Dyslipidemia in Asian Indians: Determinants and Significance

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Abstract

Data suggest that lipid fractions other than total cholesterol, i.e. serum triglycerides (TG) and high-density lipoprotein (HDL) cholesterol are important for the pathogenesis of atherosclerosis. A combination of hypertriglyceridemia, low levels of HDL-cholesterol and high levels of small dense low-density lipoprotein, termed as “atherogenic dyslipidemia”, is particularly seen in Asian Indians. Although precise reason for such dyslipidemia is unknown, genetic predisposition and characteristic body composition (excess truncal subcutaneous fat and intraabdominal fat) may be important contributors. A common interface between such body composition and dyslipidemia in Asian Indians is high tendency to develop insulin resistance, more than the other ethnic groups. The general guidelines for the management of dyslipidemia in Asian Indians should be according to National Cholesterol Education Program, Adult Treatment Panel III. However, optimal management requires consideration of ethnic-specific dietary, lifestyle and management factors to formulate individual treatment guidelines.

INTRODUCTION

Dyslipidemia refers to the derangements of one or many of the lipoproteins; elevations of total cholesterol, low-density lipoprotein (LDL) cholesterol and/or triglycerides, or low levels of high-density lipoprotein (HDL) cholesterol while elevation of lipoproteins alone is labeled as ‘hyperlipidemia’. The term ‘atherogenic dyslipidemia’ denotes a combination of elevated triglycerides and small-dense LDL particles, and low levels of HDL-cholesterol.

Dyslipidemia may result from over-production or lack of clearance of the lipoprotein particles, or may be related to other defects in the apoproteins or metabolic enzyme deficiencies. The pathways and means of lipid metabolism in the human body reflect interactions of genetics, complex biochemical processes influenced by medical disorders, medications, and/or environmental factors. A primary dyslipidemia (e.g. familial hypercholesterolemia) typically refers to a genetic defect in the lipid metabolism that causes abnormal lipid levels. A secondary dyslipidemia may be due to a variety of reasons; environmental factors (diet rich in saturated fat or a sedentary lifestyle), diseases (type 2 diabetes, hypothyroidism, obstructive jaundice etc.), and medications (thiazide diuretics, progestins, anabolic steroids etc.). Secondary dyslipidemias could be corrected or ameliorated by treating the underlying disorder.

Dyslipidemia, particularly hypercholesterolemia and atherogenic dyslipidemia, have been closely implicated in the pathogenesis of coronary heart disease (CHD). A great deal of attention has been recently given to Asian Indians because of high prevalence of CHD in this ethnic group. The following discussion will focus on the salient features and recent knowledge in dyslipidemia, particularly in reference to Asian Indians. We shall not be including discussion on lipoprotein(a) in this review. We researched the topic using the following keywords ‘Asian Indians’, ‘Asians’ ‘South Asians’ and ‘Indians’ and ‘dyslipidemia’, ‘hyperlipidemia’ ‘triglycerides’ ‘HDL-cholesterol’ from Pubmed database (National Library of Medicine, Bethesda, MD, USA) and from the non-indexed publications of relevant governmental institutions in India. We also tabulated the average levels of serum triglycerides and HDL-cholesterol in Asian Indians residing in India and compared them with those of Caucasians from pooled data of various studies in Figs. 2 and 3. These data may not be strictly comparable; nonetheless interesting differences were noticed as discussed later.

Atherogenic Dyslipidemia and Small-dense LDL

Hypertriglyceridemia is a marker for the abnormal lipoprotein pattern known as the “atherogenic lipoprotein phenotype” that consists of raised triglyceride levels and small-dense LDL particles, and low HDL-cholesterol levels. The latter two abnormalities occur due to an increase in the triglyceride component of triglyceride-rich lipoproteins and increased activity of hepatic lipase. The composition of particles within a particular class may differ significantly. In
the case of LDL particles, some are larger and more buoyant (LDL A), whereas others are smaller and denser (LDL B). The LDL A particles contain more cholesterol ester per particle than do the LDL B particles. When a triglyceride from very-low density lipoprotein (VLDL) is exchanged for a cholesterol ester in LDL by the action of the enzyme cholesterol ester transfer protein (CETP), the VLDL becomes enriched in cholesterol ester, and LDL becomes enriched in triglyceride. Further, the triglyceride in LDL is hydrolyzed by lipoprotein lipase or hepatic lipase resulting in a smaller, denser LDL particle. Thus, increased VLDL secretion results in increased generation of small-dense LDL particles, which more likely when serum triglyceride concentrations are > 1.5 mmol/L. High levels of small dense LDL promote atherogenesis by the following mechanisms: a) rapid infiltration of small dense LDL into the arterial wall than do normal-sized LDL; b) increased susceptibility to retention in the extracellular matrix and c) increased oxidation. Evidence for increased atherogenicity of small-dense LDL particle emanates from the epidemiological association studies. Low levels of HDL-cholesterol are often caused by the core lipid exchanges, as well as accelerated clearance of HDL particles, explaining frequent occurrence of hypertriglycerideremia and low HDL-cholesterol levels.

Abnormal Regional Fat Distribution and Dyslipidemia (Fig. 1)

Individuals with abnormal fat distribution, characterized by a high waist-to-hip circumference ratio or high truncal subcutaneous fat appear to be predisposed to developing insulin resistance and dyslipidemia. Such a body composition is commonly seen in Asian Indians. Patients with upper body obesity have higher levels of non-esterified fatty acids (NEFAs) than those with lower body obesity, and the effect is further enhanced in the presence of resistance to the action of insulin on abdominal adipocytes. In the presence of excess NEFAs hepatic glucose output is increased. In addition, hepatic steatosis occurs and VLDL output from liver increases markedly that reduces HDL-cholesterol due to the mechanisms outlined earlier, thus increasing concentration of small-dense LDL. Hepatic clearance of insulin is decreased causing further hyperinsulinemia. Finally, lipids tend to accumulate in the skeletal muscles (intra-myocellular lipids, IMCL) and interfere with the action of insulin. Insulin resistance, hyperglycemia and dyslipidemia are end-points of complex metabolic interactions.

Dyslipidemia in Asian Indians

Investigations from several groups, including ours, have shown that Asian Indians are predisposed to develop type 2 diabetes, proatherogenic metabolic abnormalities (metabolic syndrome, insulin resistance syndrome) and CHD. The metabolic syndrome is a constellation of risk factors such as abdominal obesity, insulin resistance, glucose intolerance, hypertriglycerideremia, low levels of HDL-cholesterol and elevated blood pressure occurring in the same individual. ‘Atherogenic dyslipidemia’ is associated with metabolic syndrome and may be responsible for accelerated atherosclerosis.

It is opined that although the total cholesterol levels in Asian Indians is similar or lower as compared to Caucasians, and atherogenic dyslipidemia is more common, which may contribute to CHD. Table 1 shows representative investigations of dyslipidemia in the Asian Indians residing in India. We have selected only those studies that were population-based and consisted of a substantial subject sample. Overall the prevalence of dyslipidemia ranged from 10-73%. Specifically, prevalence of hypercholesterolemia was 28% in urban subjects as compared to 22% in the rural subjects. In urban New Delhi, the prevalence rate of hypertriglycerideremia was 61% in non-obese subjects as compared to ~73% in obese subjects. Subjects belonging to low socio-economic stratum and residing in the urban slums also showed substantial prevalence of hypercholesterolemia (~27%) and hypertriglycerideremia (~12-17%). However, it is difficult to compare observations of the various studies due to different sampling procedures, heterogeneity in the population samples, different methodologies used for estimations of lipoproteins and different cut-offs taken to define dyslipidemia.

Figs. 2 and 3 show average levels of serum triglycerides and HDL-cholesterol from collated data from several studies in various subpopulations of Asian Indians as compared with Caucasians, respectively. The serum triglyceride levels are highest in urban Asian Indians residing in India and migrant Asian Indians. Further, even the average serum triglyceride level of rural-based Asian Indians is higher than Caucasians (Fig. 2). The highest average levels of HDL-cholesterol among Asian Indians have been reported from the physically active Asian Indians residing in rural India (Fig. 3). Gupta et al (1997) showed that ~24% of the urban population of north India had low levels of HDL-cholesterol. Our group recorded low levels of HDL-C levels in 15-16% of the people belonging to low socio-economic stratum living in New Delhi. No investigator, however, has studied isolated low HDL-C levels in healthy Asian Indians residing in India. It
appears that average HDL-cholesterol concentrations in all Asian subgroups whether residing in India or elsewhere are lower than Caucasians. For example, according to Tai et al., 34% of the subjects with isolated low HDL-cholesterol levels in the multi-ethnic population in Singapore were Asian Indians.29 They further added that a higher number of Asian Indians with low levels of HDL-cholesterol and hypertriglyceridemia had glucose intolerance, were obese, and had higher degree of insulin resistance as compared to Chinese and Malays.29 Recent data show that low levels of HDL-cholesterol may be particularly pronounced in migrant Asian Indian women as compared to Caucasians.25

All values in mmol/L. Numbers with parentheses indicate the number of males or females, respectively.

M, males; F, females, *Total number of subjects including males and females, § Only male subjects

ND: not done

Table 1: Representative studies showing average lipid levels in Asian Indians residing in India

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age group (y)</th>
<th>Total cholesterol</th>
<th>Triglycerides</th>
<th>Low-density lipoprotein cholesterol</th>
<th>High-density lipoprotein cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vikram et al, 2003</td>
<td>14-25</td>
<td>M: 3.45±0.64 (331)</td>
<td>M: 0.94±0.34 (331)</td>
<td>M: 1.8±0.61 (331)</td>
<td>M: 1.22±0.17 (331)</td>
</tr>
<tr>
<td>Lubree et al, 2002</td>
<td>30-50</td>
<td>4.26±0.88 (150) §</td>
<td>1.18 (150) §</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Bhattacharya et al, 1979</td>
<td>20-60</td>
<td>M: 5.5±1.1 (184)</td>
<td>M: 0.92±0.34 (184)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Snehlatha et al, 2000</td>
<td>≥ 40</td>
<td>M: 5.1±1.0 (396)</td>
<td>M: 1.65±1.59 (396)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Mohan et al, 2001</td>
<td>≥ 20</td>
<td>4.92±1.03 (479)*</td>
<td>1.5±0.9 (479)*</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Chadha et al, 1997</td>
<td>25-64</td>
<td>M: 5.1±1.08 (681) §</td>
<td>M: 1.62±0.54 (681) §</td>
<td>M: 3.05±1.02 (539)</td>
<td>M: 1.42±0.33 (539)</td>
</tr>
<tr>
<td>Gupta et al, 1997</td>
<td>20-60+</td>
<td>4.55±1.11 (199) §</td>
<td>1.87±0.62 (199) §</td>
<td>2.78±0.98 (199) §</td>
<td>1.11±0.31 (199) §</td>
</tr>
</tbody>
</table>

Urban Slums

| Vikram et al, 2003 | 18-65 | M: 4.67±1.02 (170) | M: 1.48±1.73 (170) | M: 3.0±1.02 (170) | M: 1.03±0.14 (170) |
| lubree et al, 2002 | | 4.66±1.22 (469) | 1.41±0.73 (469) | 2.98±1.18 (469) | 1.06±0.18 (469) |

Rural

| Gupta et al, 1997 | 20-60+ | 4.27±0.95 (202) § | 1.37±0.51 (202) § | 2.5±0.85 (202) § | 1.13±0.33 (202) § |
| Chadha et al, 1997 | 25-64 | M: 4.64±0.7 (100) | M: 1.63±0.33 (100) | M: 2.6±0.74 (100) | M: 1.30±0.29 (100) |
| | F: 4.64±0.70 (259) | F: 1.58±0.28 (259) | F: 2.57±0.62 (259) | F: 1.34±0.24 (259) |

Chinese and Malays.29 Recent data show that low levels of HDL-cholesterol may be particularly pronounced in migrant Asian Indian women as compared to Caucasians.25

Adverse anthropometric profile has been noted in hyperlipidemic Asian Indian males by our group in a case-control study. Of note, these patients were “non-obese” based on body mass index, but still had higher waist circumference (p < 0.001), waist-to-hip circumference ratio (p < 0.01), individual skinfold thicknesses (p < 0.001), sum of
Determinants of Dyslipidemia in Asian Indians

A multitude of factors may contribute to dyslipidemia in Asian Indians.

1. Physical Activity: Asian Indians are more physically inactive as compared to many ethnic groups. In particular, low level of physical activity has been reported in children and young adults. However, precise contribution of physical inactivity to dyslipidemia in the Asian Indian populations is unknown.

2. Body Composition: Migrant Asian Indians and Asian Indians residing in urban India have body composition conducive to development of dyslipidemia. Excess truncal fat and increased intra-abdominal fat accumulation have been linked to insulin resistance and consequent atherogenic dyslipidemia.

3. Genetic predisposition: It may be an important factor even for non-familial dyslipidemia in Asian Indians, however very few studies are available. Association of apolipoprotein B gene polymorphisms (Xba I and EcoRI) with hyperlipidemia has been shown in migrant Asian Indians as opposed to absence of association shown in hyperlipidemic and normolipidemic subjects by our group.

4. Diet: Asian Indian diets rich in carbohydrate and low in ω-3 polyunsaturated fatty acids may exacerbate hypertriglyceridemia. Dyslipidemic profile is commonly seen in the vegetarians. The precise role of dietary factors in genesis of dyslipidemia in Asians remains to be defined.

Management of Dyslipidemia in Asian Indians

The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) reinforced LDL as the primary target of cholesterol-lowering therapy with the optimal goal of its level below 100 mg/dL. The panel recommends treatment beyond LDL lowering for patients with triglyceride levels of 200 mg/dL and above. Non-HDL cholesterol, which is derived from subtracting HDL-cholesterol concentration from total cholesterol level, representing the sum of all atherogenic lipoproteins, has been identified as a secondary target of therapy in patients with elevated triglyceride levels. Managing and monitoring non-HDL cholesterol may be particularly important for Asian Indians. Further, the fact that the prevalence of CHD is nearly two-fold higher in the presence of combination of hypertriglyceridemia and low HDL-cholesterol levels is relevant to the management of dyslipidemia in Asian Indians. For effective lipid lowering in Asian Indians, the following principles and interventions are suggested:

1. Maintenance in regular aerobic physical activity is a simple and important measure.
2. It is advisable to increase intake of ω-3 polyunsaturated fatty acids in diets, particularly for the vegetarians. Effective lowering of serum triglyceride levels and increase HDL-cholesterol levels has been noticed with the use of moderate to high doses of ω-3 polyunsaturated fatty acids taken as fish oils.
3. HMG-CoA reductase inhibitors, (statins), are very effective in reducing LDL-cholesterol levels. The newer statins (Atorvastatin and Rosuvastatin) reduce serum triglyceride levels by nearly 15-20% and also increase the LDL particle diameter, but they do not have any significant effect on HDL-cholesterol levels.
4. Fibrates are more effective than statins in reducing serum triglyceride levels and increasing HDL-cholesterol levels. Atherogenic dyslipidemia in Asian Indians may be well managed by the use of fibrates.
5. Niacin is more effective than either statins or fibrates in increasing HDL-cholesterol levels (~35%), however it may not be tolerated by many patients. Sustained release preparations of niacin may be associated with lower adverse effects, but are not presently available in India.
6. For effective treatment of hypertriglyceridemia and low HDL-cholesterol levels, a combination of statins with fibrates or niacin may be tried although adverse drug reactions may increase. Recent evidence indicates that combination of statins and fibrates is well tolerated. Adequate spacing of administration of both the drugs by several hours, gradual upward dose titration, and careful monitoring of liver function and creatine phosphokinase levels is essential to minimize adverse effects.
7. Fibrates and ω-3 polyunsaturated fatty acids also have anti-inflammatory properties, and may be additionally useful in Asian Indians who have high prevalence of subclinical inflammation, more than that noticed in Caucasians.
Pitfalls and Future Directions

The research in this area is in preliminary stages. Concerted research efforts, clinical and experimental, need to be devoted to investigate determinants, pathogenesis and correct management of dyslipidemia in Asian Indians. An area of particular concern is knowledge and awareness of the guidelines for the management of dyslipidemia, in physicians in India. Nearly 40% of the patients prescribed lipid-lowering drugs did not meet the NCEP (ATP II) criteria for the initiation of lipid lowering drug therapy in north India. The correct knowledge of the guidelines for lipid lowering needs to be reinforced to the Indian physicians by lectures and continuing medical education. Finally, to initiate young physicians in these subjects, the undergraduate teaching curriculum should include lectures on hyperlipidemia.

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REFERENCES
