# Simvastatin Treatment on Postprandial Hypertriglyceridemia in Type 2 Diabetes Mellitus Patients With Combined Hyperlipidemia

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**Recent studies have shown that statins are effective in reducing fasting low-density lipoprotein-cholesterol (LDL-C) and triglyceride levels. However, it remains unknown if treatment with statins also lowers daily postprandial triglyceride concentrations, which may promote atherogenesis in type 2 diabetes subjects. Forty-one subjects with type 2 diabetes and combined hyperlipidemia who had stable glycemic control were randomly assigned to take simvastatin 20 mg (n = 27) or a placebo (n = 14) once daily for 12 weeks. The medication dosage was doubled after 4 weeks if a subject's LDL-C was not less than 130 mg/dL. Among these participants, 24 subjects (15 on simvastatin and 9 on placebo) agreed to take a meal tolerance test with isocaloric mixed meals (carbohydrate, 52%; fat, 33%, and protein, 15% of the daily caloric intake) and daytime hourly blood sampling from 8 AM to 4 PM. Simvastatin treatment reduced the fasting total cholesterol level from 237 ± 5 to 178 ± 6 mg/dL (−25%), the LDL cholesterol level from 150 ± 6 to 87 ± 5 mg/dL (−40%), and raised high-density lipoprotein-cholesterol (HDL-C) level from 36 ± 2 to 40 ± 2 mg/dL (+11%) (all *P* < .001). Fasting and daily ambient triglyceride concentrations from 8 AM to 4 PM decreased significantly in response to simvastatin administration (*P* < .001), but not to the placebo (*P* = .305). Simvastatin treatment not only decreased total cholesterol and LDL-C levels and increased HDL-C levels effectively, it also decreased fasting, as well as daily postprandial triglyceride concentrations, but had no effect on glycemic control in type 2 diabetes subjects with combined hyperlipidemia.**



PATIENTS WITH TYPE 2 diabetes mellitus are associated with a marked increase in the risk of death from coronary heart disease (CHD).[1-2] Among the factors contributing to this increased risk are various forms of dyslipidemia.[3] Recent studies have indicated that subjects with type 2 diabetes are characterized not only by fasting hypertriglyceridemia, lowered high-density lipoprotein-cholesterol (HDL-C) levels and predominantly small, dense low-density lipoprotein (LDL) particles, but also by abnormal postprandial lipoprotein metabolism.[4-6] Specifically, excessive production of triglyceride-rich lipoproteins, reduced postprandial lipoprotein lipase activity, and increased cholesterol ester transfer protein activity have all contributed to the differences in postprandial lipidemia between type 2 diabetic and nondiabetic subjects.[5,6] Indeed, various reports have provided evidence of a relationship between postprandial lipemia and coronary and carotid atherosclerosis.[7-10]

Previous major lipid-lowering trials, including the Scandinavian Simvastatin Survival Study (4S) and Cholesterol and Recurrent Events (CARE) studies, all indicated that therapy with hepatic hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) was effective in reducing LDL-cholesterol (LDL-C) concentrations and resultant coronary events in both diabetic and nondiabetic subjects.[11-14] Recently, accumulated evidence has suggested that statins in higher doses lower both fasting cholesterol and triglyceride concentrations in subjects with familial combined hyperlipidemia.[15,16] In fact, 1 of the statins, simvastatin, has been reported to decrease chylomicron remnants in patients with familial combined hyperlipidemia.[17] Very recently, simvastatin also been shown to decrease postprandial triglyceride-rich lipoprotein in patients with type 1 diabetes mellitus.[18] In subjects with type 2 diabetes mellitus, it was also reported that pravastatin treatment attenuated postprandial increase in very–low-density lipoprotein (VLDL) cholesterol levels 5 hours after a mixed meal.[19] However, little attention has been directed to the possible effect of statins on postprandial hypertriglyceridemia in individuals with type 2 diabetes. This study was initiated to compare the effect of simvastatin versus a placebo on fasting lipoproteins and daily ambient triglyceride concentrations in response to an isocaloric diet in type 2 diabetes subjects with combined hyperlipidemia.

## SUBJECTS AND METHODS

### *Subjects and Protocol*

Forty-one type 2 diabetes subjects with a LDL-C level exceeding 130 mg/dL and a fasting triglyceride level between 200 and 600 mg/dL were enrolled in this double-blinded, placebo-controlled study. The patients were not receiving any lipid-lowering drugs, but had been on a lipid-lowering diet for at least 6 weeks before entering the study. In addition, stable glycemic control (fasting plasma glucose less than 180 mg/dL) had been achieved with oral hypoglycemic agents in these patients for at least 3 months before entering the study. All other medications were held constant throughout the entire study. Exclusion criteria included uncontrolled hypertension, congestive heart failure, known peripheral vascular disease, a serum creatinine level exceeding 1.5 mg/dL, hepatic or thyroid disease, and the use of insulin injection. The protocol was approved by the Human Subjects Committee of Taichung Veterans General Hospital, Taiwan. Written informed consent was obtained from all subjects.

After at least 6 weeks on a lipid-lowering dietary advisory (baseline) period, treatment was started with either simvastatin 20 mg or a

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**Table 1. Clinical and Biochemical Characteristics of All Study Subjects**

| | Simvastatin | Placebo | *P* |
|---|---|---|---|
| No. | 24 | 14 | |
| Age (yr) | 62 ± 2 | 60 ± 2 | .507 |
| Sex (M/F) | 7/17 | 6/8 | .391 |
| BMI (kg/m$^2$) | 26.1 ± 0.8 | 26.6 ± 1.0 | .699 |
| Antihypertensive agents (%) | 13 (54.2%) | 5 (35.7%) | .272 |
| Sulfonylurea (%) | 20 (83.3%) | 9 (64.3%) | .620 |
| Metformin (%) | 17 (70.8%) | 5 (35.7%) | .257 |
| Fasting plasma glucose (mg/dL) | 171 ± 9 | 162 ± 16 | .606 |

placebo, taken at bedtime, in a patient ratio of 2:1. The dose of simvastatin or placebo was doubled 4 weeks later if a participant's LDL-C concentration exceeded 130 mg/dL. The total treatment period was 12 weeks. Overnight fasting blood samples were obtained for determination of plasma glucose[20] and lipoprotein values at end of the simvastatin or placebo treatment. Glycosylated hemoglobin ($HbA_{1c}$) was determined by high performance chromatography.[21] Plasma total cholesterol[22] and triglyceride[23] concentrations were measured by enzymatic analysis. HDL-C was measured after precipitation of apolipoprotein B (apo B)-containing lipoproteins by phosphotungstic acid and magnesium chloride reagent.[24] Fasting plasma LDL-C level was calculated according to the method of Friedewald et al[25] once fasting plasma triglyceride levels were below 400 mg/dL. Otherwise, the LDL-C level was determined after separation of VLDL from plasma by ultracentrifugation and precipitation of apo B-containing particles with phosphotungstic acid and magnesium chloride reagent. Cholesterol level was measured in the VLDL fraction and in the HDL-containing supernatant. LDL-C level was calculated by subtracting HDL-C and VLDL-C levels from total plasma cholesterol level.[26]

### *Mixed Meal Test*

Twenty-four subjects (n = 15 in the simvastatin group and n = 9 in the placebo group) agreed to undergo a mixed meal tolerance test, which was performed as described previously.[27] These 2 groups were relatively similar in age (62 ± 3 *v* 60 ± 4 years), sex distribution (8 men *v* 5 men), and body mass index (BMI) values (27.4 ± 1.1 *v* 29.8 ± 0.9 kg/m$^2$). In addition, their age, sex distribution, and BMI values did not differ from the entire study group. This test was performed at the baseline and at the end of the active treatment period. Blood was obtained before breakfast at 8:00 AM and then at hourly intervals until 4 PM. The test meals were isocaloric (30 kcal/kg/d), with each meal containing the following nutrients as a percentage of the total calories: 15% protein, 33% fat, and 52% carbohydrate. Meals, which were given at 8 AM, noon, and 6 PM, contained 20%, 40%, and 40%, respectively, of the day's total caloric intake. Although the average body weight of those on the placebo was slightly heavier than on simvastatin, the calories served did not significantly different (2,310 ± 65 *v* 2,190 ± 116 kcal/d, *P* = .277) during the meal tolerance test.

### *Statistical Analysis*

All descriptive data are expressed as the means ± SEM. A nonpaired *t* test was used to compare the differences between the simvastatin group and the placebo group. The effects of treatment on fasting lipoprotein levels were analyzed by paired *t* test. Plasma glucose and triglyceride concentrations in response to meals were analyzed by 2-way analysis of variance. Ambient plasma glucose and triglyceride responses under the curve were calculated by the trapezoid method. Statistical analysis was performed using a Macintosh computer with StatView IV software (Abacus Concepts, Berkeley, CA).

## RESULTS

Of 50 type 2 diabetes patients initially enrolled, 41 met the eligibility criteria. They were randomly assigned to be treated with simvastatin 20 mg (n = 27) or placed on placebo (n = 14). Three subjects in the simvastatin group discontinued treatment because of the development of pyelonephritis (n = 1) or loss of follow-up (n = 2). The dose of simvastatin was increased to 40 mg in 7 subjects who did not reach the treatment goal of a LDL-C level less than 130 mg/dL. No change in the liver enzyme tests or creatinine phosphokinase (CPK) values were reported throughout the study.

Clinical variables including age, BMI, and gender distribution were comparable between the 2 groups at baseline (Table 1). The proportion of subjects taking either sulfonylurea or metformin was not different between these 2 groups. Body weight increased slightly in subjects taking either simvastatin (59.9 ± 2.2 *v* 60.3 ± 2.3 kg, *P* = .064) or placebo (61.9 ± 3.3 *v* 62.3 ± 3.3 kg, *P* = .058). Blood glucose control, as evidence by values of $HbA_{1c}$, did not change in response to simvastatin (7.0% ± 0.2% *v* 7.3% ± 0.4%, *P* = .243) or placebo (7.4% ± 0.2% *v* 7.2% ± 0.3%, *P* = .411) administration. Table 2 summarizes the effect of treatment on fasting lipoprotein levels. The mean percent reduction from the baseline in total cholesterol and LDL-C were 25% (*P* < .001) and 40% (*P* < .001), respectively, after simvastatin administration. Simvastatin treatment reduced fasting triglyceride concentrations by 22% (*P* < .001) and raised HDL cholesterol levels by 11% (*P* < .001). Placebo administration had no effects on fasting lipoprotein concentrations.

The most interesting finding was that simvastatin administration lowered daily ambient plasma triglyceride concentrations from 8:00 AM to 4:00 PM in response to breakfast and lunch (*P* < .001), whereas the placebo had no effect on fasting or daily postprandial triglyceride levels (*P* = .305) (Fig 1). Area under the curve of triglyceride concentrations decreased significantly in subjects who took simvastatin (2,698 ± 261 *v*

**Table 2. Effect of Simvastatin or Placebo Treatment on Fasting Lipoprotein Concentrations (mg/dL) in Type 2 Diabetes Subjects With Combined Hyperlipidemia**

| | Simvastatin (n = 24) | | | Placebo (n = 14) | | |
|---|---|---|---|---|---|---|
| | Baseline | After | *P* | Baseline | After | *P* |
| Total triglyceride | 277 ± 16 | 205 ± 14 | <.001 | 254 ± 29 | 263 ± 27 | .664 |
| Total cholesterol | 237 ± 5 | 178 ± 6 | <.001 | 234 ± 9 | 250 ± 10 | .085 |
| HDL-C | 36 ± 2 | 40 ± 2 | <.001 | 34 ± 1 | 34 ± 1 | .919 |
| LDL-C* | 150 ± 6 | 87 ± 5 | <.001 | 149 ± 6 | 154 ± 9 | .506 |
| Cholesterol/HDL-C | 6.9 ± 0.3 | 4.6 ± 0.2 | <.001 | 7.0 ± 0.3 | 7.5 ± 0.4 | .159 |

*N = 22 in the simvastatin group and n = 13 in the placebo group with fasting triglyceride levels less than 400 mg/dL.

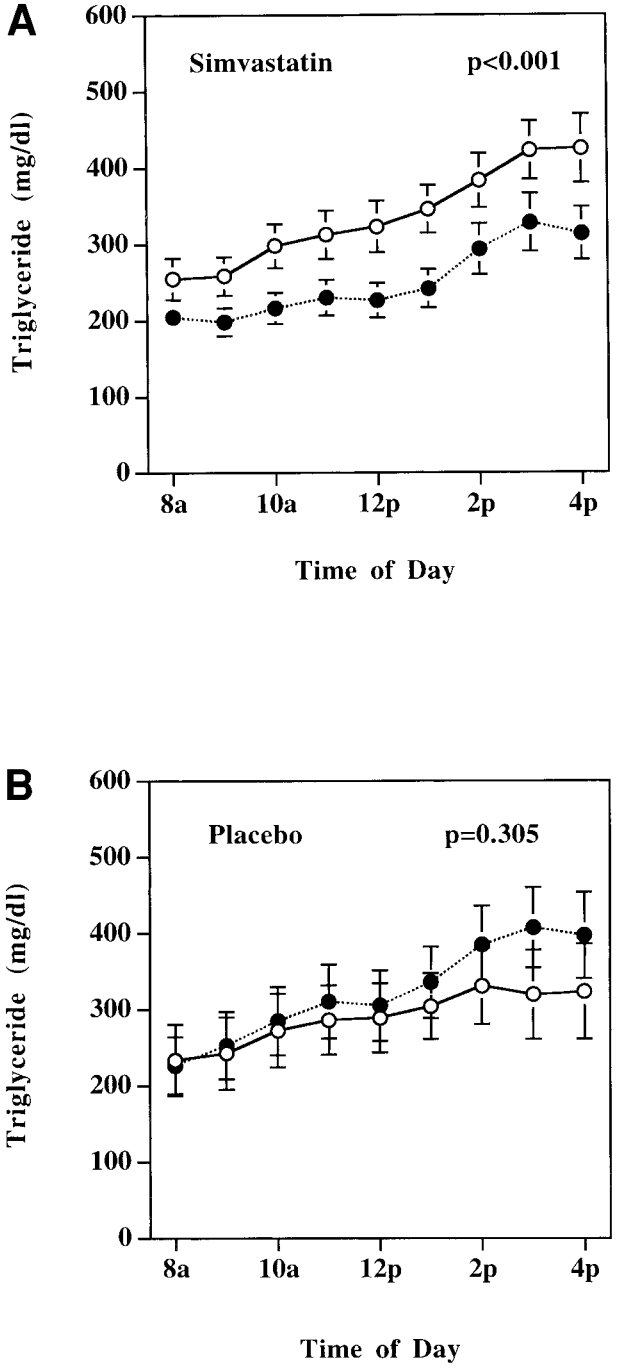


**Fig 1. Plasma triglyceride concentrations from 8 AM to 4 PM in response to breakfast (8 AM) and lunch (12 PM) in type 2 diabetes subjects with combined hyperlipidemia treated before (○) and after simvastatin treatment (●) (n = 15) (A) and before (○) and after placebo use (●) (n = 9) (B).**

1,990 ± 197 mg/dL.h, $P < .002$), but not in subjects who took placebo (2,679 ± 408 *v* 2,326 ± 388 mg/dL.h, $p = .338$). The relative increment of postchallenge triglyceride levels above fasting also reduced significantly in subjects on simvastatin (642 ± 100 *v* 358 ± 111 mg/dL.h, $p < .05$), but not in those on placebo (454 ± 86 *v* 782 ± 185 mg/dL.h, $P = .124$), which corresponds to a percentage change of 24.7% to 15.4% in the simvastatin group and 20.2% to 28.5% in the placebo group. Glucose area under the curve did not alter in response to either simvastatin ($P = .195$) or placebo ($P = .850$) administration for 12 weeks.

## DISCUSSION

The present results indicate that plasma cholesterol and LDL-C concentrations are effectively lowered when hyperlipidemic diabetic subjects are treated with simvastatin. The magnitudes of the percent of decrease were comparable to those reported in a Western population (−25% *v* −27% total cholesterol and −40% *v* −36% LDL-C levels as compared with diabetic subjects from the 4S study).[13,28] HDL-C increased approximately 11% (7% in 4S) in simvastatin-treated patients. As a result, the ratio of the total to HDL-C concentration decreased by approximately 32% in the simvastatin treatment group.

It has been well recognized that statins are ideal agents for treating subjects with hypercholesterolemia.[11,12,29] However, recent evidence has suggested that statins not only lower LDL-C, but also decrease triglyceride concentrations.[16,30,31] In a comparitive study, Stein et al[16] reported that all statins are effective in decreasing triglyceride levels, but only in hypertriglyceridemic patients. In addition, a relatively constant reduction of the ratio of triglyceride/LDL-C by statins was also found. Although the underlying mechanisms remained speculative, it was assumed that statins increased the removal of VLDL remnants via enhanced LDL receptor expressions and/or decreased hepatic secretion of triglyceride-rich lipoprotein particles.[32] In fact, Arad et al[30] have shown that VLDL assembly and production rates were inhibited by lovastatin in subjects with combined hyperlipidemia. Vega and Grundy[33] observed an enhanced uptake of VLDL remnants by LDL receptors in subjects with mixed hyperlipidemia treated with lovastatin 40 mg daily.

The novel finding of the present study was that simvastatin treatment reduced both fasting and daily ambient plasma triglyceride concentrations in type 2 diabetes subjects with combined hyperlipidemia. In 1979, Zilversmitt[7] was the first to propose that postprandial triglyceride-rich lipoprotein was involved in the development of atherogenesis. Subsequent studies have confirmed the relationship between postprandial lipemia and coronary or carotid artery disease.[8-10] Recent observations from the Atherosclerosis Risk in Community (ARIC) trial showed that the triglyceride area under the curve after a fat load was related to the intimal medial thickness of carotid arteries[34] and also to the development of exercise-induced ischemic electrocardiographic changes, although the latter relationship was only shown to be significant in nonobese men.[35] Direct evidence showed that triglyceride-rich lipoproteins can be isolated from human atherosclerotic plaques.[36] Postprandial hyperlipidemia was even more important in mediating cardiovascular complications in diabetes subjects because it involved multiple metabolic dearrangements including insulin resistance, glycemic control, substrate (free fatty acids, etc), regulation, and several enzymes participating in lipoprotein metabolism pathways.[5,6] However, little attention has been paid to the

effect of hypolipidemic agents on postprandial hyperlipidemia in diabetic individuals. Fibrate drugs have improved postprandial hyperlipidemia, as well as fasting lipid levels in subjects with type 2 diabetes.[37,38] Bhatnagar et al[19] reported that pravastatin administration attenuated postprandial increase in VLDL cholesterol levels 5 hours after a standardized mixed meal in type 2 diabetes subjects with hyperlipidemia. Very recently, simvastatin was shown to decrease the number of circulating intestinal and hepatic postprandial triglyceride-rich lipoproteins after a fatty meal in individuals with type 1 diabetes.[18] Our findings are unique and important not only because no such daytime studies have been reported, but also because they support the recent expanding evidence suggesting that statins lower both LDL-C and fasting triglyceride concentrations.

There are several possible mechanisms by which simvastatin decreases postprandial hypertriglyceridemia. As stated before, statins upregulate LDL receptors, which enhance clearance of both fasting VLDL remnants and postprandial triglyceride-rich lipoprotein particles.[32,33] In fact, it has been shown that about half of all chylomicron and VLDL remnants are cleared by the LDL receptors.[39] Other explanations come from the observation that statins reduce VLDL secretion.[33,40] In addition, enhanced lipoprotein lipase activity has been detected after simvastatin treatment in subjects with combined hyperlipidemia.[17] However, the ratio of triglyceride to apoprotein B in the flotation span ($S_f$) 20 to 400 lipoprotein did not alter in response to simvastatin treatment in subjects with type 1 diabetes, suggesting that increased lipolysis was not likely in such patients.[18] We did not measure lipoprotein lipase activity, which probably would enable us to clarify the mechnistic implications of the present study.

In summary, our studies show that simvastatin in daily doses of 20 to 40 mg is effective in lowering total cholesterol and LDL-C levels and in raising HDL-C concentrations without affecting glycemic control in type 2 diabetes subjects with combined hyperlipidemia. Our investigations further suggest that simvastatin treatment reduces fasting, as well as daily postprandial triglyceride concentrations. If statins can lower daily triglyceride significantly, we can extend the use of these potent LDL-C–lowering drugs to a far broader group of individuals at risk for CHD.

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