerosis development than HDL-C. A recent study reported that adjustment for apoA-I changes the direction of the association between HDL-C and the severity of atherosclerotic lesions as determined with coronary artery calcium score (Sung et al. 2013). Among patients treated with statin therapy, apoA-I levels are strongly associated with a reduced cardiovascular risk, even among those achieving very low LDL-C level (Boekholdt et al. 2013).

ApoA-II is the second major apolipoprotein in HDL particles. It is present in most but not all particles and the clinical significance of apoA-II-containing and apoA-II-free particles is controversial (Rosenson et al. 2011).

Some studies have reported enrichment with apoC-III in the HDL of patients with CHD (Vaisar et al. 2010; Kavo et al. 2012; Jensen et al. 2012). Interestingly, Jensen and coworkers found that HDL particles without apoC-III were inversely associated with the risk of CHD while apoC-III-containing HDL particles were directly associated with increased risk of CHD (Jensen et al. 2012). HDL with apoC-III comprised about 13 % of the total HDL-C.

16 HDL Proteomics

Several proteins circulate attached to HDL particles although most of them in much lower numbers than apolipoproteins mentioned above. The protein content of HDL particles has been characterized recently using various methods commonly described as proteomics. It has been shown that HDL2 fraction of CHD patients carries a distinct protein cargo (Vaisar et al. 2010; Gordon et al. 2010; Kavo et al. 2012; Alwaili et al. 2012).

Proteomics as a new promising approach for detecting biomarkers and mechanisms could potentially explain the beneficial characteristics of HDL particles unrelated to their cholesterol content. To this end, novel sophisticated methods have been recently developed (Gordon et al. 2010; Mazur et al. 2010;

Burillo et al. 2013; Hoofnagle et al. 2012; Mazur and Cardasis 2013; Riwanto et al. 2013). High-throughput methods are urgently needed for large-scale epidemiological studies.

17 HDL Function

Cholesterol efflux is the first step of reverse cholesterol transport. Excess cellular cholesterol from peripheral tissues is effluxed to extracellular HDL-based acceptor particles through the action of active transporters and passive diffusion. Recently, it was reported that the cholesterol efflux measured from cultured macrophages enriched with free cholesterol to apoB-depleted serum as cholesterol acceptor was inversely associated with the history of CHD independent of HDL-C levels (Khera et al. 2011). However, more recently, enhanced efflux has been associated with high cardiovascular risk (Li et al. 2013). Further studies are urgently needed to resolve the issue with conflicting results.

Antioxidative properties of HDL are mainly attributed to apoA-I although paraoxonase 1 (PON1) may also play an important role. Antioxidative activity of HDL subfractions increases with increment in density as follows: $HDL_{2b} < HDL_{2a} < HDL_{3a} < HDL_{3b} < HDL_{3c}$ (Kontush et al. 2003). The determination of the antioxidative capacity of HDL particles is technically challenging, and therefore, indirect approaches measuring arylesterase or paraoxonase activities have been used in larger cohorts.

Molecules carried by HDL particles. Recent studies have shown that short noncoding RNAs (microRNAs, miRNAs) are present in the circulation as a result of cellular damage or secretion (Laterza et al. 2009). miRNAs are ideal biomarkers since they are stable and their sequences can be easily amplified. Alterations in circulating miRNA profiles have been associated with cardiovascular risk factors such as hypertension, diabetes, and dyslipidemias as well as with cardiovascular diseases such as coronary heart disease, myocardial infarction, and heart failure (Fichtlscherer et al. 2011; de Rosa et al. 2011). However, this association has not been found in all studies (Wagner et al. 2013).

Several proteins are also attached to HDL particles. Paraoxonase 1 (PON1) is an HDL-associated enzyme that has been suggested to mediate many antiatherogenic and cardioprotective effects of HDL particles (Mackness et al. 2004; Aviram and Vaya 2013).

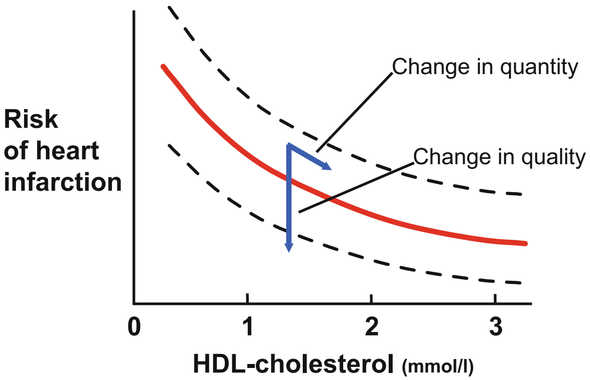

Fig. 2 Relation between HDL-C and risk of myocardial infarction. The *solid curve* shows the average risk level by HDL-C concentration. The risk of individuals, however, may vary substantially, and even at the same HDL-C level, the CHD risk could be anywhere between the *dotted lines*. Furthermore, the nearly *horizontal arrow* depicts how previous approaches have attempted to improve the atheroprotective capacity of HDL by increasing the quantity of HDL-C. Nowadays, several studies have suggested that it might be more important to change the quality of HDL particles as shown by the *arrow* down. Various biomarkers and function assays have been commonly used to determine the improved quality that ultimately could lead to lower risk of myocardial infarction

18 Pleiotropy

In addition to the antioxidative properties HDL particles have also other functions independent of the effects of HDL particles on cholesterol homeostasis. These include anti-inflammatory, anti-infective, antithrombotic, and endotoxin-neutralizing effects as well as effects on endothelial function. These pleiotropic effects have been recently reviewed (Annema and von Eckardstein 2013). The laboratory assays used for analyzing the pleiotropic effects of HDL are demanding and need to be standardized before they can be used in large epidemiological studies in order to improve the CHD risk assessment.

19 Future Approaches of Epidemiological Studies

New approaches have been used in order to resolve the complex effects of diseases, conditions, environmental factors, and genes in relation to the protective role of HDL. On one hand, there have been efforts to dissect the HDL fraction into as many well-defined subfractions and individual molecules of HDL particles as possible. On the other hand, as discussed above, the focus has been shifted from the structure and composition to the function of HDL particles (Fig. 2). Moreover, recent development in the field of "omics" (e.g., metabonomics, lipidomics, proteomics, etc.) has enabled the analysis of more holistic patterns on lipoproteins and subfractions and their relation to the risk of CHD (Ala-Korpela 2008; Rosenson et al. 2011; Würtz et al. 2012).

Dietary patterns have been used as a complementary approach to the traditional single-nutrient analysis (Randall et al. 1990; Bogl et al. 2013). Dietary patterns are, e.g., “fruit and vegetables,” “meat,” “sweets and desserts,” “junk food,” and “fish.” The “junk food” pattern is characterized by higher intakes of energy-dense nutrient-poor foods, such as hamburger, pizza, French fries, salty snacks, and liquorices and lower intakes of porridge, rye bread, and fruit. The “junk food” pattern distinguishes from the commonly used definition of “Western pattern” in that “junk food” does not contain high amounts of meat, eggs, or high-fat dairy. The healthy diet pattern has been associated with higher levels of HDL-C, whereas the fast-food dietary pattern, high in saturated fat, did not have this effect (Hamer and Mishra 2010).

The idea of analyzing the whole diet through dietary patterns is based on the fact that people do not eat single purified nutrients or simple foods, but mixed meals consisting of several foods and nutrients at a time. The term “nutritional epidemiology” depicting food patterns was coined already in the 1970s (Krehl 1977) but has only recently used more frequently.

The Mediterranean diet refers to a dietary profile commonly available in the early 1960s in the Mediterranean regions and characterized by a high consumption of fruit, vegetables, legumes, and complex carbohydrates, with a moderate consumption of fish, and the consumption of olive oil as the main source of fats and a low-to-moderate amount of red wine during meals (Sofi et al. 2010). A recent meta-analysis of 50 studies summarized the impact of the Mediterranean diet on CHD risk factors (Kastorini et al. 2011). The diet is associated with a 3 % increase in HDL-C, but many other lipid and non-lipid risk factors such as hypertriglyceridemia, blood pressure, glucose, insulin resistance, and abdominal obesity are also affected.

Conclusion

HDL-C is a strong and independent predictor of major cardiovascular events in a wide range of populations, in men and women with or without preceding CHD. As molecular biology and related approaches have revealed new biomarkers or profiles in HDL structure and function, the epidemiological research is also moving from the classical determination of total HDL-C to structure-function analyses. Recent methodological breakthroughs in HDL structure analyses have enabled their use also in large cohorts. In the future, further investigations are urgently needed for validation and clinical applications of HDL function assays.

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