THE CEYLON MEDICAL JOURNAL

Established 1887

The Official Publication of the Sri Lanka Medical Association
Volume 56, No.2, June 2011
Quarterly ISSN 0009–0875

All communications should be addressed to **The Editors, CMJ**

Continued overleaf

High density lipoprotein – quality and function

Introduction

Atherosclerosis is a focal disease of the large and medium sized arteries in areas of disturbed blood flow caused by endothelial injury, dysfunction and local inflammation [1]. Coronary heart disease (CHD) is the most common cause of death in western countries and in developing countries it accounts for over 4.5 million deaths annually [2]. Dyslipidaemia has been identified as a main cause of CHD and in particular an imbalance between the atherothrombotic (LDL-c and lipoprotein remnants) and atheroprotective (HDL-c) lipoproteins in plasma [3].

Reverse cholesterol transport has been described as a major function of high density lipoprotein (HDL) for the last few decades. In addition HDL also exerts antioxidant, antiinflammatory and antithrombotic properties. HDL functions against lipid peroxidation, alters the expression of cytokines and endothelial function, acts as an acceptor for oxidized phospholipids, blocks oxidation of apo B lipoproteins and opposes insulin resistance [4, 5]. When acute phase or chronic inflammatory response is present as in atherosclerosis, HDL can be proinflammatory and proatherogenic.

Plasma HDL level is an inverse predictor of future atherothrombotic events. The Framingham study (HDL concentrations predicting cardiovascular risk) shows that 40% of events occurred in people with normal HDL levels [6]. In some instances increased plasma HDL levels can result from reduced catabolism due to blockage in the dynamic flow of HDL lipids from peripheral tissues to the liver [7]. In this scenario, measuring HDL levels alone may not be accurate in assessing the cardiovascular risk. This has raised the question of whether measuring HDL quality rather than quantity would help in better prediction of atherosclerotic coronary artery disease.

Structure of HDL

HDL consists of a hydrophobic core made of triglycerides and cholesteryl ester. Free cholesterol, phospholipids and apolipoproteins (apo AI, AII, C,E, AIV, J and D) form an outer amphipathic layer. Apo AI is the principal protein, determines the atheroprotective function of HDL through its interaction with scavenger receptor class B type 1(SR-B1) [7]. Mature spherical HDL contains 45-55% (mass %) apoproteins, 26-32% phospholipids, 15-20% esterified cholesterol, 3-5% free cholesterol and approximately 5% triglycerides. When cholesterol in the discoid HDL particle is esterified, the HDL discs are converted into spherical HDL particles by lecithin cholesteryl acyl transferase (LCAT) (densities range from 1.063 to 1.21g/ml). Though HDL is considered as a single entity in clinical practice, recent two dimensional non denaturing electrophoresis has revealed a number of HDL subspecies and altered levels of these will predispose to CHD [8]. HDL also contains enzymes like

Published by

The Sri Lanka Medical Association
Wijerama House
6, Wijerama Mawatha
Colombo 7
Sri Lanka

Tel: +94 11 2693324

Fax: +94 11 2698802

Internet home page
http://www.sljol.info/index.php/CMJ/index

e-mail: office@cmj.slma.lk

Printed by

Ananda Press
82/5, Sir Ratnajothi Saravanamuttu
Mawatha, Colombo 13
Sri Lanka

Tel: +94 11 2435975

Fax: +94 11 2385039

e-mail: anpress@sltnet.lk

For advertising

Please contact:
Mr. Anthony
Saatchi & Saatchi
79, C W W Kannangara Mawatha
Colombo 7

Tel: +94 11 2671026
+94 772514858

This journal is indexed by BIOSIS, Elsevier SCOPUS, EMBASE, CABI, and Index Medicus/Medline

paraoxonase, lecithin cholesterol acyl transferase, cholesterol ester transfer protein and also acetyl hydrolase platelet activation factor (PAFAH) which are important in determining the antioxidant property of HDL [9]. Proteomic analyses have proved the role of HDL in innate immunity: out of 48 proteins isolated in HDL, 23 proteins are involved in immune/inflammatory functions [10].

Functions of HDL

Reverse Cholesterol Transport (RCT)

RCT is cholesterol efflux from the arterial macrophages. The lipid deposited at the site of atherosclerotic lesions are removed and transported to the liver, bile and faeces for catabolism, thus attenuating the progression of atherosclerosis. This involves specific transporters like adenosine tri phosphate - cassette binding transporter (ABCA1), ABCG1, ABCG4 and LCAT activity. The esterification of HDL by LCAT generates mature HDL particles HDL2 and HDL3. HDL3 promotes cholesterol efflux more effectively than the other HDL subclasses but plasma HDL levels measure the cholesterol content of nascent HDL, HDL2 and HDL3 and thus it becomes a marker for RCT that can be less relied upon. After cholesterol efflux, scavenger receptor B1 (SRB1), hepatocytes and steroid producing cells uptake the mature HDL particles. In addition, the cholesterol esters can be transferred to LDL and VLDL – the apo B containing lipoproteins through cholesteryl ester transfer protein (CETP). Hepatic lipase can act on the subsequent HDL rich in triglycerides and can generate small HDL particles [11].

Antioxidant property

Lipid oxidation is the key central event for the initiation of atherosclerosis. It initiates the formation of fatty streaks and the progression of atherosclerosis. A wide body of literature supports the antioxidant activity of HDL. Apo A1 protects against oxidation of LDL and is a major contributor of HDL antioxidant activity. LCAT, apart from cholesterol esterification, can hydrolyse oxidized phospholipids of LDL. The presence of antioxidant enzymes on HDL such as paraoxonase and acetyl hydrolase platelet activating factor prevent the formation of oxidized LDL. Accumulation of oxidized lipids downregulates the activity of anti oxidant enzymes present in HDL [12].

Anti-inflammatory activity

HDL has evolved as a part of the innate immune system. HDL levels fall during the progression of atherosclerosis, a condition characterised by chronic inflammation. HDL possesses antiinflammatory activity by downregulating the expression of adhesion molecules which attracts oxidized LDL in the endothelium and neutralises the effect of oxidized LDL on the vascular endothelium. A few studies have demonstrated that HDL isolated from CAD patients contain a specific myeloperoxidase driven tyrosine modification of APOA1 coinciding with attenuation of cholesterol efflux with ABCA1. HDL also reduces the platelet activation and provides anti thrombotic action thereby benefiting the late stage of atherosclerosis [13].

Anti apoptotic activity

By facilitating the efflux of oxidized lipids, HDL diminishes apoptosis in macrophages. HDL also stimulates endothelial nitric oxide synthase (eNOS) diminishing endothelial dysfunction and it inhibits the coagulation cascade through activation of factors Va and VIIa. This retards the progression of atherosclerosis. In addition, HDL stimulates glucose uptake and fatty acid oxidation thereby decreasing insulin resistance and increasing the insulin secretion by the pancreas [14].

Dysfunctional HDL

Structural and functional changes which accompany HDL during the process of atherosclerosis make it 'dysfunctional', thereby rendering HDL ineffective in its anti atherogenic function. During inflammation, HDL levels are reduced due to increased HDL catabolism, decreased apo AI synthesis and displacement of apo AI by serum amyloid A. In addition, anti oxidant enzymes, LCAT can be diminished leading to inappropriate cholesterol efflux and formation of oxidized lipids. It has been shown that 70% of South Asian immigrants with subclinical CAD had dysfunctional HDL compared to controls [15]. HDL isolated from lesions of CHD enhances the oxidation of LDL, increases lipid hydroperoxides and promotes monocyte chemotactic activity (MCP) in human arterial wall. Myeloperoxidase which is co-localised with macrophages targets apo AI, modifies and impairs its function, converts HDL into dysfunctional form in humans [16]. A cell free assay has been developed for the rapid diagnosis of dysfunctional HDL. HDL inflammatory/anti inflammatory index is used to classify HDL as pro inflammatory i.e dysfunctional [17]. Dysfunctional HDL may be converted to normal by diet, exercise, degree of fat intake and pharmacologic approaches. Therapeutic interventions may include inhibition of myeloperoxidase thereby increasing the flux rate of HDL in plasma and acceleration of RCT [18]. Statins may improve and convert proinflammatory HDL into antiinflammatory by promoting the formation of more favourable HDL subclasses [19]. Even with substantial progress in HDL genetics there is lack of information in converting the basic research into pharmaceutical designs for the treatment of dysfunctional HDL. Orally active mimetic proteins are under development and have shown clinical promise. Based on the existing literature, research directions that could be explored in an effort to create HDL-related anti-atherogenic drugs may include, (a) the development of methods to enhance HDL-mediated RCT by increasing the expression and thus activity of the lipid transporter ABCA1 and the HDL receptor SRB1, (b) the generation of recombinant forms of human apoA-I with improved biological functions or mimetic peptides with improved affinity for oxidation prone "seeding" molecules such as HPODE and HPETE and (c) the improvement of HDL subpopulation distribution by enhancing the formation of select HDL subclasses linked with increased athero protection [20].

Conclusion

In conclusion plasma concentration of HDL is an important negative predictor of CHD but does not give us the full picture of its atheroprotective properties. This necessitates a shift towards assessing HDL function rather than its quantity in CHD susceptible populations. Changing the prooxidant and pro inflammatory properties of HDL i.e. therapy to improve the HDL function may be valuable in cardio vascular disease prevention and progression in the future.

References

1. Ross R. Atherosclerosis – an inflammatory disease. *New England Journal of Medicine* 1999; **340**: 115-26.
2. Okrainee K, Banerjee DK, Eisenberg MJ. Coronary artery disease in the developing world. *American Heart Journal* 2004; **148**: 7-15.
3. Witztum IL. The oxidation hypothesis of atherosclerosis. *Lancet* 1994; **344**: 793-5.
4. Shiflett AM, Bishop JR, Pashwa A, Hajduk SL. Human high density lipoproteins are platforms for the assembly of multi component innate immune complexes. *Journal of Biological Chemistry* 2005; **280**: 32578-85.
5. Han R, Lai R, Ding Q. Apolipoprotein AI stimulates AMP-activated kinase and improves glucose metabolism. *Diabetologia* 2007; **50**: 1960-8.
6. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study. *Journal of the American Medical Association* 1986; **256**: 2835-8.
7. Tsompanidi EM, Brinkmeier MS, Fotiadou EH, Giakoumi SM, Kypreos KE. HDL biogenesis and functions: role of HDL quality and quantity in atherosclerosis. *Atherosclerosis* 2010; **208**: 3-9.
8. Aszatalos BF, Schaefer EJ. High density lipoprotein subpopulations in pathologic conditions. *The American Journal of Cardiology* 2003; **91**: 12E-7E.
9. Precourt L, Amre D, Denis M, *et al*. The three-gene paraoxonase family: physiologic roles, actions and regulation. *Atherosclerosis* 2011; **214**: 20-36.
10. Reily MP, Tall AR. HDL proteomics: pot of gold or Pandora's box. *The Journal of Clinical Investigation* 2007; **117**: 595-8.
11. Natarajan P, Kausik KR, Christopher PC. High-density lipoprotein and coronary heart disease: current and future therapies. *Journal of the American College of Cardiology* 2010; **55**: 1283-99.
12. Dodani S, Grice DG, Joshi S. Is HDL function as important as HDL quantity in the coronary artery disease risk assessment? *Journal of Clinical Lipidology* 2009; **2**: 70-7.
13. Sviridov D, Mukhamedova N, Remaley AT, Chin-Dusting J, Nestel P. Antiatherogenic functionality of high density lipoprotein: how much versus how good. *Journal of Atherosclerosis and Thrombosis* 2008; **15**: 52-62.
14. Zhao Y, Van Berkel TJ, Van Eck M. Relative roles of various efflux pathways in net cholesterol efflux from macrophage foam cells in atherosclerotic lesions. *Current Opinion in Lipidology* 2010; **21**: 441-53.
15. Dodani S, Kaur R, Mohammad N, *et al*. Can dysfunctional HDL explain excess risk of coronary artery diseases in South Asian immigrants? *The International Journal of Cardiology* 2008; **129**:125-8.
16. Smith JD. Myeloperoxidase, inflammation, and dysfunctional high-density lipoprotein. *Journal of Clinical Lipidology* 2010; **4**: 382-8.

17. Ragbir S, Farmer JA. Dysfunctional high-density lipoprotein and atherosclerosis. *Current Atherosclerosis Reports* 2010; **12**: 343-8.

18. Besler C, Heinrich K, Riwanto M, Lüscher TF, Landmesser U. High-density lipoprotein-mediated anti-atherosclerotic and endothelial-protective effects: a potential novel therapeutic target in cardiovascular disease. *Current Pharmaceutical Design* 2010; **16**: 1480-93.

19. Sorrentino SA, Besler C, Rohrer L, *et al*. Endothelialvaso - protective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy. *Circulation* 2010; **121**: 110-22.

20. Francis GA. The complexity of HDL. *Biochimica et Biophysica Acta* 2010; **1801**: 1286-93.

B Gayathri, *Department of Biochemistry, PSG Institute of Medical Sciences and Research, Coimbatore, Tamilnadu, India.*

Correspondence: BG, *e-mail <drgayukv@yahoo.co.in>.* *Competing interests: none declared.*