Effects of Combination Therapy With Glyburide and Insulin on Serum Lipid Levels in NIDDM Patients With Secondary Sulfonylurea Failure

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Objective: To compare the long-term effect of combined treatment with insulin and glyburide versus insulin alone on serum lipid levels in non-insulin-dependent diabetic (NIDDM) patients with secondary failure to sulfonylurea therapy. Research Design and Methods: The study was a randomized double-blind placebo-controlled parallel trial with a duration of 325 days. The study was conducted at a referral-based endocrinology clinic. Subjects were a sequential sample of 20 patients with NIDDM with failure to respond to glyburide treatment after at least 1 yr of adequate glucose control with this therapy. The patients were randomized to treatment with insulin and glyburide (IG) or insulin and placebo (IP). Insulin was given twice daily to all patients as a mixture of NPH and regular insulins in dosages aiming at optimal glucose control. Glyburide or placebo was taken before breakfast (7 mg) and dinner (3.5 mg). Results: Mean HbA_{1c} decreased from 11.1% (range 9.8–12.9%) before insulin to 9.1% (range 6.8–11.4%) on day 325 ($P < 0.001$) in IG patients and from 10.3% (range 8.4–13.3%) to 9.0% (range 6.3–11.8%) ($P < 0.05$) in IP patients. In both groups, there was an increase in high-density lipoprotein cholesterol of ~20% lasting throughout the study ($P < 0.01$). During the first 83 days of the study, there was a decrease in serum cholesterol ($P < 0.01$) and serum triglycerides ($P < 0.05$) in both groups. All changes in lipid variables were comparable in magnitude and duration in both treatment with insulin and glyburide in NIDDM patients with secondary sulfonylurea failure improves lipid metabolism to a similar degree as insulin therapy alone.
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The optimal treatment for patients with non-insulin-dependent diabetes mellitus (NIDDM) and secondary failure to sulfonylurea (SU) treatment remains an unsolved problem (1). Hyperglycemia is improved by insulin treatment in only ~30% of these patients (2). Combination therapy with insulin and SU may lead to better glycemic control than insulin alone (3), although this difference may be limited in time (4,5). Where lipid metabolism in these patients is concerned, the effects of combination therapy are controversial (3). In a study by Stenman et al. (6), combined treatment with insulin and glyburide resulted in lower serum levels of high-density lipoprotein cholesterol (HDL-chol) than with insulin alone. However, such a difference was not observed in earlier studies (4,5). These studies included a follow-up period of ~4 mo.

This study compared long-term effects of insulin and combined insulin and SU treatment on metabolic control in NIDDM patients exhibiting secondary failure to SU therapy. We have previously published effects on glycemic control (7), whereas in this article, we present lipid findings.

RESEARCH DESIGN AND METHODS

This study included 20 patients with NIDDM defined according to the criteria of the National Diabetes Data Group (8). Mean age was 57.1 yr (range 47–65 yr), whereas mean duration of diabetes was 14.1 yr (range

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2–25 yr). Relative body weight was 118% (range 90–165%) of normal. All patients had responded adequately in terms of glucose control to glyburide therapy during at least 1 yr. At the time of study, all patients had unsatisfactory blood glucose levels (defined as blood glucose >11 mM in >50% of premeal samples drawn in the outpatient clinic over a 1-mo period despite repeated dietary and exercise counseling and maximal glyburide treatment (14 mg/day given as 2 dosages). Renal and hepatic function tests were normal in all participants. Two patients were being treated with β-blockade for hypertension. One of these patients also received thyroxine because of a goiter.

Our study was approved by the ethical committee of the Karolinska Hospital. After the failure of SU treatment was established and the patients agreed to participate in the study, they were admitted to the hospital for metabolic studies (7). Glyburide was discontinued at least 3 wk before admission. During hospitalization, patients were given a standard diet for diabetic patients consisting of 30 kcal/kg for women and 35 kcal/kg for men. The carbohydrate, fat, and protein contents were 50, 27, and 23%, respectively. No other food intake was permitted.

On day 6, the patients were randomized in a double-blind manner into two treatment groups: insulin and glyburide (IG) and insulin and placebo (IP). There were no significant differences concerning age, duration of diabetes, or relative body weight between the groups. Insulin treatment was started on the day of randomization and was given twice daily as a mixture of NPH (Insulatard, Nordisk, Gentofte, Denmark) and regular (Velosulin, Nordisk) insulins. The criteria for acceptable glucose control were a fasting value <8 mM and postprandial values <10 mM. During hospitalization, daily adjustments of insulin dosages were undertaken to optimize glucose control. The patients received instructions about recordings of fasting blood glucose and glucose profiles (before breakfast, lunch, and dinner and at bedtime) twice weekly. They were also instructed to adjust insulin dosage according to the results of self-monitoring of blood glucose. Glyburide or placebo was given twice daily (7 mg before breakfast and 3.5 mg before dinner). In addition, all participants were recommended to keep dietary and exercise habits unchanged during the time of the study. After being discharged from the hospital on day 18, the patients were seen in the outpatient clinic on days 48, 145, 235, and 325. A second hospitalization between days 78 and 85 was also included.

Fasting blood samples for the determination of total serum cholesterol, HDL-chol, and triglycerides were obtained on the following occasions: day 3 (before insulin treatment) and days 16, 48, 83, 145, 235, and 325. HbA_{1c} was determined on all occasions except day 16. HbA_{1c} was determined by isoelectric focusing (9). Routine methods were used for analysis of serum triglycerides (10) and cholesterol (11). HDL-chol was determined by an ultracentrifugation technique (12).

Values are expressed as means with ranges in parentheses. Two-way analysis of variance (ANOVA) was used to test longitudinal effects of the two treatments and differences between the treatment groups. Apart from analyzing the entire study period (325 days), we also tested the first (days 16–83) and second parts (days 145–325) separately. Student's *t* test for independent means was used to test differences between treatment groups at single points of time. Correlation coefficients were calculated with linear regression analysis.

RESULTS

As described previously (7), initial mean HbA_{1c} was 11.1% (range 9.8–12.9%) in IG patients and 10.3% (8.4–13.3%) in the IP group (Table 1). After the start of insulin treatment, HbA_{1c} decreased markedly in both groups ($P < 0.001$) during the first part (days 48–83) of the study. HbA_{1c} remained below baseline levels in both

TABLE 1
Insulin dosages, body weight, and HbA_{1c} values in patients treated with insulin and glyburide (IG) and insulin and placebo (IP)

	Before insulin treatment	Insulin treatment (days)					
		16	48	83	145	235	325
Insulin dose (U/day)							
IG		40 (22–86)	37 (18–76)	33 (16–72)	32 (16–72)	33 (16–76)	34 (16–78)
IP		56 (24–94)	55 (26–92)	55 (24–90)	56 (22–92)	56 (24–90)	55 (24–90)
Body weight (kg)							
IG	83.5 (68–106)	83.2 (68–102)	84.7 (66–103)	84.9 (65–102)	86.6 (66–106)	88.7 (67–109)	89.6 (69–111)
IP	82.7 (62–115)	82.7 (61–114)	83.9 (63–114)	83.7 (61–114)	84.3 (61–115)	85.4 (64–119)	86.1 (64–122)
HbA_{1c} (%)							
IG	11.1 (9.8–12.9)		9.0 (6.6–11.5)	8.3 (7.1–11.5)	9.1 (7.3–11.5)	9.0 (7.0–11.8)	9.1 (6.8–11.4)
IP	10.3 (8.4–13.3)		8.3 (6.8–9.5)	8.4 (6.8–9.9)	8.6 (7.3–10.1)	9.3 (6.9–11.6)	9.0 (6.3–11.8)

Values are means with ranges in parentheses. Results of statistical testing are given in RESULTS.

TABLE 2
Serum cholesterol, high-density lipoprotein (HDL) cholesterol, and serum triglycerides in non-insulin-dependent diabetes mellitus patients treated with insulin and glyburide (IG) and insulin and placebo (IP)

	Before insulin treatment	Insulin treatment (days)					
		16	48	83	145	235	325
Serum cholesterol (mM)							
IG	6.8 (4.9–8.7)	5.6 (4.4–7.6)	6.2 (4.5–8.0)	5.8 (4.1–7.8)	6.3 (5.0–8.4)	6.3 (4.6–8.6)	6.4 (4.4–9.7)
IP	6.6 (5.0–9.1)	5.3 (4.3–6.7)	6.2 (4.6–7.5)	6.0 (4.7–7.2)	6.4 (5.6–7.9)	6.5 (5.5–8.4)	6.3 (4.3–7.3)
HDL-cholesterol (mM)							
IG	1.0 (0.6–1.3)	1.1 (0.7–1.5)	1.2 (0.9–1.7)	1.0 (0.7–1.5)	1.2 (0.8–1.8)	1.2 (0.7–1.9)	1.0 (0.7–1.6)
IP	0.8 (0.6–1.0)	1.0 (0.7–1.4)	1.0 (0.8–1.8)	1.0 (0.6–1.6)	1.0 (0.8–1.7)	1.0 (0.8–1.9)	1.0 (0.8–1.6)
Serum triglycerides (mM)							
IG	2.4 (1.1–4.7)	1.7 (0.9–3.0)	1.8 (1.0–3.1)	1.7 (0.6–2.4)	1.7 (1.3–2.5)	1.7 (2.0–2.8)	1.7 (1.2–2.3)
IP	1.7 (1.0–2.6)	1.2 (0.7–2.0)	1.5 (0.6–2.7)	1.3 (0.8–1.9)	1.8 (0.8–2.9)	2.0 (0.8–3.8)	1.8 (0.7–2.6)

Values are means with ranges in parentheses. Results of statistical testing are given in RESULTS.

IG ($P < 0.001$) and IP patients ($P < 0.05$) during the last part of the study (days 145–325). No differences were found between the treatment groups.

Body weight tended to increase in both groups after initiation of insulin therapy. A statistically significant increase was only observed in the IG group between days 145 and 325 ($P < 0.05$).

Baseline levels of total serum cholesterol were comparable in IG and IP patients (Table 2). The start of insulin treatment caused a reduction in cholesterol levels that was significant by ANOVA during days 16–83 ($P < 0.01$) but not during the last part of the study. Over the entire study period, the reduction of serum cholesterol did not reach statistical significance. No differences were found between IG and IP patients.

HDL-chol levels were slightly higher in IG than IP patients before insulin treatment (1.0 [0.6–1.3 mM] vs. 0.8 mM [0.6–1.0 mM], $P < 0.05$). In both groups, the start of insulin therapy resulted in an increase of ~20%. This change was statistically significant by ANOVA for the entire study ($P < 0.01$), the first 83 days ($P < 0.01$), and days 145–325 ($P < 0.05$). However, in the IG group, mean HDL-chol level had returned to baseline at day 325. No differences were detected between the treatment groups during insulin therapy. There was no correlation between changes in HDL-chol and HbA_{1c}.

Before insulin treatment, serum triglycerides tended to be higher in IG groups than IP patients (NS). Insulin treatment caused a reduction of serum triglycerides during the first part of the study ($P < 0.05$). However, during the last part of the study, serum triglycerides had returned to baseline levels in the IP patients, whereas mean levels tended to be reduced in IG patients. There was no difference between the groups by ANOVA. Changes in triglycerides did not correlate with changes in body weight, HbA_{1c}, or HDL-chol. In addition, there were no correlations between initial values of triglycerides and body weight or HbA_{1c} levels.

CONCLUSIONS

In this study, we demonstrated that insulin therapy in NIDDM patients with secondary failure to SU treatment led to improvement of several aspects of lipid metabolism. Combination therapy with glyburide and insulin exerted similar effects on serum lipid concentrations as insulin alone.

The increase in HDL-chol levels after the start of insulin treatment is in agreement with most (13–17) but not all (18–20) previous studies in NIDDM. However, except for Paisey et al. (13), who followed six NIDDM patients for 12 mo, all previous studies were of limited duration (6 wk to 6 mo). Thus, like Paisey et al., we demonstrated that insulin treatment led to a sustained increase in HDL-chol.

The most important result of this study is that combination therapy led to a rise in HDL-chol that appeared comparable to that caused by insulin alone. Although Osei et al. (4) and Groop et al. (5) also found no differences in HDL-chol between combination therapy and insulin alone, a negative effect of combination therapy with glyburide and insulin has been demonstrated (6). However, note that in our study the mean HDL-chol value at day 325 had returned to baseline in IG patients. Thus, even though HDL-chol levels were significantly increased determined by ANOVA during the entire study period, there was a possibility that this increase may not have been sustained beyond 8 mo in patients on combination therapy. In this connection, it is of interest that SU treatment alone is associated with lower HDL-chol levels than insulin treatment in several cross-sectional studies of NIDDM patients (21–25). Furthermore, a change from insulin to chlorpropamide treatment results in a reduction of HDL-chol (26). Obviously, this is a question of great concern, because a low HDL-chol level constitutes an independent risk factor for cardio-

vascular disease (27), the prevalence of which is increased in NIDDM (28).

There are several possible explanations for the divergent effects of combination therapy on HDL-chol levels in different studies, such as choice of SU and differences in study populations and design and the time of sampling. Glyburide was used by Osei et al. (4), Groop et al. (5), and Stenman et al. (6) and in this study. However, although in all previous studies an older formulation (HB 419) was administered, we used a microcrystalline form of glyburide (HB 420).* A dose of 3.5 mg HB 420 has a comparable (29,30) or more pronounced (31,32) hypoglycemic effect in NIDDM patients than 5 mg HB 419. To our knowledge, there are no comparative studies on the effects of the two glyburide formulations on lipid metabolism. There were no obvious differences regarding age, duration of diabetes, and body weight between the patients of Stenman et al. (6) and those of the other studies. Nevertheless, all patient populations displayed considerable variation regarding clinical and metabolic variables. For study design, Stenman et al. (6) treated their patients with insulin for 4 mo before randomization to glyburide, whereas our patients had been treated with diet alone for at least 3 wk when randomized to insulin or combination therapy. Thus, there exists a possibility that this difference in experimental design could contribute to the differences in results. Furthermore, our follow-up period was 325 days, whereas follow-up periods were 56–112 days in the three other studies (4–6). In our study, the different findings could not be accounted for by different sampling times, because a significant increase in HDL-chol was already found during the initial period (days 16–83).

In contrast to HDL-chol, both total serum cholesterol and serum triglycerides displayed only a temporary decrease during the first part of the study. Because HbA_{1c} was decreased in both groups throughout the study, insulin, with or without glyburide, had a more limited effect on these variables than on glucose metabolism. Part of the reason for such a limited effect of insulin on serum lipid levels may have been the tendency to gain weight observed in both groups. These findings are in agreement with previous studies demonstrating a beneficial effect of insulin treatment on serum lipids (13–16,19,33). In addition, like this study, no previous investigation has shown any difference in serum levels of cholesterol or triglycerides when combination therapy is directly compared to insulin given alone (4–6,34,35).

In conclusion, this study showed that the beneficial effects of insulin treatment on serum lipid levels in NIDDM patients with secondary SU failure are not influenced by addition of glyburide. Thus, where lipid metabolism is concerned, combination therapy is comparable to insulin given alone.

*HB 420 was introduced in Sweden in 1985 and is distributed in tablets containing 1.75 and 3.5 mg glyburide. When 3.5 mg HB 420 is administered, higher peak serum glyburide levels are attained than when 5 mg HB 419 is given (29,32). In addition, both mean and peak glyburide levels tend to be less variable for HB 420 than HB 419 (29). The effects of the two formulations on serum levels of insulin and C-peptide do not differ (29,31,32).

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