Dyslipidaemia in ethnic populations: special considerations

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Abstract

There is extensive evidence of an increased risk of coronary heart disease (CHD) amongst South Asians (Indo-Asians) compared with Caucasians. This increased risk is not explained by conventional risk factors for CHD, such as smoking, hypertension and elevated total cholesterol levels. Studies have consistently demonstrated an increased prevalence of metabolic abnormalities including insulin resistance, diabetes, impaired glucose tolerance and dyslipidaemia, characterised by low plasma levels of high-density lipoprotein cholesterol (HDL-C) and high levels of triglycerides and lipoprotein a (Lp[a]), amongst South Asians. Together these factors predispose to accelerated atherosclerosis, and this is accentuated by adoption of a Western lifestyle. Nicotinic acid is the most potent lipid-modifying therapy for increasing HDL-C (by up to 30%), and is also effective in reducing triglycerides and Lp(a). Clinical studies in Caucasian patients have shown that nicotinic acid can also be safely used in patients with controlled type 2 diabetes. Long-term intervention studies have demonstrated the clinical benefits of nicotinic acid treatment, reducing cardiovascular morbidity and mortality in Caucasian patients with CHD. Nicotinic acid could potentially offer important therapeutic benefits in South Asians. Further clinical studies in this patient group are needed to substantiate this potentially useful treatment strategy and identify specific groups that would derive most benefit.

Key words: South Asians, coronary heart disease, dyslipidaemia, lipid-modifying therapy, nicotinic acid.

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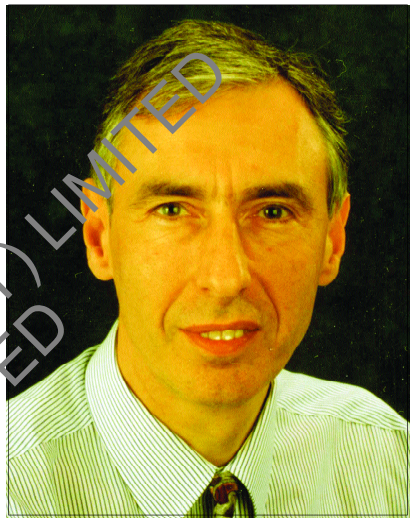
Introduction

Men and women from the Indian sub-Continent (Indo-Asians or South Asians) are at increased risk of coronary heart disease (CHD) compared with individuals of European descent, irrespective of whether they have recently migrated or not.[1-3] This increased susceptibility has been demonstrated in groups living in a variety of countries including the United Kingdom (UK), South Africa, Singapore, the USA and Canada.[3] Based on a recent comprehensive review of UK data, the excess CHD risk in South Asians compared with the population of England and Wales is estimated to be at least 40%.[4] Conversely, even though people of black African origin have a relatively high incidence of stroke and end-stage renal failure compared with people of European origin, CHD is far less common.[5] Chinese immigrants have a lower rate of CHD compared with other ethnic groups.[6] Given that there are over 15 million South Asians living outside India, including over 1.5 million in the UK and over one million in the USA, the factors implicated in this increased CHD risk have been the subject of extensive research.



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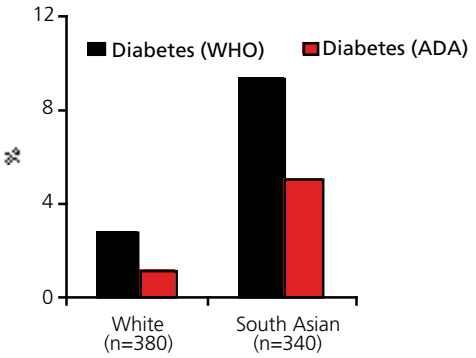
South Asians: factors implicated in excess CHD risk

The increased risk of CHD in South Asians compared with Caucasians cannot be explained on the basis of conventional risk factors for CHD such as smoking, hypertension and elevated total cholesterol. Instead, the pattern of risk factors in South Asians is more complex. Insulin resistance is regarded as the underlying factor responsible for the high rates of CHD in South Asians.[7] Studies have consistently identified an increased preva-

Figure 1. Diabetes is far more common in South Asians (both men and women) than in Caucasian subjects

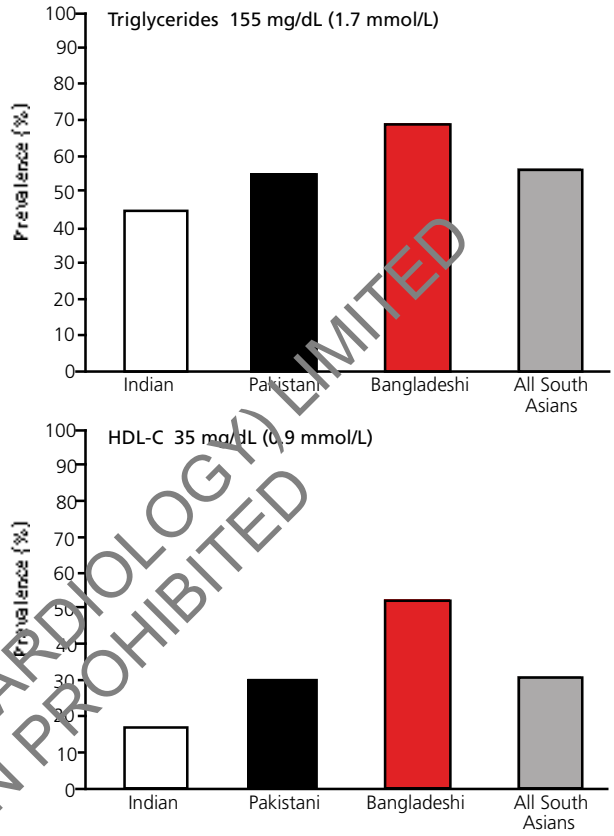


World Health Organisation (WHO) definition of diabetes: fasting plasma glucose ≥ 7.0 mmol/L or two-hour post-glucose load ≥ 11.1 mmol/L

American Diabetes Association (ADA) definition of diabetes: fasting plasma glucose ≥ 7.0 mmol/L

Adapted from Cappuccio *et al.*[5]

Figure 2. Prevalence of lipid abnormalities in South Asians (data from Bhopal *et al.*[7])



lence of a number of closely related metabolic abnormalities amongst South Asians, including insulin resistance, impaired glucose tolerance and dyslipidaemia. Both insulin resistance and type 2 diabetes are far more common amongst South Asians than Caucasians (figure 1). South Asians living in the UK and Canada, for example, have a four-to-five fold higher rate of type 2 diabetes than Caucasians.[6,7] Moreover, studies in the UK have shown that the tendency among British South Asian adults to develop insulin resistance is present even in early life, even though it is not associated with overt glucose intolerance at that stage.[8]

In addition, lipid abnormalities that predispose to accelerated atherosclerosis, specifically an atherogenic lipid profile characterised by low high-density lipoprotein cholesterol (HDL-C) and hypertriglyceridaemia, are also common in South Asians. Studies[9-11] have consistently shown that although South Asians living in the UK or USA have similar total cholesterol levels to those observed in Caucasians, plasma levels of HDL-C are consistently significantly lower. Low HDL-C is well established as an independent risk factor for cardiovascular disease. Epidemiological studies[12] have demonstrated an inverse relationship between serum HDL-C and risk of CHD, with a 2–3% increase for every 1% decrease in HDL-C, independent of low-density lipoprotein cholesterol (LDL-C) and triglyceride concentrations. In addition, South Asians also tend to have elevated levels of lipoprotein(a) (Lp[a]),[13] a cholesterol-rich lipoprotein that is a genetic variant of plasma LDL. Lp(a) may play an important role in promoting coronary atherosclerosis and thrombosis as increased levels of Lp(a) have been associated with an increased propensity for atherosclerosis, thrombogenesis and clinical events.[13,14]

Data from the UK, however, indicate that this pattern of lipid abnormalities is not uniform amongst South Asians. In one study[7] that investigated CHD risk factors in a heterogeneous population of South Asians and Caucasians, Bangladeshis were reported to have the highest concentrations of triglycerides and lowest plasma levels of HDL-C (see figure 2). Additionally, a higher proportion of Pakistani and Bangladeshi men had diabetes compared with other South Asians.[7]

This clustering of metabolic abnormalities conferring increased cardiovascular risk is characteristic of the metabolic syndrome, as defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) Criteria[15] (see table 1). The metabolic syndrome is particularly prevalent in South Asians and individuals of black African origin. South Asians, however, commonly exhibit an atherogenic profile (as described above), whereas individuals of black African origin exhibit a more protective lipid profile, specifically low serum levels of triglycerides and high plasma levels of HDL-C.[5] The relatively high prevalence of this atherogenic lipid profile and its association with insulin resistance in South Asians is implicated in their higher CHD risk compared with other ethnic groups.

Table 1. Risk factors associated with the metabolic syndrome, as defined by the National Cholesterol Education Program Adult Treatment Panel III Criteria[15]

- Central obesity:
  Waist circumference > 102 cm (men) and > 88 cm (women)
- Elevated triglycerides: > 150 mg/dL (1.7 mmol/L)
- Low high-density lipoprotein cholesterol:
  < 40 mg/dL (1.04 mmol/L) in men and < 50 mg/dL (1.30 mmol/L) in women
- Elevated blood pressure: ≥ 130/85 mmHg
- Elevated fasting blood glucose: ≥ 110 mg/dL (6.11 mmol/L)

Moreover, this predisposition to accelerated atherosclerosis is further enhanced by adoption of Western lifestyle.

What is appropriate lipid-modifying therapy in South Asians?

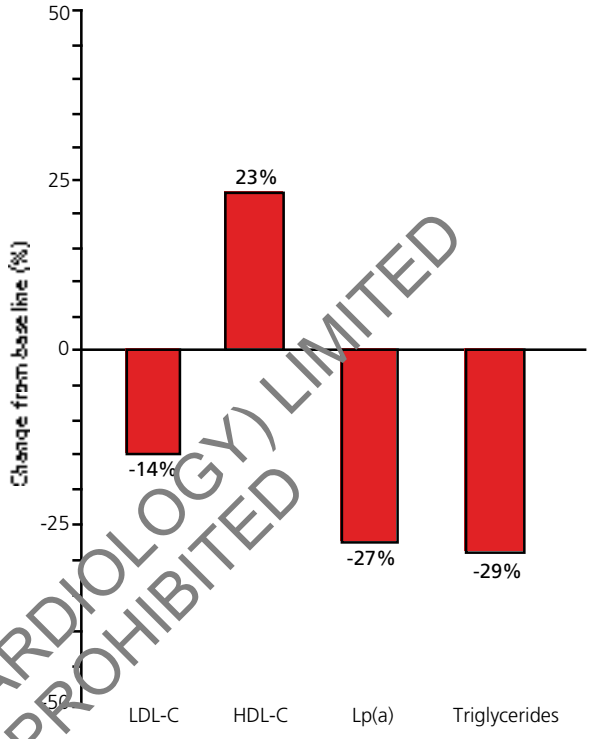
Clinical management of South Asians poses a particular challenge. Lipid-modifying therapy should address the specific needs of this patient group. Statin therapy should be the primary pharmacological intervention in patients at high cardiovascular risk and in those with elevated background levels of cholesterol, as indicated in recent guidelines.[15-17] Statins are highly effective in reducing LDL-C, decreasing levels by up to 50%,[18,19] although treatment effects on HDL-C and triglycerides are less robust. Typically, increases in HDL-C of 5–10% and decreases in triglycerides of 7–30% have been reported.[15] Fibrate therapy has been shown to be effective in reducing triglycerides (typically decreasing levels by 25–30%) and increasing HDL-C plasma levels, although the magnitude of the treatment effect on HDL-C observed in clinical studies was generally less than 10%.[20,21] Moreover, as an additional caveat, neither statin nor fibrate therapy is effective in reducing Lp(a).

Nicotinic acid is the most potent therapeutic agent available for increasing plasma HDL-C, and is also effective in decreasing serum triglycerides and LDL-C.[22] Nicotinic acid is also the only lipid-modifying therapy that substantially lowers Lp(a). Thus, the pharmacological profile of nicotinic acid suggests that it may be appropriate, in addition to primary statin therapy, for treatment of South Asians with this characteristic lipid profile of low HDL-C, high triglycerides and high Lp(a).

A prolonged-release formulation of nicotinic acid has been developed to improve the tolerability of earlier formulations. Clinical data in predominantly Caucasian patients[23] demonstrate that prolonged-release nicotinic acid is as effective as immediate-release nicotinic acid in increasing HDL-C and decreasing LDL-C, triglycerides and Lp(a). At doses of 1–2 g daily, it resulted in increases in HDL-C of 17–23%, as well as decreases of 14% in LDL-C, 27% in Lp(a) and 29% in triglycerides (figure 3).[24]

In a direct comparative trial,[25] prolonged-release nicotinic acid 2 g daily was significantly more effective than gemfibrozil 600 mg daily in increasing HDL-C plasma levels (26% *vs.* 13%). Moreover, despite concerns about reduced glycaemic control with nicotinic acid therapy, recent data from the Assessment of Diabetes control and Evaluation of the Efficacy of Niaspan Trial (ADVENT)[26] show that prolonged-release nicotinic acid can be safely used in Caucasian patients with controlled type 2 diabetes, with only transient effects on glycaemic control that are manageable by adjusting the dose of antidiabetic medication.

Figure 3. Treatment with prolonged-release nicotinic acid (2 g/day) was effective in increasing HDL-C, and decreasing LDL-C, Lp(a) and triglycerides in predominantly Caucasian patients



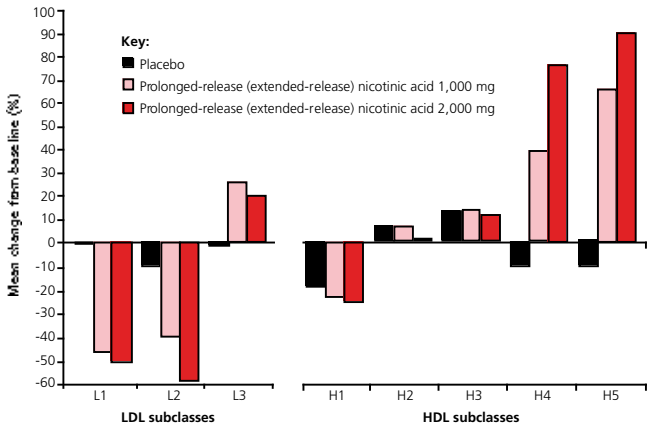
Key: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a)

Adapted from Morgan *et al.*[24]

Clinical benefits of nicotinic acid therapy

Data from long-term intervention studies provide support for the clinical benefits of nicotinic acid for secondary prevention of CHD in Caucasian patients. In the Coronary Drug Project, a long-term study involving 8,341 men with previous myocardial infarction (MI), treatment with nicotinic acid reduced the incidence of non-fatal MI by 26% and cerebrovascular events by 24% at six years compared with placebo. Follow-up data after 15 years demonstrated a significant reduction in mortality with nicotinic acid (11% *vs.* placebo, $p<0.001$).[27,28] Additionally, the Stockholm Ischaemic Heart Disease Secondary Prevention Study[29] demonstrated a significant reduction in total mortality (by 26%, $p<0.05$)

Figure 4. Effect of prolonged-release nicotinic acid on lipoprotein subclasses



Key: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

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and CHD mortality (by 36%, p<0.01) with the combination of immediate-release nicotinic acid and clofibrate.

The effects of nicotinic acid on lipoprotein subclasses may explain its beneficial effects. A recent analysis[30] showed that nicotinic acid produces potentially important effects on lipoprotein subclasses, specifically by reducing the more atherogenic small, dense LDL particles (characteristic of the diabetic atherogenic lipid profile) and increasing the larger cardioprotective HDL particles (figure 4). Together, these effects may contribute to the reduction in CHD morbidity and mortality observed with nicotinic acid therapy.

Conclusion

There is much evidence of an increased CHD risk amongst South Asians compared with Caucasians. Epidemiological studies have consistently demonstrated an increased prevalence of a specific atherogenic dyslipidaemia characterised by low plasma levels of HDL-C and high levels of triglycerides and Lp(a), which predispose to accelerated atherosclerosis. Additionally, South Asians have an increased prevalence of insulin resistance, diabetes and impaired glucose tolerance compared with Caucasians, which accentuates this CHD risk. This predisposition to accelerated atherosclerosis in South Asians is further enhanced by adoption of Western lifestyle.

Lipid-modifying therapy should address the specific needs of this patient group. Nicotinic acid is the most potent agent for increasing HDL-C and is also effective in reducing triglycerides, LDL-C and Lp(a). The addition of nicotinic acid to primary statin therapy has been suggested as a potentially useful treatment strategy in South Asians. Further clinical studies in this important patient group are needed to substantiate this potentially useful treatment strategy and identify specific groups that would derive most benefit.

Key messages

- South Asians (Indo-Asians) are at increased risk of coronary heart disease (CHD) compared with Caucasians. This excess risk cannot be explained by conventional risk factors
- South Asians have an increased prevalence of metabolic abnormalities including insulin resistance, diabetes, impaired glucose tolerance and atherogenic dyslipidaemia, characterised by low plasma levels of high-density lipoprotein cholesterol (HDL-C), high levels of triglycerides and an increase in the number of small, dense, low-density lipoprotein (LDL) particles, which predispose to accelerated atherosclerosis
- Nicotinic acid, which is the most potent agent currently available for increasing HDL-C and is also effective in reducing LDL-C, triglycerides and lipoprotein(a), combined with primary statin therapy may be a useful lipid-modifying strategy in this patient group

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Conflict of interest

AHB has received fees for lectures and advisory work for Merck Pharmaceuticals.

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