Protection from Cardiovascular Disease Due to Increased High-Density Lipoprotein Cholesterol in African Black Populations: Myth or Reality?

Nicholas J. Woudberg, Bsc Hons[1];
Julia H. Goedecke, PhD[2]; Sandrine Lecour, PhD[1]

The burden of cardiovascular disease (CVD) in sub-Saharan Africa has increased over the last decade. Despite this, African Black populations present with relatively low incidences of coronary heart disease and ischemic heart disease, which may be attributed to their lower total cholesterol, triglycerides and low-density lipoprotein cholesterol concentrations, compared with White populations. Commensurate with these lower lipid levels, it was believed that high-density lipoprotein cholesterol (HDL-C) concentrations would be higher in Black populations compared with their White counterparts. This is based on data from previous studies of African and African American populations; however, recent studies conducted in Africa found similar or lower HDL-C concentrations in Black compared with White individuals. Current research, therefore, suggests that HDL-C may not be a good indicator of cardiovascular risk and future research should focus on HDL quality (vs quantity), by measuring HDL functionality and subclass. *Ethn Dis.*2016;26(4):553-560; doi:10.18865/ed.26.4.553.

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[1]Hatter Institute for Cardiovascular Research in Africa and South African Medical Research Council Inter-University Cape Heart Group, Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
[2]Non-Communicable Disease Research Unit, South African Medical Research Council

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide.[1] In Sub-Saharan Africa, although the leading cause of death remains communicable diseases, the prevalence of CVD is increasing.[1–3] Progressive changes in socioeconomic status and a Westernized lifestyle contribute to the burden of preventable CVD.[4–6]

Since first demonstrated in the Framingham Heart study, it is now generally accepted that high-density lipoprotein cholesterol levels (HDL-C) are inversely correlated with CVD risk.[7–9] Much of the benefits of HDL are thought to be related to its antiatherogenic functions including reverse cholesterol efflux, anti-oxidative, anti-inflammatory and anti-thrombotic properties.[10]

Since HDL-C is traditionally believed to be an accurate risk factor for CVD, it is hypothesized that ethnic groups with lower risk of coronary artery disease and ischemic heart disease may then have higher HDL-C than their higher risk counterparts. Does this hold true in an African setting?

Address correspondence to Nicholas Woudberg; University of Cape Town, Hatter Institute, Chris Barnard Building, Anzio Road, Observatory, 7801, Western Cape, South Africa; nicholaswoudberg@gmail.com

Ethnic Diversity in Cardiovascular Disease Risk

A systematic review of cardiovascular risk factors in North Americans concluded that African American populations exhibit higher obesity, diabetes and high blood pressure than White American populations[11] resulting in a greater risk for coronary artery disease, stroke and cardiovascular outcomes than their White American counterparts.[12–14] The review attributes the higher risk in African Americans to poor socioeconomic status, lack of education and lack of access to adequate health care compared with White Americans.[15] Interestingly, the aforementioned factors would apply to most Black populations living in Africa.

Despite possessing similar risk factors as African Americans, the Black Africans present with different CVD compared with African Americans, most likely due to a difference in epidemiological transition between Africa and America.

Indeed, Black Africans present with higher blood pressure, diabetes mellitus, hypertension and cerebrovascular disease, compared with their White counterparts.[5,16–19] In contrast, coronary heart disease remains less common in Black African populations. Less than 10% of Black African patients present with ischemic heart disease, a CVD much more routinely associated with White patients in developed countries.[4,20–23] Within South Africa, cholesterol-attributable mortality was higher in White compared with Black populations, with only 1.8% mortality attributable to 'sub-optimal' cholesterol levels in the South African Black population.[24] Notably, the White Afrikaaner population in South Africa, for example, are affected by founder effects relating to genetic aberrations in genes encoding for low density lipoprotein receptors, increasing their risk for ischemic heart disease.[22,25]

Despite these ethnic differences in CVD risk, there has been a notable rise in non-communicable diseases throughout Africa,[5] which are largely driven by an aging population, urbanization, unhealthy diet and reduced levels of physical activity.[4,5] These effects can be clearly "illustrated by the so-called immigrant" effect. For example, the prevalence of type 2 diabetes shows a rising gradient from Black Africans to African American and African migrants.[26] A comparison of local Cameroonians and migrants showed a younger age of diagnosis of type 2 diabetes in the migrant patients.[27] This may be attributed to earlier diagnosis of metabolic disorders, due to an improved access to health care, or may be due to marked changes in the socioeconomic environment, including shifts in dietary intake toward a Westernized diet.[27] Conversely, access to drugs might improve some health outcomes. Notably, African diabetic migrants displayed greater HDL-C concentrations than matched African diabetic patients, most likely due to access to statin therapy, which is available in more developed countries.[27]

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Protective Lipid Profiles in Black African Population

Differences in the susceptibility to cardiometabolic diseases in Africa may be a result of distinct ethnic-specific lipid profiles. Populations of African descent have more favourable lipid profiles than White populations, characterized by lower total-cholesterol, LDL-cholesterol and triglycerides.[20,28,29] It was also generally thought that the lower incidence of coronary heart disease in Black African populations may be attributed to their greater HDL-C, which has been consistently shown in African American, compared with White Americans.[30–32] Within Africa, high HDL-C concentrations were associated almost exclusively with Black African populations.[4,33–36] For example, studies from the early 1990s in South Africa indicated that the majority of the Black population presented with high protective HDL-C/triglyceride ratios.[34,35] However, recent South African studies from the last decade have shown that HDL-C does not differ in the Black population, compared with White and other ethnic groups. (Table 1)

In the Heart of Soweto study, Black African patients had significantly lower total-cholesterol, LDL-cholesterol and triglycerides compared with Indian, White and mixed ethnic groups; however, HDL-C did not differ between ethnic groups.[6] Similarly in 2001, Punyadeera et al showed that South African White women presented with higher total cholesterol, triglycerides and LDL-cholesterol concentrations than Black women, but HDL-C concentrations did not differ by ethnicity.[37] In contrast, Goedecke et al showed that Black women from the Western Cape region in South Africa presented with lower HDL-C than their

Table 1. Findings of South African population studies comparing HDL-C levels

Population	Population age	Sex (%)	Finding	Reference
Black, n=458	16-69 years	Men (52%) and women (48%)	Protective high HDL/ triglyceride ratio in the majority of patients	Seedat et al[34]
Black, n=15; White, n=14	Pre-menopausal	Women	No difference in HDL-C values across ethnicities	Punyadeera et al[37]
Black, n=1823; White, n=142; Mixed race, n=87; Indian, n=133	40-75 years	Men (53%) and women (47%)		Sliwa et al[6]
Black, n=28; White, n=28	18-45 years (pre-menopausal)	Women	HDL-C significantly lower in Black vs White women	Goedecke et al[38]
Black, n=209; White, n=234	18-45 years (pre-menopausal)	Women		Ellman et al[39]

White counterparts, despite lower triglycerides and total cholesterol.[38] This was further confirmed by Ellman et al in 2015, even after adjusting for differences in total fat mass and visceral adipose tissue mass.[39] These studies consistently showed that HDL-C concentrations are similar or lower in Black African women compared with White pre-menopausal women. In their 2010 study, Nwagha et al found reduced HDL-C concentrations in post-menopausal Nigerian women compared with their pre-menopausal counterparts; however, no ethnic comparisons have been made in African populations in this regard.[40] There is an emerging body of evidence from population studies suggesting that any protective lipid profile in Black populations cannot be linked to a higher HDL-C, as previously shown in American populations.

The change in the HDL-C phenotype of Black African populations over the years may be attributed to changes in lifestyle and nutrition transition. Lower HDL-C concentrations are associated with obesity, cigarette smoking and sedentary behavior.[41–43] Conversely, moderate exercise, adherence to the Mediterranean diet and moderate alcohol consumption are associated with increases in HDL-C.[44–46] For example, a long-term lifestyle intervention program employing the Mediterranean diet and exercise in patients with metabolic syndrome indicated that HDL-C, independent of changes in other lipids, was raised in response to the intervention.[47]

These observations, however, are limited to the quantity of the HDL-C, which may not, in fact, confer reduced CVD risk. The validity of the relationship between total HDL-C levels and CVD risk has been questioned recently, with the disappointing results of the AIM-HIGH[48] and dal-OUTCOMES[49] trials. In both trials, drug treatment increased HDL-C levels but failed to reduce cardiovascular risk or secondary outcomes. A possible explanation for these unexpected results may be a selective increase of particular HDL subclasses, which play functionally distinct roles. However, the contribution of individual HDL subclasses to HDL function is not yet fully understood.

We postulate that a "protective lipid profile" observed in Black Africans may be related to the quality of the HDL rather than the quantity.

Quality over Quantity of HDL

It is important to consider that the HDL particles themselves can be fully or partially loaded with cholesterol, implying that functional HDL is not directly related to a measure of total HDL-C.[50] Another important consideration is that of dysfunctional HDL. Dysfunctional HDL relates to a total loss of HDL function where the normal anti-atherogenic lipoprotein starts displaying pro-atherogenic properties, often as a result of structural changes.[51,52] Accordingly, although two individuals may have equivalent quantities of HDL-C, the quality of an individual's HDL may differ, consequently affecting CVD risk profiles.

The quality of an individual's HDL in this case refers to both the anti-atherogenic functionality and distribution of HDL subclasses (Figure 1). HDL displays a broad range of anti-atherosclerotic functions, the

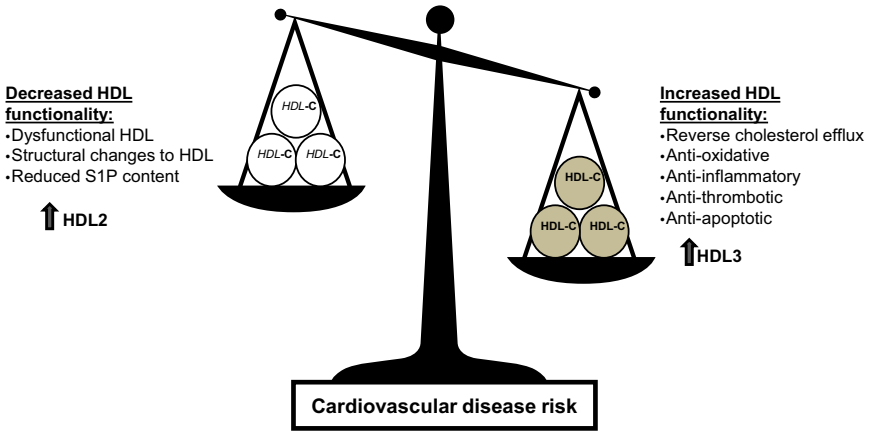

Figure 1. Quality vs quantity of HDL
Despite equivalent concentrations of HDL-C, CVD risk may be different. This is related to improved HDL functionality, namely reverse cholesterol efflux, antioxidative, anti-inflammatory, anti-thrombotic and anti-apoptotic functions. Decreased CVD risk may be associated with shifts in HDL subclass distribution, with decreased HDL2 and increased HDL3. Increased CVD risk may be associated with dysfunctional HDL and a reduction in sphingosine-1-phosphate (S1P) content.

most fundamental of which is reverse cholesterol efflux. Peripheral cells are unable to catabolize free cholesterol and as a means of attenuating cholesterol cytoxicity, it is effluxed to carriers like HDL.[53,54] HDL then delivers excess cholesterol to the liver where it is excreted into the bile.[54] While reverse cholesterol efflux is the primary and most well characterised function of HDL, many other functions have been demonstrated.

Most of the additional functions of HDL center on controlling the pro-atherogenic influence of oxidized LDL (OxLDL). OxLDL increases the expression of monocyte chemotactic protein, triggering inflammatory cell intrusion through the endothelial cell layer and the downstream formation of atherosclerotic plaques.[55–57] HDL inhibit metal ion induced LDL oxidation and performs antioxidant functions primarily by the paraoxonase enzyme.[58–62] HDL also performs anti-inflammatory functions through inhibition of endothelium expressed monocyte adhesion molecules.[63–65] HDL is a functionally diverse molecule, as summarized in Figure 1. While HDL function has been well characterized, new and accurate methods have allowed quantification of HDL subclasses.

Using agarose gel electrophoresis, HDL can be separated into two distinct subclasses, HDL2 and HDL3.[66–68] The two HDL subclasses differ on the basis of charge, size, composition and as shown recently, by functionality.[66,69,70] It is a matter of extensive debate as to which of the subclasses, HDL2 or 3 is functionally superior.[71] Epidemiological data suggest that CVD is associated with lower HDL2; however, preclinical studies appear to indicate that HDL3 is functionally superior to HDL2.[69,70,72–75] Due to the structural associations of HDL3 with antioxidant enzymes, as well as sphingosine-1-phosphate, a known cardioprotective lipid, we propose that the smaller HDL3 serves as the superior HDL subclass.[73,76,77] Certainly, in patients with myocardial infarction, long-term clinical events were associated with low levels of HDL3.[78]

New methods are now available to facilitate the quantification of HDL subclass distribution including the Lipoprint system (Quantimetrix, Redondo Beach, CA).[79] Using this system, we have recently studied the HDL subclasses in an African population. Although our preliminary data did not highlight a difference in HDL subclass distribution between Black and White South African women, a difference in HDL antioxidant and anti-inflammatory activities was noted, with a better HDL protective profile for the Black population compared with White women.[80] In addition, obese women had decreased levels of large HDL compared with their normal-weight counterparts.[80] These preliminary data indicate the importance of a

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focussed approach on HDL subclass and functionality, which may provide further novel insights into CVD risk in African populations.

Conclusions

The protective lipid profile associated with Black African populations does not include elevated HDL-C concentrations as originally thought. Cardiovascular risk due to lifestyle changes is increasing in Black African populations, which may then contribute to lower HDL-C concentrations. It is, however, unclear how this may relate to HDL functionality and subclass distribution. Failure of clinical trials to show a cardioprotective effect of raised HDL-C levels suggests that measurement of total HDL-C alone is not a sufficient measure for assessment of CVD risk. It is therefore critical to consider the functionality of HDL as well as the distribution of HDL subclasses. Although HDL-C levels are similar or lower in Black African compared with White populations, differences in HDL subclass and superior HDL function may confer protection against coronary artery disease and ischemic heart disease in Black populations. In order to better understand why different ethnicities are more susceptible to certain types of CVD, assessing the quality of HDL should be considered. Many of these techniques, while established further afield, have not been used in an African setting and these are essential to our understanding of the role of HDL in preventing CVD and metabolic diseases in Africa.

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Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Woudberg, Goedecke, Lecour; Data analysis and interpretation: Goedecke; Manuscript draft: Woudberg, Lecour; Acquisition of funding: Lecour; Supervision: Goedecke, Lecour; Administrative: Goedecke

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