Vol 5 | Issue 1 | Pages 140-145

Annals of Heart
ISSN: 2578-6520

Review Article

DOI: 10.36959/652/405

High Density Lipoprotein as a Biomarker, Potential Therapeutic Target and Therapy

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HDL, LDL and how they correlate within acute/chronic phase response

HDL is a plasma lipoprotein with the function of reverse cholesterol transport and inflammation modulation. Studies suggest that HDL can function as both anti inflammatory and proinflammatory depending on absence or presence of inflammation and chronic disease. Functions of HDL may not always match its cholesterol levels. LDL on the other hand is one of the main lipoproteins in plasma which is in charge of extracellular lipid transportation. With its major protein group being apolipoprotein B, LDL is capable of binding to extracellular matrix molecules within subendothelial spaces of arteries, causing a secretion of chemotactic agent, monocyte chemotactic protein 1 (MCP-1), which in turn triggers an inflammatory response of the type seen in atherosclerosis, all of these occur due to LDL lipid oxidation [1-3]. Such responses can be abolished by HDL due to HDL's anti inflammatory properties which prevent LDL oxidation [4].

HDL's anti inflammatory properties are beneficial, however during an acute phase response, such abilities are altered since the HDL itself becomes pro inflammatory. Our group conducted a research using two groups of HDL lipoproteins from the same humans and normal rabbits; one isolated before an elective surgery and the other at the peak of an acute phase response. HDL from both groups was tested by their inflammation response on cultures of human artery wall cells. The research on HDL showed not only a shift from anti to proinflammatory during acute phase, but also a decrease in two HDL enzymes, paraoxonase-1 (PON1) and platelet activating acetylhydrolase (PAF-AH) [5]. It was concluded that these enzymes are partly responsible for inhibiting proinflammatory features of HDL [6-8].The Ability of HDL to prevent LDL induced lipid oxidation found to be a major factor in determining HDL anti-inflammatory properties [9,10] (Figure 1).

Can proinflammatory HDL be found in chronic disease?

It has been stated that a vast number of chronic disease exhibit a chronic acute phase response [11]. These responses are associated with persistent elevation of acute phase agents such as C-reactive proteins [12-14]. Examples of these diseases are diabetes, visceral abdominal obesity and a number of autoimmune diseases.

There are numerous studies regarding HDL's inflammatory properties in chronic diseases. Hedrick, et al. [15], found that under hyperglycaemic conditions in diabetes, glycation of HDL and its enzymePON1 occurs. This leads to HDL's failure to inhibit the inflammatory response induced by LDL oxidation within endothelium. The subjects studied by these investigators were individuals with either type 1 or type 2 diabetes with coronary artery disease. Comparing subjects with either abnormal glucose intolerance test or well controlled diabetes or poorly controlled diabetes with normal control group, showed that the first group had 40% reduction of PON1 activity as well as HDL's loss of anti-inflammatory abilities. It must be noted that HDL cholesterol levels were not significantly different amongst the different groups [15]. A study on south Asian immigrants with high incidence of metabolic syndrome and with a high risk of coronary heart disease, showed a correlation between HDL inflammatory properties and the thickness of carotid intima-media [16].

Persegol, et al. have studied subjects with abdominal obesity and also subjects with diabetes (both type 1 and 2) in separate studies [17-19]. They found that in comparison to normal subjects, the HDL from diabetics was unable to prevent LDL oxidation likely due to inflammation. Regardless of the type of diabetes, both types 1 and 2 had dysfunctional HDL [19,20]. A research by Cancello, et al. [21], proved a significant increase in the numbers of macrophages within omental adipose tissue when compared to subcutaneous adipose tissue. This was correlated with fasting glucose, insulin levels and insulin sensitivity as well as hepatic fibro inflammatory lesions [18]. It is concluded that macrophage cytokines play a role in insulin resistance and also in alterations in HDL inflammation properties.

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Accepted: December 23, 2021

Published online: December 27, 2021

Citation: Amini S (2021) High Density Lipoprotein as a Biomarker, Potential Therapeutic Target and Therapy. Ann Heart 5(1):140-145

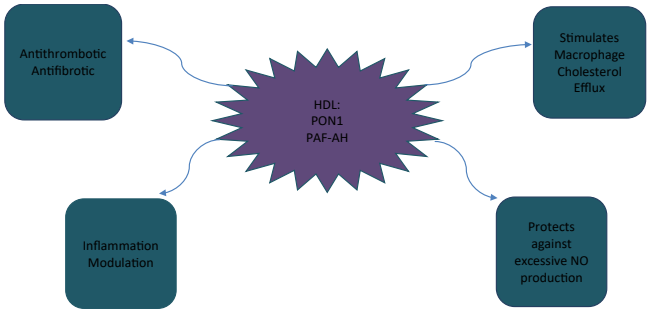

Figure 1: HDL under normal conditions.

An article by Roberts et al. also claims that HDL cholesterol levels cannot be reliable when it comes to detecting HDL's inflammatory properties [20]. Subjects of their studies were obese men with features of metabolic syndrome that underwent a three week diet treatment and an aerobic exercise program. These subjects showed an improvement in HDL inflammatory properties in spite of a decline in HDL cholesterol levels [20].In patients with familial hypercholesterolemia, LDL apheresis improved HDL inflammatory properties whereas HDL cholesterol levels had fallen due to this treatment [21]. HDL was found to be proinflammatory in 44.7% of women with systemic lupus erythematosus, 20.1% of women with rheumatoid arthritis (RA) and only in 4.1% of healthy women. These properties were significantly decreased in patients with RA who had taken atorvastatin with a daily dose of 80 mg [22,23].

HDL's response to inflammation can also be altered in patients with coronary heart disease (CHD). During a study, HDL from patients with CHD was found to be dysfunctional in preventing MCP-1 production and LDL oxidation in cultures of human artery cell wall compared to HDL from normal subjects. None of the subjects had abnormal lipid levels or diabetes [24].

What is HDL inflammatory index and how is it related to chronic diseases?

HDL inflammatory index (HII) was originally introduced by our group [25]. We measured the ability of LDL from normal subjects to induce MCP-1 both in the absence or in the presence of HDL in cultures of human aortic wall cell. The value in presence of LDL and absence of HDL was normalised to 1.0. The values measured in presence of both LDL and HDL were divided by the values obtained in the presence of LDL and absence of HDL. This new value was named HII. A sample with HII above 1.0 would be considered pro-inflammatory and one with HII below 1.0 would be classified as anti-inflammatory. HII of plasma samples from 26 subjects with CHD and with normal plasma lipid was calculated before and after treatment witha daily dose of 40mg simvastatin for 6 weeks [26]. HII before the medications was 1.38 plus minus 0.91 while HII after treatment was 1.08 plus-minus 0.71. A healthy Control group had HII of 0.38 plus-minus 0.14. In conclusion, HII showed a significant improvement after taking statin albeit still categorized as proinflammatory. (Above 1.0) Ansell, et al. also stated that inflammatory/ anti-inflammatory properties of HDL can be more reliable in distinguishing patients from control subjects in comparison to HDL cholesterol levels [25].

Chronic renal disease is associated with chronic acute phase response, therefore 189 patients on hemodialysis were followed for 30 months and their HII was measured [26]. Patients with HII above 1.0 had a significantly higher mortality despite experiencing no difference in total cholesterol levels, LDL cholesterol levels, triglyceride levels or HDL cholesterol levels [27].

Leprosy exhibits cellular events that are similar to atherosclerosis. A study by Cruz, et al. [28], reported that HDL from patients with leprosy was less effective in promoting the conversion of monocytes into CD1B+ dendritic cells and they were found to be proinflammatory (HII > 1.0) when the results were compared to normal anti inflammatory HDL.

The HDL inflammatory properties was tested on inbred strains of mice and rabbits by our group [29,30]. It was found that HDL from atherosclerosis resistant mice was anti inflammatory which was in contrast to HDL from atherosclerosis susceptible mice [29]. We also detected a significant correlation between levels of both HII and serum amyloid A -an acute phase reactant- and with the lesion area in rabbits [29,30] (Figure 2).

HDL, Apo-J and oxidative stress

In a study, oxidised phospholipids were injected into atherosclerosis resistant or into atherosclerosis susceptible mice [31]. The susceptible group had a significant increased HDL-associated acute phase reactant, apo-J, and a significant decline in PON1 levels. There was no change in HDL properties in the resistant group [31].

According to Bhattacharyya, et al. [32], the oxidative stress enzyme, myeloperoxidase, which is present at sites of inflammation is associated with HDL and its enzyme PON1and causes oxidative damage to apoA-I. This damage results in reduced cholesterol efflux by HDL [33].

A specific tyrosine residue is found to be the preferred target for this oxidative modification [34]. Apo-E is found within HDL of CHD patients [35]. In the past, statin and niacin combination appeared to reduce the Apo-E content of HDL in

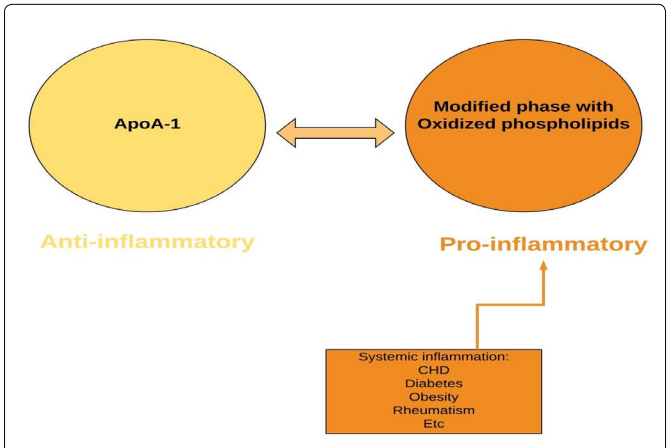

Figure 2: Anti-Inflammatory HDL vs. Pro-Inflammatory.

CHD patients and to contribute to an HDL proteome similar to that of healthy individuals [36].

Determination of the inflammatory properties of HDL

In the absence of hemolysis, a small amount of haemoglobin (Hb) is present outside of erythrocytes and in the plasma. Based on a research conducted by Watanabe, et al. [37], an atherogenic diet resulted in association of plasma Hb with HDL in mice. Such HDL was found to be proinflammatory in mice and in humans whereas there was no increase in the concentration of plasma Hb [37,38]. The main protein responsible for such association is haptoglobin (Hp) which increases during the acute phase response. The same atherogenic diet on mice with no Hp did not develop proinflammatory HDL. Humans have 2 alleles and 3 genotypes for Hp which are 1-1, 1-2 and 2-2 [39]. Hp 2-2 paired with diabetic patient (present in 40% of diabetics) increases the risk for CHD [39]. In contrast to humans, mice only have 1 genotype for Hp which is 1-1. Levy and colleagues [39], genetically engineered mice to express 2-2 genotype. The result was that HDL impaired reverse cholesterol transport. It was reported that in both 2-2 diabetic humans and 2-2 diabetic mice HDL was unable to promote cholesterol efflux from macrophages when compared to Hp 1-1 subjects [40].

Is HDL cholesterol level a reliable predictor of risk for atherosclerosis and CHD?

For decades HDL cholesterol level was assumed to be a strong predictor of clinical events associated with atherosclerosis [41]. However many studies reported that subjects with normal levels of HDL cholesterol presented with coronary atherosclerosis and related events [29]. Briel, et al. [42], reported that the risk of CHD events and total deaths would not always be decreased simply by increasing the amounts of HDL cholesterol levels. This can be true in patients with apoA-1 Milano [43]. This mutant apoA-1 leads to decreased HDL cholesterol levels even though the patients are not in higher risk for CHD [43]. With all this taken into account, we can see that the composition, functionality and inflammatory properties of HDL are as important as its cholesterol levels when it comes to determining risk for CHD.

Can HDL be used as a therapy and therapeutic target?

In various studies, HDL and apoA-1 have been efficacious in the treatment of atherosclerosis in both animal models as well as human beings, even in diabetic subjects [44-47]. In a study, infusion of recombinant HDL particles increased AMP-activated protein kinase in skeletal muscles, increased plasma insulin and decreased plasma glucose in type 2 diabetic subjects [48]. ApoA-1 is a large protein with 243 amino acids, which makes it a difficult target for large scale production. While millions of atherosclerotic and diabetic patients would need long term treatment with apoA-1, the cost of such therapy makes it economically prohibitive.

ApoA-1 mimetic peptides may be used as a treatment for atherosclerosis

Segrest and Anantharamaiah designed an 18 amino acid residues peptide with a class A amphipathic helix which it had in common with apoA-1. This peptide was named 18A. This name was updated to 2F when 2 phenylalanine residues were added on the hydrophobic face in order to increase stability and ability to bind non oxidized lipids. The 2F failed to improve atherosclerosis in a mouse model [49-52] since oxidized lipids derived from LDL play a major role in atherosclerosis and 2F could not bind them. A number of amino acids were substituted in 2F to enhance its effectiveness. As a result, a peptide with 5 phenylalanine residues on the hydrophobic face was generated (and thus termed 5F) which significantly improved atherosclerosis in a mouse model [52,53]. A peptide with 4 phenylalanine (4F) was also effective in mouse models to improve atherosclerosis lesions [54]. After these findings, many additional studies were conducted in animal models to indicate 4F efficacy in improving inflammation-based disease such as influenza A pneumonia [55], Type 1 and 2 diabetes, and obesity [56-59]. The 4Fpeptide increased survival in septic rats by inhibiting the inflammatory response [60]. The 4F peptide was found to be synergic with statin resulting in regression of atherosclerotic lesions in mouse models [61]. Moreover, 4F was capable of increasing HDL anti inflammatory properties in the plasma from end-stage renal disease patient [62]. In all the above studies, HII was significantly improved. The 4F peptide binds oxidized lipids 5 million fold better than human apoA-1 [63]. This feature makes 4F extremely capable of removing oxidized lipids from inflamed tissue hence leading to resolution of the inflammatory changes [64].

Four F peptide administration

At first, it was observed that only peptides containing D-amino acids are effective in an oral dose since L-amino acids would be degraded by intestinal proteases [60]. Nonetheless, if oral L-amino acid peptides are combined with niclosamide [61], they will be efficacious [61]. In acidic PH,niclosamide forms a complex with 4F, protecting it from degradation [61]. If the 4F peptide was to be given by injection, it would not matter whether it is made out of the L or the D amino acid [30].

Summary

In conclusion, relying merely on cholesterol levels of HDL does not provide accurate understanding of its composition, functionality and anti inflammatory properties. Currently, there are no tests widely available to measure these features, however, it seems they are directly related to conditions inducing a chronic acute phase response (e.g., diabetes, visceral obesity CHD). Studies on HDL mimetics as therapeutic agents are in progress. Our therapeutic approach must continue to emphasise lifestyle modification, to control diseases such as diabetes, obesity, hyperlipidemia and conditions including oral inflammation.

Plus the inclusion of an appropriate use of aspirin, statins, ACE inhibitors and beta blockers for CHD patients are always recommended (Figure 3).

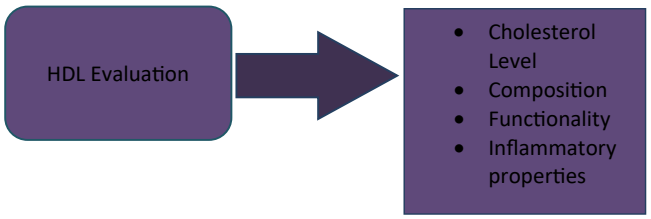

Figure 3: Evaluation of HDL by its properties.

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DOI: 10.36959/652/405