

The Effect of Fenofibrate on Insulin Sensitivity and Plasma Lipid Profile in Non-diabetic Males with Low High Density Lipoprotein/Dyslipidaemic Syndrome

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Abstract

Non-diabetic males, particularly those with very low levels of high density lipoprotein (HDL) type cholesterol and high levels of very low density type lipoprotein (VLDL), are associated with insulin resistance and decreased insulin sensitivity. The evidence that elevation of HDL cholesterol and diminution of triglycerides with drugs, with improvement in insulin sensitivity is still lacking. In the treatment of the dyslipidaemic syndromes with hypolipidaemic drugs, the associated metabolic abnormality of insulin resistance/sensitivity has to be addressed. We investigated the degree of decreased insulin sensitivity in 23 patients with low HDL and/or raised triglycerides by measuring the fasting, first and second hour insulin levels during an oral glucose tolerance test (OGTT) and repeated the measurements after a 6-month course of fenofibrate. The insulin levels were correlated with the OGTT, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides measured before and at the end of the trial. The serum insulin at the second hour of the OGTT fell from 100.79 ± 42.79 mU/l to 54.56 ± 25.43 mU/l ($P < 0.0005$) even though there was no change in the blood glucose level at this point. Our study shows that fenofibrate (Lipanthyl®) 300 mg daily significantly raises the pretreatment low HDL cholesterol (from 0.64 ± 0.1 mmol/l to 0.99 ± 0.2 mmol/l) as well as lowers the triglyceride level (from 2.17 ± 1.1 mmol/l to 1.43 ± 0.64 mmol/l) in patients with low HDL/dyslipidaemic syndrome. The data also support the conclusion that treatment with fenofibrate increases insulin sensitivity as measured by the corresponding insulin levels of the OGTT in the study subjects who presented with very low HDL cholesterol level. There was also a decrease in blood pressure readings in our study subjects. Throughout the trial, there was no significant change in body weight or exercise level in the subjects studied.

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Introduction

Hyperinsulinaemia and insulin resistance have been postulated to relate directly to both hypertension and coronary artery disease in type II diabetes and possibly also in those with the dyslipidaemic syndrome as first described by Reaven.¹ This syndrome (also known as Syndrome X in endocrinology) comprises of some or all of the following features: insulin resistance, glucose intolerance, dyslipidaemia (increased very low density type lipoproteins/VLDL, decreased high density type lipoprotein/HDL cholesterol), hypertension and central obesity.^{2,3} The possibility that insulin resistance and hyperinsulinaemia cause or is strongly associated with both hypertension and atherosclerosis⁴⁻⁶ may explain why some forms of antihypertensive therapy do not produce the expected decrease in atherosclerotic disease.⁷ Furthermore, hyperinsulinaemia predisposes to hypertension by various mechanisms.⁸⁻¹² In this study,

we evaluated whether a decrease in VLDL triglyceride and an increase in HDL with the drug fenofibrate would improve insulin sensitivity and decrease fasting hyperinsulinaemia with a decrease in blood pressure. We also studied the oral glucose tolerance test (OGTT) of these subjects and measured the corresponding serum insulin levels at the fasting, first and second blood glucose levels of the OGTT.

Materials and Methods

Twenty-three male patients were recruited from the outpatient clinics. All of them were under 65 years old without a past history of diabetes and all had a fasting HDL cholesterol of less than 0.9 mmol/l with or without a raised triglyceride level of >1.9 mmol/l and a raised LDL cholesterol level of >3.4 mmol/l. Four patients were cigarette smokers and 14 of them were on antihypertensive medication (stable BP on beta-blockers or

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ACE inhibitors) for at least a year prior to the trial. All patients were stabilised on a low cholesterol diet of less than 300 g of cholesterol (NIH step I diet) for 6 months prior to initiation of fenofibrate. They were all counselled on dietary control and advised to remain on diet during the trial. All subjects were initiated on fenofibrate 300 mg once a day before dinner for 6 months and liver function tests were evaluated every 3 months to exclude fenofibrate-induced hepatotoxicity. For the duration of the trial, all patients were strongly advised to maintain their usual lifestyle, smoking pattern (if applicable) and exercise programme (if they exercised) as before and not to take any other new medication or change their medication profile without prior consultation with the trial coordinator. The frequency of exercise per week was recorded if they exercise regularly. All subjects were started on fenofibrate in accordance with the American National Cholesterol Education Programme (NCEP) Adult Treatment Panel II guidelines.¹³ Particular emphasis was paid to the HDL cholesterol level. The following endpoints were measured:

- Weight at 0 and 6 months
- Body mass index at 0 and 6 months
- Exercise schedule (if any): hours per week
- Systolic and diastolic BP at 0 and 6 months
- Fasting blood glucose at 0 and 6 months
- HbA1c at 0 and 6 months
- Uric acid at 0 and 6 months
- Total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol (calculated from the Friedewald equation) at 0, 3 and 6 months
- Oral glucose tolerance test (75 g) and corresponding 0, 1st hour and 2nd hour serum insulin at 0 and 6 months

Assays

Blood pressure was measured manually twice at each visit, both at the beginning and at the end of the consultation visit (approximately 30 min). The lower of two values was used to reflect actual resting blood pressure.

Insulin was measured with the MEIA assay¹⁴ (Micro Particle Enzyme ImmunoAssay) manufactured by Abbott® Laboratories. This assay has a sensitivity better than or equal to 1.0 mU insulin/ml and a specificity of almost 100% with minimal cross-reactivity (<0.005% with proinsulin and only in specimens containing low levels of insulin). The correlation coefficient¹⁴ compared to standard insulin radioimmunoassay (Pharmacia®) is 0.982.

Lipids were measured using enzymatic methods¹⁵ (Greiner Diagnostica®). Wet chemistry methods were used. The fasting blood for lipid analysis were collected into a plain tube without the use of tourniquet, immediately centrifuged and serum isolated for deep freeze

storage at -70°C. Batch analysis was performed within 6 months of collecting the first sample. The LDL cholesterol level was determined using the Friedewald equation subject to the equation's limitations. Serum glucose was measured in the hospital laboratory using the Beckmann glucose analyser. The glycosylated haemoglobin was measured using the Glytrac® glycosylated haemoglobin set.¹⁶

Statistical Analysis

Student's paired t-test was used to directly compare the means between before and after treatment results. Normality of data was assessed by Kolmogorov-Smirnov method (with Lilliefors' correction). All the parameters except the blood pressure and weight passed the test for normality set at $P < 0.05$. Wilcoxon signed rank test was done for the blood pressure and weight analysis. Statistical significance was taken at $P < 0.05$. Statistical analysis was computed using SPSS® version 7.5 and Sigmatat® programmes.

Ethical Considerations

All subjects gave their informed consent to the study.

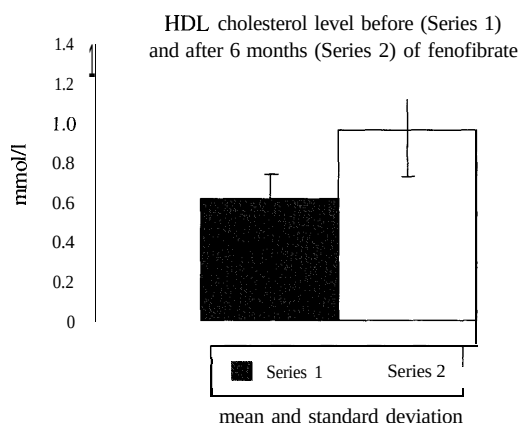


Fig. 1. Mean HDL cholesterol levels before and after 6 months of fenofibrate.

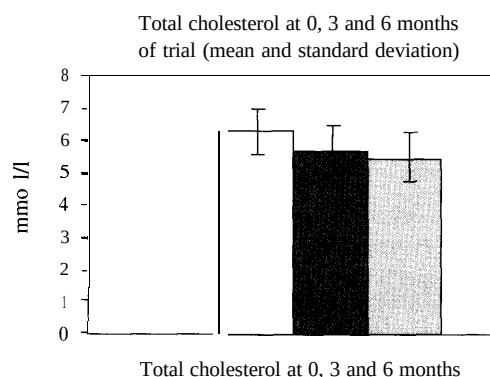


Fig. 2. Mean total cholesterol levels at start, after third month and at sixth month of trial.

Results

Means of parameters studied $\pm$ standard deviations

Time after fenofibrate	0 month	3rd month	6th month	P value
Age (years)	42 $\pm$ 9.7			
Weight (kg)	72.506 $\pm$ 12.33		72.33 $\pm$ 11.46 kg	ns
BMI	26.17 $\pm$ 3.57		26.11 $\pm$ 3.25	ns
No. of subjects who exercise	5	5	5	ns
Total duration of exercise (hours per week)	6	6.5	6	ns
Systolic BP (mmHg)	140 $\pm$ 14.14		131 $\pm$ 13.64	<0.05
Diastolic BP (mmHg)	88.5 $\pm$ 10.57		80.5 $\pm$ 7.26	<0.05
HbA1c	5.433 $\pm$ 0.78		5.36 $\pm$ 0.8	ns
Total cholesterol (mmol/l)	6.3 $\pm$ 0.69	5.66 $\pm$ 0.88	5.48 $\pm$ 0.84	<0.005
TG (mmol/l)	2.17 $\pm$ 1.10	1.42 $\pm$ 0.52	1.43 $\pm$ 0.639	<0.05
HDL (mmol/l)	0.64 $\pm$ 0.098	0.96 $\pm$ 0.18	0.99 $\pm$ 0.21	<0.0001
LDL (mmol/l)	4.69 $\pm$ 0.88	4.05 $\pm$ 0.75	3.85 $\pm$ 0.74	<0.0001
Fasting (0 hour OGTT) glucose (mmol/l)	4.73 $\pm$ 0.75		4.23 $\pm$ 0.69	<0.001
1 st hour OGTT glucose (mmol/l)	8.26 $\pm$ 3.0		7.33 $\pm$ 1.19	ns
2nd hour OGTT glucose (mmol/l)	6.8 $\pm$ 1.9		6.3 $\pm$ 1.28	ns
0 hour insulin (mU/L)	10.24 $\pm$ 3.22		7.34 $\pm$ 2.56	<0.005
1st hour insulin (mU/L)	94.02 $\pm$ 40.89		92.41 $\pm$ 57.27	ns
2nd hour insulin (mU/L)	100.79 $\pm$ 42.79		54.56 $\pm$ 25.43	<0.0005

BMI : body mass index

BP : blood pressure (mmHg)

TG : triglycerides (mmol/l)

HDL : high density lipoprotein (mmol/l)

LDL : low density lipoprotein (mmol/l)

OGTT : oral glucose tolerance test

ns : not significant

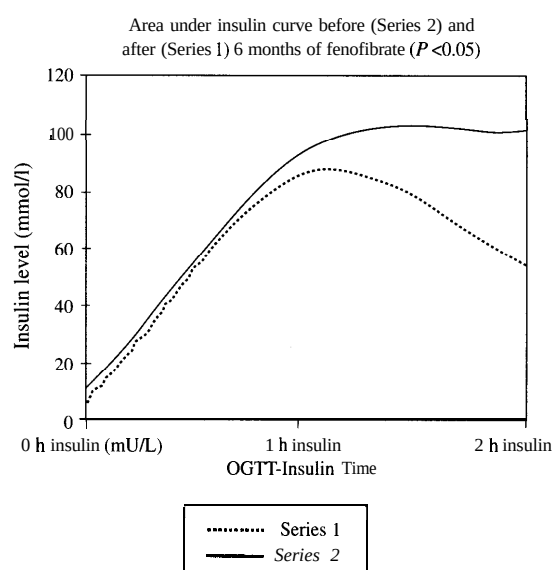


Fig. 3. Area under insulin curve before and after 6 months of fenofibrate.

Discussion

Our study subjects did not show any improvement in weight and BMI after six months of fenofibrate. However, the resting systolic and diastolic blood pressure showed a statistically significant small decrease with the systolic of 140 mmHg and diastolic of 88.5 mmHg falling

to a systolic of 131 mmHg and diastolic of 80.5 mmHg. This could be the result of improved insulin sensitivity or lipid abnormalities as both of them are intricately linked to blood pressure as suggested by De Fronzo³ and others.^{8,17}

The total cholesterol, LDL cholesterol and triglycerides all showed a marked decrease with the greatest fall occurring just after three months of initiating fenofibrate. Total cholesterol, LDL cholesterol and triglyceride levels showed a drop of 13%, 18% and 34% over their pre-treatment levels respectively. HDL cholesterol showed a statistically significant rise of 50% over its pre-treatment level. The degree of improvement in lipid profile (with the exception of HDL cholesterol) is consistent with most studies on fenofibrate. The rise in the HDL cholesterol level by about 50% was higher than previous studies which document on average a 30% increase. It is likely that because our subjects had very low levels of HDL cholesterol (mean 0.6 $\pm$ 0.1 mmol/l) initially, any absolute increase with treatment contributed to a greater percentage rise over its pre-treatment value. In absolute measurements, the increase in HDL (mean of 0.3 $\pm$ 0.2 mmol/l) is not inconsistent with previous published studies on fenofibrate ability to significantly raise the HDL levels.¹⁸⁻²¹

In our study, the majority (18 out of 23) led relatively sedentary lifestyle and do not exercise. Only 5 subjects exercise at least once a week without any change in the duration of exercise workout before and during the study period. Although a change in exercise pattern/intensity cannot be ruled out entirely, this is less likely as corroborated by the lack of change in body weight or

body mass index since the initiation of therapy.

Although most of the subjects (61%) did not achieve the target LDL cholesterol level of less than 3.4 mmol/l, the majority (65%) attained a HDL level of greater than 0.9 mmol/l after the six months treatment period.

The fall in the fasting glucose level i.e. 4.73 ± 0.75 mmol/l to 4.23 ± 0.75 mmol/l was significant ($P < 0.001$) but there was no difference between the first and second hour OGTT glucose corresponding levels. The HbA1c level also did not show a statistically significant decrease.

As for insulin dynamics, the fasting and second hour OGTT insulin levels showed a statistically significant decrease (both $P < 0.0005$) after six months. This is further borne out by the significant decrease for the insulin area under the curve ($P < 0.01$)²² for the amount of insulin that was required for the disposal of the 75 g of glucose of the OGTT. There was no significant difference for the area under the curve for the pre and post-treatment glucose excursion curve of the OGTT. This fall in insulin requirement is most likely due to an increase in insulin sensitivity with fenofibrate treatment. As there was no significant change in exercise levels (among subjects who exercise regularly) or body weight of the subjects under treatment, the increase in insulin sensitivity could be attributed solely to fenofibrate therapy. Furthermore, the improvement in insulin sensitivity was seen throughout, both in subjects who were sedentary and active.

We were unable to infer if this increase in insulin sensitivity was due to either a fall in the triglyceride level or a rise in the HDL cholesterol since their metabolic regulations are closely inter-related (by its modulation via lipoprotein ligands and the combined actions of lipoprotein lipase, hepatic lipase, and cholesterol ester transfer protein). As various authors have linked a probable causal effect of dyslipidaemia on decreased insulin sensitivity, any improvement in these lipid abnormalities should theoretically lead to an improvement in insulin sensitivity. Similarly, the fall in blood pressure readings could also be due to the improvement in insulin sensitivity,⁹⁻¹² as high insulin levels itself are known to be sympathomimetic and sodium retentive.¹¹

The other possible explanation for the improved insulin sensitivity could be a sudden cessation of cigarette smoking²³ among some of our subjects but this is unlikely as they were told not to change their lifestyle or decrease their smoking intake during the trial. In the 4 patients who were cigarette smokers, the number of packets of cigarettes smoked daily were the same in the short period before and after the period that they were on fenofibrate. Moreover, there were only 4 cigarette smokers among our subjects and the improvement in insulin sensitivity and lipid profile was seen in both the smokers as well as in the non-smokers

Conclusion

The risks for coronary artery disease in non-diabetic patients are dependent on blood pressure, a dyslipidaemic profile, smoking history, poor family history and possibly a hyperinsulinaemic state together with a degree of insulin resistance.⁴⁻⁶ The combination of a moderately elevated triglyceride,²⁴ low HDL cholesterol and elevated small dense LDL has been associated with an approximately four- to seven-fold increase in risks for development of CAD.^{25,26} This is the pattern frequently encountered in patients with the dyslipidaemic syndromes as described by Kaplan and De Fronzo.^{2,3} Furthermore, a low HDL cholesterol level in particular, is a very strong risk factor for the development of coronary artery disease.²⁷⁻³⁰ In our study, the use of fenofibrate resulted in an improvement in the lipid profile particularly in the HDL cholesterol level. The improvement in insulin sensitivity and the decrease in both the systolic and diastolic blood pressure occurred independent of any change in body weight or BMI and also probably exercise workload duration. This is most probably due to the increase in HDL cholesterol and decrease in triglyceride levels which resulted in an improvement in insulin sensitivity and subsequent drop in blood pressure readings.⁷⁻¹⁰ Further large scale studies are needed to confirm our findings. The study conclusions also support current suggestions by certain authors³¹⁻³³ that aggressive drug treatment be started earlier in patients with low HDL cholesterol particularly in those with extremely low HDL cholesterol (< 0.6) levels associated with hypertriglyceridaemia.

Limitations of the Study

The authors acknowledged that there are certain limitations to this study. The number of patients studied was small. Although this might have reduced the power of the study, the results were in most instances still statistically significant.

Although the universal standard of measuring insulin sensitivity is the hyperinsulinaemic-euglycaemic clamp method, this is not adopted for our study as it is time- and labour-consuming, expensive and its invasive nature is a deterrent for voluntary patient recruitment.

Hence, we adopted the abovementioned approach which has also been widely used in insulin sensitivity studies.

Although the subjects were not blinded to the medication, care was taken to ensure uniformity of dietary and smoking lifestyle throughout the short period under trial. Moreover, certain prolonged effects of hypolipidaemic drugs (even after cessation) make short-term placebo double-blind cross-over studies less feasible.

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REFERENCES

- Reaven G. Role of insulin resistance in human disease. *Diabetes* 1988; 37:1595.
- Kaplan N M. The deadly quartet: Upper body obesity, glucose intolerance, hypertriglyceridaemia, and hypertension. *Arch Intern Med* 1989; 149:1514-5.
- De Fronzo R A, Ferrannini E. Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia and atherosclerotic cardiovascular disease. *Diabetes Care* 1991; 14:173-94.
- Stout R W. Insulin and atheroma: 20-year perspective. *Diabetes Care* 1990; 13:631.
- Modan M, Or J, Karasik A, Drory Y, Fuchs Z, Lusky A, et al. Hyperinsulinaemia, sex and risk of atherosclerotic cardiovascular disease. *Circulation* 1991; 84:1165-75.
- Sowers J R, Sowers P S, Edelson G W. Insulin and premature ischaemic heart disease. *J Myocardial Ischemia* 1993; 5(Suppl 1):45-8.
- Moan A, Os I, Hjermann I, Kjeldsen S E. Hypertension therapy and risk of coronary heart disease: how do antihypertensives affect metabolic factors? *Cardiology* 1995; 86:89-93.
- Pollare T, Lithell H, Berne C. Insulin resistance is a characteristic feature of primary hypertension independent of obesity. *Metabolism* 1990; 39:167-74.
- Reaven G M. Insulin Resistance, hyperinsulinaemia and hypertriglyceridemia in the etiology and clinical course of hypertension. *Am J Med* 1991; 90(Suppl 2A):7-12.
- Swislocki A L M, Hoffman B B, Reaven G M. Insulin resistance, glucose intolerance and hyperinsulinaemia in patients with hypertension. *Am J Hypertens* 1989; 2:419-20.
- Weber M A. Cardiovascular and metabolic characteristics of hypertension. *Am J Med* 1991; 91(Suppl 1A):4.
- Tan C E, Chew L S, Sum C F, Fok A C, Wang K W. Metabolic abnormalities in young non-obese males with hypertension. *Ann Acad Med Singapore* 1994; 23:1:2-5.
- Expert Panel on the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993; 269:3015-23.
- Imx® Insulin Reagent (Abbot Imx® Insulin Assay) Pack Manual. USA: Abbot Laboratories, 1993. List No. 2A10:10.
- Lopes-Virella M F, Stone I, Shelton E, Cohwell J A. Cholesterol determination in high density lipoproteins separated by three different methods. *Clin Chem* 1977; 22:882-4.
- Menard L, Dempsey M E, Blankstein L A, Aleyassine H, Wacks M, Soeldner J S. Quantitative determination of glycosylated hemoglobin A1 by agar gel electrophoresis. *Clin Chem* 1980; 26:1598-1602.
- Ferrannini E, Haffner S M, Stern M I. Essential hypertension. An insulin resistant state. *J Cardiovasc Pharmacol* 1990; 15(Suppl 5):18-25.
- Bairaktari E T, Tzallas C S, Tsimihodimos V K, Liberopoulos E N, Miltiades G A, Elisaf M S. Comparison of the efficacy of atorvastatin and micronized fenofibrate in the treatment of mixed hyperlipidemia. *J Cardiovasc Risk* 1999; 6:113-6.
- Gholami K, Tavakoli N, Maleki M, Shafiee A J. Comparison of the efficacy and safety of fenofibrate and lovastatin in patients with primary type IIa or IIb hyperlipidaemia. *Clin Pharm Ther* 1998; 23:213-21.
- Davignon J. Advances in drug treatment of dyslipidemia: focus on atorvastatin. *Can J Cardiol* 1998; 14:28B-38B.
- Adkins J C, Faulds D. Micronised fenofibrate: a review of its pharmacodynamic properties and clinical efficacy in the management of dyslipidaemia. *Drugs* 1997; 54:615-33.
- Le Floch J I, Escuyer P, Baudin E, Baudon D, Perlemuter L. Blood glucose area under the curve. *Diabetes Care* 1990; 13:172-5.
- Axelsen M, Eliasson B, Joheim E, Lenner R A, Taskinen M R, Smith U. Lipid intolerance in smokers. *J Intern Med* 1995; 237:449-55.
- Tenkanen L, Pietila K, Manninen V, Manttari M. The triglyceride issue revisited. Findings from the Helsinki Heart Study. *Arch Intern Med* 1994; 154:2714-20.
- Austin M A, Breslow J L, Hennekens C H, Buring J E, Willett W C, Krauss R M. Low density lipoprotein subclass patterns and risk of myocardial infarction. *JAMA* 1988; 260:1917-21.
- Griffin B A, Freeman D J, Tait G W, Thomson J, Caslake M J, Packard C J, et al. Role of plasma triglyceride in the regulation of plasma LDL subfractions: relative contribution of small dense LDL to coronary heart disease. *Atherosclerosis* 1994; 106:241-53.
- Lavie C J, Milani R V. National Cholesterol Education Program's recommendations and implications of "missing" HDL cholesterol in cardiac rehabilitation programs. *Am J Cardiol* 1991; 68:1087-8.
- Zeiger A M, Schachlinger V, Hohnloser S H, Saurbier B, Just H. Coronary atherosclerotic wall thickening and vascular reactivity in humans: elevated HDL cholesterol ameliorate abnormal vasoconstriction in early atherosclerosis. *Circulation* 1994; 89:2525-32.
- Kitamura A, Iso H, Naito Y, Iida M, Konishi M, Folsom A R, et al. High density lipoprotein cholesterol and premature coronary artery disease in urban Japanese men. *Circulation* 1994; 89:2533-9.
- Corti M C, Guralnik J M, Salive M E, Harris T, Field T S, Wallace R B, et al. HDL cholesterol predicts coronary heart disease mortality in older persons. *JAMA* 1995; 274:539-44.
- Milani R V, Lavie C J. Assessment and management of patients with low levels of HDL cholesterol. *J Myocardial Ischemia* 1992; 4:27-45.
- Rubins H B, Robins S J, Collins D, Iranmanesh A, Wilt T J, Mann D, et al. Distribution of lipids in 8,500 men with coronary artery disease. Department of Veterans Affairs HDL Intervention Trial Study Group. *Am J Cardiol* 1995; 75:1196-201.
- Kashyap M L. Cholesterol and atherosclerosis: a contemporary perspective [review]. *Ann Acad Med Singapore* 1997; 26:517-23.