Endocrinology & Metabolic Syndrome

Dodani, Endocrinol Metab Synd 2015, 4:1
DOI: 10.4172/2161-1017.1000e124

Editorial Open Acces

Coronary Artery Diseases in South Asian Immigrants: Philosophy behind HDL Function

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Rec Date: Jan 03, 2015, **Acc Date:** Jan 06, 2015, **Pub Date:** Jan 08, 2015

Editorial

Even though coronary artery disease (CAD) event rates have decreased by 50% in the US over the past 30 years, CAD still is #1 killer in both developed and developing world [1]. Moreover, CAD is a complex, multi-factorial disease. It involves multiple pathophysiologic processes including inflammation, cellular proliferation, lipid metabolism, hypertension, hyperglycemia, coagulation, and oxidation, all of which interact and each of which involves multiple genetic and environmental factors. Epidemiologic studies of ethnic minorities in general and South Asian immigrants (SAIs) in particular in developed countries have documented markedly increased rates of CAD and CAD mortality compared to whites [2]. South Asians residing in urban environments in the Indian subcontinent also show increased CAD prevalence [3,4]. Compared to Caucasians and other ethnic groups, CAD presents at younger ages in SAIs, with more diffuse and aggressive disease, and more deaths [5]. Other groups that migrate to developed areas also show increased rates of CAD and CAD mortality but the increases in SAIs exceed them in both prevalence and severity [3]. Differences in CAD outcomes between SAIs in the US and South Asians in India show that migration adversely affects established CAD risk factors and may even reveal new ones [6]. For example, the prevalence of dyslipidemia and type 2 diabetes (T2D) among SAIs has been increasing over the past decade [7].

Among all Asians in the US, SAIs has the highest rates of overweight/obesity (25% among men; 37% among women) [8]. They develop insulin resistance at a lower body mass index (BMI [kg/m^2]) than do other racial/ethnic groups. As a result, they have a higher prevalence of T2D, metabolic syndrome (MS) and CAD. In one study, an MS prevalence of 29.7% in adult SAIs was seen, which is much higher than in any other immigrant population in the US [9]. In response to the increased risk for co-morbid conditions in Asian populations, the WHO in 2002 recommended establishing new BMI standards for Asian populations: normal (18.5 to <23.0), a moderate-risk public health action point (23.0), and a high-risk public health action point (27.5) [10]. The primary adipose tissue compartment (superficial subcutaneous adipose tissue) is less developed in SAIs, resulting in earlier use of secondary compartments (visceral adipose tissue), which might explain why at a similar BMI, the waist-to-hip ratio of SAIs is greater, and the atherogenic lipoprotein profile and hyperglycemia are more pronounced in SAIs. Even so, conventional risk factors and insulin resistance parameters, although important in predicting CAD risk, do not fully account for the increased CAD risk in SAIs. Hence, other, less- or non-conventional risk factors are likely involved. It is important to identify these factors in SAIs because they are the key to primary prevention and early detection of CAD, and development of a validated prediction tool similar to the Framingham Risk Scoring (FRS) tool. Among the many factors contributing to excess CAD risk in SAIs, dyslipidemias appear to play major roles.

Dyslipidemias

Epidemiological studies have identified Low Density Lipoprotein (LDL) and high density lipoprotein (HDL) as independent CAD risk factors and there is an inverse relationship between HDL levels and prospective CAD risk [1]. According to the practice guidelines, lowering LDL levels has been the major target in cardiovascular protection strategies, and clinical trials have clearly established that reductions in LDL are associated with a 30-45% reduction in clinical events [1]. However, even with optimal treatment for LDL, at best only 25-35% is relative risk reduction for subsequent CAD events. LDL and non-HDL are not the only lipoprotein to predict CV outcomes and there must be some other factors- high residual risk of CAD [10]. There is less evidence for the salutatory effects of raising HDL. In the NCEP ATP III guidelines (NCEP ATP IV 4 guidelines not yet released), HDL is important in risk stratification in primary prevention, influencing the need for and intensity of treatment of LDL [11] Moreover, guidelines clearly define an HDL level of 40 mg/dL as an independent risk factor for CAD, and low HDL is often present in high-risk patients with CAD [1,11].

HDL Role in CAD-Dysfunctional HDL (Dys-HDL)

HDL is a heterogeneous lipoprotein, containing several surface apolipoproteins (Apo A-I, AII, C, E, AIV, J, and D). Apolipoprotein A-I (Apo A-I) is the principle protein of HDL, which also carries enzymes, such as Paraoxonase 1 (PON 1), Platelet Activating Factor (PAF) – acetyl hydrolase, Lecithin Cholesterol Acyl Transferase (LCAT), and Cholesteryl Ester Transfer Protein (CETP). Differences in HDL particle size result mainly from the number of apolipoprotein molecules and the volume of the cholesterol ester in the core of the particle.

HDL has antioxidant, anti-inflammatory, and anti-thrombotic properties that contribute to its function as an anti-atherogenic agent [12]. HDL protects against CAD via several mechanisms, including its involvement in (a) the reverse cholesterol transport process, (b) protection of LDL from oxidation, and (c) selective reduction of endothelial cell adhesion molecules, which increases the release of nitric oxide (NO) and prostacyclin, and maintains endothelial function Epidemiological studies suggest that a 1 mg/dL increase in HDL is associated with a 2% to 4% reduction in CAD risk [11]. However, HDL can have this protective effect only if it functions normally. In recent studies in Caucasians, and few SAIs, HDL was not only found to be ineffective as an antioxidant but, paradoxically, appeared to be pro-oxidant [9,13,14]. The presence of Dys-HDL has

also been found in MS, diabetes, Systemic Lupus Erythematosus (SLE) and other diseases that cause systemic infection. This pro-inflammatory HDL, or Dys-HDL, accumulates oxidants that (i) inhibit HDL-associated antioxidant enzymes, (ii) render apo A-I, the main protein component of HDL, unable to promote ABCA1-mediated cholesterol efflux, and (iii) promote the formation of LDL-derived oxidized lipids [14].

Conclusion

Given that SAIs are known to carry a disproportionately high risk for CAD and those traditional CAD risk factors may not fully explain the excess risk, there is a need to explore and understand other non-traditional risk factors. SAIs is under-represented in major clinical trials, and evidence-based management strategies of CAD in this population are lacking. Most clinicians are aware of the low HDL levels in this group, but whether this is due to isolated low HDL levels, high total cholesterol/HDL ratio, or an elevated non-HDL level, is not known. Moreover, the quality of HDL and its role in CAD protection is rapidly emerging. The time has now come for CAD to be considered the number one public health problem in SAIs, the second largest Asian immigrant population in the US. Emerging data from some well-planned community-based investigations have emphasized the gravity of this rapidly increasing epidemic. The good news is that the epidemiologic studies have already shown that the bulk of the CAD can be prevented or at least its manifestations can be delayed. A multidisciplinary approach towards improving lifestyle methods involving the population at risk, healthcare personnel, and the government is required to diminish the incidence.

From SAIs' perspective, there is a need for implementation of newer guidelines as well as lowering the threshold for initiating therapeutic interventions. There is an increasing body of evidence that the function of HDL, including its anti-atherogenic properties and its reverse cholesterol transport activity, has a greater impact on CVD risk compared with levels of HDL alone. Targeting HDL has become a growing interest. Nevertheless, raising HDL pharmacologically has failed to show a considerable, if any, impact on cardiovascular outcome. Efforts should focus on improving HDL quality in addition to raising HDL levels when developing new therapies. Ongoing and future research will help determine the most safe and effective approach to improve cardiovascular outcome and establish the safety, efficacy and impact on atherosclerosis of the emerging HDL-raising therapies. Moreover, a greater understanding of mechanisms of action of HDL and its altered vascular effects is therefore critical within the context of HDL-targeted therapies.

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