The effect of lipid-lowering drugs on serum lipids and apolipoproteins in hypercholesterolemic non-insulin dependent diabetes mellitus (NIDDM)

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Coronary artery disease is an important complication of diabetes mellitus[1,2]. In the general population, the concentrations of total cholesterol and low-density lipoprotein (LDL) are positively associated with the prevalence of coronary heart disease[3]. It is well known that hyperlipidemia as a metabolic abnormality is frequently associated with diabetes[4-7]. These suggest that coronary heart disease in the diabetic is partly related to abnormalities of lipid metabolism. Unlike the microvascular complications which occur more frequently in IDDM, the macrovascular complications are more frequently observed in NIDDM. Thus the treatment of abnormalities of lipid metabolism in NIDDM may reduce the rates of morbidity and mortality from arteriovascular disease. Probucol, a cholesterol-lowering agent with uncertain mode of action, and pravastatin, an inhibitor of the rate-limiting enzyme of cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are now used frequently to treat hypercholesterolemia. However, the effect of these drugs on lipid metabolism in diabetic patients with hypercholesterolemia remains to be fully elucidated. In the present study, the effect of small doses of probucol and pravastatin on concentrations of serum lipids and apolipoproteins was investigated in non-obese NIDDM patients (frequently observed in Japan) with hypercholesterolemia.

Subjects and methods

Subjects

Thirty subjects of NIDDM with hypercholesterolemia (above 240mg/dl) were selected and divided randomly into two groups. The patients were hypercholesterolemic despite

of being received low fat and low cholesterol diet. The diabetes was stable prior to entry into the study. One group of fifteen patients (ten type IIa and five type IIb hyperlipidemia) were administered probucol (250mg twice a day) and the other group of fifteen patients (ten type IIa and five type IIb hyperlipidemia) were administered pravastatin (5mg twice a day) for twelve months. They have not been taken any drugs to lower plasma lipid concentrations. Patients with evidence of abnormal hepatic or renal function and a history of excessive ethanol consumption were excluded. Quality of diet and dose of insulin or oral hypoglycemic agents (OHA) were not changed during the study. The venous blood sample was taken after a 12-14 hr fast, and concentrations of serum lipids and apolipoproteins were measured. Determinations of blood cell count, serum creatinine, blood urea nitrogen, transaminases, creatine phosphokinase, alkaline phosphatase and lactic dehydrogenase were performed at each blood sampling. No adverse drug experiences were reported. Besides, no drug-related side effect was revealed in clinical and laboratory examinations. Clinical characteristics of diabetic subjects were shown in Table 1.

Measurements

The percentages of the HbA1 and HbA1c contents were measured by affinity chromatography (normal ranges, HbA1 6-8% and HbA1c 4-6%). Serum total cholesterol[8] and triglyceride[9] were determined enzymatically. HDL cholesterol was determined by measurement of the lipid in the supernatant after precipitation of VLDL and LDL in 1ml of serum with 50μl of 2mol/l $MnCl_2$ and 50μl of sodium heparin. Apolipoproteins were measured by immuno-nephelometry using the commercially available kit of Daiichi Chemical Pharmaceutical Co., Tokyo. Intraassay coefficients of variation were 4-8% for apolipoproteins. Friedewald equation was used for calculation of LDL cholesterol.

Statistical analyses

Analysis of variance, non-parametric statistics and two-tailed Student's non-paired t test were used for statistical analyses, The data are expressed as the mean ± SD.

Results

Clinical characteristics in NIDDM patients

As shown in Table 1, NIDDM subjects were similar in their clinical characteristics before probucol or pravastatin treatment. BMI was not changed during the study in either group.

Changes in serum lipid concentrations

As shown in Table 2, the concentrations of serum lipids were similar before probucol or pravastatin treatment. Treatment with probucol or pravastatin resulted in a significant decrease in plasma total and LDL cholesterol concentrations after six months, and the decrease remained till twelve months. HDL cholesterol was significantly reduced by probucol treatment after twelve months. Triglyceride levels were not altered in either group.

Changes in serum apolipoprotein concentrations

Apolipoprotein B (apo-B) concentrations were significantly decreased by probucol or pravastatin treatment. Serum apo-E level was significantly decreased by pravastatin treat-

Table 1 Clinical characteriscs of subjects

	probucol-treated	pravastatin-treated
Mean age (years)	58 ± 12	56 ± 11
Sex ratio (f : m)	10 : 5	10 : 5
duration of diabetes (years)	14.1 ± 5.7	12.5 ± 5.1
Treatment		
insulin	5/15	6/15
tablets	5/15	5/15
diet only	5/15	4/15
FBG (mg/dl)	144 ± 28	147 ± 32
HbA_1 (%)	10.0 ± 1.5	9.8 ± 1.5
HbA_1c (%)	7.7 ± 1.2	7.7 ± 1.2
BMI (kg/m^2)	17.6 ± 2.6	18.6 ± 4.4
complications		
neuropathy	9/15	10/15
retinopathy	6/15	6/15
nephropathy	3/15	2/15

The values are expressed as mean ± SD. The number of subjects in each group was fifteen

FBG : fasting blood glucose, BMI : body mass index (kg/m^2).

Clinical characteristics were not different from each other before probucol- and pravastatin-treatment.

ment. Serum levels of apo-AI, AII, CII and CIII were not significantly altered in either group.

Changes in various indices

The ratio of apo-AI to apo-AII was not altered in either group. The ratio of apo-B to apo-AI was significantly decreased by pravastatin treatment. The ratio of HDL cholesterol to apo-AI was slightly decreased by probucol treatment but slightly increased by pravastatin treatment. Consequently, at six or twelve months after the treatment, the ratio of HDL cholesterol to apo-AI in pravastatin-treated group was significantly higher than that in probucol-treated group. The ratio of the difference between total and HDL cholesterol to HDL cholesterol was significantly decreased by pravastatin treatment, though not changed by probucol treatment.

Changes in glycemic control

Glycosylated hemoglobin concentration was not changed during the study in either group.

Table 2 Changes in serum lipids and apolipoproteins concentrations after treatment

	probucol treatment			pravastatin treatment		
	before	6 months	12 months	before	6 months	12 months
T. ch	300±40	247±44**	245±45**	295±33	243±37**	231±36**
TG	150±71	146±60	143±60	153±87	147±54	147±52
HDL	53±19	41±16	38±16*	48±13	51±11	50±10
LDL	217±47	177±45*	178±43*	201±38	153±31**	145±33**
apoprotein						
A I	128±28	114±23	110±25	113±33	115±16	114±18
A II	31.8±7.4	26.8±3.5	27.0±3.6	31.3±8.7	27.2±4.8	28.0±4.9
B	189±44	143±58*	140±60*	162±61	111±23*	108±26
C II	4.8±1.5	4.3±2.4	4.4±2.0	5.8±1.7	4.6±1.6	5.0±1.7
C III	13.0±8.3	11.5±6.0	11.8±6.2	12.7±4.0	11.9±2.8	12.0±3.1
E	6.0±2.1	5.8±1.9	5.8±2.0	6.1±2.1	4.4±1.6*	4.5±1.5
T. ch-HDL / HDL	4.7±2.8	5.0±2.3	5.4±2.5	5.1±2.1	3.8±1.4*	3.6±1.3*
A I/A II	4.4±0.8	4.3±0.8	4.1±0.7	4.2±1.0	4.2±0.7	4.1±0.8
B/A I	1.5±0.5	1.3±0.5	1.3±0.3	1.4±0.6	1.0±0.2*	0.9±0.2*
HDL/A I	0.41±0.07	0.36±0.10#	0.35±0.08§	0.42±0.05	0.44±0.07#	0.44±0.06§
LDL/B	1.15±0.26	1.24±0.46	1.27±0.34	1.24±0.45	1.38±0.18	1.34±0.20
HbA_1	10.0±1.5	10.4±1.8	10.4±1.8	9.8±1.5	10.4±1.8	10.2±1.6
HbA_1c	7.7±1.2	7.9±1.4	7.8±1.3	7.7±1.2	7.9±1.4	7.9±1.3

T. ch : total cholesterol, TG : triglyceride. The values are expressed as mean ± SD. The number of subjects in each group was fifteen. * $p < 0.05$, ** $p < 0.02$, significantly different from that before treatment. #-# and §-§ $p < 0.05$, significantly different from each other.

Discussion

Non-obese NIDDM patients were selected in this study, because non-obese NIDDM is frequent in Japan, and obesity itself, rather than diabetes mellitus, has an important role in abnormality of lipid metabolism. Probucol and pravastatin treatments similarly decreased serum total and LDL cholesterol levels, suggesting that these drugs are useful for the treatment of hypercholesterolemia in NIDDM patients. There have been no reports regarding the influence of the mode of diabetic therapy on the cholesterol-lowering effect of probucol or pravastatin. Although the number of subjects was too small to say clearly in the present study, probucol or pravastatin exhibited similar cholesterol-lowering effects in diet-, OHA- and insulin-treated NIDDM. It has been reported that therapy with inhibitors of HMG-CoA reductase was associated with a 20-30% decrease in the plasma concentration of triglyceride in hypercholesterolemic patients[10-12] and in NIDDM patients[13,14]. However, serum triglyceride levels were not significantly changed after

treatment in either group probably because non-obese NIDDM patients had relatively low serum levels of triglyceride in the present study. Probucol has been reported to decrease HDL cholesterol in familial hypercholesterolemia[15-18]. In the present study, HDL cholesterol concentrations were significantly decreased by probucol treatment. This result was in agreement with the report of Hattori et al., which showed a significant reduction in HDL-cholesterol level by probucol treatment in NIDDM patients[19]. Therefore, probucol effect on HDL-cholesterol may be similar in familial hypercholestrolemia and NIDDM patients. Serum levels of apo-B were significantly decreased by probucol or pravastatin treatment. Because it has been suggested that apo-B may be a better predictive factor than lipids for coronary heart disease[20,21], probucol or pravastatin treatment may reduce coronary heart disease in NIDDM. Although Yoshino et al.[14] have reported that apo-AI level was significantly increased by pravastatin treatment in NIDDM patients after 12 months, apo-AI level was not altered in the present study. One of the reasons for this discrepancy may be that HbA1c concentration after treatment was slightly decreased in their NIDDM patients, while it remained constant in our treatment. Serum apo-E concentration was significantly decreased by pravastatin treatment. This result was in agreement with the report of Yoshino et al.[14]. Pravastatin treatment may enhance the rate of metabolic clearance of chylomicron remnant.

The ratio of apo-B to apo-AI has been suggested as a helpful parameter for assessing the relative risk of coronary heart disease[22]. This ratio and the ratio of the difference between total and HDL cholesterol to HDL cholesterol, atherogenic indices, were significantly decreased by pravastatin treatment, but not by probucol treatment. Therefore, pravastatin, rather than probucol, may be more useful for the treatment of hypercholesterolemia associated with NIDDM. Interestingly, the ratio of HDL cholesterol to apo-AI after treatment was significantly different between probucol-treated and pravastatin-treated group, suggesting that composition of HDL cholesterol may be different between probucol treatment and pravastatin treatment. Because HDL cholesterol has been suggested to have a protective effect on atherosclerosis[23,24], this phenomenon may have an important clinical significance. Further studies should be necessary.

Probucol and pravastatin treatment did not affect the glycemic control. No adverse drug experiences were reported and clinical and laboratory examinations did not reveal any drug-related side effect. Thus probucol and pravastatin are safely available for hypercholesterolemia associated with diabetes mellitus. Although there was only a small number of male patients, the changes in serum lipids and apolipoproteins after treatment were similar in male and female subjects.

Summary

To elucidate the effect of small doses of probucol and pravastatin on serum concentrations of lipids and apolipoproteins in hypercholesterolemic patients (above 240 mg/dl) associated with non-obese non-insulin dependent diabetes mellitus (NIDDM), comparison was made between fifteen subjects treated with probucol (250mg twice a day) and fifteen subjects treated with pravastatin (5mg twice a day) for twelve months. Serum levels of

total cholesterol (from 300 ± 40 to 245 ± 45 mg/dl and from 295 ± 33 to 231 ± 36 mg/dl, mean ± SD), LDL-cholesterol (from 217 ± 47 to 178 ± 43 mg/dl and from 201 ± 38 to 145 ± 33 mg/dl), and apolipoprotein B (apo-B, from 189 ± 44 to 140 ± 60 mg/dl and from 162 ± 61 to 108 ± 26 mg/dl) were significantly decreased in the probucol- and pravastatin-treated groups, respectively. Glycosylated hemoglobin concentrations were not altered during the study in either group, and clinical and laboratory examinations did not reveal any drug-related side effect during the study. We conclude that small doses of probucol or pravastatin may be useful for the treatment of hypercholesterolemia associated with non-obese NIDDM patients.

References

1. Garcia MJ, McNamara PM, Gordon T and Kannell WB, Diabetes, **23**, 105-111, 1974.
2. Steiner G, Diabetes, **30** (Suppl 2), 1-7, 1981.
3. Castelli WP, Am J Med, **76**, 4-12, 1984.
4. Santen RJ, Willis PW and Fajans SS, Ann Intern Med, **130**, 833-843, 1972.
5. Stalenhoef AFH, Demacker PNM, Lutterman JA and van'tLaar A, Diabetologia **22**, 489-491, 1982.
6. Taylor KG, John WG, Matthews KA and Wright AD, Diabetologia, **23**, 507-510, 1982.
7. Briones ER, Mao SJT, Palumbo PJ, O'Fallon WM, Chenoweth W and Kottke BA, Metabolism **33**, 42-49, 1984.
8. Richmond W, Clin Chem, **19**, 1350-1356, 1973.
9. Barr SI, Kottke BA and Mao SJT, Clin Chem **27**, 1142-1144, 1981.
10. Illingworth DR and Sexton GJ, J Clin Invest **74**, 1972-1978, 1984.
11. Hoeg JM and Brewer Jr HB, Am Med Assoc, **258**, 3532-3536, 1987.
12. Tobert JA, Circulation **76**, 534-538, 1987.
13. Garg A and Grundy SM, New Engl J Med **318**, 81-86, 1988.
14. Yoshino G, Kazumi T, Iwai M, Matsushita M, Matsuba K, Uenomiya R, Iwatani I and Baba S, Atherosclerosis **75**, 67-72, 1989.
15. Durrington PN and Miller JP, Atherosclerosis **55**, 187-194, 1985.
16. Mellies MJ, Gartside BS, Glatfelter L, Vink P, Guy G, Schonfeld G and Glueck CJ, Metabolism **29**, 956-964, 1980.
17. Mettinen TA, Huttunen JK, Naukkarinen V, Strandberg T and Vanhanen H, Am J Cardiol, **57**, 49H-54H, 1986.
18. Franceschini G, Sirtori M, Vaccarino V, Gianfranceschi G, Rezzonico L, Chiesa G and Sirtori CR, Arteriosclerosis **9**, 462-469, 1989.
19. Hattori M, Tsuda K, Taminato T, Nishi S, Fujita J, Tsuji K, Kurose T, Koh G, Seino Y and Imura H, Curr Therap Res **42**, 967-973, 1987.
20. Avogaro P, BittoloBon G, Gazzolata G and Quinci GB, Lancet **1**, 901-903, 1979.
21. DeBacker G, Rosseneu M and Deslypere JP, Atherosclerosis **42**, 197-203, 1982.

22. Freedman DS, Srinivasan SR, Shear CL, Franklin FA, Webber LS and Berenson GS, N Eng J Med **315**, 721-726, 1986.
23. Stein Y, Glangeaud MC, Fainaru M and Stein O, Biochim Biophys Acta **380**, 106-118, 1975.
24. Ho YK, Brown MS and Goldstein JL, J Lipid Res, **21**, 391-398, 1980.

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