The Effect of Improved Diabetic Control on Plasma Lipid and Lipoprotein Levels

A Comparison of Conventional Therapy and Continuous Subcutaneous Insulin Infusion

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SUMMARY

We studied short-term changes in plasma lipid levels in type I diabetics treated with either a conventional insulin regimen or continuous subcutaneous insulin infusion. Mean plasma glucose dropped from 260 ± 18 to 134 ± 8 mg/dl when conventional treatment was used and from 194 ± 18 to 108 ± 8 mg/dl with CSII. Both forms of therapy were associated with a significant fall in plasma triglyceride levels. However, only CSII treatment produced significant changes in total plasma cholesterol and LDL cholesterol levels. Total cholesterol fell from 195 ± 17 mg/dl to 161 ± 11 mg/dl and LDL cholesterol fell from 129 ± 13 mg/dl to 102 ± 9 mg/dl.

We conclude that improved diabetic control by any method is effective in lowering plasma triglyceride levels, but it requires almost perfect metabolic control to affect plasma cholesterol and LDL cholesterol levels. The changes in plasma lipid and lipoprotein achieved with CSII may favorably alter the prediction for the development of premature atherosclerosis in our patients. DIABETES 29:1001–1005, December 1980.

Diabetes mellitus is associated with an increased incidence of atherosclerosis.[1,2] Hyperlipidemia, a common problem in insulin-dependent diabetic patients,[3] appears to contribute to the development of the accelerated atherosclerosis seen in these patients.[4] The exact relationship between degree of metabolic control, plasma lipid levels, and atherosclerosis has been difficult to dissect, but recent epidemiologic studies suggest that there may be an increased risk of atherosclerosis even in persons with minimal alterations in glucose tolerance.[5–7] Because of the important relationship between diabetic control and plasma lipid levels, we compared the effects of 2–3 wk of improved glucoregulation either with a conventional insulin regimen or continuous subcutaneous insulin infusion (CSII) on plasma lipids and lipoproteins.

We show that near normalization of plasma glucose levels, which is possible with CSII but not with conventional treatment, produces a marked reduction in total plasma cholesterol and low density lipoprotein cholesterol levels. These changes do not occur with conventional insulin treatment. Either method of diabetic control is effective in lowering plasma triglyceride levels.

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MATERIALS AND METHODS

Twenty-three nonobese patients presenting with typical insulin-dependent (type I) diabetes mellitus for at least 5 yr were studied. All patients were ketosis-prone and had been previously treated with insulin. None had hyperlipidemia and there was no evidence of renal, hepatic, or thyroid disease. No patient had a family history of hyperlipidemia. All drugs except insulin were withheld during the study. Each patient gave informed consent before participation.

The study was conducted in the General Clinical Research Center of Parkland Memorial Hospital. The investigation was performed in two phases, an initial phase representing "poor" diabetic control and a subsequent period of 3 wk of "improved" diabetic control. Throughout the study the patients consumed a constant metabolic diet, with calories distributed as 40–45% carbohydrate, 15–20% protein, and 35–40% fat (polyunsaturated to saturated fat ratio = 0.35, cholesterol 500 mg/day). Caloric intake was sufficient to maintain stable body weight throughout the study.

Conventional insulin treatment protocol. This protocol was followed in 14 of the 23 patients, mean age 25 ± 2 yr. During the "poor control" phase, each patient was treated with his/her usual daily dose of insulin. After completion of the poor control phase, the patients' diabetes was aggressively treated in an attempt to achieve euglycemia. Insulin was given by conventional methods, being administered subcutaneously as a combination of intermediate-acting

(NPH) and short-acting (Regular) insulin 30 min before breakfast and dinner. Each patient's daily insulin dose was determined by the glycemic response to the previous day's insulin dose. This "improved control" phase lasted 21 days.

Diabetic regulation was assessed by measurement of a 24-h "glucose profile," which consisted of measurement of plasma glucose concentrations from blood samples obtained 5 times daily (before each meal and at 0300 h) from which a mean glucose level was calculated. The mean plasma glucose concentration for the poor control phase was taken from the glucose profile done on the third day of hospitalization after 2 days of equilibration to the metabolic diet. The mean plasma glucose concentration for the improved control phase was the average plasma glucose level from profiles done on day 14 and day 21 after institution of improved glucoregulation. From the mean value for each individual a mean of the entire group was calculated.

CSII treatment protocol. This protocol was followed in 9 patients, mean age 25 ± 3 yr. During the poor control phase, each patient was maintained on his/her usual daily insulin dose. On the third hospital day, after 2 days of stabilization to the metabolic diet, the initial glucose profile was performed.

On the day after the initial profile, continuous subcutaneous insulin infusion (CSII) by a portable battery-powered pump was started. In all patients except one, the Auto-Syringe pump model AS2C (Auto-Syringe, Inc., Hooksett, New Hampshire) was used; in the remaining patient the Mill-Hill Infuser (Muirhead Ltd., Beckingham, Kent, England) was employed.[8] The CSII protocol has been previously described.[9] The glucose profile was repeated on days 14 and 21 and the mean plasma glucose level for the improved control phase is the average of these two values.

For both treatment protocols, fasting plasma lipoprotein levels were obtained at 0700 h after an overnight fast on each profile day. The value for the improved control phase represents the average of the 14- and 21-day values. No significant differences in mean plasma glucose or fasting lipoprotein levels were found between the 14- and 21-day samples in patients receiving either treatment protocol.

Sample collection and analysis. Samples for plasma glucose determination were collected through an indwelling 19-gauge butterfly needle placed in a large forearm vein. Glucose was measured in each sample immediately by the glucose-oxidase method on a Beckman Glucose Analyzer.

Blood for lipid determination was obtained after an overnight fast from an anticubital vein without use of a tourniquet, with the patient in the recumbent position. Blood was collected in 1% EDTA and immediately centrifuged at 4°C to separate plasma from cells. Plasma was stored at 4°C until determination of lipid and lipoprotein levels (3–5 days).

Plasma lipoprotein concentrations were estimated by standard ultracentrifugation techniques[10] combined with heparin-manganese precipitation to estimate the content of high density lipoprotein cholesterol.[11] Plasma cholesterol and triglyceride determinations were performed with commercially available enzyme methods (Boehringer-Mannheim Biochemicals, Indianapolis, Indiana) on a Gilford 3500 Autoanalyzer. Lipid determinations were standardized by commercially available sets of cholesterol (BMC Preciset Cholesterol, Boehringer-Mannheim Biochemicals, Indianapolis, Indiana), and triglyceride (Triolein Standards, Sigma Chemical Company, St. Louis, Missouri) standards. The interassay coefficient of variation was 3.6% for cholesterol and 5.5% for triglyceride assays.

For comparisons within groups the Student's *t* test for paired groups was used, and for comparison between groups the nonpaired analysis was used.

RESULTS

Table 1 shows the results of this study. The 14 diabetics treated with a conventional insulin regimen had a mean blood sugar of 260 ± 18 mg/dl (± SEM) during the "poor control" phase. This decreased significantly ($P < 0.01$) to 134 ± 8 mg/dl during the "improved control" phase. The 9 patients treated with CSII had a baseline plasma glucose level of 194 ± 18 mg/dl. This was significantly less than the baseline value for the conventional treatment group ($P < 0.01$). The mean plasma glucose level decreased significantly ($P < 0.01$) to 108 ± 8 mg/dl after 2–3 wk of CSII. The mean plasma glucose levels during the improved control phase in those patients treated with CSII were significantly less ($P < 0.05$) than the mean plasma glucose levels during the improved control phase in the conventionally treated group, demonstrating the advantage of CSII treatment in achieving normal glucoregulation.

TABLE 1
Changes in mean plasma glucose, lipid, and lipoprotein levels during periods of poor control and after 2–3 wk of improved control in type I diabetics treated with either conventional insulin therapy or continuous subcutaneous insulin infusion

Treatment	Glucose (mg/dl)	Cholesterol (mg/dl)				Total triglyceride (mg/dl)
		Total	VLDL	LDL	HDL	
CSII						
Poor control	194 ± 18‡	195 ± 17	21 ± 11	129 ± 13	40 ± 2	134 ± 23
Improved control	108 ± 8*§	161 ± 11*	11 ± 1†	102 ± 9*	42 ± 2	84 ± 8†
Conventional therapy						
Poor control	260 ± 18	195 ± 8	14 ± 2	128 ± 9	42 ± 4	100 ± 9
Improved control	134 ± 8*	189 ± 8	10 ± 2*	127 ± 8	44 ± 5	84 ± 6†

* $P < 0.01$ vs "poor control" phase.
† $P < 0.02$ vs "poor control" phase.
‡ $P < 0.01$ "poor control" conventional therapy vs "poor control" CSII.
§ $P < 0.05$ "good control" conventional therapy vs "good control" CSII.

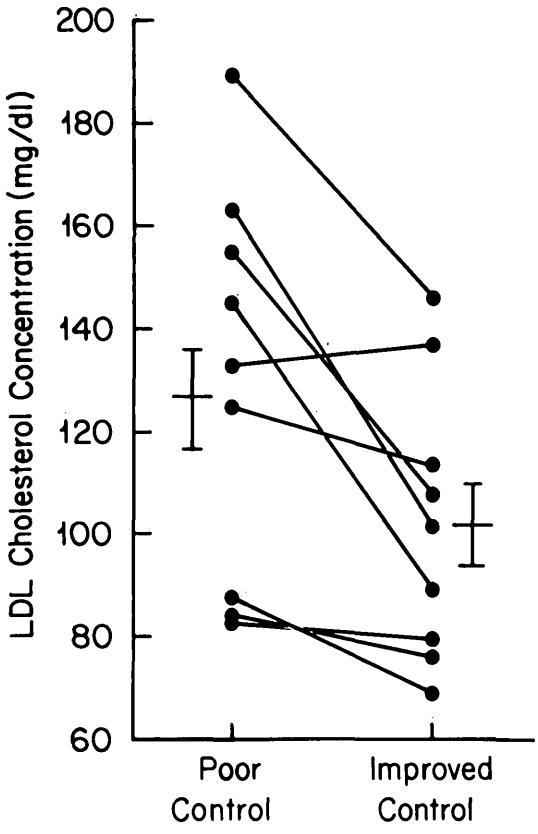

FIGURE 1. The effect of conventional insulin therapy on LDL cholesterol levels in type I diabetics.

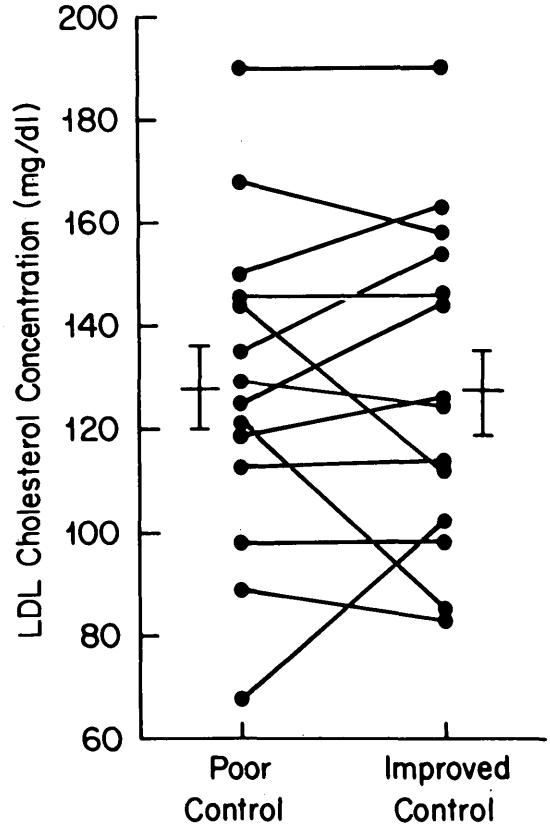

FIGURE 2. The effect of continuous subcutaneous insulin infusion on LDL cholesterol levels in type I diabetics.

Table 1 also shows the effect of the two kinds of treatment on plasma lipid and lipoprotein levels. There were no statistical differences between the two groups in baseline lipid or lipoprotein levels despite the differences in the baseline mean plasma glucose levels. In the conventional treatment group, improved diabetic control resulted in a significant decrease in plasma triglyceride levels from 100 ± 9 to 84 ± 6 mg/dl ($P < 0.02$) with 12 patients showing a decline in total plasma triglyceride concentration and 2 patients showing a small rise. Very low density lipoprotein (VLDL) levels fell from 14 ± 2 to 10 ± 2 mg/dl ($P < 0.01$). Eleven of the group showed a decline, 2 patients rose, and one had no change. There was no significant change in total cholesterol, low density lipoprotein (LDL), or high density lipoprotein (HDL) cholesterol levels. LDL cholesterol levels in individual patients are shown in Figure 1.

By contrast, the CSII-treated group showed significant reductions in total plasma cholesterol and LDL cholesterol values. Total plasma cholesterol levels fell from the baseline value of 195 ± 17 mg/dl to 161 ± 11 mg/dl ($P < 0.01$) after 2–3 wk of CSII. All but 1 patient showed a decrease in total plasma cholesterol levels. The 1 patient who did not show a decline had only a 2-mg/dl rise in cholesterol concentration. The fall in plasma cholesterol level was largely due to a fall in the LDL cholesterol concentration from 129 ± 13 mg/dl to 102 ± 9 mg/dl ($P < 0.02$), with 8 of the 9 patients showing a decrease (Figure 2). VLDL cholesterol also fell in eight of the nine patients from a mean of 21 ± 11 to 11 ± 1 mg/dl ($P < 0.02$). Triglyceride levels decreased from 134 ± 23 mg/dl to 84 ± 8 mg/dl ($P < 0.02$). All 9 patients had a decrease in plasma triglyceride levels with CSII. HDL cholesterol levels did not change.

DISCUSSION

The present study shows that significant reductions in plasma lipids occur with CSII treatment. This confirms the results obtained by Tamborlane et al.[12,13] showing decreases in plasma cholesterol and triglyceride levels with CSII. However, these workers did not measure lipoprotein levels. We have shown that the fall in total plasma cholesterol is due largely to a reduction in the LDL cholesterol, a fact that could have significance in slowing the development of premature atherosclerosis.[4]

Although it is generally agreed that improved control results in decreases in levels of triglycerides in diabetics, its effect on plasma cholesterol levels has been a matter of debate. Kaufmann et al.[14] examined plasma cholesterol levels in juvenile diabetics while in summer camp. They found that reductions in plasma cholesterol levels were related more to the diet consumed than to the degree of diabetic control. Billimoria et al.,[15] studying lipoprotein profiles in diabetics, reported that treatment produced no changes in total cholesterol, LDL, or VLDL cholesterol levels. Nikkila et al.[16] also could find no change in LDL cholesterol levels with good diabetic control. However, Bennion and Grundy,[17] working with Pima Indians, reported a fall in plasma cholesterol levels in maturity-onset diabetics after improved diabetic control.

It is possible that the different results in these studies are due to different degrees of "good control." In our patients,

aggressive treatment by conventional means did not produce significant lowering of plasma cholesterol despite a drop in the mean plasma glucose to 134 ± 8 mg/dl, only 26 mg/dl higher than the group on CSII. This suggests that exquisite metabolic control is required to produce substantial changes in total cholesterol and LDL cholesterol levels. The changes in lipid levels observed with CSII treatment could also be the result of the more physiologic means of insulin delivery and need not necessarily be attributed solely to improved metabolic control. The difference in plasma lipid response between our two groups cannot be accounted for by differences in diet, since both groups received the same diet. Also, the initial mean plasma lipid and lipoprotein levels were the same in both groups. Since the group of diabetic patients treated by conventional means had a higher initial mean plasma glucose level than those diabetics treated with CSII, it is possible that differences appeared between the 2 groups with the 2 forms of treatment because the 2 groups of patients were not homogenous. The conventional treatment groups may have responded differently in respect to their plasma cholesterol levels irrespective of the treatment used, or they may have required a longer treatment period for their cholesterol levels to fall. Obviously, this possibility cannot be excluded by this study. However, by all other criteria except the initial mean plasma glucose level, the two groups were indistinguishable.

Sosenko et al.[18] recently followed a group of diabetics for 1 yr and found a correlation between degree of diabetic control and plasma triglycerides, cholesterol, and LDL cholesterol. However, their study differs from ours for several reasons. First, they were dealing with a population of younger diabetics that had much lower initial cholesterol values than our patients. Second, they compared groups of patients according to degree of diabetic control rather than individual patients studied under 2 levels of diabetic control. Finally, the changes in plasma lipid and lipoprotein levels they reported, although statistically significant, were quite small. We observed changes approximately twice those of Sosenko et al. in our patients treated with CSII.

The mechanism responsible for the observed changes in lipoprotein levels with improved diabetic control is not clear. The increases in VLDL levels often seen in insulin-deficient patients is thought to be due to decreases in lipoprotein lipase activity[19] though increases in VLDL synthesis may also occur.[20] The change in LDL levels might be due to a decrease in total body cholesterol synthesis[17] or an increase in LDL catabolism.[21] It is not surprising that HDL cholesterol levels did not change after 2–3 wk of improved diabetic control, since the turnover rate of HDL is the slowest of the various lipoproteins[22] and changes in HDL levels usually do not occur until several weeks after a therapeutic intervention.[23]

In conclusion, improved diabetic control by any method is effective in reducing plasma triglyceride levels. However, it may require almost perfect metabolic control to reduce total plasma and LDL cholesterol levels. The changes in total plasma cholesterol and LDL cholesterol levels achieved with CSII may be significant enough to alter the rate of development of atherosclerosis, if sustained. Whether or not these changes in lipid and lipoprotein levels will persist with a more prolonged period of CSII treatment remains to be determined.

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