EFFECTS OF INSULIN, GLIMEPIRIDE AND COMBINATION THERAPY OF INSULIN AND METFORMIN ON BLOOD SUGAR AND LIPID PROFILE OF NIDDM PATIENTS

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ABSTRACT

In the present study the efficacies of therapy with insulin, sulphonylurea or insulin + metformin on NIDDM patients are compared. One group which was on a definite dose of insulin therapy, but with uncontrolled diabetes was treated by doubling the insulin dose, a second group whose diabetes was not controlled by glibenclamide was switched over to another sulphonylurea viz; glimepiride and a third group whose diabetes was not controlled by insulin therapy was switched over to a combination therapy with insulin +metformin. After recording their initial blood parameters all the groups were treated as above for 3 months, and the parameters were again determined. The fasting blood sugar and serum lipids of the first group were controlled significantly, but the values were far above normal range. However HDL Cholesterol and atherogenic index were near normal range. In glimepiride treated group, none of the parameters showed any amelioration. In the combined therapy group, control of blood sugar and atherogenic index was more or less the same as for group 1, but hyperlipidemia remained slightly above that of the same. From the findings we can infer that in long term diabetes treatment higher doses of insulin and combined therapy with insulin and metformin may be more beneficial than with low doses of insulin or sulfonyl urea alone

KEY WORDS

Insulin, Glimepiride, Metformin, Blood sugar, Combination therapy, NIDDM.

INTRODUCTION

When maturity onset diabetics or Non insulin dependent diabetes mellitus (NIDDM) patients do not show reasonable improvement of the disease within 1.5 to 3 months of intervention with diet and exercise pharmacology should be used in the treatment plan. The pharmacological treatment of hyperglycemia in most NIDDM patients begins with low doses of sulphonylurea, biguanide (metformin) or glucose inhibitors. While each agent is effective in monotherapy, there are several factors that have to be considered before writing the prescription. The physician should review each of the drug option and learn the benefits of each drug against cost,

contraindications, case of compliance, duration of action, patient's weight and lipid profile.

In most patients, consideration of combination therapy is the next step if one agent fails to control hyperglycemia. Each agent has a different effect on body weight, serum lipid levels, plasma insulin levels and insulin resistance. Glimepiride is a second generation sulphonyl urea and studies (1) have shown that it does not restore defective first phase insulin secretion, but significantly increases second phase insulin secretion. It also increases whole body glucose uptake and increases insulin sensitivity. Glimepiride has been shown to have significantly fewer harmful effects on cardiovascular system than by glyburide (2).

Insulin is not usually a first line treatment for NIDDM, but nearly 50% of patients of this group eventually need insulin to control their hyperglycemia. Insulin therapy can correct or improve many of the metabolic abnormalities present with NIDDM. Insulin regulates plasma glucose levels by decreasing hepatic glucose production (3) and increasing glucose uptake (4) by

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peripheral tissues. Normal physiological regulation of glucose level involves a basal level of insulin secretion followed with increased secretion by meals. Basal insulin secretion regulates hepatic glucose production and post prandial secretion increases glucose uptake. Insulin also lowers the abnormal lipoprotein composition commonly seen in patients with insulin resistance. Insulin therapy may also decrease or eliminate the effects of glucose toxicity by reducing hyperglycemia to improve insulin and B cell secretory function (5).

Combination therapy usually refers to the use of oral antidiabetic agents together with a single injection of intermediate acting insulin at bed time. Combination therapy is introduced in cases where the patients are poorly controlled with large doses of insulin. Even though metformin enhances insulin sensitivity, it is associated with weight loss and does not cause hypoglycemia or an increase in plasma insulin level. The combination of insulin sensitizers such as pioglitazone with metformin may be an attractive therapeutic option for NIDDM patients (6). A number of studies have demonstrated that primary antiglycemic action of metformin results from improved insulin sensitivity, primarily in the liver and secondary in muscle.

MATERIALS AND METHODS

A total of sixty patients aged 35-70 years who have been diagnosed as diabetic patients for about 20 years were included from a tertiary care hospital. The study was carried out at the out patient unit after all the patients gave informed consent to the doctor for using their blood parameters data determined in the course of treatment at the hospital for this purpose.

They were groups of twenty each of the categories of therapy- NIDDM patients using insulin, NIDDM patients using sulphonylurea and NIDDM patients undergoing combination therapy of insulin and metformin.

The fasting blood sugar (FBS) and lipid profile of these patients were estimated before and after three months on regularization of the dose. The initial samples were collected while the patients were admitted to the hospital for glycemic control. Their FBS and serum lipid profile were determined by standard methods. After admission of the patients, doses of the drugs were adjusted or treatments were altered and fasting blood sugar monitored for a week, Once control was achieved three monthly appointments were given and their FBS (7), serum total cholesterol (8), HDL-C (9), VLDL-C and LDL-C (10) and triacylglycerol (11), were determined at that time. Group 1

patients were initially on 24-30 units of insulin (8-10 units thrice a day). Since they did not achieve good glycemic control their doses were increased to 60 units (20 units thrice a day). Group 2 patients were initially on glibenclamide treatment (15-20mg/day) for a year.

Since they did not show much response to this therapy the drug was changed to glimepiride (1-4 mg twice a day). The patients in group 3 were initially on 60 units of insulin (20 units thrice a day). Since they did not achieve good glycemic control a biguanide metformin (15 mg/day) was introduced along with insulin. The insulin used was Huminsulin and it was administered as a mixture of short acting (30%) and long acting insulin (70%). Statistical analysis of the blood parameters data obtained was carried out by one- way analysis of variance (ANOVA) and difference between the means of treated groups were determined by Bonferroni multiple comparison procedure (12). The results are given in tables for comparison with level of significance obtained for each parameter ($P < 0.05-0.001$).

RESULTS

A group wise comparison of FBS, serum total cholesterol and TAG variations between initial and final values is made in Table 1 and those of lipoproteins and atherogenic index are given in Table 2. Majority of patients on insulin treatment (Group 1) before regularization of the dose showed no good control of their FBS or lipid profile. After regularization of the insulin dose and 3 months treatment they showed a highly significant FBS fall of 20% ($p < 0.001$). Similarly total cholesterol, TAG and LDL-C decreased significantly i.e. cholesterol by 9%, TAG by 13%, ($p < 0.05$) and LDL-C by 15% ($p < 0.01$) respectively. On the contrary VLDL-C decreased only non-significantly by 9% and good cholesterol HDL-C increased significantly by 25% ($p < 0.01$).

However after regularization of insulin and on treatment in the above group only 2 out of 20 patients showed a good control of FBS (< 150 mg/dl) and only 7 out of 20 showed a good control of cholesterol (< 200 mg/dl). Again only 11 out of 20 improved their HDL-C (> 50 mg/dl). Similarly 14 out of 20 showed a good control of LDL-C (< 130 mg/dl) and only 7 out of 20 patients showed a good control of TAG (< 140 mg/dl) and only 9 out of 20 showed a good control of VLDL-C (< 30). However treatment improved the general well being of the patients to a great extent even though their mean blood sugar and serum lipids were not brought down to normal levels. With respect to atherogenic index (AI) it decreased significantly for all the treated patients of this group.

Table 1: Fasting Blood Sugar and serum total cholesterol and Triacylglycerol values of Insulin, glimepiride or Insulin + metformin treated NIDDM patients, before and after regularization of treatment for a three month duration. Mean values $\pm$ SD for 20 patients in each group are given in terms of mg /100ml

Groups	FBS		Total Cholesterol		TAG	
	Initial	Final	Initial	Final	Initial	Final
Insulin treated	218.7 $\pm$ 12.8 ^a	174 $\pm$ 9.7 [*]	222.4 $\pm$ 12.07 ^a	203.0 $\pm$ 11.37 ^c	180.1 $\pm$ 14.8 ^d	154 $\pm$ 16.3 ^c
Glimepiride	221.45 $\pm$ 26.05 ^a	215 $\pm$ 21.5 ^a NS	217.4 $\pm$ 15.5 ^a	218.4 $\pm$ 20.7 ^a NS	190.75 $\pm$ 10.12 ^d	184.86 $\pm$ 16.5 ^d NS
Insulin + Metformin	243.45 $\pm$ 11.8 ^b	178.65 $\pm$ 15.5 [*]	228.4 $\pm$ 5.8 ^a	207 $\pm$ 8.5 ^c	205.1 $\pm$ 8.6 ^a	180.95 $\pm$ 8.70 ^c

ANOVA * P<0.001 ° P<0.05 as compared to initial values.

Values with the same superscript in the vertical columns; are not significantly different from each other.

None of the patients of group 2 showed any control of their FBS or lipid profile before the regularization of treatment with glimepiride. Even after glimepiride treatment 7 patients out of 20 actually showed an increase and others showed only a non significant decrease in their FBS. Only 7 out of 20 showed any control of cholesterol (<200mg/dl) and others showed a non significant rise in their cholesterol level. With respect to HDL-C only 1 out of 20 showed a good elevation of it (>50 mg/dl) and only half of this group showed a normal level of LDL-C (<130 mg/dl). However 8 of the remaining showed a non significant increase in their values. Similarly only 2 out of 20 showed a good control of TAG (<140 mg/dl) and 10 of them showed a rise in their values. Only 4 out of 20 showed a normal level of VLDL-C (<30 mg/dl) and 5 of the remaining actually showed a non significant rise in their values. With respect to AI, there was no significant change on treatment.

FBS, serum lipids and lipoproteins of group 3 initially on insulin treatment were not well controlled. After combination therapy with insulin and metformin, the FBS of this group significantly reduced by 27% (p<0.001). However only 1 out of 20 showed a good glycemic control (<150 mg/dl). With respect to serum total cholesterol, it reduced just significantly by 9.4 % (p<0.05). Only 7 out of 20 showed a good control of cholesterol (<200 mg/dl).

HDL-C of this group increased significantly by 18.3% (p <0.01).

14 out of 20 patients showed a good level of HDL-C (>50mg/dl). With respect to LDL-C it decreased significantly by 15 % (p<0.01). All the patients of this group had a good control of LDL-C (<130 mg/dl). Even though their VLDL-C reduced by 11 % it was non significant. Only 4 out of 20 showed a good control of VLDL-C (<30 mg/dl). TAG level of this group reduced significantly by 12% (p<0.05). However only 1 out of 20 patients showed a good control of TAG (<150 mg/dl). With respect to AI, it showed a significant reduction in this group (p<0.01). In Tables 1 and 2 values with the same superscripts in the same vertical column are not significantly different from each other.

DISCUSSION

For the NIDDM group even after doubling the dose of insulin a satisfactory control of FBS was not achieved in our study as these patients had a high mean value of FBS initially. However some of the lipid parameters in serum viz; HDL-C and LDL-C were found to be controlled significantly, even though total cholesterol and TAG levels remained above normal after regularization of the dose (See Tables). A general improvement after the high dose insulin treatment is reflected in reducing the AI from 5.85 to 4.06 significantly. This supports the claim that insulin therapy helps in controlling some lipid abnormalities (13, 14). Previous reports also showed an increase in HDL-C after insulin therapy (15, 16), but which may not necessarily control all the serum lipid components as found in this study.

Table 2: Serum lipoprotein and atherogenic index values of different groups of NIDDM Patients as given in Table 1 before and after regularization of treatment for three months duration. Mean values $\pm$ SD for 20 patients in each group are given in terms of mg / 100ml

Groups	HDL Cholesterol		VLDL cholesterol		LDL Cholesterol		Atherogenic Index (AI) Total chol./HDL chol.	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final
Insulin treated	38.0 $\pm$ 10.2 ^a	50.2 $\pm$ 8.09 ^c	35.57 $\pm$ 6.9 ^a	32.4 $\pm$ 8.76 ^a NS	147 $\pm$ 14.4 ^b	123.83 $\pm$ 11.34 ^c	5.85 $\pm$ 0.2 ^a	4.06 $\pm$ 0.15 ^c
Glimepiride	42.3 $\pm$ 3.8 ^a	43 $\pm$ 4.06 ^a NS	38.15 $\pm$ 3.4 ^a	36.93 $\pm$ 5.31 ^a NS	137.0 $\pm$ 12 ^b	138 $\pm$ 20 ^b NS	5.13 $\pm$ 0.1 ^a	5.06 $\pm$ 0.06 ^a NS
Insulin+Metformin	41.7 $\pm$ 5.4 ^a	51.05 $\pm$ 4.6 ^c	40.72 $\pm$ 2.39 ^a	36.19 $\pm$ 2.14 ^a NS	137.21 $\pm$ 10.6 ^b	116.4 $\pm$ 11.4 ^c	5.48 $\pm$ 0.15 ^a	4.05 $\pm$ 0.05 ^c

ANOVA ° P<0.01 as compared to initial values. Values with the same superscript in the vertical columns are not significantly different from each other.

For the sulphonylurea group a change over of the drug from glibenclamide to glimepiride did not improve the blood or serum parameters considerably. This may be because control by sulphonylurea may fail on long term application of the same and particularly so with serum lipids (17). In the insulin + metformin group even though FBS fell very significantly glycemic control was not better than that of the insulin treated group. TAG and VLDL-C levels remained above that of the insulin group, but LDL-C level remained the lowest among the treated groups. However reports are available showing the merits of metformin therapy for a better control of lipid profile in NIDDM patients (18, 19). In one of our studies (6) recently when we used an insulin sensitizer pioglitazone in place of insulin in combination therapy with metformin for NIDDM patients, their FBS level was reduced from 235 mg to 97 mg accompanied by a 50 % fall in glycosylated Hb, during a three months treatment. Therefore the decreased effect of insulin +metformin therapy on FBS and lipid parameters in the present study may be due to some degree of insulin resistance and it warrants the need for the introduction of insulin sensitizers in combination therapies for their success in future. Metformin may act both directly and indirectly to inhibit hepatic gluconeogenesis. In addition to its effect on the liver, metformin also appears to reduce glucose concentration by reducing peripheral insulin resistance and augmenting insulin mediated glucose uptake. Further metformin corrects dyslipidemia also (20).

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