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Improving HDL Functions – A New Version of The Quest of SANCGREAL?

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ABSTRACT

HDL complex has multiple functions. There is some parallelism between the plasma HDL-cholesterol (HDL-C) concentrations and the HDL complex atheroprotective function, but those values only measure the reverse C-transport. Multiple epidemiological studies have shown that a high HDL-C level is a strong marker of protection against atherosclerotic vascular disease (AVD) development, but in about 10% of patients, there is no correlation between AVD presence or absence and low or high HDL-C values, respectively. Plasma HDL-C concentrations have multiple genetic determinants, but most of the genetic profiles responsible for the association of high HDL-C levels with atheroprotection are not yet identified. A meta-analysis demonstrated that the HDL capacity of C-acceptance from macrophages is inversely associated with AVD prevalence but is independent of HDL-C values. CETP-inhibition therapies, in spite of up to 133% HDL-C increases, failed to improve AVD secondary prevention. As a consequence, the main focus of research has changed and resides now on attempts to improve HDL complex functionality. Elderly AVD-free aortic stenosis patients represent a natural laboratory terrain for use in studies to identify the HDL complex components responsible for successful atheroprotection. However, the reasons why HDL complex, competent for AVD protection for several decades, fails to prevent aortic sclerosis/calcification in the same patients, remain unknown.

High density lipoproteins (HDL) complex is a multiple and diverse set of proteins, lipoproteins, enzymatic pathways and cell structures (cell receptors and transporters) presenting with multifarious body functions, concerning atheroprotective, anti-inflammatory, antioxidant, vasoprotective, anti-infectious, and anti-apoptotic actions. When we measure the HDL-cholesterol (HDL-C) concentrations, we are actually analysing only a small part of the multiple HDL complex functions. Measuring the plasma HDL-C concentration – that is, merely measuring certain subpopulations of discrete particles rich in cholesterol but that differ quantitatively and qualitatively in apolipoprotein and lipid composition[1] -- gives us an idea (not a truly accurate one, indeed) of the reverse cholesterol transport (just one among the multiple HDL complex functions), but very little about the other actions of this fascinating physiological complex. However, there is not unfrequently some parallelism between the plasma HDL-C concentrations and the atheroprotective function of the HDL complex.

Considering the study populations as a whole, multiple epidemiological studies have shown that a relatively high HDL-C

plasmatic level is a strong marker of protection against the early development of atherosclerotic vascular disease (AVD), and specially coronary artery disease (CAD)[2-4]. Nevertheless, in an analysis of data from the original Framingham Study (5), it was found that nearly half of the men and women who suffered a clinical event had what we could call 'normal' HDL-C values[6]. On the other hand, a recent CANHEART substudy has shown that the protective effect against cardiovascular events of a plasma HDL-C value over 90 mg/dl exhibited a hazard ratio of only 0.87 for women and 0.73 for men[4].

In a previous work from our Group, an observational prospective cohort study of 264 patients aged over 59 consecutively undergoing surgical aortic valve replacement for severe calcific aortic valve disease (CAVD)[7], 'CAD-free' CAVD patients (that is, patients with normal coronary angiograms, classified as subjects without significant CAD, and representing 52 per cent of the whole group) had a mean HDL-C level of 59+-16 mg/dl, showing only a mean increase of 20.4 per cent in regard to the individuals with CAD evidence (49+-19 mg/dl). This relatively modest increase in plasma HDL-C levels (as long as it could be representative of a long-life lipidemic behaviour) had apparently been fully effective in protecting against CAD for several decades until the elderly phase of life (the mean age was 72 years), even when 27 per cent of patients had developed long-standing type 2 diabetes. Other interesting findings of our study were: 1) although diabetes and low plasma HDL-C concentrations were the sole independent CAD risk factors in elderly CAVD patients (in multivariate analysis), about five per cent of patients with normal coronary angiograms had plasma HDL-C levels below 40 mg/dl (which could not be attributed to a component of CAVD-induced cardiac cachexy); 2)) six per cent of CAVD patients presenting with CAD had plasma HDL-C levels above 70 mg/dl; 3) fourty per cent of diabetic patients in our population had normal coronary angiograms, displayed a weak expression of metabolic syndrome, and had high HDL-C values (54+-17 mg/dl in men and 56+-18 mg/dl in women). Thus, in more than ten per cent of our patients there was no correlation between the presence or absence of CAD and low or high HDL-C levels, respectively. On the other hand, in more than one third of subjects who became diabetic, an apparently highly functioning HDL complex resisted to the deteriorating actions of type 2 diabetes, and, despite the shrinkage of the gap usually seen between mean HDL-C values of women and men in the general population (shrinkage due to an eleven per cent HDL-C decrease in women while the values remained stable in men), the patients persisted CAD-free and showing relatively high plasma HDL-C concentrations.

Plasma HDL-C concentrations have multiple genetic determinants, and the polygenic nature of HDL-C regulation involves dozens of single nucleotide polymorphisms (SNPs), which small effects are frequently present and eventually combine in up to 50 per cent of the general population[1]. Presumably, most of SNPs combinations responsible for the association of high or relatively high plasma HDL-C concentrations with a potent atheroprotective effect are not yet identified.

Extreme rare mutations in apolipoprotein A-I (the major structural component of HDL), responsible for extremely low plasma HDL-C levels, have been described and are either responsible for potent atheroprotection and no signs of AVD[8,9] or early AVD or CAD (1). Epidemiologically, these rare variants are not important, but in the general population with low HDL-C concentrations, a relevant number of subjects (more than one fifth) are carriers of potentially pathogenic mutations in the apoA-I or ABCA1 genes, and overt or subclinical evidence of atherosclerosis in the mutation carriers is twice as frequent as in the non-carrier individuals with plasma low HDL-C values[10].

The reverse cholesterol transport (RCT) by HDL is initiated with the transference of cholesterol from the peripheral macrophages to the nascent (lipid-free) HDL particles, and the cholesterol efflux capacity is regulated by the apoA-I gene (in plasma) and ABCA1 gene (in cells). Then, the reverse cholesterol transport to the liver proceeds, mainly regulated by CETP, LCAT and SR-BI genes[12]. A meta-analysis of 15 studies[11] recently demonstrated that the HDL capacity to accept cholesterol from the macrophages is inversely associated with the prevalence of cardiovascular events but is *independent* from plasma HDL-C values[11]. Nevertheless, in the last fifteen years, CETP (cholesteryl ester transfer protein) inhibition had become a main focus for a therapeutical concept involving the combination of classical LDL-reducing treatment with HDL pharmacological increase, in order to promote the improvement of CAD secondary prevention in high-risk patients. However, four successive clinical trials with CETP inhibitors (compared to placebo), despite up to 133 per cent increases in plasma HDL-C concentration, failed to demonstrate further reduction of cardiovascular events[13-15] or showed only very modest results (16). The reasons of these failures are probably multifactorial and genetically complex, but lays on a basis constituted by HDL-C particles that were functionally poor in promoting anti-inflammatory and antioxidant effects before the therapeutical intervention. Since most patients involved in the clinical trials had suffered cardiovascular events previously, the simple fact of increasing the quantity of HDL-C particles in circulation did not decisively guarantee a qualitative improvement of their functional capabilities to prevent the initiation or aggravation of atheromatous lesions.

Accompanying the sequential presentation of the

results of CETP inhibitors clinical trials, the debate on which HDL subclass is the most important for the atheroprotective HDL actions has been re-launched. Until then, the predominant theory pointed towards the HDL2 fraction (HDL2b and HDL2a, the very large and large HDL subclasses, respectively[17]) as the central player[7]: if a potent cholesterol efflux capacity (CEC) is fundamental to promote an effective RCT as the key player of atheroprotection – and since HDL2 is a major participant in RCT and exerts together with HDL3 a prominent influence on CEC through its interaction with the macrophage ABCG1 transporter – then a high plasma HDL2 concentration should have a key role; it was even postulated that the ABCG1 transporter might be the mechanistic link between high HDL-C and the low risk of atherogenic disease[18]. Indeed, early epidemiological studies suggested that the atheroprotective HDL action resides mainly on HDL2 subclasses[19], a theory supported by the significantly higher HDL2 values seen in female gender[19]; subsequently, several and even modern studies continued to argue for HDL2 as a negative cardiovascular risk factor, despite some conflicting and confusing results[19-21]; however, the majority of preclinical studies have demonstrated evidence of stronger beneficial effects of HDL3 (HDL3a, HDL3b, HDL3c, or medium, small or very small HDL particles, respectively[17]), and the biochemical basis for this more beneficial effect pointed to the higher contents of paraoxonase 1, apolipoprotein J and sphingosine-1-phosphate as HDL3 components, while HDL2 contains apolipoprotein C-IV (which has been associated with a higher risk of cardiovascular events)[19]. Meanwhile, data from the CETP inhibitors clinical trials (known only for torcetrapib and anacetrapib) have shown that the impressively higher plasma HDL concentrations obtained were predominantly due to an increase in HDL2 values (HDL2b, in case of anacetrapib)[19]; the absence of relevant clinical results following those impressive increments in HDL2 conflict seriously with the far-back predominant theory. Concomitantly, the results of two modern clinical studies – AIM-HIGH clinical trial[22] and Ludwigshafen Risk and Cardiovascular Health Study[23] – indicated that HDL3 represents a protective HDL subpopulation. Finally, the strongest evidence for HDL3 being the functionally superior HDL fraction came from a study by Camont et al[24], in which several functionality assays demonstrated that CEC, antioxidant, antithrombotic, anti-inflammatory, and anti-apoptotic HDL properties are predominantly associated with the small dense HDL3 particles; these activities are strongly inter-correlated, and significantly correlated with multiple components of HDL phosphsphingolipidome[24]. At this point, one must recall that, as long as the commonly used lipid-lowering drugs are concerned, they have non-interesting effects on HDL3 fraction[19,25]: statins promote a mild (dose-dependent for simvastatin and rosuvastatin) HDL-C increase (5-10%), due to a HDL2 elevation, however accompanied by a HDL3 decrease; niacin determines a mild to moderate HDL-C increase (10-30%), predominantly due to a 40-100% increase in HDL2 (HDL3 is not affected or shows a small decrease); the mild increment in HDL-C promoted by fibrates (up to 15%) is due to a modest 2-20% increase in HDL3 values, with a null effect on HDL2 particles.

Following this conceptual turning point, the lack of credible oral HDL3-increasing drug therapy led the main focus of research to change and to reside now on other ways of improving HDL functionality rather than simply increasing the circulating HDL-C particles. Thus, efforts are being made to achieve the development of reconstituted HDL, apoA-I mimetic drugs or the upregulation of hepatic apolipoprotein A-I production[26]. However, a large-scale clinical use will be hampered while orally effective substances are not available. Nevertheless, recent work on the experimental oral use of transgenic tomatoes (expressing an apoA-I mimetic peptide) in mice is promising[27]. In the future, other possibilities could reside on an 'insulin-like' kind of parenteral administration.

Meanwhile, we believe that the elderly CAD-free populations with calcific aortic stenosis proposed to or undergoing aortic valve replacement – constituted by patients protected from coronary atheromatous disease for several decades – should represent a natural laboratory terrain prone to be used in extensive biochemical, immunochemical and genetic studies pointed towards the identification of the main components of HDL complex responsible for the successful atheroprotection in those individuals. These investigations would guide the constitution of a therapeutical armamentarium composed of several specific drugs which should be capable of enriching specifically the secondary prevention in selected high-risk patients, especially those with recurrent cardiovascular events.

Another important question raised by our article[7] is the apparent discrepancy between the capacity of high plasma HDL-C levels to prevent CAD occurrence and the 'inefficacy' in preventing the aortic valve sclerosis and calcification.

The etiology and pathophysiology of calcific aortic valve disease are not fully understood. Three facts are relevant: a polygenic genetic heritage plays a role[28,29], type 2 diabetes is the main pathogenic co-factor[30,31], and there is some similarity between the atherogenic process and the initial steps of aortic valve sclerosis: aortic leaflet interstitial cells-derived macrophages and oxidized LDL particles co-play a role in the initiation of the chronic inflammatory process that culminates later in the intensive formation and activation of osteoblast-like cells[29,32,33]. In animal models, where hypercholesterolemia plays a major role in the pathogenesis of calcific aortic stenosis (vitamin D2

added to an atherogenic diet), the aortic valve calcification and stenosis can be reverted by a treatment with an apoA-I mimetic peptide[34]. On the other hand, in humans with Tangier disease (a very rare condition caused by a mutation in ABCA1 gene, producing severe HDL deficiency, with a phenotype characterized by extremely low plasma levels of apoA-I and HDL)[35], the adult patients may develop severe aortic stenosis[36].Thus, it would be expectable that the HDL complex would also play a role in the prevention of human AVCD. However, that is not the case in the human 'common world', as our work has once more demonstrated[7].

Hypercholesterolemia is an AVCD risk factor, but it plays a relatively minor role as suggested by the AVCD trials with statins[37], yet it is apparently more relevant in the early phases of aortic valve sclerosis[38]. In our work, most cachexy- and statin-free patients have shown normal or only mildly elevated plasma LDL values[7], and high plasma HDL-C concentrations in CAD-free patients apparently had what we have called a 'bystander behaviour' before the chronic inflammatory process occurring in the aortic valve[7].

Recent work on HDL genetics and HDL functionality did not provide any clues allowing to predict the risk of developing aortic stenosis in human beings[39]. Data about the action of apoA-I and HDL complex in patients with aortic stenosis continue to be controversial, and some data apparently suggest a partially defective role in protecting against the oxidized LDL infiltration of the aortic leaflets and its consequences[40,41,42]. In our article, we have raised another possibility: the aortic leaflet myofibroblast-derived macrophages (which have different cellular origin, as compared with the macrophages usually seen in the vascular atheromatous processes[43]) may exhibit differences or an anomaly involving the ABCA1 or ABCG1 transporters[7]; this hypothesis has not been discarded until now.

Meanwhile, the renin-angiotensin-aldosterone system[44] and lipoprotein (a)[45] have emerged as probable major players in the pathogenesis of aortic stenosis.

In summary, the reasons why a highly functioning HDL complex, capable of protecting against coronary artery disease for several decades, fails to prevent the development of aortic stenosis in the same patients, remain unknown.

Conflict of Interests

The author has given non-payed lectures sponsored by Pfizer, Abbott, Merck Sharp & Dohme, Merck Serono, Novartis, and Medinfar Laboratories.

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