

# Association between Isolated Hypercholesterolemia, Isolated Hypertriglyceridemia and Coronary Artery Disease in South Indian Type 2 Diabetic Patients

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## Summary

Very high prevalence rates of coronary artery disease have been reported among Indians. The aim of this study was to determine the relative importance of isolated hypercholesterolemia, isolated hypertriglyceridemia, isolated high low-density lipoprotein and isolated low high-density lipoprotein in coronary artery disease among South Indian type 2 diabetic subjects. The study group comprised of 17,885 type 2 diabetic patients attending our institute. A history of documented myocardial infarction was considered as the diagnostic criteria for coronary artery disease. Isolated hypercholesterolemia was defined as serum cholesterol over 200 mg/dL with normal serum triglyceride levels ( $\leq 200$  mg/dL); isolated hypertriglyceridemia was defined as serum triglyceride level over 200 mg/dL with normal serum cholesterol levels ( $\leq 200$  mg/dL). Isolated low high-density lipoprotein was defined as one below 35 mg/dL with normal serum triglyceride levels. Isolated high low-density lipoprotein cholesterol was defined as one over 150 mg/dL with normal serum triglyceride levels. Normolipidemia was defined as serum cholesterol and serum triglyceride both upto 200 mg/dL, high-density lipoprotein 35 mg/dL or above and low-density lipoprotein upto 150 mg/dL. The prevalence of coronary artery disease was significantly high among patients with isolated hypercholesterolemia (4.1%;  $p < 0.001$ ), isolated high low-density lipoprotein (4.5%;  $p < 0.001$ ) and isolated low high-density lipoprotein (3.9%;  $p = 0.005$ ) compared to normolipidemic individuals (2.8%), but not in those with isolated hypertriglyceridemia (3.4%). The odds ratios for coronary artery disease increased with each quartiles of isolated cholesterol, isolated low-density lipoprotein cholesterol and total cholesterol to high-density lipoprotein ratio and reached statistical significance in the last quartile ( $p < 0.05$ ). There was no significant increase in the odds ratios for coronary artery disease in relation to quartiles of isolated triglycerides. For isolated low high-density lipoprotein, when the last quartile was taken as the reference, the odds ratio for coronary artery disease in the first quartile reached statistical significance ( $p = 0.03$ ). Multivariate regression analysis revealed age (odds ratio 1.06;  $p < 0.001$ ), male sex (odds ratio 1.7;  $p < 0.001$ ), hypercholesterolemia (odds ratio 1.26;  $p = 0.07$ ) and high low-density lipoprotein levels (odds ratio 1.22;  $p = 0.043$ ) to be strongly associated with coronary artery disease. Among South Indian type 2 diabetic subjects, serum isolated hypercholesterolemia and high low-density lipoprotein cholesterol but not isolated hypertriglyceridemia appear to be associated with coronary artery disease (*Indian Heart J* 2000; 52: 400-406).

## Introduction

The prevalence of coronary artery disease (CAD) is higher among patients with both diabetes and impaired

glucose tolerance compared to the general population<sup>1,2</sup>. Several studies have shown that the prevalence of CAD is considerably higher among migrant Asian Indians compared to Europeans<sup>3-5</sup>. Recently, the SHARE study reported significantly higher risk of cardiovascular events among Asian Indians compared to Europeans and Chinese<sup>6</sup>. It has also been predicted that in India due to westernisation, a dramatic increase in CAD may occur in forthcoming years<sup>7</sup>. However, earlier studies have revealed that the conventional risk factors for CAD

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like hypertension, obesity, smoking and family history of CAD do not explain the excess CAD rates seen among Asian Indians<sup>8,9</sup>. An increased thrombogenic risk profile due to high triglycerides, low high-density lipoprotein (HDL) cholesterol, glucose intolerance, insulin resistance, abdominal obesity and higher lipoprotein(a) (Lp[a]) levels have been suggested to explain the increased prevalence of CAD among Indians<sup>10</sup>.

The role of serum triglycerides as a risk factor for CAD remains controversial<sup>11,12</sup> and some studies have shown a strong association of serum triglyceride. Triglycerides alone are not a good predictor of CAD<sup>11-13</sup>. A very recent report generated from the analyses of data from the Multiple Risk Factor Intervention Trial and three other trials concluded that triglyceride measurements do not provide clinically meaningful information about coronary heart disease (CHD) risk beyond that obtained by cholesterol measurements<sup>14</sup>.

Ethnic differences have also been reported for both prevalence and risk factors of CAD<sup>15,16</sup>. On account of these differences, studies on the risk factors for CAD in different ethnic populations is of great interest. However, there is very little data on the relative importance of serum lipids for CAD among native Indians and virtually none on Indian type 2 diabetic subjects. Here, we report on the association between isolated hypercholesterolemia, isolated hypertriglyceridemia, isolated low HDL cholesterol and CAD in a large group of type 2 diabetic patients attending a referral centre for diabetes in South India.

### Material and Methods

The study group comprised of 17,855 type 2 diabetic patients attending the M.V. Diabetes Specialities Centre, Chennai. The centre caters to approximately 15 percent of the diabetic population of Chennai. Recent epidemiological studies suggest that the clinical profiles of the patients seen at our centre are fairly representative of Chennai<sup>17</sup>. The diagnosis of diabetes and the classification as type 2 diabetes were based on the WHO study group criteria<sup>18</sup>. A detailed clinical history was taken in all patients including the duration of diabetes mellitus, age of onset, history of angina/infarction and a history of smoking. All the patients underwent a thorough clinical examination which included recording of height and weight, body mass index (BMI) and elicitation of ankle and knee jerks.

A resting 12-lead ECG was done in all cases using a computerised machine. A fasting blood sample was drawn after an overnight fast of 12 hours, for plasma glucose and lipid estimation. Biochemical analysis was

done on Corning Express Plus Auto Analyser (Corning, Medfield, MA, USA) using kits supplied by Boehringer Mannheim (Mannheim, Germany). Fasting plasma glucose (glucose oxidase method)<sup>19</sup>, serum cholesterol (CHOD-PAP method)<sup>19,20</sup>, serum triglycerides (GPO-PAP method)<sup>19,21</sup> and serum creatinine (modified kinetic method of Jaffe)<sup>22</sup> were measured in all patients after an overnight fast of at least 10 hours. Glycosylated haemoglobin (HbA1c) was estimated by high pressure liquid chromatography using the Variant machine (Bio Rad, Hercules, CA, USA). HDL cholesterol was estimated by CHOD-PAP method after precipitating low-density lipoprotein (LDL) and chylomicron fractions by addition of phosphotungstic acid in the presence of magnesium ions and very low-density lipoprotein (VLDL)<sup>19,20,23</sup>. LDL cholesterol was calculated using the Friedwald formula<sup>24</sup> namely,

$$\text{LDL cholesterol} = \text{Total cholesterol} - \left( \frac{\text{Triglycerides}}{5} + \text{HDL} \right)$$

The coefficients of variation for cholesterol, triglyceride and HDL cholesterol assay were 2.6 percent, 3.3 percent and 3.9 percent, respectively.

The following definitions were used for the study.

1. *Coronary Artery Disease*: Only if the individuals had prior myocardial infarction (MI) determined by history of prolonged chest pain, hospital records documenting treatment for MI including raised enzyme levels and presence of pathological Q waves in anterior or inferior leads.
2. *Hypertension*: If the blood pressure was greater than 140/90 (JNCV criteria)<sup>25</sup>.
3. *Isolated Hypercholesterolemia*: Total serum cholesterol levels above 200 mg/dL (>5.2 mmol/L) and serum triglyceride levels upto 200 mg/dL ( $\leq$ 2.26 mmol/L).
4. *Isolated Hypertriglyceridemia*: Serum triglyceride levels over 200 mg/dL (>2.26 mmol/dL) and serum cholesterol levels upto 200 mg/dL ( $\leq$  5.2 mmol/L).
5. *Isolated Low HDL*: HDL cholesterol levels less than 35 mg/dL (0.91 mmol/L) and serum triglyceride levels upto 200 mg/dL ( $\leq$  2.26 mmol/L).
6. *Isolated High LDL*: LDL cholesterol level more than 150 mg/dL and serum triglyceride levels upto 200 mg/dL.
7. *Combined Hyperlipidemia*: Serum cholesterol above 200 mg/dL and triglyceride levels above 200 mg/dL.
8. *Normolipidemia*: Serum cholesterol level of 200 mg/dL or lower, serum triglyceride upto 200 mg/dL, HDL levels over 35 mg/dL and LDL cholesterol upto 150 mg/dL.

**Statistical Analysis.** Analyses were performed using SPSS Program (Version 4.0.1) on an IBM compatible computer. Chi-squared tests were used to compare frequencies and t-tests were used to compare means. Serum lipid levels were categorised into quartiles. The prevalence of CAD in each quartile was determined. To determine the association of serum lipids with CAD, the first quartile was taken as the reference and the relative odds ratios (ORs) for the other quartiles of serum cholesterol, LDL cholesterol, triglyceride and total cholesterol to HDL ratio were determined. To determine the association of serum HDL cholesterol with CAD, the OR for CAD was calculated taking the last quartile as the reference. Univariate regression analysis was performed using CAD as the dependent variable and age, sex, hypertension, smoking, hypercholesterolemia, hypertriglyceridemia, low HDL levels and high LDL levels as independent variables. Multivariate regression analysis was performed using CAD as the dependent variable. The variables which turned out to be significant in the univariate analysis were taken as independent variables for the multivariate regression analysis.

## Results

Table 1 outlines clinical and biochemical features of patients with and without CAD. There was a male preponderance in subjects with CAD compared to subjects without CAD ( $p < 0.001$ ). The subjects with CAD were older than the non-CAD subjects ( $p < 0.001$ ) and also had significantly longer duration of diabetes ( $p < 0.001$ ). The prevalence of smoking and hypertension were high among the subjects with CAD compared to subjects without CAD ( $p < 0.05$ ). Serum cholesterol ( $p = 0.002$ ), LDL cholesterol ( $p < 0.001$ ) and total cholesterol to HDL ratio ( $p = 0.02$ ) were higher in the CAD group compared to the non-CAD group. Serum HDL cholesterol levels in the CAD group were significantly lower compared to non-CAD group ( $p = 0.03$ ). Among the CAD patients 85 percent were on aspirin and 10 percent on statin therapy.

The prevalence of CAD was significantly high among patients with combined hyperlipidemia (4%) compared to normolipidemic individual (2.8%;  $p = 0.005$ ) (Fig. 1). However, the prevalence of CAD was equally high in those with isolated hypercholesterolemia (4.1%;  $p < 0.0001$  compared to normolipidemic patients). Patients with isolated low HDL cholesterol levels had a significantly higher prevalence of CAD (3.9%) compared to those with normal lipid levels ( $p = 0.005$ ). The prevalence of CAD in subjects with isolated LDL cholesterolemia was significantly higher than the

TABLE 1  
Clinical Characteristics of the Study Groups

| Parameters                           | CAD (n=641) | Non-CAD (n=17214) | p-Value |
|--------------------------------------|-------------|-------------------|---------|
| Male (%)                             | 481 (75%)   | 10921 (63%)       | <0.001  |
| Age (years)                          | 61±10       | 54±11             | <0.001  |
| Body mass index (kg/m <sup>2</sup> ) | 24.5±4.0    | 24.8±4.3          | NS      |
| Smoking (%)                          | 112 (17.5%) | 2564 (14.9%)      | 0.07    |
| Hypertension (%)                     | 174 (27.1%) | 3688 (21.4%)      | <0.001  |
| Duration of diabetes mellitus        | 13±8        | 9±8.0             | <0.001  |
| Fasting plasma glucose (mg/dL)       | 196±77      | 195±72            | NS      |
| Glycosylated haemoglobin (%)         | 9.3±2.2     | 9.2±2.2           | NS      |
| Serum cholesterol (mg/dL)            | 209±46      | 204±44            | 0.002   |
| Serum triglycerides (mg/dL)          | 183±126     | 183±143           | NS      |
| HDL - cholesterol (mg/dL)            | 39±9        | 40±12             | 0.03    |
| LDL - cholesterol (mg/dL)            | 136±39      | 130±37            | <0.001  |
| Total cholesterol/HDL ratio          | 5.6±1.6     | 5.4±1.5           | 0.02    |
| Statins (%)                          | 64 (10.0%)  | 637 (3.7%)        | <0.0001 |
| Aspirin (%)                          | 545 (85.0%) | 1751 (10.2%)      | <0.001  |

normolipidemic subjects (4.5%;  $p < 0.001$ ). Total cholesterol to HDL cholesterol ratio more than 4.5 was also significantly associated with CAD (3.8%;  $p = 0.002$ ). However, prevalence of CAD in those with isolated hypertriglyceridemia (3.4%) was not significantly different from those with normolipidemia.

Fig. 2 shows the relative odds for CAD in relation to the quartiles of serum cholesterol levels. The prevalence of CAD increased linearly with increase in quartiles of serum cholesterol level. Taking the first quartile as the reference the OR for second quartile was 1.0, third quartile 1.4 ( $p = 0.009$ ) and fourth quartile 1.3. This, however, reached statistical significance only in the third quartile.

The relative odds for CAD in relation to the quartiles of serum triglyceride levels is presented in Fig. 3. Taking the first quartile as the reference, the OR for second

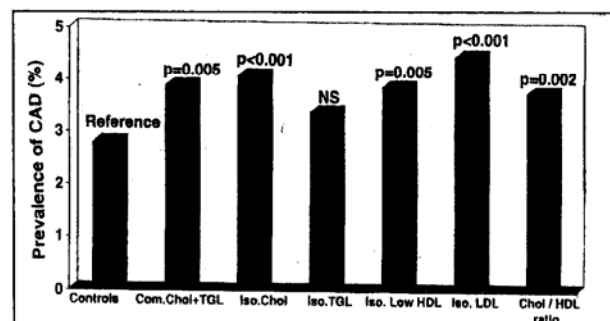


Fig. 1. Prevalence of CAD (myocardial infarction) in different categories of lipidemia.

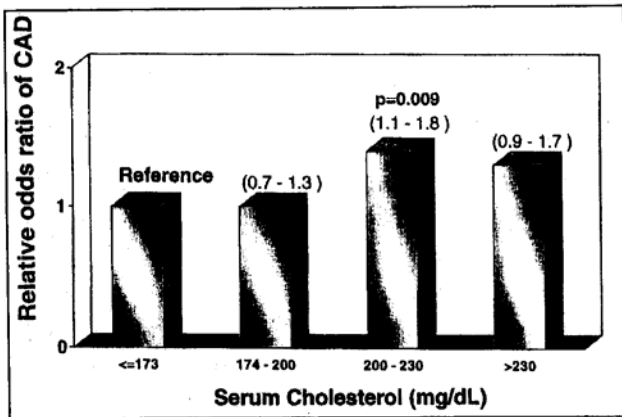


Fig. 2. Relationship of isolated serum cholesterol with CAD.

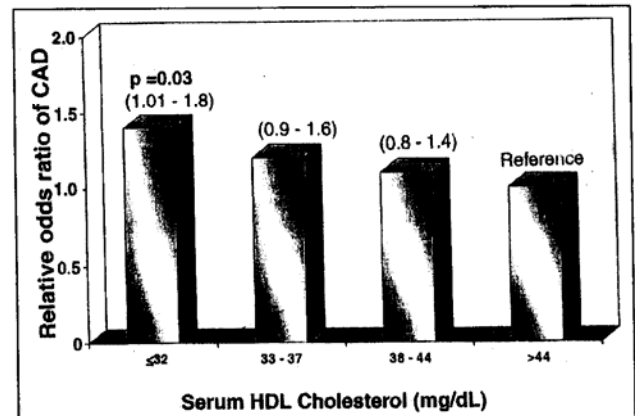


Fig. 4. Relationship of isolated HDL cholesterol with CAD.

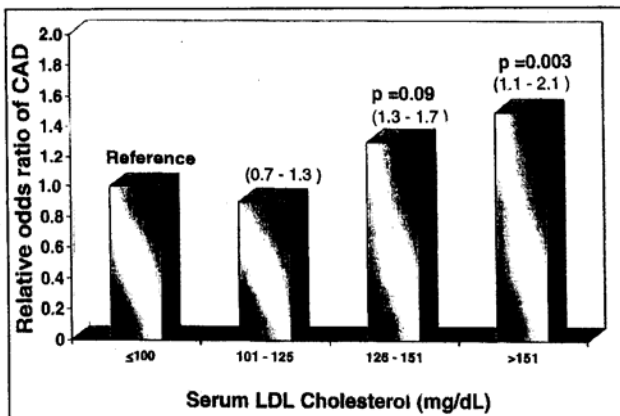


Fig. 3. Relationship of isolated LDL cholesterol with CAD.

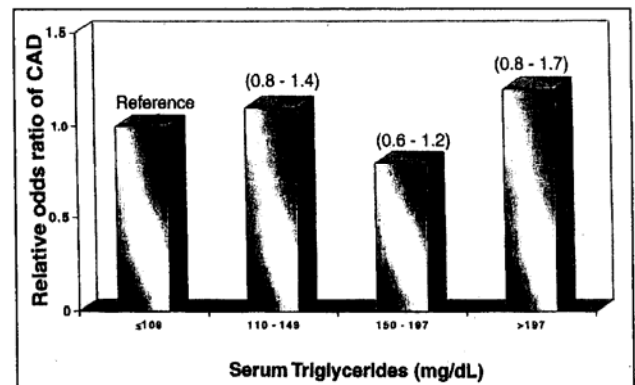


Fig. 5. Relationship of isolated serum triglycerides with CAD.

quartile was 1.1, third quartile 0.8, fourth quartile 1.2; none of these differences reached statistical significance. Fig. 4 shows the relative OR for CAD in relation to the quartiles of HDL cholesterol. The last quartile was taken as the reference. The OR for the third quartile was 1.1, second quartile 1.2 and first quartile 1.4. The odds ratio for the first quartile reached statistical significance ( $p=0.03$ ). Fig. 5 presents the relative OR for CAD in relation to the LDL cholesterol levels. The first quartile was taken as the reference. The OR for second quartile was 0.9, third quartile 1.3 and fourth quartile 1.5. Statistical significance was reached in the third ( $p=0.09$ ) and fourth quartiles ( $p=0.003$ ). Fig. 6 presents the relative OR for CAD with respect to quartiles of the cholesterol to HDL ratio. The first quartile was taken as the reference. The OR for the second quartile was 0.9, third quartile 1.4 and fourth quartile 1.4. The odds ratios reached statistical significance in the third ( $p=0.005$ ) and fourth quartile ( $p=0.003$ ).

Table 2 presents the results of univariate regression analysis. Age (OR 1.06;  $p<0.0001$ ), male sex (OR 1.7;

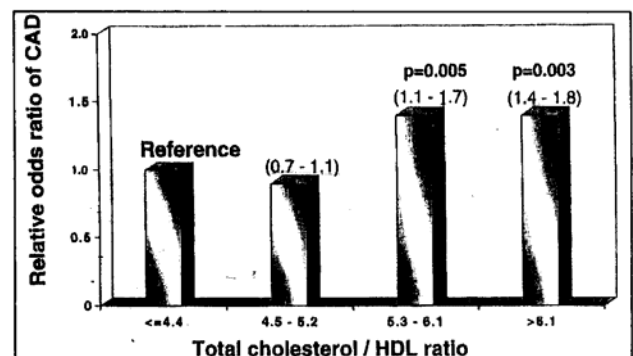


Fig. 6. Relationship of total cholesterol/HDL ratio with CAD in normo-triglyceridemic individuals.

$p<0.001$ ), hypercholesterolemia (OR 1.29;  $p=0.0024$ ), LDL cholesterol (OR 1.34;  $p=0.0009$ ), total cholesterol to HDL ratio (OR 1.38;  $p=0.0001$ ), hypertension (OR 1.29;  $p=0.006$ ) and smoking (OR 1.25;  $p=0.043$ ) had a strong association with CAD. Table 3 presents the results of multivariate regression analysis. In order to avoid colinearity among the variables, total cholesterol to HDL ratio was not included as an independent variable in

**TABLE 2**  
Univariate Regression Analysis of Risk Factors for Coronary Artery Disease

| Variable   | $\beta$ | S.E.  | p-Value | OR (95% CI)       |
|--|---------|-------|---------|-------------------|
| Age  | 0.05    | 0.004 | <0.0001 | 1.061 (1.05-1.06) |
| Sex (1-male, 0 - female)                               | 0.53    | 0.095 | <0.0001 | 1.71 (1.42-2.05)  |
| Smoking  | 0.22    | 0.110 | 0.043   | 1.25 (1.007-1.55) |
| Hypertension   | 0.26    | 0.094 | 0.006   | 1.29 (1.08-1.56)  |
| Obesity (BMI > 25)                                     | 0.13    | 0.084 | 0.117   | 1.14 (0.97-1.35)  |
| Hypercholesterolemia (serum cholesterol > 200 mg/dL)   | 0.25    | 0.083 | 0.0024  | 1.29 (1.09-1.51)  |
| Hypertriglyceridemia (serum triglycerides > 200 mg/dL) | 0.05    | 0.094 | 0.590   | 1.05 (0.87-1.3)   |
| Low HDL levels (< 35 mg/dL)                            | 0.12    | 0.085 | 0.1644  | 1.12 (0.95-1.32)  |
| High LDL levels (> 150 mg/dL)                          | 0.29    | 0.088 | 0.0009  | 1.34 (1.10-1.6)   |
| High total cholesterol/HDL cholesterol ratio (> 5.0)   | 0.33    | 0.080 | <0.0001 | 1.38 (1.17-1.63)  |

OR - Odds ratio, CI - Confidence interval, BMI - Body mass index.

this analysis. The results revealed age, male sex, hypercholesterolemia and high LDL levels as strong risk factors for CAD.

### Discussion

The occurrence of CAD is substantially increased in patients with type 2 diabetes<sup>26</sup>. CAD mortality and the incidence of non-fatal CAD events are two to four times higher in type 2 diabetic patients than in age-matched non-diabetic subjects<sup>27,28</sup>. Both hypercholesterolemia and hypertriglyceridemia have been shown to be related to CAD in diabetic patients in many prospective studies<sup>29</sup>. In the WHO Multinational study<sup>29</sup> and the Paris Prospective study<sup>30</sup>, hypertriglyceridemia was the only factor that correlated with the occurrence of CAD in diabetic patients. But many studies also support the opposite conclusions. The United Kingdom Prospective Diabetes Study (UKPDS), the largest ever study on type 2 diabetes<sup>31</sup> analysed the risk factors for CAD in 3055 type 2 diabetic patients; CAD was significantly associated with increased concentrations of LDL cholesterol, decreased concentrations of cholesterol, hyperglycemia, hypertension and smoking. However, serum triglycerides were not associated with CAD in this study. In the Lipid Research Clinics Coronary Primary Prevention Trial<sup>32</sup>, treatment with diet and cholestyramine resulted in 19 percent reduction in the risk of CHD, in spite of an increase in serum triglyceride concentrations averaging 2.5 percent. Oestrogen treat-

**TABLE 3**  
Multiple Logistic Regression Analysis of Risk Factor for Coronary Artery Disease

| Variable   | $\beta$ | S.E.  | p-Value | OR (95% CI)       |
|--|---------|-------|---------|-------------------|
| Age  | 0.05    | 0.004 | <0.0001 | 1.057 (1.05-1.07) |
| Sex (1-male, 0-female)                               | 0.55    | 1.003 | <0.0001 | 1.73 (1.42-2.01)  |
| Smoking  | 0.16    | 0.115 | 0.160   | 0.17 (0.94-1.47)  |
| Hypertension   | 0.02    | 0.097 | 0.810   | 1.02 (0.85-1.24)  |
| Hypercholesterolemia (serum cholesterol > 200 mg/dL) | 0.23    | 0.116 | 0.049   | 1.26 (1.003-1.53) |
| High LDL levels (Serum LDL > 150 mg/dL)              | 0.20    | 0.099 | 0.043   | 1.22 (1.006-1.48) |

Abbreviations same as in Table 2.

Coronary artery disease was taken as the dependent variable. The following categories were taken as independent variables: categorical - sex, hypertension, smoking, hypercholesterolemia and high LDL levels; continuous variable - age.

ment is also associated with increased triglyceride concentrations and a reduced risk of CHD<sup>33</sup>. Even in the PROCAM study<sup>34</sup>, Helsinki Heart Study<sup>35</sup> and the Framingham study<sup>36</sup> where strong association between serum triglycerides and CAD were shown, the association was more powerful in the presence of low HDL or high LDL cholesterol levels, rather than with serum triglycerides per se.

The aim of the present study was to see the relative importance of cholesterol and its subfractions and serum triglycerides with the risk of CAD. Only those with MI were included in order to make the endpoint a stronger and more robust one. This study clearly brings out that the serum total cholesterol, LDL cholesterol and total cholesterol-HDL ratio are independent risk factors for CAD. Moreover, those with combined hyperlipidemia (raised cholesterol and triglycerides) did not have any higher risk compared to those with isolated hypercholesterolemia (prevalence rate of CAD in those with combined hypercholesterolemia 4.0% vs isolated hypercholesterolemia 4.1%; p=NS).

The importance of serum cholesterol in Indians has probably been underplayed because of evidence from migrant Indians that triglycerides/low HDL are more important for CAD<sup>5</sup>. However, it is possible that risk factors could differ considerably in migrant and native Indians due to differences in income, lifestyle, body weight, waist-hip ratio and differences in prevalence of diabetes and other components of the metabolic syndrome<sup>8</sup>.

Many studies have demonstrated the effectiveness of cholesterol lowering therapy in reducing the risk of CAD. The Scandinavian Simvastatin Survival Study<sup>37</sup> demonstrated that the risk for CHD events was significantly reduced by cholesterol lowering with simva-

statin in patients with angina pectoris and previous MI. Post-hoc subgroup analysis on diabetic patients included in the trial showed that benefit of cholesterol lowering in terms of reduction in the risk of serious CHD events was at least as marked in diabetic patients as in non-diabetic patients<sup>38</sup>. This is in accordance with the results of the Cholesterol And Recurrent Events (CARE) trial which showed that treatment with pravastatin reduced the risk of CAD events upto 25 percent in patients with diabetes<sup>39</sup>.

The recent American Diabetes Association Position Statement recommends that firstline lipid lowering therapy in diabetic subjects should be statins<sup>40</sup>. Given the high prevalence of silent infarction in diabetics and the greater mortality rates, primary prevention of CAD in diabetic patients appears to be justified. Despite the lack of association between triglycerides and CAD in this study, the importance of serum triglycerides cannot be ignored. It is well known that high serum triglyceride can increase the small dense LDL particles and lead to greater oxidised and glycated LDL<sup>41</sup> and can also impair fibrinolysis<sup>42</sup>. All of these are very important in the causation of CAD<sup>41-44</sup>.

One limitation of this study is, it is a cross-sectional one. Moreover it is clinic-based and is restricted to survivors of MI. One could argue that among those who succumbed to infarction, serum triglycerides would have been high. However, it is equally plausible that they could have had even higher serum cholesterol levels. More studies, especially prospective longitudinal population-based ones, are needed to assess the relative importance of hypercholesterolemia and hypertriglyceridemia in Indian diabetic patients.

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