A COMPARATIVE STUDY ON THE EFFECTS OF DIET AND EXERCISE, METFORMIN AND METFORMIN + PIOGLITAZONE TREATMENT ON NIDDM PATIENTS

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ABSTRACT

A comparative study on two groups of newly diagnosed nonobese and obese NIDDM patients who were 15 in each group and treated by diet cum exercise and metformin monotherapy respectively and a third group of 15 obese NIDDM patients whose hyperglycemia was not first controlled by a combination therapy of metformin and sulfonylurea and therefore changed over to a different combination therapy of metformin and pioglitazone, was carried out before and after a period of three months treatment. The mild hyperglycemia in the 1st group and the moderate or severe hyperglycemia with accompanied disorders of serum enzymes such as AST, ALT, GGT and the level of HbA_{1c} observed with 2nd and 3rd groups of obese NIDDM patients were significantly ameliorated by the respective mode of treatments. Here the efficacies of the three types of treatment are substantiated and further it specifically depicts the success with the choice of combination therapy with metformin and pioglitazone in the third group of obese diabetics.

KEY WORDS

NIDDM patients, Diet cum exercise, Metformin, Pioglitazone, FBS, Enzymes, Hb A_{1c}.

INTRODUCTION

Diet restriction is the corner stone of all the therapeutic regimes for type II diabetes. Proper dietary choice along with exercise therapy is important for all patients with NIDDM. Unfortunately dietary habits are often difficult to change (1) without the help of a dietician who shall formulate a proper diet with choices of the patient (2). Approximately 80% of the patients with NIDDM are overweight (3). Moderate weight loss, calorie restriction and exercise are beneficial for obese diabetic patients to control their blood sugar. In terms of calories 50 to 60 percent should be complex carbohydrates, 15 to 20% should be biologically rich proteins and 20 to 25 percent should be fat with a ratio of 2:1 for unsaturated to saturated fat (4). Those with renal diseases may require a diet with less protein and those with carbohydrate induced hypertriglyceridemia may require more unsaturated fat and fewer carbohydrates (5). Increased physical activity decreases insulin resistance and

improves glucose metabolism. However the effectiveness of exercise therapy is limited because of poor compliance or disability level (6). Brisk walking for 2 km or gardening work for 30 minute is sufficient, but patients with retinopathy should avoid isometric exercises and weight lifting (7).

Oral hypoglycemic agents are often effective in patients with NIDDM after diet and exercise therapy have failed; Sulfonylurea drugs are not suitable for obese patients. They suffer from allergy and bone marrow depression. Some patients also suffer from gastrointestinal distress, anorexia lethargy, dizziness etc. (8). Biguanides are suitable for obese diabetics and they are highly effective in lowering the blood sugar (9). The former groups of drugs stimulate the pancreas for secretion of insulin while the latter group have no such action but they increase peripheral up take of glucose, impair its absorption from the bowel and decrease its output from the liver. Advantages of biguanides are that they are useful in middle aged obese diabetics and that they keep down the body weight (10). However they have a disadvantage that they promote lactic acidosis. Biguanids like metformin potentiate insulin action also (9) and that in turn reduces fasting and postprandial hyperglycemia and glycosylated hemoglobin (Hb A_{1c}). UK prospective study group report (10) shows that obese patients with metformin therapy alone had a 32 percent

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lower risk of developing any diabetes related complications e.g. macro and micro vascular complications. Side effects of metformin therapy include anorexia, diarrhoea, nausea and abdominal discomfort (11). It is effective in non obese diabetics also (12).

A class of oral drugs called thiazolidinediones sensitize insulin action and decrease hepatic gluconeogenesis. Some side effects reported for a member of this group viz; pioglitazone are headache, upper respiratory tract infection, sinusitis and myalgia (13). Pioglitazone is peroxisome proliferators-activated receptor agonist that increases transcription of insulin-responsive genes and increases insulin sensitivity. Pioglitazone like other members of this group ameliorates insulin resistance associated with NIDDM without stimulating insulin release or hypoglycemia (14). The mean serum half life of pioglitazone ranges from 3 to 7 hours (15). The major aim of the study was to show the beneficial effects of pioglitazone + metformin therapy, in obese diabetic patients. This was compared with the effects of diet control cum exercise and also that of monotherapy with metformin. For this the parameters measured are fasting blood sugar (FBS), Glycated Hemoglobin (HbA_{1c}), Aspartate transaminase (AST), Alanine transaminase (ALT) and γ glutamyl transferase (GGT) and the general well being of the patients are also assessed.

MATERIALS AND METHODS

Forty five diabetic patients in the age range of 40-65 years and under the treatment of Dr.Varghese Chemmanur at S.H.Medical Centre, Kottayam have been diagnosed as NIDDM patients and they were selected for the present study. These patients gave the formal consent and participated in the study. They were classified into three groups containing 15 in each on the basis of the therapy they were asked to follow. Groups I & II were newly diagnosed patients and group III were under treatment for one year with sulfonylurea and metformin combination therapy which ultimately didn't control the diabetes. Standard doses of drugs were used.

- Group I : Newly diagnosed 15 NIDDM patients were asked to follow diet control and exercise (8 males of age range 40-55 years and 7 females of 45-60 years)
- Group II : Newly diagnosed 15 NIDDM patients with obesity. They were put on metformin therapy (9 males of age range 40-60 years and 6 females of 42-65 years)
- Group III : 15 NIDDM obese patients who were under combined therapy of sulfonylurea and metformin for one year and switched over to combination

therapy of metformin and pioglitazone. (7 males of age range 50-65 years and 8 females of 45-65 years) Diets of all groups consisted of whole wheat, unpolished rice, potatoes, peas, beans, skimmed milk, lean meat and fish as formulated by a dietician.

Obesity was determined based on minimum grade BMI values $>25\text{kg/m}^2$.

The initial blood samples were collected from patients after an overnight fasting while they were admitted to the hospital for glycemic control. Blood was withdrawn from the median cubital vein in the antecubital fossa or crook of the elbow is the preferred site. The puncture site was then cleaned with an antiseptic spirit and tourniquet was placed around the upper arm, i.e. 4 inches above the intended puncture site to obstruct the return of venous blood to heart and to distend the vein. A needle was inserted into the vein and blood was collected using a syringe. During the procedure, the tourniquet was removed and samples of blood were collected into clean labeled capped tubes for estimation of various parameters FBS (16), HbA_{1c} (17), AST (18), ALT (19) and GGT (20).

For estimation of FBS blood was collected into tubes containing potassium oxalate and sodium fluoride in the ratio 2:1. The samples were centrifuged and plasma was collected for the estimation of glucose. For the estimation of HbA_{1c}, a haemolysate of the blood was prepared and the labile fraction was eliminated when Hbs were retained on a column of cationic exchange resin. HbA_{1c} is specifically retained on washing away other Hbs by two reagents viz; (1). 30 ml potassium biphosphate buffer, 50 mmol/L, pH 5.0 and (2) 50ml phosphate buffer, 48 mmol/L, pH 6.5 with sodium azide 0.95/L. HbA_{1c} was then eluted by a IIIrd reagent (3) 450ml phosphate buffer 72 mmol/L, pH 6.4 with sodium azide 0.95g/L.

The absorbance of this elute at 415nm was read against distilled water. Total Hb was estimated by adding reagent 3 to initial haemolysate and taking the absorbance (O.D) at 415 nm. Then the percentage of HbA_{1c} was calculated. The various enzymes mentioned above were also estimated by the standard methods in the remaining serum.

After hospital admission, doses of the drugs were adjusted so that a good glycemic control was achieved. After a week these patients were sent home with instructions to take medicines as the case may be and follow a life style and dietary habit befitting a diabetic patient i.e. eat only the initially

formulated diet by the dietitian (4,5) at home at definite time intervals and do moderate work or walk up to 2km daily if they can. A three month appointment was fixed for them and their blood was collected again after overnight fasting for measuring all the parameters as before. The results were analyzed according to the student's t test and the levels of significances were noted.

RESULTS

Results are given in Table I

In diet control and exercise group I, the FBS level decreased very significantly by 24 % ($P<0.001$). However in their enzyme levels viz. AST, ALT and Gamma glutamyl transferase and HbA_{1c} level there was no significant variation in a period of three months treatment.

In metformin treated group II, their FBS decreased very significantly by 45%($P<0.001$) after the treatment of 3 months. With respect to enzyme levels only AST decreased significantly by 22%($P<0.01$) and other enzyme levels showed only non significant decreases. However their HbA_{1c} level decreased very significantly by 33 % ($P<0.001$).

In metformin + pioglitazone treated group their FBS decreased very significantly by 58 % ($P<0.001$) after treatment. Their enzyme levels also decreased significantly i.e.AST by 15 % ($P<0.01$), ALT by 21 % ($P<0.01$), and Gamma GT by 41 % ($P<0.001$). Along with the above improvements their HbA_{1c} also decreased very significantly by 50 % ($P<0.001$). When we consider the initial FBS values between groups, group II values are very significantly higher over group I values and group III values are very significantly higher over group II values($P<0.001$). However no such differences are found in

final FBS values. With respect to initial enzyme levels we find that only AST in groups II and III are significantly higher over group I ($P<0.001$). Similarly HbA_{1c} levels in groups II and III are significantly higher over group I ($P<0.001$). With respect to final levels of enzyme values group III shared a significantly higher AST over groups I and II ($P<0.001$) and for the other two enzymes ALT and Gamma GT, group II showed significantly higher values over group I and group III showed significantly higher values over group II ($P<0.01 - 0.001$).

With respect to the initial levels of HbA_{1c} group II has significantly higher value over group I and Group III has a significantly higher value over group II($P<0.01$). However no such variations are found in their final values.

DISCUSSION

The results show that for NIDDM patients with mild hyperglycemia, diet control and exercise are sufficient to control their FBS to normal range. Their serum enzymes and HbA_{1c} levels are more or less in the normal range, where as in the case of obese NIDDM their FBS and HbA_{1c} levels are far above the normal range but their serum enzyme levels are only non significantly elevated. By metformin monotherapy their FBS, HbA_{1c} and AST level are well controlled to the near normal values, but the other two enzymes ALT and Gamma GT are non significantly elevated. Metformin is contraindicated in population who take alcohol and the fact that some of them were alcoholic might have caused a marginal elevation of those two enzymes in serum. The results showed that the metformin therapy is very effective for obese NIDDM patients.

The group III patients showed a marked amelioration of hyperglycemia with combination therapy of pioglitazone and

Table I : Comparative effects of Diet Control and Exercise Therapy, Metformin Therapy and Combination therapy of Metformin and Pioglitazone on NIDDM patients for 3 months.(Values are mean of 15 patients $\pm$ SD in each group

Groups	FBS (mg/dl)		AST (U/L)		ALT (U/L)		GGT (U/L)		HbA _{1c} (% of Total Hb)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Diet control & exercise therapy	121.6 $\pm$ 6.04	93.86 $\pm$ 7.3** 24%	25.31 $\pm$ 7.1	25.13 $\pm$ 7.06 1.50% NS	27 $\pm$ 7.7	26.5 $\pm$ 7.67 2.1% NS	12.19 $\pm$ 3.78	11.8 $\pm$ 3.63 1.5% NS	4.73 $\pm$ 0.32	No change
Metformin therapy	167.86 $\pm$ 16.55 *	92.5 $\pm$ 9.25* 45%	36.6 $\pm$ 3.3	30.0 $\pm$ 2.17* 22%	33.0 $\pm$ 3.02	35.66 $\pm$ 3.39 8% NS	15.73 $\pm$ 3.0	17.06 $\pm$ 2.84 9% NS	6.72 $\pm$ 0.23	4.7 $\pm$ 0.176** 33%
Metformin + pioglitazone therapy	235.8 $\pm$ 7.9	97.0 $\pm$ 6.69** 58%	34.0 $\pm$ 3.77	40.2 $\pm$ 1.85* 15%	34.0 $\pm$ 4.32	43.46 $\pm$ 2.61* 21%	15.66 $\pm$ 3.55	26.6 $\pm$ 4.5** 41%	8.92 $\pm$ 0.132	4.87 $\pm$ 0.23** 50%

* Initial versus final ** $P<0.001$.

* $P<0.01$.

metformin. These patients previously failed to respond to a combination therapy of sulfonylurea and metformin. The tremendous improvement observed in their blood sugar control is mainly due to the insulin sensitizer pioglitazone. However this type of combined therapy adversely affected the serum enzymes AST, ALT and Gamma GT i.e. all three enzymes increased their levels in serum very significantly. Pioglitazone treatment showed previously also an adverse effect on serum transaminases and Gamma GT level (21). The highest fall of FBS(58%) observed in combined therapy may be due to two factors. i.e. due to very high pretreatment level of FBS and also due to insulin sensitizer action of pioglitazone. Similarly the comparatively higher FBS fall (45%) for metformin group over the diet control cum exercise group (24%) may be due to fact that the pretreatment level of FBS in the former group was about 37% higher than of the latter and that for the obese group metformin is the drug of choice that worked here also as it enhances the peripheral uptake of glucose. In the last two groups we can observe a parallel decrease of HbA_{1c} level along with FBS fall i.e. 33% in the metformin group and 50% in the combined therapy group. Therefore combination therapy is far more effective than monotherapy for controlling NIDDM, but the adverse effect of pioglitazone on the liver should also be taken into account and proper adjustment of its dose is warranted. In order to get a better control of diabetes mellitus combination therapy may be encouraged but dose adjustment with periodic monitoring of the level of the affected enzymes is very necessary to control the bad effects of the insulin sensitizer.

There are many other studies which support the beneficial effects of pioglitazone in combination with hypoglycemic agents or insulin. In an observational report trioglitazone, rosiglitazone and pioglitazone were compared in a limited number of patients; changes in HbA_{1c} were similar for the three agents, whereas the effects on lipoprotein metabolism were different. Pioglitazone reduced serum triglycerides and increased HDL-C to a greater extent than either trioglitazone or rosiglitazone. In addition, trioglitazone and rosiglitazone increased LDL-C whereas pioglitazone did not (22, 23). Interestingly trioglitazone was shown to decrease the proportion of dense LDL in obese subjects despite its LDL-C raising effect (24).

In a recent study on NIDDM patients by Dorsa et al (25); the combination of glimepiride with pioglitazone (G+P) or rosiglitazone (G+R) significantly improved glycemic control in the study patients. This treatment also controlled plasma HbA_{1c} satisfactorily. However only G+P controlled the lipid profile particularly the lipoprotein variables. On the contrary combination therapy of G+R experienced a significant increase

in most of the lipid risk factors for Coronary Vascular Disease (CVD). Overall no significant changes were observed with respect to plasma aminotransferase activities. Only three out of forty five patients, with G+P group and five out of forty five in G+R group experienced mild to moderate adverse effects, that did not cause withdrawal from the trial. In another study with pioglitazone in combination with insulin on NIDDM patients by Mattoo et al (26) they observed that only in those patients whose disease was inadequately controlled with insulin monotherapy, that pioglitazone + insulin combination therapy improved the glycemic control. All these studies and our present findings stress the importance of pioglitazone in combination therapy but with all the required precautions.

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