Effect of Intensive Glycemic Control on Fibrinogen, Lipids, and Lipoproteins

Veterans Affairs Cooperative Study in Type II Diabetes Mellitus

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Background: The Veterans Affairs Cooperative Study in Type II Diabetes Mellitus prospectively studied insulin-treated patients with type 2 (non–insulin-dependent) diabetes mellitus, achieving 2.1% glycosylated hemoglobin separation between intensive- and standard-treatment arms (P<.001) for 2 years.

Objective: To assess the effect of intensive therapy on serum fibrinogen and lipid levels, compared with standard treatment.

Methods: One hundred fifty-three male subjects with type 2 diabetes mellitus and who required insulin treatment were recruited from 5 Veterans Affairs medical centers. The subjects were divided into intensive- and standard-treatment arms for a randomized prospective study. Dyslipidemia was managed identically in both arms (diet, drugs). Fibrinogen levels and lipid fractions were measured in the full cohort. Lipid fractions are separately reported in patients not treated with hypolipidemic agents.

Results: There were no baseline differences between arms. Fibrinogen levels rose in the intensive-treatment arm at 1 year (from 3.34 ± 0.12 to 3.75 ± 0.15 g/L; P<.001) but returned to baseline at 2 years (3.47 ± 0.12 g/L). There was no change in the standard-treatment arm. Triglyceride levels decreased in the intensive-treatment arm from 2.25 ± 0.27 to 1.54 ± 0.14 mmol/L (199 ± 24 to 136 ± 12 mg/dL) at 1 year (P = .004) and to 1.74 ± 0.18 mmol/L (154 ± 16 mg/dL) at 2 years (P = .03); there was no change in the standard-treatment arm. Cholesterol levels decreased in the intensive-treatment arm at 1 year from 5.4 ± 0.21 to 4.99 ± 0.13 mmol/L (207 ± 8 to 193 ± 5 mg/dL) (P = .02); there was no change in the standard-treatment arm. Levels of low- and high-density lipoprotein cholesterol decreased in the standard-treatment arm only by 2 years, from 3.44 ± 0.13 to 3.16 ± 0.10 mmol/L (133 ± 5 to 122 ± 4 mg/dL) (P = .02) and from 1.10 ± 0.03 to 1.00 ± 0.03 mmol/L (42 ± 1 to 38 ± 1 mg/dL) (P<.001) for low-density and high-density lipoprotein cholesterol, respectively. Levels of apolipoprotein B decreased in both treatment arms (P<.001), and apolipoprotein A1 levels decreased in the standard-treatment arm (P<.01). Lipoprotein (a) levels did not change in either treatment arm. Lipid results were essentially identical whether examined in the full cohort or excluding those patients receiving hypolipidemic agents.

Conclusions: Intensive insulin therapy led to a potentially beneficial reduction in serum triglyceride levels and preservation of high-density lipoprotein cholesterol and apolipoprotein A1 levels. However, it caused transient elevation in plasma fibrinogen levels, a possible thrombogenic effect.

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MATERIALS AND METHODS

SUBJECTS

Subjects were male, aged 40 to 69 years, with type 2 diabetes mellitus for 15 years or less and receiving maximum-dose sulfonylurea and/or any dose of insulin. At entry, each patient had an Hb A1c level greater than 3 SDs above the mean of normal (5.05% ± 3[0.3%] = 6.55%). Fasting C-peptide levels were greater than 0.21 mmol/mL. Criteria for exclusion have been detailed elsewhere; briefly, patients were excluded if they had conditions that would have precluded intensive treatment, end points evaluation, or continuation into a proposed long-term study.

STRATIFICATION AND RANDOMIZATION

Subjects were stratified by participating hospital (5 strata) and by presence or absence (2 strata) of any previous complication (myocardial infarction, angina pectoris, congestive heart failure, or cerebrovascular event). Within these 10 strata, patients were then randomized to intensive glycemic control or standard treatment. This stratification was done to ensure that both treatment arms would be balanced by participating hospital and presence or absence of any previous complications.

MANAGEMENT OF HYPERGLYCEMIA

In the standard-treatment arm, the aim of treatment was good general medical care and well-being while avoiding excessive hyperglycemia (Hb A1c, less than 13% or 2 SDs above mean diabetic values in participating centers). Ketonuria, or hypoglycemia. This was generally accomplished with 1 morning injection of insulin per day.

In the intensive-treatment arm, the goal was to maintain the Hb A1c levels within 2 SDs of the mean of those of nondiabetic subjects (4.0%-6.1%). Details of management have been published. Briefly, this was a 4-step treatment, with subjects moving to the next step only if operational goals were not met. This provided the simplest possible regimen for each subject. The steps were as follows: (1) evening intermediate or long-acting insulin only; (2) evening insulin with daytime glipizide; (3) twice daily insulin with no glipizide; and (4) more than 2 injections of insulin with no glipizide. Dietary treatment and management of dyslipidemia, hypertension, and smoking were identical in both treatment arms. Lipid levels were first managed by diet and by meeting the glycemic objectives of each treatment arm. If preset criteria were not achieved, then drug therapy was initiated. The preset levels were LDL cholesterol of at least 4.14 mmol/L (160 mg/dL), serum total cholesterol level of at least 6.21 mmol/L (240 mg/dL), and serum triglyceride level of at least 2.82 mmol/L (250 mg/dL).

GLYCEMIC CONTROL

Details of the efficacy of the step-up therapy approach in achieving and maintaining separation in glycemic control between the standard- and intensive-treatment arms have been reported elsewhere. Briefly, patients in the standard-treatment arm began with an Hb A1c level of 9.5% ± 0.2% (mean ± SEM; n = 78) and a fasting serum glucose level of 12.6 ± 0.4 mmol/L (227 ± 7 mg/dL) (n = 78). These levels did not vary significantly from baseline for the entire 2-year follow-up. The patients in the intensive-treatment arm started with a similar Hb A1c level of 9.3% ± 0.2%, but the Hb A1c level decreased steadily to levels lower than those of the standard-treatment arm by about

RESULTS

BASELINE CHARACTERISTICS

Seventy-eight subjects were randomized into the standard-treatment arm and 75 into the intensive-treatment arm. The mean age of the patients was 60.0 ± 6.0 years, and mean duration of diabetes was 7.8 ± 4.0 years. There was no difference between treatment arms at baseline in fibrinogen levels or in any of the lipid parameters measured.

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2.1% (below 7.3%) from 6 months onward ($P<.001$). The fasting serum glucose level in the intensive-treatment arm began at $11.4 \pm 0.4$ mmol/L ($206 \pm 7$ mg/dL) and was reduced to $7.3 \pm 0.3$ mmol/L ($131 \pm 6$ mg/dL) by 3 months. This was approximately 4.2 mmol/L ($75 \pm 24$ mg/dL) lower than in the standard-treatment arm throughout ($P<.001$ vs standard-treatment arm). Insulin dose increased in both treatment arms, but was significantly higher in the intensive-treatment arm. Body mass index did not differ between treatment groups or from baseline.

### PLASMA FIBRINOGEN

Plasma fibrinogen levels rose significantly in the intensive-treatment arm after 1 year, from $3.34 \pm 0.12$ to $3.75 \pm 0.15$ g/L ($P<.001$). Plasma fibrinogen levels returned to levels no different from baseline by 2 years of intensive therapy ($3.47 \pm 0.12$ g/L). There was no change in plasma fibrinogen levels in the standard-treatment arm (Figure 1). These data were based on analyses of the full cohort. There was no correlation between change in insulin dose and change in fibrinogen level in either treatment arm or in the entire cohort. Likewise, there was no correlation between change in body mass index and change in fibrinogen level.

### LIPID MEASUREMENTS

We analyzed lipid level changes in the 57 patients in the standard-treatment arm and the 54 patients in the intensive-treatment arm who did not receive hypolipidemic agents during the study. There was no difference between these subcohorts at baseline in any of the lipid measurements.

Serum triglyceride levels in the intensive-treatment group decreased significantly from $2.25 \pm 0.27$ mmol/L to $1.54 \pm 0.14$ mmol/L ($190 \pm 24$ to $136 \pm 12$ mg/dL) at 1 year ($P = .004$ vs baseline) and to $1.74 \pm 0.18$ mmol/L ($154 \pm 16$ mg/dL) at 2 years ($P = .03$ vs baseline). In contrast, serum triglyceride levels in the standard-treatment arm were unchanged (Figure 2).

Serum total cholesterol levels decreased significantly in the intensive-treatment arm during the first year of therapy, from $5.35 \pm 0.21$ to $4.99 \pm 0.13$ mmol/L ($207 \pm 8$ to $193 \pm 5$ mg/dL) ($P = .02$), while levels in the standard-treatment arm were unchanged. At 2 years, the intensive-treatment arm sustained a decrement in cholesterol levels at $5.04 \pm 0.13$ mmol/L ($195 \pm 5$ mg/dL) ($P = .06$ vs baseline). After 2 years, cholesterol levels decreased significantly in the standard-treatment arm to $5.04 \pm 0.13$ mmol/L ($195 \pm 5$ mg/dL) ($P = .04$ vs baseline) (Figure 3). The LDL cholesterol levels decreased in the standard-treatment arm only, at 2 years, from $3.44 \pm 0.13$ to $3.16 \pm 0.10$ mmol/L ($133 \pm 5$ to $122 \pm 4$ mg/dL) ($P = .02$). There was no change in LDL cholesterol levels in the intensive-treatment patients (Figure 4, A). Plasma Apo B levels decreased in both treatment arms ($P < .001$ vs baseline in each arm) (Figure 4, B). The LDL cholesterol/Apo B ratio increased in the standard-treatment arm from $1.03 \pm 0.03$ at baseline to $1.22 \pm 0.05$ at 2 years ($P < .003$). In the intensive-treatment patients, the LDL cholesterol/Apo B ratio rose from $1.04 \pm 0.03$ to $1.40 \pm 0.06$ ($P < .001$). The increase in ratios was approximately 2-fold higher in the intensive- than in the standard-treatment arm, and this difference was of borderline statistical significance ($P = .07$). Serum Lp(a) levels did not change in either group during the study (Figure 4, C). Serum HDL cholesterol levels decreased by 2 years in the standard-treatment arm only, from $1.11 \pm 0.03$ mmol/L ($43 \pm 1$ mg/dL) at baseline to $1.01 \pm 0.03$ mmol/L ($39 \pm 1$ mg/dL) at 2 years ($P < .001$). There was no change in HDL cholesterol levels in the intensive-treatment arm ($1.09 \pm 0.05$ mmol/L).

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**Figure 1.** Fibrinogen levels. STD indicates standard-treatment arm; INT, intensive-treatment arm; and asterisk, $P<.001$ compared with 0 years in INT.

**Figure 2.** Triglyceride levels. STD indicates standard-treatment arm; INT, intensive-treatment arm; asterisk, $P<.03$ compared with 0 years in INT; and dagger, $P<.004$ compared with 0 years in INT.

**Figure 3.** Total cholesterol levels. STD indicates standard-treatment arm; INT, intensive-treatment arm; asterisk, $P = .06$ compared with 0 months in INT; dagger, $P<.04$ compared with 0 years in STD; and double dagger, $P<.02$ compared with 0 years in INT.
[42 ± 2 mg/dL] at baseline vs 1.03 ± 0.05 mmol/L [40 ± 2 mg/dL] at 2 years), although the latter were nearly identical in both treatment arms (Figure 5, A). Levels of Apo A₁ decreased at 2 years in the standard-treatment arm only ($P < .01$ vs baseline); but by that time, levels were almost identical to those seen in the intensive-treatment patients (1.22 ± 0.04 g/L in the standard- and 1.20 ± 0.04 g/L in the intensive-treatment arms) (Figure 5, B).

Because the main point of our analysis was to examine the effect of glycemic control on the lipid measurements, we excluded patients receiving hypolipidemic agents. However, when the full cohort was analyzed, including these patients, the findings were almost identical to those in the subcohort analysis. The only difference between both analyses involved Apo A₁. In the full cohort analysis, Apo A₁ levels were significantly reduced from baseline in both treatment arms, whereas in the subcohort analysis, there was a significant decline of Apo A₁ from baseline levels only in the standard-treatment arm.

**COMMENT**

The VA CSDM Feasibility Trial was successful in attaining a clinically and statistically significant difference in Hb A₁c and fasting serum glucose levels between treatment arms, which was maintained throughout the entire study. Both arms were well-matched in baseline characteristics; at baseline, there were no significant differences in plasma fibrinogen, serum lipid, or lipoprotein levels between treatment arms.

Plasma fibrinogen level has been found to be a potent, independent risk factor for cardiovascular disease and stroke in several prospective epidemiological studies conducted at Framingham,9 Coteberg,10 and London.11 In fact, some studies have shown that fibrinogen level is a stronger risk factor than cholesterol level for acute and chronic cardiovascular disease.12-14 Meade et al11 showed that a fibrinogen level elevation of 0.6 g/L was associated with an 84% increased risk of stroke within the next 5 years. Cross-sectional studies have usually reported that fibrinogen levels are increased in individuals with diabetes mellitus compared with nondiabetic subjects,10,13,15-17 and that these fibrinogen levels correlate positively with insulin dosages18 and fasting serum insulin levels.19 Also, studies have
shown a correlation between levels of fibrinogen and the presence of microvascular and macrovascular complications of diabetes mellitus.\textsuperscript{10,11,20}

The VA CSDM is the first interventional study of which we are aware that has prospectively examined the effect of intensive insulin therapy on levels of fibrinogen. The results showed that intensive insulin therapy led to a significant, albeit transient, increase in fibrinogen levels (Figure 1). This is not entirely surprising, since insulin stimulates the secretion of fibrinogen by isolated hepatocytes.\textsuperscript{21} High levels of plasma insulin have been shown to correlate with high levels of plasma fibrinogen in otherwise healthy, overweight individuals.\textsuperscript{22} The observation that intensive insulin therapy transiently raises an important cardiovascular risk factor is disturbing. Of additional pertinence is that previously reported analyses of other data from the VA CSDM have shown a statistically borderline relationship between levels of Hb A\textsubscript{1c} and combined cardiovascular events, with lower Hb A\textsubscript{1c} levels possibly being associated with an increased frequency of such events.\textsuperscript{23} Such data, while not statistically compelling, are troublesome. They suggest that institution or maintenance of intensive glycemic control with insulin in a relatively elderly population with type 2 diabetes mellitus could have, at least initially, deleterious consequences on the cardiovascular system. If such a relationship were confirmed in a larger and longer trial, one could hypothesize that the mechanism of such an effect is, at least in part, through transient elevation of plasma fibrinogen levels.

The sustained and significant reduction in plasma triglyceride levels (Figure 2) in the intensive-treatment patients is consistent with data from other studies\textsuperscript{24,25} and is likely due to insulin-induced enhancement of triglyceride clearance.\textsuperscript{26}

The sustained decrease in cholesterol levels induced by intensive therapy (Figure 3) is also in accord with the data of others, including the Diabetes Control and Complications Trial (DCCT)\textsuperscript{25} in type 1 diabetes and other studies in type 2 diabetes mellitus,\textsuperscript{29,33} and represents, in addition to the effects on triglycerides, a beneficial effect of intensive therapy on this important cardiovascular risk factor. By the end of the 2-year follow-up, however, patients in the standard-treatment arm also had significant reductions in cholesterol level, and reached cholesterol levels that were virtually identical to those seen in the intensive-treatment subjects. Since this analysis was performed on subjects not taking any hypolipidemic agents and with continued high glycemic levels, it might appear that the higher insulin doses above baseline of the standard-treatment arm along with dietary advice and enforcement, which was common to that of the intensive-treatment arm, might have contributed to this outcome.

There was no reduction in LDL cholesterol level at any point in the intensive-treatment patients (Figure 4, A). In fact, LDL cholesterol levels decreased slightly but significantly at 2 years of therapy in the standard-treatment group only. The DCCT, in contrast, reported small but significant decrements in LDL cholesterol levels in intensively treated subjects in the primary and secondary intervention cohorts.\textsuperscript{25} Similarly, Cusi et al\textsuperscript{24} (as well as others) have observed that intensive insulin treatment reduced LDL cholesterol levels in type 2 diabetes mellitus. The reason for this difference between the VA CSDM and DCCT as well as other studies is not clear, especially since comparable levels of glycemic control were seen in intensive-treatment subjects in our report, the DCCT, and the study by Cusi et al.\textsuperscript{24} However, others have shown that there are important compositional changes in LDL cholesterol particles depending on triglyceride and glucose levels.\textsuperscript{27-32} Specifically, when triglyceride levels are maintained below 1.69 mmol/L (150 mg/dL), LDL cholesterol particles that are less atherogenic emerge. This is pertinent, since intensive glycemic control maintained mean serum triglyceride levels approximately at or below 1.69 mmol/L (150 mg/dL), whereas those in the standard-treatment group remained above 1.69 mmol/L (150 mg/dL). Furthermore, it seems likely that intensive-treatment subjects with lower average serum glucose levels had a lower proportion of glycated LDL cholesterol.\textsuperscript{32,33} Since it has been demonstrated that glycated LDL cholesterol is more prone to oxidation than nonglycated LDL cholesterol,\textsuperscript{32,33} it is also reasonable to assume that the intensive-treatment subjects had less oxidized LDL cholesterol.\textsuperscript{34-36} These points are important, since glycated and oxidized LDL cholesterol may be more atherogenic than unmodified LDL particles. Therefore, although the standard-treatment subjects had slight reductions in LDL cholesterol levels, it is possible that the LDL particles in these subjects may be of a more atherogenic type.

Ninety percent of circulating Apo B is attached to LDL particles, with the remainder associated with very LDL cholesterol, which we did not measure.\textsuperscript{37,38} The LDL cholesterol/Apo B ratios may reflect the size and density of LDL particles. Higher ratios suggest larger, less dense, less atherogenic particles. In both treatment arms, LDL cholesterol/Apo B ratios increased significantly. In the intensive-treatment arm, the LDL cholesterol/Apo B ratio rose almost twice as much as in the standard-treatment arm, and the difference was of borderline statistical significance.

Lipoprotein (a), an LDL-like lipoprotein, is another important independent cardiovascular risk factor.\textsuperscript{39-41} Cross-sectional data and those from a small longitudinal study have not suggested a consistent relationship between glycemic control and Lp(a) in type 2 diabetes mellitus.\textsuperscript{42,43} Similarly, in our larger longitudinal study, intensive glycemic control did not have an effect on Lp(a) levels (Figure 4, C).

Levels of HDL cholesterol were preserved in intensive-treatment patients, whereas there was a slight, but significant, reduction in the standard-treatment group (Figure 5, A). Apolipoprotein A\textsubscript{1} is the major apoprotein of HDL cholesterol.\textsuperscript{37,44} The lack of change in Apo A\textsubscript{1} levels (Figure 5, B) in the intensive-treatment subjects, coupled with the reduction in Apo A\textsubscript{1} levels in standard-treatment subjects, reflect and support the HDL findings.

In summary, in a well-characterized and carefully observed cohort of patients with type 2 diabetes mellitus, we showed that, after intensive glycemic control, there was a transient rise in fibrinogen levels coupled with sustained decreases in serum triglyceride and cholesterol levels and a preservation of serum HDL cholesterol and Apo A\textsubscript{1} levels. Therefore, intensive glycemic control leads to potentially beneficial effects (ie, reduced Hb A\textsubscript{1c}, triglyceride, and cholesterol levels) on the progression of vascular disease, but to possible adverse effects (ie, increased fibrinogen levels) on thrombosis. The risk-benefit ratio of intensive gly-
cemic control on progression of macrovascular disease in the population with type 2 diabetes mellitus so prone to macrovascular disease needs to be clarified in a longer, longer trial. Such a trial has been approved with very high scientific priority by the Veterans Affairs Cooperative Studies Program, but awaits funding and implementation.

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