The Effects of Glibenclamide on Serum Lipids and Lipoproteins in Type II Non-Insulin Dependent Diabetes Mellitus

Muhammad Azhar Mughal, Kausar Aamir, Mehari Ali, Wali Muhammad Maheri, and Muhammad Jan

Abstract

Objective: To examine the effects of glibenclamide treatment on plasma lipids and lipoprotein levels.

Settings: Out patients of Type II diabetics from department of Baqai Diabetes and Endocrine Centre and two other diabetic clinics of Karachi.

Methods: The effects of glibenclamide on blood glucose and various aspects of lipoproteins has been studied in 26 (14 male, 12 female) Type II Diapetes patients before and after 12 weeks of glibenclamide therapy. Treatment was initiated with 5 mg oral glibenclamide with diet control. The initial dosage of glibenclamide was 5 mg/day taken half an hour before meal; this was increased to 5 mg per week and was adjusted according to the patient’s tolerance to the drug and their glycemic control.

Results: The results demonstrated that fasting blood glucose declined from 221.53+7.84 to 165.02+5.12 mg/dl, (P<0.001). There was a statistically significant increase in the plasma high-density lipoprotein cholesterol from 33.60+1.00 to 37.07+1.05 mg/dl, (P<<0.05). Total cholesterol, triglycerides, low-density lipoprotein cholesterol and very-low-density lipoprotein cholesterol did not change significantly.

Conclusion: Improved glycaemic control in patients treated with glibenclamide with Type II Diabetes was achieved which lead to changes in lipoprotein metabolism. There was no evidence of changes in lipoproteins in. directions associated with an increased risk for atherosclerosis OPMA 49: 89, 1999).

Introduction

Subjects with type II diabetes are characterized by a very high cardiovascular morbidity and mortality rate. Plasma lipoprotein abnormalities of concentration, composition, or subfraction distribution are one of the main factors for the enhanced cardiovascular risk. The major cause of morbidity and mortality of patients with diabetes is macrovascular disease. The mechanisms by which diabetes accelerates atherosclerosis are not well understood. One of the significant risk factors for atherosclerosis in the diabetic population is dyslipidemia. Moreover, it is well known that blood glucose optimization (reached by diet, hypoglycemic drugs, or insulin therapy) influences lipoprotein metabolism positively in Type II diabetic patients, although a complete normalization in plasma lipoprotein concentration and composition abnormalities is seldom obtained with this type of diabetes. Lipoprotein abnormalities in Type II patients involve all classes of lipoprotein and may consist of chylomicronemia, high levels of very-low density lipoprotein (VLDL) and low-density lipoproteins (LDL). Also elevated triglycerides levels are commonly seen in type II diabetic subjects. Low concentrations of High Density Lipoprotein (HDL) cholesterol appear to be an outstanding lipoprotein predictor of cardiovascular diseases. The true nature of the relationship between diabetic conditions and increased Coronary Artery Disease (CAD) still remains unclear and
the role of HDL has not been adequately proven\(^6\). However, only a few data are available of the effect of glibenclamide on the changes in lipid and lipoprotein metabolism in patients with non-insulin dependent diabetes mellitus. Sulfonylureas stimulate insulin secretion from pancreatic B-cells and are widely used in the treatment of type 11 diabetes\(^7\). This study investigated the effects of glibenclamide therapy on glycemic control, lipids and lipoprotein concentrations in non-insulin-dependent diabetic patients.

**Patients and Methods**

This study was conducted in the department of Pharmacology and Therapeutics, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi. Thirty NIDDM (type II) patients were initially recruited in the study, from the out-patients department of Baqai Diabetes and Endocrine Centre and two other diabetic Clinics of Karachi. The diagnosis of diabetes was made using World Health Organization criteria\(^8\). Patients having no history of significant ketosis, to whom no previous antidiabetic medication had been given, or previous treatment consisted of diet and an oral hypoglycemic agent (Sulfonylurea) were included. The exclusion criteria were conditions requiring insulin treatment, significant renal, hepatic or thyroid disease by history, physical examination, or by laboratory evidence. Patients with severe diabetic complications, allergies to the sulfonylurea or concurrent medical illness needing immediate treatment were excluded.

All hypoglycemic medications were discontinued at least 10 days prior to admission to the study, during that period patients were treated with individualized weight maintaining diets with caloric content adjusted to the patient’s age, body weight and physical activity. After the 10 days period, selected patients with NIDDM received glibenclamide (Daonil) orally (each tablet of Daonil contains as active ingredient 5 mg glibenclamide) with diet control for 12 weeks. The initial dosage of glibenclamide was 5 mg/day taken half an hour before meal; this was increased by 5 mg per week and was adjusted according to the patient’s tolerance to the drug and glycemic control. Dietary recall information was obtained by the dietitian and the patients were advised isocaloric weight maintaining diet consisting (as percent of calories) or 15-20% protein, 50-55% carbohydrate and 30-40% fat. This dietary programme was followed throughout the study and compliance to the diet was evaluated in the patient’s follow-up visits. All patients were advised light exercise four to five times per week for 30-60 minutes.

The study period was 12 weeks (90 days) with weekly patient’s follow up visits. Alt patients were assessed for glycemic control by estimating 12 hours fasting blood glucose and were questioned on drug compliance, side effects of drug and symptoms related to hyperglycemia or any other unusual symptoms. Patients were also motivated to keep their nutritional habits, physical activity and general life style as constant as possible throughout the study period. Subjects were forbidden to take any other medication during the study. Fasting serum lipids, blood glucose and weight were determined at entrance (day 0) and a similar assessment was taken at day 90.

**Determination of blood glucose, lipids and lipoproteins**

Fasting blood glucose was determined by capillary blood with the Accutrend blood glucose analyzer (Boehringer Mannheim, Germany). Serum total cholesterol, triglycerides and high-density lipoprotein cholesterol were measured by the enzymatic colorimetric method by using kits Spinreact, S.A. Spain. Low-density lipoprotein cholesterol was calculated according to the Friedwald et al\(^9\) and very-low-density lipoprotein cholesterol according to formula proposed by Wilson, cited by DeLong et al\(^10\).

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\text{VLDL - cholesterol (mg/dl)} = 0.20 \times \text{triglycerides}
\]

**Statistical Analysis**

All data are expressed as mean±SEM. Groups of data were compared using student’s paired t-test. Differences were considered to be significant if P<0.05.
Results

Thirty patients were included in the trial, of which four were withdrawn due to non-compliance. The remaining 26 patients (14 male, 12 female) were studied, who had a mean age of 51.77±9.76 years. Their mean duration of diabetes was 2.84±1.41 years, and the body mass index of 27.7±1.7 kg/m2, which remained stable. Their dietary intake during the 12-weeks period of glibenclamide administration was kept constant. In the twenty six patients fasting blood glucose concentration declined from 221.53±7.84 to 165.02±5.12 mg/dl; this reduction was statistically highly significant (P<<0.001). Glibenclamide therapy significantly raised HDL-cholesterol from 33.60±1.00 to 37.07±1.05 mg/dl (P<0.05). While insignificant decrease was observed with glibenclamide therapy in fasting serum total cholesterol, serum total triglycerides, LDL-cholesterol and VLDL-cholesterol concentrations, as depicted in Table.

### Table. Effects of glibenclamide treatment on mean (+SEM) fasting blood glucose, plasma lipids and lipoproteins in Type II diabetic patients (n=26).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>At day 0</th>
<th>At day 90</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>221.53±7.84</td>
<td>165.02±5.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum total cholesterol (mg/dl)</td>
<td>215.12±5.97</td>
<td>204.83±5.97</td>
<td>N.S.</td>
</tr>
<tr>
<td>Serum total triglycerides (mg/dl)</td>
<td>190.05±7.19</td>
<td>177.18±8.43</td>
<td>N.S.</td>
</tr>
<tr>
<td>High density lipoproteins cholesterol (mg/dl)</td>
<td>33.60±1.00</td>
<td>37.07±1.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (mg/dl)</td>
<td>143.39±5.51</td>
<td>132.57±5.29</td>
<td>N.S.</td>
</tr>
<tr>
<td>Very low density lipoprotein cholesterol (mg/dl)</td>
<td>37.90±1.43</td>
<td>35.40±1.69</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Values are mean+SEM, N.S = Non significant.

Discussion

Diabetes is frequently associated with the combination of hypertriglyceridemia and low HDL-cholesterol levels a known risk factor for cardiovascular disease\(^\text{11}\). The results of Jenkins et al suggested that HDL is more important than the other lipoproteins in influencing atherosclerosis, this finding needs to be interpreted since there is a close metabolic interrelation between lipoprotein species. Recent epidemiological studies have elucidated the importance of individual lipoproteins in predicting future clinical coronary heart disease. 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 events. However, we attempted to study the effect of glibenclamide on lipids and NIDDM (type II) patients with glibenclamide significantly (P<0.05) increased the HDL cholesterol concentrations, though it remained below the desired level. It is apparent that these patients had unequivocal fasting hyperglycemia before therapy and that this was associated with elevated plasma triglyceride and reduced HDL-cholesterol concentrations. Recently, Frenais et al reported an increased catabolism of HDL apoA-I to be completely responsible for the lower HDL concentrations in NIDDM with a pronounced diabetic dyslipidemia, hypertriglyceridemia and low MDL cholesterol and poor metabolic control when compared with non-diabetic subjects. This was the probable cause of a reduction in HDL-cholesterol in our study and the effects of glibenclamide therapy on mean HDL-cholesterol concentrations remained modest in magnitude. The objective of this study was not to look at normalization of HDL-cholesterol, but was to see any effect of glibenclamide on lipid profile. To gain further insight into the metabolic etiology of low HDL in NIDDM further studies are required.

Information available on the effects of sulfonylurea therapy on lipoprotein concentrations in non-insulin-dependent diabetes mellitus is more limited. Greenfield et al found that glipizide therapy significantly lowered total triglycerides. Ratzmann et al showed no significant change in total cholesterol or triglyceride concentrations with glibenclamide therapy from that seen with diet alone. Howard et al also reported a slight trend towards alteration of high-density lipoprotein composition in their study. However, the effects on plasma low-density lipoprotein levels are more variable and range from no effect to a modest reduction. Again, in no case was there any tendency for low-density lipoprotein levels to rise during glibenclamide therapy. Similarly, Tamai et al found no significant change in very-low-density lipoprotein or low-density lipoproteins values but did not report a decrease in high density lipoprotein cholesterol during Glibenclamide therapy. Although we observed a non-significant reduction in low density lipoprotein cholesterol in NIDDM patients. Clinically glibenclamide was well tolerated. No gastrointestinal complaints and no skin rashes or other side effects were noted; or reported in the present study over 12 weeks treatment.

The purpose of the present study was to provide insight into the apparent controversy regarding the importance of effects of sulfonylurea drugs in their mediation of biologic effects/or on lipid and lipoprotein metabolism. The magnitude of the changes was small, and it is certainly not our intention to overemphasize the possible beneficial effects of glibenclamide in this regard. However, in view of these observations, we do feel that we can safely say that glibenclamide treatment did not have an adverse effect on either LDL or HDL cholesterol metabolism. However, we could find no evidence that glibenclamide led to changes in lipid metabolism that would be expected to increase the risk of CAD and atherosclerosis. Although the patients group in our study was small and not randomized, however, the results need to be confirmed in future studies.

References