Acta Diabetol (1999) 36:93-97

ORIGINAL

N. Güvener • O. Gedik

Effects of combination of insulin and acarbose compared with insulin and gliclazide in type 2 diabetic patients

Received: 29 January 1999 / Accepted in revised form: 19 May 1999

Abstract In this prospective study we aimed to compare insulin plus acarbose with insulin plus gliclazide with respect to their effect on insulin requirement, lipid profiles and body mass index (BMI) while achieving good glycemic control. Forty patients with type 2 diabetes mellitus who were on conventional insulin therapy (subcutaneous insulin therapy consisting of regular and NPH insulin, two times a day) were included in the study. They were randomized to double blind treatment with insulin in combination with gliclazide or acarbose for 6 months. For both groups, acceptable glycemic control was achieved at the end of study period. The mean HbA_{1c} levels decreased from 8.32±0.26 to 7.13±0.18% in acarbose group and 8.6±0.15 to 7.48±0.21% in the gliclazide group. The difference between groups was not significant (*P* 0.29). In the acarbose group, total cholesterol and LDL concentration decreased significantly while other parameters did not change. In the gliclazide group, HDL levels decreased significantly from 46.6±2.48 mg/dl to 41.3±2.09 mg/dl (*P* 0.001) BMI increased significantly from 27.60±1.21 kg/m^2 to 28.69±1.26 kg/m^2. (*P* 0.003) Total daily insulin dose was not changed in the acarbose group significantly, but increased from 42.6±2.73 to 49.27±3.58 U/day, which was significant in gliclazide group of (*P* 0.016). In the acarbose group, there were no significant differences between responders and nonresponders with respect to fasting and stimulated C-peptide, HbA_{1c} levels and baseline BMI values. But in the gliclazide group, baseline BMI values were significantly higher in the nonresponding group compared to responders (*P* 0.02). In conclusion, combination of insulin with acarbose can be a good alternative for type 2 diabetic patients on insulin therapy; seems more beneficial than combination with gliclazide; may have advantage of achieving good glycemic control without increasing insulin dose and BMI; also may have the advantage of providing a decrease in LDL level, which are all important to prevent atherosclerosis.

Key words Type 2 diabetes mellitus • Insulin • Acarbose • Gliclazide

N. Güvener (✉) • O. Gedik
Hacettepe University Faculty of Medicine,
Department of Internal Medicine, Section of Endocrinology,
Mesnevi sok. 38/3, TR-06540, A. Ayranci-Ankara, Turkey

Introduction

Secondary failure to therapy with oral hypoglycemic agents is a common problem in the management of patients with type 2 diabetes mellitus (DM) [1]. Insulin therapy is required to achieve adequate glycemic control in many of these patients. The frequent association of obesity, hypertension, hyperlipidemia and hyperinsulinemia with atherosclerosis is well known in type 2 diabetic patients [2]. There is type 2 increasing evidence to suggest that high circulating levels of insulin constitute an atherogenic risk factor [3]. Vigorous insulin therapy generally leads to peripheral hyperinsulinemia. This generates alternative treatment programs for reducing hyperinsulinemia.

Sulphonylurea agents enhance the pancreatic β-cells ability to secrete insulin and they decrease peripheral insulin resistance by ameliorating some as yet undefined post-receptor defect [4]. But this effect may be due to a decrease in glucose toxicity associated with glycemic control rather than direct effect of SU on insulin sensitivity. Type 2 diabetic patients are both insulin deficient and insulin resistant. In these patients using insulin plus SU agent has been proposed to help to maximize endogenous insulin secretion and to enhance the response to both endogenous and exogenous insulin [5].

Besides this acarbose, which is a glucosidase inhibitor, by slowing down the digestion of complex carbohydrates

and sucrose, is able to reduce the amount of insulin needed to control postprandial hyperglycemia, since it prevents abnormally high increments of postprandial glucose levels [6].

Based on these facts combining insulin with oral drugs is postulated to decrease exogenous insulin requirements producing less peripheral hyperinsulinemia that may be atherogenic for diabetic patients [3].

Starting from that point, in this prospective study, we aimed to compare insulin plus SU and insulin plus acarbose therapy with respect to their effect on insulin requirement, lipid profiles and body mass index (BMI) while achieving adequate glycemic control.

Patients and methods

Forty patients with type 2 DM (as defined by National Diabetes Data Group criteria) who failed on therapy with maximum doses of oral hypoglycemic agents and for that reason were on conventional insulin therapy (subcutaneous insulin therapy consisting of regular and NPH insulin, two times a day), were included in the study. None of the patients had secondary DM or clinical evidence of hepatic, renal or pulmonary dysfunction. At the beginning of the study, they had all failed to achieve good glycemic control with fasting plasma glucose levels >140 mg/dl and postprandial glucose levels >200 mg/dl.

Patients were divided randomly into two groups. They were randomized to a double-blind treatment with insulin in combination with gliclazide or acarbose for 6 months. Starting dose for gliclazide was 240 mg and for acarbose 150 mg, doses were increased to a maximum of 320 mg and 600 mg/day, respectively according to plasma glucose levels. All patients were given diet treatment designed according to patient's ideal body weight and activity (consisting of 50-60% carbohydrate, 10-15% protein and ≈30% lipid). In each visit all were asked to use diet.

At the beginning, basal and glucagon stimulated C-peptide levels were measured for all patients. During the entire study period, the patients visited the outpatient unit every 4 weeks or more often if necessary. Doses of drugs and insulin were regulated in each visit according to glucose profiles. Insulin dose was kept constant at the beginning until the maximum dose of oral drug was achieved. Then insulin dose was changed to obtain adequate glycemic control.

HbA_{1c}, lipid profiles, and BMI were determined at the beginning and end of study period. This study was approved by our local ethics committee and all the persons gave informed concent prior to their inclusion in the study.

Assays

Plasma glucose was measured by the glucose oxidase method (Glucose Enzymatique PAP kit, BioMerieux, France). HbA_{1c} concentration was determined by cation exchange microcolumn chromatography (Isotech). The normal range for HbA_{1c} was 4.2-6.2%. Serum C-peptide concentration was measured by RIA (DSL).

Statistical analysis

All data are expressed as means ± SEM. All statistical comparisons within and between the groups were made with the paired and unpaired Student's *t*-test respectively. Mann-Whitney U test was used to compare the responders with nonresponders. *P*-value < 0.05 is accepted as statistically significant.

Results

Table 1 shows the clinical and laboratory features of both groups. In the gliclazide group 2 patients were lost to follow up, so excluded from the study.

In the acarbose group of 20 patients; 16 of them were female and the remaining 4 were male, while in gliclazide group, 14 of them were female and the other 4 were male. Mean ages of patients in the acarbose and gliclazide groups were 59.61 ± 2.07 and 53.10 ± 1.37 (*P* 0.01) and the mean durations of DM were 10.15 ± 1.75 and 11.86 ± 1.56 years, respectively (*P* 0.47). Except for age, HDL and fasting plasma glucose, for all these parameters, the differences between groups were not statistically significant. Table 1 shows the laboratory values obtained at the beginning and the end of 6 months for each group.

In the acarbose group

There were no significant differences between baseline and 6-month fasting glucose levels, BMI, HDL, VLDL and triglyceride levels. But total cholesterol and LDL concentrations were decreased significantly at the end of the study period (*P* 0.001 for both).

Postprandial glucose levels decreased from 224.3 ± 11.68 mg/dl to 131.65 ± 6.44 mg/dl and again that was statistically significant (*P* 0.001). The mean HbA_{1c} concentration decreased significantly from 8.32 ± 0.26% to 7.13 ± 0.18% (*P* 0.01). But there were not any significant change in total daily insulin dose, which were 40.45 ± 3.18 U at the beginning and 43.50 ± 4.22 U at the end of the study (*P* 0.31). Hypoglycemic episodes were observed in two patients. Only six patients had flatulence and bloating, which were relieved with simethicon. Nobody had diarrhea.

In the gliclazide group

Fasting plasma glucose levels decreased significantly from 202.24 ± 13.4 to 141.61 ± 6.19 (*P* 0.001). The mean postprandial glucose and HbA_{1c} levels were 137.61 ± 10.8 and 7.48 ± 0.21, respectively and the amount of decrements were statistically significant (*P* values 0.001 and 0.01, respectively).

Table 1 Comparison of before and after treatment values in each group

	Group I (before)	Group I (after)	*P*-value	Group II (before)	Group II (after)	*P*-value
BMI (kg/m^2)	27.60 ± 1.21	28.69 ± 1.26	0.03	28.04 ± 1.01	28.31 ± 1.13	0.47
HbA_{1c} (%)	8.6 ± 0.15	7.48 ± 0.217	0.01	8.32 ± 0.26	7.13 ± 0.182	0.01
Fasting plasma glucose (mg/dl)	202.22 ± 13.4	141.61 ± 6.19	0.001	163.65 ± 10.35	141.35 ± 6.51	0.06
Postprandial plasma glucose (mg/dl)	230.39 ± 12.73	137.61 ± 10.8	0.001	224.30 ± 0.68	131.65 ± 6.43	0.001
Total cholesterol (mg/dl)	231.94 ± 7.34	220.44 ± 10.35	0.3	231.55 ± 12.8	213.26 ± 9.75	0.01
Triglyceride (mg/dl)	158.89 ± 20.3	158.83 ± 19.74	0.9	174.05 ± 22.93	192.0 ± 27.24	0.43
HDL (mg/dl)	46.61 ± 2.48	41.3 ± 2.09	0.01	38 ± 3.06	36.21 ± 2.29	0.9
LDL (mg/dl)	153 ± 6.89	137.72 ± 8.28	0.09	159.45 ± 10.69	141.63 ± 11.11	0.01
VLDL (mg/dl)	31.72 ± 4.06	31.72 ± 4.03	0.99	34.45 ± 4.68	37.79 ± 5.36	0.49
Total daily insulin dose (U)	42.67 ± 2.73	49.28 ± 3.57	0.016	40.45 ± 3.18	43.55 ± 4.21	0.31

We obtained a statistically significant increase in BMI (*P* 0.003) while there were no significant changes for LDL, VLDL, total cholesterol and triglyceride values. But HDL levels decreased from 46.61 ± 2.48 mg/dl to 41.33 ± 2.09 mg/dl and that was significant statistically (*P* 0.01).

One of the most important points is that, total daily insulin dose was increased from 42.6 ± 2.73 U to 49.27 ± 3.58 U (*P* 0.016).

Hypoglycemic episode was seen in only one patient in this group.

Comparison of two groups at the end of study period

At the end of 6 months duration of therapy HbA_{1c} values for acarbose and gliclazide groups were 7.13 ± 0.18% and 7.48 ± 0.21%, respectively and the difference was not significant statistically (*P* 0.22). Again the differences between groups for fasting and postprandial glucose, HDL, LDL, VLDL, triglyceride and total cholesterol concentrations and total daily insulin dose were not significant statistically.

In each group patients were divided into two groups who were responders and nonresponders. If the total daily insulin dose was not changed or decreased while good glycemic control was achieved the patient was accepted as responder.

In that respect; in the acarbose group 11 of 20 patients, and in the gliclazide group 7 out of 18 patients were responders. For each group responders and nonresponders were compared with respect to fasting and glucagon stimulated C-peptide levels, baseline BMI and baseline HbA_{1c} levels. Mean values for these characteristics in responders and nonresponders in each group we summarized in table 2.

In the acarbose group there were no significant differences in responding and nonresponding groups with respect to fasting and stimulated C-peptide, HbA_{1c} levels and BMI.

In the gliclazide group, again there were no significant differences in basal and stimulated C-peptide and HbA_{1c} levels. But in this group, baseline BMI values were significantly higher in the nonresponding group compared to responders (*P* 0.02).

Discussion

In this prospective study, we aimed to compare the effects of combination therapies on lipid profiles, BMI and total daily insulin requirements while achieving good glycemic control. For both groups, at the end of study period HbA_{1c} levels decreased and acceptable glucose levels were obtained. But this goal was achieved at the expense of increase of total daily insulin dose for the gliclazide group, while total insulin dose was not changed in the acarbose group significantly.

With respect to lipid profiles, again acarbose seems to be more beneficial, since significant decreases in LDL lev-

Table 2 Comparison of responders with nonresponders in each group

	Insulin + acarbose		Insulin + gliclazide	
	Responders	Nonresponders	Responders	Nonresponders
HbA_{1c} (%)	8.09 *P* 0.36	8.60	8.34 *P* 0.17	8.77
C-peptide (ng/ml) 0’	1.45 *P* 0.11	2.00	1.53 *P* 0.40	1.99
6’	2.47 *P* 0.27	3.44	2.52 *P* 0.30	3.46
BMI (kg/m^2)	27.61 *P* 0.65	28.56	24.22 *P* 0.02	29.75

els were obtained in this group, while in the gliclazide group HDL levels decreased significantly, which is not desired.

In the gliclazide group, BMI also increased at the end of the study period, probably related with the increase in total daily insulin dose. SU itself may also be the contributing factor since it has been shown to be associated with weight gain, even in the absence of insulin treatment [7].

The difference between groups with respect to age has been found to be statistically significant. The impact of this factor to the end result of the study is not clear since there are studies on the effect of aging on insulin resistance with conflicting results. In most of these studies the major factor effecting insulin sensitivity with aging is the change in fat mass with aging rather than the age itself at least up to 60 to 70 years [8-12]. We did not evaluate insulin sensitivity in our study, but based on these reports we don’t think that the difference between groups with respect to age has a great effect on the results.

Another difference between the two groups was the HDL levels at the beginning. Low HDL level has been reported to be a indicator of insulin resistance [13, 14]. In our study there were no significant differences between groups with respect to C-peptide, HbA_{1c} levels and total daily insulin dosage at the beginning of the study. These may reflect that there was no major difference in insulin sensitivity for the two groups at the beginning.

Fasting plasma glucose has been found to be significantly higher in the gliclazide group and the levels decreased in this group at the end of study period with the cost of increase in total daily insulin dosage. So it is difficult to determine the effect of SU on fasting plasma glucose level.

During the last 10 years, increasing numbers of reports dealing with combined insulin-sulphonylurea therapy appeared in the literature [15-17]. The rationale behind this combination resides in the synergistic action of the two agents [18]. In some studies, it has been shown that insulin requirement to achieve good glycemic control can be reduced by 10-50%. However some studies failed to report such a reduction in insulin requirement similar to our results. Besides this, weight gain with the combined treatment was frequently greater than the insulin therapy alone [19]. Also similar to our results regarding the decrease in HDL level that we obtained in the gliclazide group was reported in Groop’s study [20]. All these imply rather unwanted effects of combination therapy with SU.

In our study, it is impossible to say that insulin and gliclazide combination therapy is not beneficial at all, since we did not compare the group with insulin therapy alone. Although acarbose treatment seems more beneficial with respect to BMI and insulin requirements considering baseline values, in another study, adding an arm with insulin treatment only, will be helpful to define net benefits of treatment modalities.

In the literature, studies done especially in a type 1 DM group reported that insulin requirements decrease by adding acarbose to treatment [18]. This has also been observed in type 2 diabetes but the data are scarcer. In one study, acarbose treatment resulted in improved metabolic control and a small reduction in insulin requirement [21].

In our study, we have shown that with combination of insulin and acarbose therapy, a significant decrease in LDL level was obtained as a beneficial effect. In some studies, no effect on HDL, LDL or triglyceride levels have been shown [2]. However in Reaven’s study, TG and total cholesterol levels were shown to be decreased with acarbose treatment [22]. Most reported lipid changes are moderate.

We analysed the groups with respect to their total daily insulin requirement at the end of the study period and divided them into two groups as responders and nonresponders. In both the acarbose and gliclazide groups basal and glucagon stimulated C-peptide levels were slightly higher in nonresponders compared to responders but the difference was not significant. In the acarbose group, there was no significant difference with regard to baseline BMI and HbA_{1c} values. But in the gliclazide group, mean BMI were significantly higher in nonresponders. Also in the nonresponding group,

basal an stimulated C-peptide levels were higher compared to responders. These results must be verified in larger groups. There are reports in the literature contradictory to our findings. In four studies, glycemic control was most improved in the patients who initially had the worst glycemic control and the greatest degree of obesity and had a high initial C-peptide level. But in another four studies, no difference was found between groups taking insulin plus SU and insulin plus placebo with respect to these parameters. In one small study, two patients with the highest initial fasting plasma glucose levels were nonresponders [1, 23]. So predicting which patients will respond clinically is difficult.

In conclusion, the combination of insulin with acarbose can be a good alternative for those type 2 diabetic patients who remain hyperglycemic despite treatment with insulin and in whom a further increase in insulin dose is considered. This combination may take the advantage of achieving good glycemic control without increasing insulin dose, without increasing BMI and also may have the advantage of providing decrease in LDL level, which all may be very important factors that must be achieved to prevent atherosclerosis.

Acknowledgements We thank to Alper Gürlek M.D. and Yahya Büyükasik M.D. for their assistance in statistical analysis.

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