

The Effect of Metformin on Glycemic Control, Serum Lipids and Lipoproteins in diet alone and Sulfonylurea-treated type 2 Diabetic Patients with Sub-Optimal Metabolic Control

Muharnniad Azhar Mughal (Department of Pharmacology and Therapeutics, Ziauddin Medical University, Clifton, Karachi.)

Muhammad Jan (Department of Pharmacology Avub Medical College, Abbottabad.)

Wali Muhammad Maheri (Department of Physiology, Liaquat Medical College, Jamshoro, Karachi.)

Muhammad Yousuf Memon (Departments of Biochemistry, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Center, Karachi.)

Mehar Ali (Departments of Pharmacology and Therapeutics, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Center, Karachi.)

Abstract

Objective: TO see if Metformin Monotherapy affects glycemic control, serum lipid or lipoprotein levels in the treatment of type 2 diabetes who were poorly controlled with diet alone or despite maximal doses of (sulfonyl urea) oral glucose lowering agents.

Design: A prospective, clinical intervention trial conducted between 1996-1997, **Setting:** two outpatient diabetic clinics of Karachi.

Patients and Methods: A 12-week prospective clinical intervention trial, A total of 30 type 2 diabetic subjects were enrolled of whom 21 (12 men and 9 women) completed the study period. Their ages ranged between 35 and 70 years, (mean $\pm$ SD 53.3 ± 9.31) years, with a mean duration since diagnosis of diabetes was 4.5 ± 2.3 years, body mass index (mean $\pm$ SD) 26.8 ± 3.53 kg/m². They were previously treated with diet alone or had already been taking maximum doses of sulfonylurea monotherapy with suboptimal glycemic control, i.e., raised fasting blood glucose concentrations of 6-15 mmol/L or (108—270 mg/dL) on two occasions, with significant hyperglycemic symptoms. The patients were treated with metformin monotherapy with a follow up of 12 weeks. The initial dosage was 500 mg twice daily and the dosage was increased to two or three tablets depending on the metabolic changes. By comparing before and after 12 weeks therapy with metformin we assessed the importance of baseline parameters (glycemic control, serum lipid and lipoprotein concentrations, and measures of change in body weight and body mass index).

Results: Metformin therapy significantly decreased fasting blood glucose levels in all patients $\pm$ SD) 227.2 ± 37.5 to 168.6 ± 20.5 mg/dL, $p < 0.001$). Serum total cholesterol decreased marginally (mean $\pm$ SD) 200.3 ± 18.7 to 181.4 ± 19.4 mg/dL, $p < 0.01$). Serum total triglycerides concentration also decreased ($\pm$ SD) 195.9 ± 31.9 to 174.2 ± 26.6 mg/dL, $P < 0.01$). Low-density lipoproteins declined ($\pm$ SD) 123.5 ± 16.9 to 105.5 ± 19.1 mg/dL, $P < 0.01$), and very-low density lipoprotein cholesterol also decreased (mean $\pm$ SD) 39.2 ± 6.4 to 34.8 ± 5.3 mg/dL, $P < 0.01$). Whereas, high-density lipoprotein cholesterol tended to increase ($\pm$ SD) 37.7 ± 5.1 to 39.5 ± 4.9 mg/dL, $p < 0.01$) / while no significant changes occurred in body weight and body mass index.

Conclusion: Metformin treatment was effective, safe, and generally well tolerated (J PMA 50:381, 2000).

Introduction

Type 2 diabetes mellitus results from impaired insulin secretion and reduced peripheral insulin sensitivity. It is frequently found to coexist with other conditions, such as obesity, dyslipidemia, atherosclerotic vascular disease, and hypertension, which contribute to morbidity and mortality. The major clinical objective in the management of type 2 diabetes is to control hyperglycemia; the long-term objective is to prevent microvascular and macrovascular complications, although hyperglycemia

may be adequately controlled. Cardiovascular disease is the major cause of death in type 2 diabetes². In particular, type 2 diabetes usually presents with concomitant elevations in plasma triglyceride (TG) levels³. The United Kingdom Prospective Diabetes Study (UKPDS) report also revealed that cardiovascular disease was the major cause of complications, and the risk factors included raised LDL-Cholesterol concentrations. Low HDL-Cholesterol concentrations, elevated blood pressure and HbA_{1c} concentrations, and smoking⁴. Life style changes, dietary and exercise modification, weight loss, and smoking cessation have been shown to have a positive effect on cardiovascular disease risks although glycemic control prevents several of the long-term complications of diabetes⁶. Treatment options include diet, oral antihyperglycemic agents, and insulin. Metformin has been used for over 40 years as an effective glucose lowering agent in type 2 (non-insulin dependent) diabetes mellitus⁷. Metformin is an oral biguanide, it ameliorates hyperglycemia by improving peripheral sensitivity to insulin, and reducing gastrointestinal glucose absorption and hepatic glucose production. Treatment with metformin in patients^{8,9}. Therefore, one could speculate that improvement of glycemic control could beneficially influence the lipid profiles. However, outcome data potentially beneficial effect of metformin, is not yet available. This study was designed to see if the treatment of type 2 diabetes with metformin affects glycemic control, serum lipid or lipoprotein levels with suboptimal glycemic control with diet alone or sulfonylurea monotherapy.

Patients and Methods

The study was carried out in the Pharmacology and Therapeutics, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi, during 1996-97. The Patients were selected from two outpatient diabetic clinics of Karachi. A total of 21 adult subjects, 12 males and 9 females, who had sub-optimal glycemic control and were previously treated with diet alone or maximal doses of sulfonylureas alone were included in the study.

The diagnostic criterion was based on clinical history and the finding of a fasting blood glucose concentration higher than 6.0-15.0 mmol/L or (108—270 mg/dL) on two occasions and hyperglycemic symptoms while receiving diet therapy alone or sulfonylurea. Age was recorded at the beginning of the study for all subjects. Entry criteria was: Type 2 diabetic patients in concomitant dietary follow-up, body mass index (BMI) < 35 kg/m², BMI was calculated as BMI weight (kg)/height (m²). Informed consent was obtained from all study participants.

Patients were excluded, if they had severe diabetic complications or any history of significant ketosis, or myocardial infarction in the previous year, current angina or heart failure, or a severe underlying illness likely to limit life or require systemic therapy. Those taking medications known to affect lipid or carbohydrate metabolism, and a significant gastrointestinal, cardiovascular or renal disease were also excluded.

All Patients entered a 14 days run-in period. Study protocol included screening visits to assess patient eligibility. Patients underwent a standardized baseline assessment, in which cardiovascular and relevant risk factors were assessed. All medications were discontinued 10 days before admission to the study, if the patients were already on antidiabetic medications. During that period patients were treated with individualized weight maintaining diets (carbohydrate, 60%; fat, <30% protein, 12-20%) with caloric content adjusted to the patient's age, body weight, and physical activity as recommended by the dietitian.

The study period consisted of 2 weeks with weekly follow-up visits. All the patients were prescribed tablets Glucophage (metformin hydrochloride) as monotherapy taken orally for 12 weeks.

Subjects were requested not to change any habits that could alter blood lipid levels during the study including physical activity and diet. Patients were also forbidden to take any other medication during the study. Therapeutic compliance was monitored at each clinic visit by taking "pill count", eating habits were assessed by three-day dietary records: caloric intake was assessed by dietitian, Detailed analyses of these food records were recorded: body weight assessed with patients' coats and shoes

removed, All patients were followed up for assessment of glycemic control: 12-14 hours thsting blood glucose was measured usually in the morning at baseline and at each weekly visit up to 12 weeks.

Lipids and lipoproteins were measured only at baseline and week 12.

Fasting blood glucose was nicasured by using Accutrend Blood Glucose Analyzer (Boehringer Manpheim Mannheim, Germany). Venous blood from an antecuhital vein was drawn from subjects in the seated position. and the plasma was rapidly separated and refrigerated. Serum total cholesterol, high—density lipoprotein cholesterol and serum total triglyceride concentrations were assayed by standard enzymatic colorimetric methods using commercial kits (Spin react, S. A. Spain). Low-density' lipoprotein cholesterol levels were calculated usiiiig a standard formula Very—low density lipoprotein cholesterol was calculated, according to formula proposed by Wilson. cited by Delong et al¹².

Statistical Analysis

All data are expressed as means $\pm$ SI). Changes in variables have been calculated as values at the end of a 12week, minus values at the baseline; a negative and positive value implies a lowering or increasing of that value. Differences between means of parameters within groups were tested for significance using the Paired Student's t—test. For all analyses. P values less than 0.05 was considered significant.

Results

Of 30 selected patients 9(30%) having type 2 diabetes discontinued the study. during the first 3 weeks of the treatment period. The reasons for discontinuation were two subjects poor compliance (2). refusal to participate further (4) lost to fol low—up (2) and diarrhea (I). total of 2 1 subjects completed the study, of whom 11 (52.3%) previously used dietary treatment alone. 10 (47.6%) were on maximum dosage of sulfonylureas. Of the sulfonylureas treated patients. 7 received glibenclamide. 5 received 15 mg/d, and 2 were on 20mg/d of glihenclamide dosage. 3 patients were taking chlorpropamide 500mg/d, all were taking maximum dosages of sulfonylureas previously. Demographic variables of the 2 1 subjects with type 2 diabetes, who received metformin therapy alone in this study are presented in Table 1.

Table 1. Baseline characteristics of study subjects.

Demographic Profile	All Patients (n=21)	Diet Alone treated (n=11)	Glibenclamide treated (n=7)	Chlorpropamide treated (n=3)
Age (years)	53.3 ± 9.3	51.1 ± 8.7	54.4 ± 10.5	59.0 ± 7.1
Sex				
Male (n)	12	6	5	1
Female (n)	9	5	2	2
Body Weight (kg)				
Baseline	76.1 ± 7.3	77.0 ± 8.1	73.3 ± 7.0	79.7 ± 3.4
End of treatment	75.8 ± 7.5*	76.8 ± 8.0*	72.7 ± 7.5*	79.8 ± 3.4*
BMI (kg/m ²)				
Baseline	26.8 ± 3.5	26.1 ± 3.0	27.1 ± 4.8	28.7 ± 1.4
End of treatment	26.6 ± 3.4*	26.0 ± 2.9*	26.9 ± 4.7*	28.4 ± 1.2*
Duration of Diabetes (years)	4.5 ± 2.3	3.5 ± 2.0	5.6 ± 2.5	5.7 ± 1.7

Data are means ± SD. Figures in parentheses shows the number of patients. BMI= body mass index. For values marked with an asteric shows insignificant p value at the end of 12-week metformin treatment.

The mean duration of diabetes was 3.5 years, 5.6 years and 5.7 years in patients previously treated with diet alone, glibenclamide and morning and chlorpropanide respectively. At the end of follow-up, mean body weight did not change significantly: this reflects insignificant reduction in mean body mass index, indicating that all individuals were compliant with the study protocol. The dosage of metformin was individualized, with the therapeutic response being monitored by blood glucose determinations during the follow up visits. We initiated metformin therapy with a low dose and gradual increased it. Therapy was started with a dosage of 500 mg twice daily administered with the Morning and evening meals). Increase in dose was made weekly (500 mg tablets) as divided doses three times daily. and was also adjusted according to patient's clinical and metabolic response. The metformin dosage was assessed weekly, mean daily dose was 1000 mg/day at the start of therapy week- I and mean daily dose was 1333 mg/day at the end of study week-12. The average dose remained throughout the study was 1243 mg/day.

Table 2. Effects of metformin treatment on fasting blood glucose levels in patients with type 2 diabetes previously treated with diet alone, glibenclamide, and chlorpropamide therapy.

Treatment Group	Baseline	At 12 week	Difference	P Value*
All Patients (n=21)	227.2±37.5	168.6±20.5	-58.6	< 0.001
Diet Alone treated (n=11)	219.3±43.6	166.9±22.4	-52.4	< 0.01
Glibenclamide treated (n=7)	236.4±35.3	170.7±20.6	-65.7	< 0.002
Chlorpropamide treated (n=3)	234.7±8.1	169.7±15.9	-65.0	< 0.01

Data are means ± SD. Figure in parenthesis shows the number of patients. All observations were measured in mg/dl. Difference between baseline and after the treatment at week 12.

*P value comparing changes from baseline to last visit at week-12.

Table 2 shows that fasting blood glucose density lipoprotein cholesterol LDL-C Low-density lipoprotein cholesterol concentrations progressively decreased in all patients (n=21) 21) mean 12-week difference from baseline was -58.6, (P 0.001). Whereas, glucose concentrations tended to fall in patients previously treated with diet alone (n=11) difference from baseline was -52.4. (P<0.01). Glibenclamide (n= 7) difference from baseline -65.7. (P<0.002) and chlorpropamide (n=3) difference From baseline was -65.7. (N10.002).

As shown in Table 3.

Table 3. Changes in plasma lipid and lipoproteins for all patients with type 2 diabetes treated with metformin alone (n=42).

Parameters	Baseline	At 12-week	Difference	P value*
T-CHOL (mg/dl)	200.3 ± 18.7	181.4 ± 19.4	-18.9	< 0.01
TRIG (mg/dl)	195.9 ± 31.9	174.2 ± 26.6	-21.7	< 0.01
HDL-C (mg/dl)	37.7 ± 5.1	39.5 ± 4.9	+1.8	< 0.01
LDL-C (mg/dl)	123.5 ± 16.9	105.5 ± 19.1	-18.0	< 0.01
VLDL-C (mg/dl)	39.2 ± 6.4	34.8 ± 5.3	- 4.3	< 0.01

Data are means ± SD. Figure in parenthesis shows the number of patients. All observations were measured in mg/dl. Difference between baseline and after the treatment at week-12.

*P value comparing changes from baseline to last visit at week-12. T-CHOL= Serum total cholesterol; TRIG= Serum total triglycerides; HDL-C= High-density lipoprotein cholesterol; LDL-C= Low-density lipoprotein cholesterol.

treatment with metformin monotherapy resulted in favorable trend in lipid and lipoprotein profiles in that there was a trend for decreases in serum total cholesterol, serum total triglycerides, LDL cholesterol, and VLDL-cholesterol while high-density lipoprotein cholesterol concentration was significantly increased at the end of 12 week. 'treatment with metformin was not associated with adverse changes in any of the lipid parameters that were monitored. The effect of the study drug on all lipid and lipoprotein parameters were statistically significant at the end of metformin treatment (P 0.01).

Over 12 weeks, more upper-gastrointestinal (GI) symptoms were observed with metformin. 4(19%) of patients reported mild, transient gastrointestinal side effects include diarrhea, nausea, epigastric discomfort and anorexia none of which required cessation of metformin therapy. The majority of the studied subjects 11 (52.38%) were previously treated with diet alone and 10(47.61%) with sulfonylureas. No blood glucose values in the hypoglycemic range were observed during the study.

Discussion

In subjects with type 2 diabetes, both defects of insulin secretion and insulin resistance contribute to the development of hyperglycemia. The major goals of treatment are to optimize blood glucose control, and normalize the associated lipid disturbances and elevated blood pressure. Pharmacological treatment is often necessary¹³.

The treatment of type 2 diabetic patients with secondary failure to sulfonylurea is a common problem¹⁴. Metformin has been shown to be safe and effective in improving glycemic control in type 2 diabetes when diet or sulfonylureas alone have been inadequate¹⁵⁻¹⁷. Metformin alleviates hyperglycemia of type 2 diabetes by inhibiting hepatic glucose production and improving peripheral insulin sensitivity¹⁸. Review of literature shows that metformin interferes with several processes linked to hepatic glucose production (gluconeogenesis, glycogenolysis and their regulatory mechanisms), lowering glucose production and resensitizing the liver to insulin. The hepatic drug effect is largely favored by prevailing glycemia. In peripheral tissues, metformin potentiates the effects of both hyperglycemia and hyperinsulinemia. Increase in glucose-mediated glucose transport is mainly mediated by an improvement in the glucose transporter's intrinsic activity. Potentiation of the hormone effect relates to an increase in insulin receptor tyrosine kinase activity¹⁹. Both mechanisms (insulin signaling and glucose transport) result in the activation of glycogen synthase, a limiting enzyme in the causal defects of type 2 diabetes¹⁹. In this study we did not directly assess these parameters, but the results indicating that metformin certainly has positive effect on these physiological mechanisms, as we found significant decline in all the biochemical parameters of the study.

Current studies suggest that controlling hyperglycemia, LDL-cholesterol, and blood pressure are important to protect the diabetic from atherosclerosis, although low-density lipoprotein (LDL) cholesterol is a critically important factor in the development of atherosclerosis²⁰. Low-density lipoprotein (LDL) oxidation has been suggested to play a key role in the pathogenesis of atherosclerosis, a major complication of diabetes mellitus²¹. High-density lipoproteins (HDLs) appear to exert the greatest influence independently of other lipoproteins, with low-density lipoproteins (LDLs) having a weaker, though still significant, independent relation with coronary heart disease. This correlates negatively with HDL and positively with LDL so probably HDL retards while LDL accelerates the development of clinical events²². In addition, reductions in weight, triglyceride, LDL-cholesterol, insulin resistance, and an increase in HDL-cholesterol have also been reported with metformin in treatments²³⁻²⁶. Defranzo and Goodman reported that metformin treatment is associated with reduced plasma lipids in patient with marked hyperglycemia. As expected, fasting blood glucose concentrations were significantly higher in the diet failure and sulfonylureas treated group in the present study: in that group plasma levels of total cholesterol, LDL-Cholesterol triglycerides and very low density lipoprotein cholesterol were also significantly elevated, while HDL-Cholesterol was decreased at baseline Table 2 and 3.

Although, fasting blood glucose did not reach the acceptable level in this study, but this might be expected, since the patients have mean fasting blood glucose concentrations ranged between 154.2 and 280 mg/dl at baseline. It becomes increasingly more difficult to attain near normal glycemic control, this could be related to type 2 diabetes, which is characterized by steady deterioration of glucose control due to progressive β -cell dysfunction²⁷. In this study, we found significant decrease in serum cholesterol, triglycerides, LDL-Cholesterol and VLDL-Cholesterol levels, they still remained higher and were not optimized, and the reason could be higher levels at baseline. The reduction in LDL-Cholesterol associated with metformin in this study is of interest because of the strong association between LDL-Cholesterol level and the development of ischemic heart disease. There also apparent change in HDL-cholesterol was observed; mean change 1.8 at 12 week (P 0.01).

Our results are consistent with some previous studies, where an increase in HDL-Cholesterol has been

associated with metformin therapy^{24,28,29}. A significant decrease in serum cholesterol levels was also found at the end of studies.

Only longer-term studies can determine whether metformin will help to prevent late complications of type 2 diabetes. Although the patients group in our study was small and not randomized, however, the results need to be confirmed in future studies.

It may be concluded from the results of this study that metformin improves glycaemic control, irrespective of the patient's baseline fasting blood glucose concentration, obesity, or previous therapy. It also has beneficial effects on lipid and lipoprotein concentrations. Metformin can be used safely and effectively as first-line monotherapy in type 2 diabetes or when diet alone or sulphonylurea monotherapy agent fails. It can be particularly suitable when hyperlipidemia especially with respect to plasma lipid profile. HDL cholesterol, LDL cholesterol and hypoglycemia are clinically important issues. Metformin that provides these effects, when administered to carefully selected patients and monitored appropriately, may prove to be valuable in altering its cardiovascular sequelae. Metformin is not associated with weight gain, and does not produce hypoglycemia.

These differential effects may be important in planning therapy when hyperlipidemia accompanies type 2 diabetes. These data suggest that metformin therapy in subjects with poorly controlled type 2 diabetes offer an advantage in terms of glycaemic control and plasma lipid profile.

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