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EVALUATION OF INSULIN-SULFONYLUREA COMBINATION VERSUS INSULIN ALONE IN THE TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM)

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ABSTRACT

Lowering the glucose level in diabetic patients reduces the risk of many consequences which are usually reported in these patients. Non-insulin dependent (type II) diabetes which cannot be controlled with sulfonylureas alone can be controlled with a combination of sulfonylurea and insulin. In an open randomized trial 58 patients were divided into three groups. The first group received only insulin based on their blood glucose level. The second group received a set amount of insulin plus the required amount of glibenclamide and the third group received a set amount of insulin plus the required amount of chlorpropamide based on their glycemic control. All three groups had a significant reduction of blood glucose, total cholesterol and triglyceride levels. The best long term glycemic control was in the second group with the lowest HbA_{1c}(%). In these patients bedtime insulin and daytime sulfonylurea (BIDS) gives better glycemic control. This method of therapy is a valuable option for patients with NIDDM whose hyperglycemia cannot be controlled by sulfonylureas and do not have compliance with more than one injection a day.

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INTRODUCTION

The initial treatment of NIDDM is diet and exercise.[1] However, in many patients this approach does not result in normalization of blood glucose values. Patients with NIDDM who remain persistently hyperglycemic can be offered a course of therapy with an oral hypoglycemic agent. In most NIDDM patients these agents control the blood glucose level. In some NIDDM patients these agents may initially control blood glucose levels but later lose effectiveness (secondary failure), whereas in other NIDDM patients oral hypoglycemic agents are never able to control blood glucose levels adequately (primary failure).[2] In these cases when the patient remains severely hyperglycemic and symptomatic, the only therapy left is addition of insulin to their regimen.[3,4]

NIDDM is characterized by a state of peripheral insulin resistance.[5,6,7] Many patients with NIDDM are also obese, a factor that increases insulin resistance.[8,9] Although the exact mechanism of action of sulfonylurea agents is uncertain, evidence exists which suggests that these agents enhance peripheral insulin sensitivity,[9-13] and reduce hepatic glucose production,[13-15] whereas exogenous insulin is thought to increase insulin resistance at the level of the receptor.[16] The possibility exists, therefore, that a patient with NIDDM who is treated with

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insulin actually becomes more insulin resistant. A number of studies have examined the possibility of enhancing insulin sensitivity in patients with NIDDM who are treated with insulin, by treating them simultaneously with a sulfonylurea agent. If enhancement of insulin sensitivity is an important mode of action for sulfonylureas as has been suggested, combining a sulfonylurea with insulin should improve glycemic control, while allowing patients to use lower doses of insulin. Several studies have demonstrated a modest improvement in glycemic control using this approach.[13] Recent studies suggest that hyperinsulinemia contributes to hypertension and lipid profile changes,[17,18] therefore adequate control of blood glucose with the lowest concentration of blood insulin is the essential goal of therapy. The majority of the studies demonstrated that combination therapy needs lower doses of insulin.[18,20]

In this study BIDS therapy was evaluated on Iranian diabetic patients. To the best of our knowledge, this type of study has not been done in Iran. In our study BIDS was compared with insulin therapy in NIDDM patients whose glycemic control with insulin therapy was poor. Among sulfonylureas, glibenclamide and chlorpropamide were selected.

MATERIALS AND METHODS

Inclusion criteria for patients in our study were:
1- Non-insulin dependent diabetes mellitus (NIDDM); all patients were selected by a single endocrinologist.
2- Poor glycemic control in spite of insulin therapy (FBS>200 mg/dL).
3- Daily insulin dosage of 20 u/day or more.
Exclusion criteria for patients in this study were:
1- Evidence of liver or kidney disease.
2- Evidence of cardiovascular disease.
3- Serious infection.
4- Allergy to sulfonylureas.
5- Evidence of pregnancy.

The study was done in a private office from January to March 1996. Fifty-eight patients who met the inclusion criteria were selected for the study and randomly placed in "Insulin" (I), "Insulin+Glibenclamide" (I+G) and "Insulin+Chlorpropamide" (I+C) groups. General information regarding these patients at the beginning of the study are presented in Table I.

Each patient was followed for three months and visited three times; at the beginning of the study, one and a half months and three months later. In each visit, the following clinical tests were recorded in individual medical profiles: fasting blood sugar (FBS), BS (4 pm blood sugar), HbA_{1c}, serum total cholesterol and triglycerides. These tests were done in a single laboratory. Throughout the study, the insulin dose administered to the treatment groups [i.e., (I+G) and (I+C)] was constant and the dose of sulfonylurea (i.e., glibenclamide and chlorpropamide) was changed according to the glycemic control. In the control group (I), the insulin dose was changed according to the glycemic control. Also, in each visit, patients were asked about adverse effects of drugs. Diet and exercise were recommended to all of the patients.

Table I. Characteristics of the patients in the beginning of the study

Parameter	(I)	(I+G)	(I+C)
Number of patients	19	19	20
Ratio of female to male	12/7	9/10	14/6
Age (years)	44±13	42±8	47±17
Weight (kg)	77±20	77±21	80±15
Height (cm)	166±10	163±14	160±11
History of disease			
a) Less than 5 years	52%	57%	75%
b) More than 5 years	47%	42%	25%
Daily dosage of insulin (u/day)	38±18	37±14	31±11
FBS (mg/dL)	365±118	352±102	325±55
Postprandial blood sugar (mg/dL)	360±150	350±86	345±96
Hemoglobin A_{1c} (%)	11.2±2.5	10.9±2.4	10.6±1.4
Total cholesterol (mg/dL)	260±92	236±101	195±42
Serum triglycerides (mg/dL)	216±93	237±130	169±39

Values reported in this table are Mean±SD.
All parameters of the three groups are similar with regard to Levene's test for comparison of variances and the two tailed t-test for comparison of means and are not significantly different ($p>0.05$).

Statistical methods which were used for analysis included Levene's test for comparison of variances, the two tailed t-test for comparison of means (these two tests were used for comparing the parameters [except for sex & disease history] between the two different groups in each visit), the paired t-test (this test was used for evaluation of parameters [except for sex & disease history] between two different visits of each group), and the chi-square test (this test was used for comparison of sex and disease history between the two different groups at the beginning of the study).

RESULTS

Comparing the last visit (Table II) with the first visit (Table I) showed that in all three groups, at the end of the study, mean FBS, BS (4 pm blood sugar) and HbA_{1c}

Table II. Characteristics of the patients at the end of the study

Parameter	(I)	(I+G)	(I+C)
FBS (mg/dL)	147±22	167±45	175±45
	(n= 19)	(n= 18)	(n= 20)
BS	168±35	159 28	252±100
	(n= 15)	(n= 13)	(n= 17)
HbA_{1c} (%)	6.8±0.6	5.9 0.9	6.5±0.8
	(n= 19)	(n= 19)	(n= 20)
Total cholesterol (mg/dL)	178±64	164±61	174±62
	(n= 7)[a]	(n= 6)[a]	(n= 7)[a]
Serum triglycerides (mg/dL)	149±31	151±49	153±49
	(n= 8)[a]	(n= 6)[a]	(n= 7)[a]
Daily dosage of insulin (u/day)	52±18	fixed	fixed
	(n= 19)	(n= 18)	(n= 20)
Daily dosage of oral	0	10 2	50±6
hypoglycemic agent (mg/day)		(n= 19)	(n= 20)

Number in parenthesis show the number of patients in the statistical calculations.
(a) denotes the number of patients in each group which did not use any antihyperlipidemic drugs.

values were significantly lower than the beginning of the study ($p<0.05$). At the end of the study, the mean daily insulin dose in group (I) was significantly higher than the beginning of the study ($p<0.001$).

Results of comparing these parameters in third visits [(I), (I+G)], [(I), (I+C)] and [(I+G), (I+C)] are described below:

1- FBS:

A-(I) and (I+G)

At the end of the study mean FBS values in (I) and (I+G) groups were similar ($p>0.05$).

B- (I) and (I+C)

At the end of the study mean FBS values in group (I) were significantly lower than group (I+C) ($p= 0.021$).

C-(I+G) and (I+C)

At the end of the study, mean FBS values were similar in (I+G) and (I+C) groups ($p>0.05$).

2- BS (4 p.m. after meal)

A-(I) and (I+G)

At the end of the study, mean BS values were similar in (I) and (I+G) groups ($p>0.05$).

B-(I) and (I+C)

At the end of the study, mean BS values were significantly lower in group (I) compared to group (I+C) ($p= 0.004$).

C-(I+G) and (I+C)

At the end of the study, mean BS values were significantly lower in group (I+G) compared to group (I+C) ($p= 0.002$). (mg/dL)

3- HbA_{1c}

A-(I) and (I+G).

At the end of the study, mean HbA_{1c} levels in group (I+G) were significantly lower than group (I) ($p=0.003$).

B-(I) and (I+C)

At the end of the study, mean HbA_{1c} levels were similar in (I) and (I+C) groups ($p>0.05$).

C-(I+G) and (I+C)

At the end of the study, mean HbA_{1c} levels were significantly lower in group (I+G) compared to group (I+C) ($p= 0.044$).

4- Total cholesterol and serum triglycerides

At the end of the study, total cholesterol and serum triglyceride levels were significantly lower ($p<0.001$) than the beginning of the study in all three groups.

A-(I) and (I+G)

At the end of the study, these parameters were not significantly different in (I) and (I+G) groups ($p>0.05$).

B-(I) and (I+C)

At the end of the study, these parameters were also not significantly different in (I) and (I+C) groups ($p>0.05$).

C-(I+G) and (I+C)

At the end of the study, these parameters were not significantly different in (I+G) and (I+C) groups ($p>0.05$).

5-Insulin dosage

A-(I) and (I+G)

At the end of the study, comparison of mean daily insulin dose between (I) and (I+G) groups showed that mean daily insulin dosage in group (I) was significantly higher than group (I+G) ($p= 0.01$).

B-(I) and (I+C)

At the end of the study, comparison of mean daily insulin dose between (I) and (I+C) groups showed that mean daily insulin dose in group (I) was significantly higher than group (I+C) ($p<0.005$).

C-(I+G) and (I+C)

At the end of the study, comparison of mean daily

Table III. Incidence of adverse effects among the study groups.

Adverse effects	%incidence in (I)	%incidence in (I+G)	%incidence in (I+C)
Hypoglycemia	42	42	45
Redness & itching of injection site	21	15	--
Skin rash	5.3	5.3	5
Lipodystrophy	5.3	--	5
GI adverse effects	--	5.3	--
None	36	36	45

insulin dose between (I+G) and (I+C) groups showed that mean daily insulin dose was similar in both groups ($p>0.05$).

6- Adverse effects

Incidence of adverse effects among all three groups are almost the same (Table III).

7- Cost

Cost of treatment for a month in group (I+G) at the third visit was lower than group (I) (3654.8 rials versus 4222.8 rials). Also the cost of a month's treatment in group (I+C) at the third visit was less than group (I) (3557.3 rials versus 4222.8 rials). It should be noted that the parameters of the patients at the second visit were also recorded, but were not analyzed in this paper because they didn't affect the final results of the study.

DISCUSSION

Improvement in glycemic control with a combination of insulin and sulfonylurea is not a new subject. For the first time some researchers (about 38 years ago) reported the benefits of combining talbutamide and insulin in the treatment of NIDDM. These reports showed that combining insulin and talbutamide in some NIDDM patients resulted in improvement of glycemic control, lowering of insulin dosage and improvement in life style.

Studies performed in the United States and Europe showed that combination therapy with insulin and sulfonylurea can improve glycemic control and perhaps lower insulin dosages. Most of these studies were done in a small number of patients (6 to 22) and in short periods of time (16 weeks or less). In these studies insulin dosages or sulfonylurea dosages were adjusted with regard to blood glucose.[16]

1) Comparison of glycemic control

In some specialist opinions BIDS therapy results in relative glycemic control but does not give perfect control.[21] A few double blind placebo-controlled studies have even reported poor improvement in glycemic control with combination therapy.[13]

In this study, we concluded that, with regard to mean FBS and BS values, glycemic control in group I was better than group (I+C), but glycemic control in (I) and (I+G) groups were similar.

With regard to HbA_{1c} levels the recorded values showed that long term glycemic control in group (I+G) was better than group (I) but was similar in (I) and (I+C) groups.

According to BS and HbA_{1c} values at the end of the study, we concluded that glycemic control in group (I+G) was better than group (I+C).

2) Comparison of lipid profiles

In comparing insulin with BIDS therapy in NIDDM patients, most researchers report no difference in serum lipids or triglycerides.[22] In our study, evaluation of serum lipids showed that in all three groups, effects on serum lipids were similar.

3) Comparison of daily insulin dosage and number of daily injections of insulin

Most studies have proven that with BIDS therapy lower doses of insulin are required.[18-20] Also, Kabadi showed that one of the benefits of this method is to lower the number of daily insulin injections.[20]

At the end of this study, comparing mean daily insulin dosage values showed that in group (I) this parameter was significantly higher than each of the combination therapy groups ($p<0.05$). However, the mean number of daily insulin injections was not significantly different between the three groups ($p>0.05$).

4) Adverse effects and cost of therapy

In most of the double blind placebo-controlled studies, glycemic control with BIDS therapy has shown poor improvement.[13] In combination therapy, hypoglycemia

was more common (2-4 times) but mild, which was treated by reducing insulin dosage.[22] Generally, adverse effects in this method of therapy are lower. Mild hypoglycemic reactions generally occur and are the most important adverse effects with this method of therapy.[23] Weight gain was greater with combination therapy than with insulin therapy alone. However, insulin therapy alone also generally causes weight gain.[22]

Comparing the incidence of adverse effects in this study did not show a significant difference between these three groups. (p>0.05).

Comparison of therapeutic cost (in rials/month) in the third visit showed that the cost of combination therapy in this study was lower than insulin therapy alone. In other studies it was reported that the cost of drugs used in BIDS was more than insulin therapy alone. However, this increase in cost of drugs is not important because the reduction in the number of daily insulin injections will decrease other peripheral expenses.[20]

With regard to the results of this study, glycemic control in the (I+G) group is better than the (I+C) group; however, their effects on serum lipids are not significantly different. Also, the results show that in NIDDM patients who are using insulin (at least 20 u/day) but their BS is poorly controlled (FBS>200 mg/dL), glibenclamide should be added to their therapeutic regimen.

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