The effect of a small dose pravastatin on plasma lipids in postmenopausal hypercholesterolemia associated with non-insulin dependent diabetes mellitus

Tadasu IKEDA

The Department of Nursing, Tottori University, College of Medical Care Technology, Nishi-machi 133-2, Yonago 683

The common cause of death in non-insulin-dependent diabetes mellitus (NIDDM) is ischemic heart disease. It is known that the increase in the occurrence of coronary heart disease in the diabetic is particularly striking among women, and here diabetes appears to reduce the favored status of women[1,2]. In the general population the concentrations of plasma total cholesterol and low-density lipoprotein (LDL) cholesterol are positively associated with the prevalence of coronary heart disease[3]. In practice, postmenopausal women have high levels of plasma cholesterol than men of the same age[4], and several investigators[5~8] and we[9] have observed higher levels of plasma cholesterol in diabetic women than those in diabetic men. Despite the potential importance of elevated plasma cholesterol in postmenopausal women, hypercholesterolemia in this population has received less attention. Pravastatin, an inhibitor of the rate-limiting enzyme for cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, is now used for treatment of hypercholesterolemia. However, the effect of pravastatin on lipid metabolism in postmenopausal hypercholesterolemia associated with NIDDM patients remains to be fully elucidated. The present study was designed to determine whether or not hypercholesterolemic women respond effectively to low doses of pravastatin.

Subjects and methods

Subjects

The postmenopausal state was defined as the absence of menses for at least 1 year before enrollment into the study. Sixty-one postmenopausal hypercholesterolemic subjects (above 240 mg/dl) associated with NIDDM were selected from a large number of patients in our diabetic clinic, and divided into three groups; group 1 was 50-59 yr (n=11), group 2 was 60-69 yr (n=25) and group 3 was 70-79 yr (n=25). The patients were hypercholesterolemic despite low fat and low cholesterol diet. The diabetes was stable before entry into the study. None of the postmenopausal subject was on estrogen replacement therapy. Eight premenopausal hypercholesterolemic NIDDM patients (40-49 yr) were selected as a control group. Clinical characteristics of diabetic subjects were shown in Table 1. The subjects were administered pravastatin (5 mg twice a day) for 12 months. They were not taking any drugs to lower plasma lipid concentrations. Patients with evidence of abnormal hepatic or

renal function and of heavy drinkers (alcohol intake was above 50 g/day) were excluded. Diet and the dose of insulin or oral hypoglycemic agents were not changed during the study.

Measurements

The venous blood sample was taken after a 12-14 hr overnight fast, and plasma lipids were measured. Determinations of blood cell count, plasma creatinine, blood urea nitrogen, transaminases, creatine phosphokinase, alkaline phosphatase and lactic dehydrogenase were performed at each blood sampling. The percentage of the glycosylated hemoglobin (HbA_{1C}) content was measured by affinity chromatography (normal range is 4-6%). Plasma total cholesterol[10] and triglyceride[11] were determined enzymatically. High density lipoprotein (HDL) cholesterol was measured in the supernatant after precipitation of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) in 1 ml of plasma with 50 μl of 2 mol/l $MnCl_2$ and 50 μl of sodium heparin. Friedewald calculation was applied to LDL cholesterol determination.

Statistical analyses

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

Results

Clinical characteristics in NIDDM patients

Clinical characteristics of subjects were similar in pre- and postmenopausal NIDDM before treatment, as shown in Table 1. Body mass index (BMI, kg/m^2) was not changed during the study in all groups.

Table 1 Clinical characteristics in NIDDM patients

	premenopausal	postmenopausal		
	control	group 1	group 2	group 3
number	8	11	25	25
age(yr)	44.9±3.1	55.7±2.7	64.7±3.0	73.5±2.7
time since menopause(yr)		6.2±2.3	13.5±2.6	23.4±2.1
HbA_{1c}(%)	7.6±1.4	8.6±2.5	8.6±1.4	7.8±2.2
BMI	24.5±4.4	23.8±4.4	24.7±3.4	23.8±4.1
neuropathy	2/8	1/11	6/25	4/25
retinopathy	2/8	1/11	6/25	6/25
nephropathy	1/8	1/11	4/25	4/25
diet	4/8	6/11	12/25	11/25
sulfonylurea	2/8	3/11	12/25	10/25
insulin	2/8	2/11	1/25	4/25

The values are mean ± SD.
BMI : body mass index

Changes in plasma lipids

Basal levels of total cholesterol in group 2 were significantly lower than those in controls and group 3, as shown in Fig 1. The basal levels of high density lipoprotein (HDL) cholesterol in group 3 were significantly higher than those in controls and basal levels of LDL cholesterol in group 2 were significantly lower than those in control, as shown in Figs. 2 and 3. The basal levels of triglyceride were similar in all groups, as shown in Fig. 4. Treatment with pravastatin resulted in a significant decrease in plasma total cholesterol and LDL cholesterol concentrations, though LDL cholesterol level in control was significantly higher than that in postmenopausal subjects at one month. This hypocholesterolemic effect continued for 12 months (Figs. 1 and 3). On therapy, total cholesterol decreased by 29.8, 20.3, 21.8 and 21.0% in controls, group 1, 2 and 3, respectively, and LDL cholesterol decreased by 40.6, 27.7, 27.2 and 32.4% in controls, group 1, 2 and 3, respectively. Triglyceride and HDL cholesterol levels were not significantly changed in all groups (Figs. 2 and 4).

Glycemic control

HbA_1c concentration was not changed during the study in all groups.

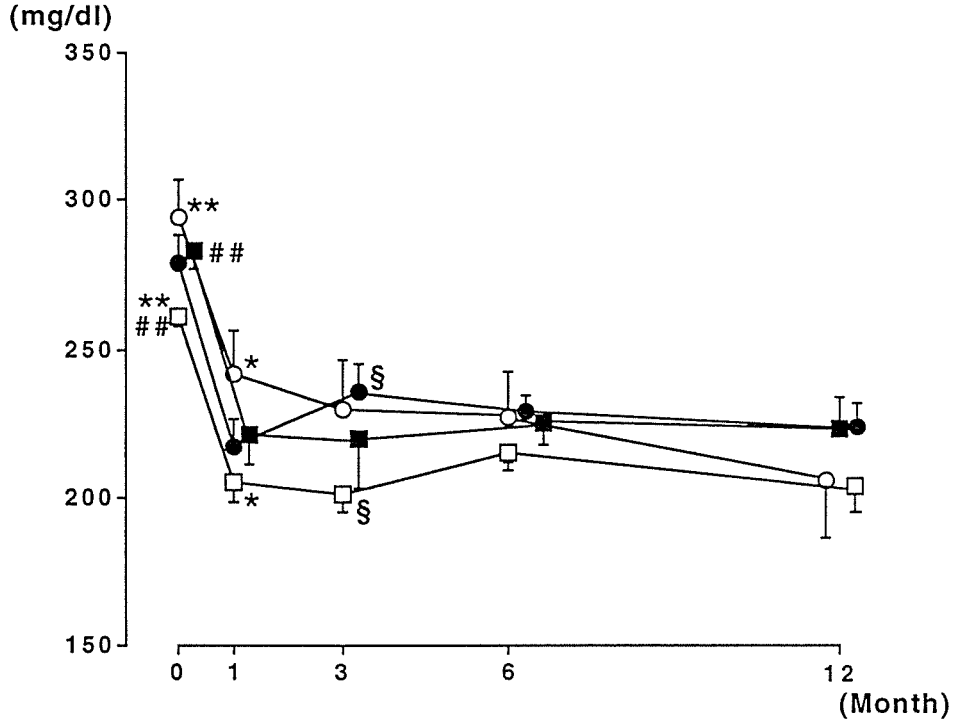

Fig. 1. Changes in total cholesterol levels
The bars represent means ± SD.
○ : control (40–49 yr, n = 8), ● : group 1 (50–59 yr, n = 11),
□ : group 2 (60–69 yr, n = 25), and ■ : group 3 (70–79 yr, n = 25).
– and §–§, $p < 0.05$, **–** and ##–##, $p < 0.01$.

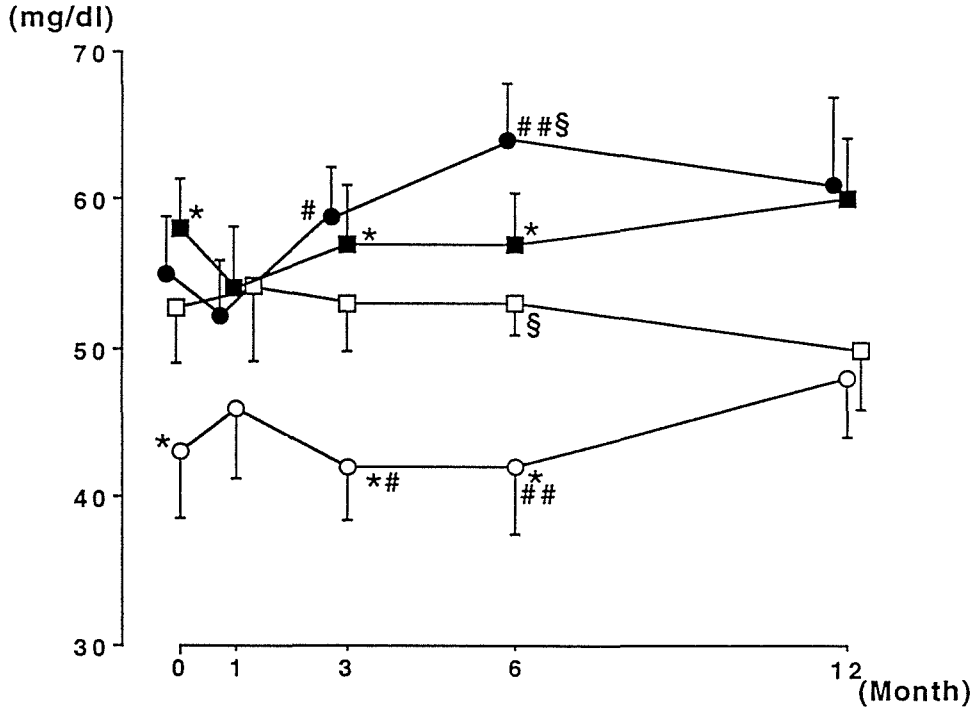

Fig. 2. Changes in HDL cholesterol levels
The bars represent means ± SD.
○ : control (40-49 yr, n = 8), ● : group 1 (50-59 yr, n =11),
□ : group 2 (60-69 yr, n =25), and ■ : group 3 (70-79 yr, n =25).
-, #-#, and §-§, $p < 0.05$, ##-##, $p < 0.01$.

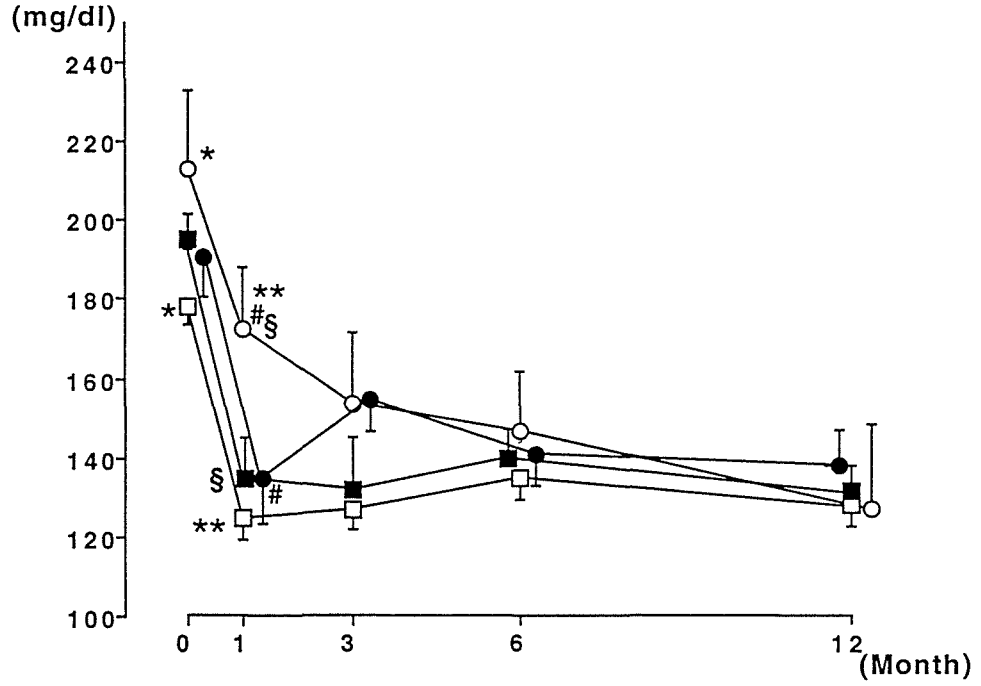

Fig. 3. Changes in LDL cholesterol levels
The bars represent means ± SD.
○ : control (40-49 yr, n = 8), ● : group 1 (50-59 yr, n =11),
□ : group 2 (60-69 yr, n =25), and ■ : group 3 (70-79 yr, n =25).
-, #-#, and §-§, $p < 0.05$, **-**, $p < 0.01$.

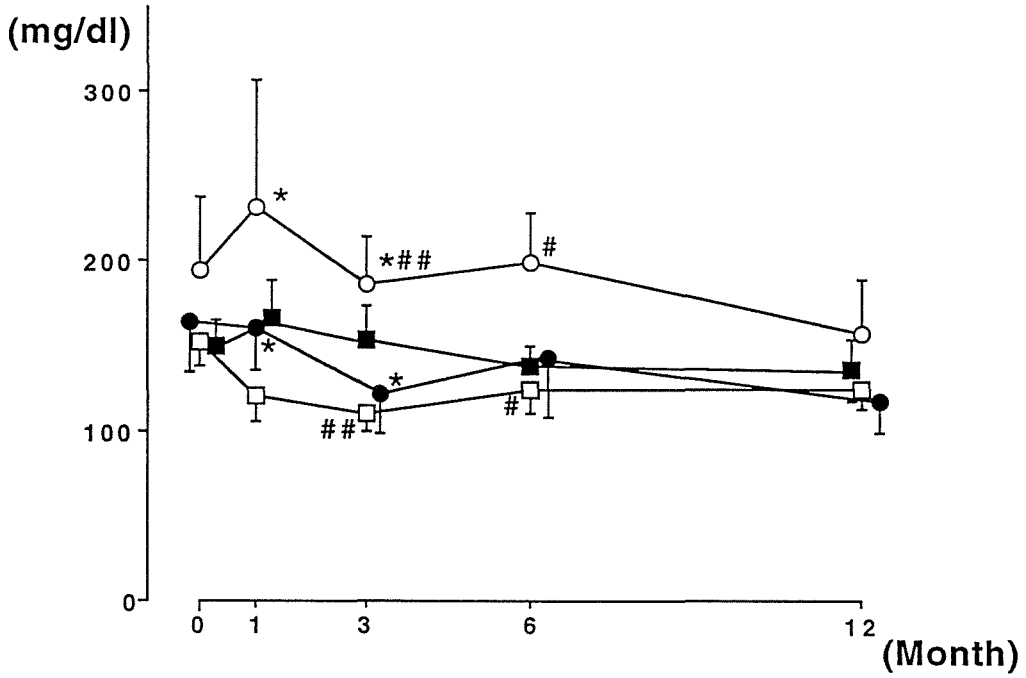

Fig. 4. Changes in triglyceride levels
The bars represent means ± SD.
○ : control (40–49 yr, n = 8), ● : group 1 (50–59 yr, n =11),
□ : group 2 (60–69 yr, n =25), and ■ : group 3 (70–79 yr, n =25).
– and #–#, $p < 0.05$, ##–##, $p < 0.01$.

Discussion

Effects of a small dose of pravastatin treatment on plasma lipid levels were not significantly different from each other between premenopausal and postmenopausal hypercholesterolemic diabetic subjects, though the decreasing effects of pravastatin on total cholesterol and on LDL cholesterol were slightly weak in postmenopausal diabetic subjects compared with in premenopausal diabetic subjects. These results suggest that a small dose of pravastatin is useful for the treatment of postmenopausal hypercholesterolemia in NIDDM patients. The present study demonstrates the fact that time since menopause does not affect the hypocholesterolemic effect of a small dose of pravastatin.

There have been no reports whether or not the mode of diabetic therapy influences the cholesterol-lowering effect of pravastatin. Although the number of subjects was very small in the present study, pravastatin showed similar cholesterol-lowering effects in diet-, sulfonylurea-, and insulin-treated NIDDM subjects. It has been reported that therapy with inhibitors of HMG-CoA reductase caused a 20–30% decrease in the plasma concentration of triglyceride in familial hypercholesterolemic patients[12~14] and in NIDDM patients[15,16]. Plasma triglyceride levels, however, were not significantly changed after treatment in the present study. This may be because the present NIDDM patients have relatively low plasma levels of triglyceride.

Pravastatin treatment did not affect the glycemic control because HbA_{1c} concentration

did not change during the study. No adverse drug experiences were reported. Clinical and laboratory examinations did not reveal any side effect of pravastatin. Thus pravastatin is safely available for postmenopausal hypercholesterolemia associated with diabetes mellitus.

Postmenopausal diabetic women have high levels of plasma cholesterol[4~9], and subsequently may have high risk for ischemic heart disease. Thus the potential importance of elevated plasma cholesterol in postmenopausal diabetic women should be received more attention. The author concludes that a small dose of pravastatin (5 mg twice a day) is useful for the treatment of hypercholesterolemia associated with postmenopausal NIDDM, and prevents diabetic women from higher incidence of ischemic heart disease.

Summary

To elucidate whether a small dose of pravastatin will correct postmenopausal hypercholesterolemia associated with NIDDM, sixty-one postmenopausal hypercholesterolemic women with NIDDM were treated with pravastatin (5 mg twice a day) for twelve months. The subjects were divided into three groups; group 1 was 50-59 yr (n=11), group 2 was 60-69 yr (n=25) and group 3 was 70-79 yr (n=25). Twelve months after treatment, plasma levels of total cholesterol decreased by 20.3, 21.8 and 21.0% in group 1, 2 and 3, respectively, and LDL cholesterol decreased by 27.7, 27.2 and 32.4% in group 1, 2, and 3, respectively. Serum levels of triglyceride and HDL cholesterol were not significantly changed in any group during the study. This cholesterol-lowering effect of pravastatin was slightly weak, but not significantly different compared with that in eight premenopausal hypercholesterolemic patients associated with NIDDM (total cholesterol decreased by 29.8% and LDL cholesterol decreased by 40.6%). HbA_1c concentrations were not altered during the study, and clinical and laboratory examinations did not reveal any side effects during the study. The author concludes that a small dose of pravastatin appears highly effective for treatment of postmenopausal hypercholesterolemia associated with NIDDM patients.

References

1. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR, Ann Intern Med, **87**, 393-397, 1977.
2. Barrett-Connor E, Wingard D, Amer J Epidemiol, **118**, 489-496, 1983.
3. Castelli WP, Am J Med, **76**, 4-12, 1984.
4. Sempos CT, Cleeman JI, Carroll MD, Johnson CL, Bachorik PS, Gordon DJ, Burt VL, Briefel RR, Brown CD, Lippel K, Rifkind B, JAMA, **269**, 3009-3014, 1993.
5. Zimmerman BR, Palumbo PJ, O'Fallon WM, Ellefson RD, Osmudson PJ, Kazmier FJ, Mayo Clin Proc, **56**, 233-242, 1981.
6. Taylor KG, John WG, Matthews KA, Wright AD, Diabetologia, **23**, 507-510, 1982.

7. Briones ER, Mao SJT, Palumbo PJ, O'Fallon WM, Chenoweth W, Kottke BA, Metabolism, **33**, 42-49, 1984.
8. Walden CE, Knopp RH, Wahl PW, Beach KW, Strandness E, New Engl J Med, **311**, 953-959, 1984.
9. Ikeda T, Ohtani I, Fujiyama K, Hoshino T, Tanaka Y, Takeuchi T, Mashiba H, Diab & Metabol, **17**, 373-378, 1991.
10. Richmond W, Clin Chem, **19**, 1350-1356, 1973.
11. Barr SI, Kottke BA, Mao SJT, Clin Chem, **27**, 1142-1144, 1981.
12. Illingworth DR, Sexton GJ, J Clin Invest, **74**, 1972-1978, 1984.
13. Hoeg JM, Brewer Jr HB, Am Med Assoc, **258**, 3532-3536, 1987.
14. Tobert JA, Circulation, **76**, 534-538, 1987.
15. Garg A, Grundy SM, New Engl J Med, **318**, 81-86, 1988.
16. Yoshino G, Kazumi T, Iwai M, Matsushita M, Matsuba K, Uenomiya R, Iwatani I, Baba S, Atherosclerosis, **75**, 67-72, 1989.

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