

THE STUDY OF BIOCHEMICAL PARAMETERS AND EFFECT OF GLIBENCLAMIDE IN TYPE 2 DIABETES MELLITUS

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Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract:



India is a country known for its rich and varied cultural heritage. It is also one of the oldest civilizations (Indus Valley Civilization) in the world. India is the seventh largest country in the world, divided into 29 states and 7 union territories (Figure 1). Since its independence from the British in 1947, India has achieved an all-round progress socio-economically. It is also self-sufficient in agricultural production and one of the emerging top industrialized countries of the world [1,2].

Knowledge of diabetes dates back to centuries before Christ. The Egyptian Ebers Papyrus [ca. 1500 B.C.] described an illness associated with the passage of much urine. Celsus [30 B.C. to 50

A.D.] recognised the disease but it was not until two centuries later that another Greek physician, the renowned Aretaeus of Cappadocia, gave the name diabetes [a siphon]. He made the first complete clinical description, describing it as "a melting down of the flesh and limbs into urine". In the 3rd to 6th centuries A.D., scholars in China, Japan and India wrote of a condition with polyuria in which the urine was sweet and sticky. However, although it had been known for centuries that diabetic urine tasted sweet, it remained for Willis in 1674 to add the observation "as if imbued with honey and sugar". The name diabetes mellitus [mellitus = honey] was thus established. A century after Willis, Dobson demonstrated that the sweetness was, indeed, due to sugar. From the time of the earliest recorded history of diabetes, progress in the understanding of the disorder came slowly until the middle of the 19th century [3].

However, over these centuries gradually the course and complications of the disease were recognised. Gangrene had been described by Avicenna, an Arab physician, in about 1000 A.D. Its hereditary tendency was described ["Passed with the seed"] as well as two general varieties, one with the classic acute symptoms noted above [Type I or IDDM in today's terminology] and the other with "torpor, indolence and corpulence" [Type II or NIDDM]. Within the past century an association was established with a disturbance in the beta cells. These islets were first noted in fish by Brockman early in the 19th century, but they bear the name of Langerhans who described them in mammals in 1869. Soon after, the German scientists, von Mering and Minkowski, found that surgical removal of the pancreas produced

diabetes in the dog. At the turn of the century, an American, Opie, noted the beta cells in the islets to be damaged in humans dying of the disease. Finally in 1921 Banting and Best, Canadians, prepared active extracts of pancreas which lowered the elevated glucose levels of diabetic dogs^[4].

Type 2 diabetes mellitus is often characterized by hyperglycemia as a result of increased insulin resistance in hepatic, peripheral tissues and pancreatic β -cell dysfunction. Approximately 92% of patients with type 2 diabetes mellitus demonstrate insulin resistance; however hyperglycemia is always a consequence of insulin deficiency. This study was done on 75 patients newly diagnosed diabetes type 2 characterized by dyslipidaemia that is increased triglycerides and decreased HDL. Hypoglycemia and weight gain are common problems with oral sulfonylurea drugs. In this study two different oral hypoglycemic drugs Glibenclamide (insulin secretagogues) were used for treatment of patients with type 2 diabetes mellitus. The effects of these drugs on fasting and postprandial blood glucose levels, lipid profiles (TC, TG, and HDL) were studied. Two groups of newly diagnosed type 2 diabetic patients, group 1 (75 patients) were subjected to treatment with Glibenclamide (5 mg once daily), Fasting and postprandial blood glucose levels, lipid profiles (TC, TG, and HDL) were analysed for these patients before and after 90 days of oral hypoglycemic drug treatment. The results demonstrated that Glibenclamide has a greater postprandial glucose regulator. Glibenclamide produces greater percent reduction with respect to fasting blood glucose levels, postprandial blood glucose levels

Key words: Glibenclamide, lipid profile lipoprotein a and lipoprotein lipase Type 2 diabetes mellitus

Introduction:

Type 2 Non insulin dependent diabetes mellitus (NIDDM) is heterogeneous metabolic disorder with multiple underlying pathophysiological processes, which include relative deficiency in insulin secretion, resistance to the action of insulin in the muscle and increased hepatic glucose output. These pathophysiological defects lead to the development and progression of hyperglycemia, the hallmark of diabetes mellitus^[4-5].

Although non-pharmacological measures such as diet and exercise are considered as important components of the management of type -2 diabetes^[5, 6] most of the patients are unable to achieve adequate glycemic control with these interventions alone. In such patients therapy with a single oral hypoglycemic agent can be tried.

The pharmacological therapy of diabetes has undergone unprecedented expansion in the past decade. With the recent development of new classes of antidiabetic agents, the opportunities as well as the challenges of managing patients with diabetes have both increased. Multiple pharmacological agents with distinct mechanism of action are now available for achieving euglycemia. It is now possible to individualize management by attempting to match the appropriate agents to the underlying

pathophysiology of type 2 diabetes thus allowing a larger number of patients to achieve optimum glycemic goals.

When pharmacology therapy becomes necessary, most physicians use sulfonylureas or the bigunides, metformin. However, the real challenge lies in the optimizing glycemic control with the minimum number of available medications while taking into consideration the adverse effect profiles, the ease of administration and urgency for blood sugar normalization. Insulin resistance plays a key role in type 2 diabetes mellitus and linked to a cluster of cardiovascular risk factors^[8]. Thus, an ideal therapeutic agent for type 2 diabetes should not only aim at achieving glycemic control with minimal adverse effect but also without reducing serum insulin levels.

The sulfonylureas exert hypoglycemic action primarily by stimulating endogenous insulin secretion from the beta cells of the islets of Langerhans of pancreas, both in the basal state and in response to a glucose load. The sulfonylureas interact with specific receptors present on the plasma membrane of the insulin-releasing beta cells of pancreatic islets. This interaction leads to closure of adenosine triphosphate-sensitive potassium (K_{ATP}) channel. Reduced K^+ conductance results in the depolarization of the cells membrane, opening of

voltage sensitive calcium channels, increase in intracellular may further increase insulin levels by reducing hepatic clearance of the hormone^[5].

Differences in the pharmacokinetic and pharmacodynamics characteristics of the various sulfonylureas compound produce different therapeutic and side effect profiles. Second generation sulfonylureas like Glibenclamide and Glipizide are more potent and better tolerated than first generation sulfonylureas like chlorpropamide and tolbutamide^[5]. Glibenclamide (glyburide) may have an additional mechanism of action suppressing hepatic glucose production more than glipizide in patients of non-insulin dependent diabetes mellitus (NIDDM)^[9]. Glipizide –mediated increase in meal stimulated insulin secretion may contribute to its antidiabetic action^[9-11].

Glimepiride is new low dose oral sulfonylurea that provides 24 hours glycemic control in patients of type 2 diabetes with the convenience of once daily dosing. Glimepiride has shown benefit over existing agents of the same class in vitro and in animal studies. In experimental animal model, Glimepiride lowered blood glucose by stimulating insulin release from the pancreas^[12]. It has also been shown to possess and insulin sensitizing action in an in vitro intrinsic extra-pancreatic action^[13], which may add to its therapeutic effects. This drug is well tolerated, with fewer episodes of hypoglycemia as compared to Glibenclamide. Thus glimepiride possesses several benefits including lower dosage, good safety profile, rapid onset and long duration of action and lower insulin levels, possibly due to less stimulation of secretion of insulin and more extra-pancreatic effects^[12].

Diabetic dyslipidaemia is characterized by an increase in fasting triglycerides (TG), a decrease in HDL cholesterol (HDL-C), and an increase in small dense LDL particles.^[14] Whether plasma TG concentrations are considered an independent cardiovascular risk factor is still controversial. TG-rich lipoproteins have a shorter residence time than LDL particles within the circulation^[15] and, therefore, TG measurements exhibit a high intra- and inter-individual variability^[16] which would confound any association. However, in type 2 diabetes (T2DM), increases in plasma TG-

rich lipoproteins are associated with the qualitative and quantitative alterations of other lipoprotein species (i.e. low HDL-C, small dense LDL particles)^[15] indicating that TG-rich lipoproteins contribute to cardiovascular risk. 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).^[16] Also elevated triglycerides levels are commonly seen in type II diabetic subjects.^[17] 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^[17]. 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 β -cells and are widely used in the treatment of type 2 diabetes.^[18]

The present study was conducted to investigate the effects of Glibenclamide on fasting, 2hr postprandial blood glucose, serum insulin, lipid profile, in type 2 diabetic patients. Evaluation of the correlation between fasting and postprandial blood glucose in patients treated with, Glibenclamide separately were also conducted.

MATERIALS AND METHODS

Patients: 75 consecutive type 2 diabetes patients (mean age, 50.15 years) in Mumbai, these 75 were treated with drug of Glibenclamide 5 mg, they met the inclusion and exclusion criteria. *The criteria for inclusion/exclusion were:*

- ❖ Newly diagnose patient of non Insulin Dependent Diabetes Mellitus.
- ❖ Diagnosed patients of diabetes also include having no any history medication.
- ❖ Having either sex or age between 30 to 60 years.
- ❖ Diagnosed patients who will be Non Insulin Dependent Diabetes Mellitus, who will be treated with Pioglitazone.

- ❖ Diagnosed patients who will be Non Insulin Dependent Diabetes Mellitus, who will be treated with drug Glibenclamide.
- ❖ Patients suffering from blood pressure.
- ❖ Patients suffering from liver diseases.
- ❖ Patients suffering from cardiac disease.
- ❖ Pregnancies and lactating women.
- ❖ Patients suffering from renal disorders.

Biochemical parameters studies will be performed by standard methods using internationally accepted techniques.

Collection of Sample Venous blood samples (10 ml from each patient) will be collected into fluoride, plain and heparin bulbs. The samples will be centrifuged at 3000 rpm for 10 minutes and plasma/serum will be separated. Fluoride plasma will be used for Glucose estimation. Serum will be used for lipid profile, insulin, and other biochemical tests Seventy five patients who met the inclusion criteria had their baseline, fasting and postprandial blood sugars, and lipid profiles were done. They were treated with

Glibenclamide 5 mg/day. They were advised to repeat their plasma glucose every three weeks and report for follow-up. They were educated regarding hypoglycaemia and were to report it telephonically if they experienced it before their follow-up date. Fasting and postprandial plasma glucose level and biochemical measures of safety, including chemistry tests lipid profile (TC, TG, HDL), were performed at 3-week intervals throughout the study. Self-monitoring of blood glucose level was encouraged. Determination of blood glucose, lipids and lipoproteins. Fasting blood glucose was determined by capillary blood with the Accutrend blood glucose analyser (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 al⁹ and very-low-density lipoprotein cholesterol according to formula proposed by Wilson, cited by DeLong et al¹⁰.
 $VLDL - cholesterol (mg/dl) = 0.20 \times triglycerides$

OBSERVATION AND RESULTS

Table: Effect of Glibenclamide treatment on Group

Parameters	At day 0	At day 90	P value
Fasting blood glucose(mg/dl)	222.11±9.59	137.12±9.66	< 0.001
2 hr post prandial glucose (mg/dl)	257.34±3.49	201.54±5.19	< 0.001
Serum total cholesterol(mg/dl)	217.44±8.31	201.77±6.06	< 0.001
Serum Triglycerides (mg/dl)	188.69±5.64	168.31±5.61	< 0.001
High density lipoprotein (mg/dl)	33.37±1.90	41.61±1.44	< 0.001
Low density lipoproteins(mg/dl)	141.97±3.96	125.75±4.19	< 0.001
Very low density lipoproteins(mg/dl)	37.04±3.10	33.15±1.41	< 0.001
LP(a) (mg/dl)	35.21±3.03	54.89±3.93	< 0.001
LPL(U/L)	27.58±6.91	28.22±6.72	< 0.001

P< 0.001 indicates the significance of parameter after 90 days of Glibenclamide treatment.
 N.S. indicates the insignificance of parameter after 90 days of Glibenclamide treatment

In the present study they compare effect of oral hypoglycemic drugs Glibenclamide on the group of 75 patients in type 2 diabetic mellitus. The mean age of the group was 50.15±5.14. Out of these 75 patients treated with Glibenclamide. The table showed the effect of Glibenclamide on group 1 at 90 days of treatment on fasting and 2 hr post prandial blood glucose level in diabetic

patient treated with Glibenclamide Significant reduction in fasting and post prandial blood glucose levels and TG were observed in treated patients when compared with zero level values (before treatment). reduction in TG were observed in treated patients when compared with zero level values (before treatment). The same table also showed that Glibenclamide

significantly increases HDL-C after 90 days of treatment at 5 % level of significance. The insignificant decrease was observed with Glibenclamide therapy in Serum total cholesterol, LDL-C and VLDL –cholesterol concentration.

DISCUSSION

Diabetes mellitus comprises of a group of disorders that share a phenotype of hyperglycemia. The complications are an important cause of morbidity and mortality in the diabetic patients. The complications are a result of interaction of multiple metabolic, genetic and other factors⁽¹⁹⁾. The increased risk of vascular disease in diabetics is in part due to the lipid abnormalities, which are twice as common in type 2 diabetes compared to non-diabetics and are more complex than in type 1 diabetics. The most common lipid abnormality seen is hypertriglyceridemia and reduced HDL cholesterol level. An atherogenic constellation of lipid abnormalities including elevated small dense LDL, IDL and apo –B level and reduced Apo- A levels also occur commonly in type 2 diabetics. Glycated LDL can be more atherogenic than native LDL. Hence, the study of these risk factors of Diabetes Mellitus became essential following the usage of different therapeutic hypoglycemic agents.

Disturbance in the structure and function of the endothelium are associated with vasoconstriction and intravascular thrombosis (Vanhoutte PM 1985)²⁰. These alteration appear early in the courses of hyperlipidemia, hypertension and diabetes Mellitus and may contribute to the pathogenesis of atherosclerosis and to its manifestation, such as Coronary Artery Disease (Bessenge et al 1990)²¹.

In the present study Group with Glibenclamide, there was a significant fall of FBS, PPBS, TC, TG and rise of HDL, Lp (a) and LPL level. (Nghyen C et al)²² in their studies shows Glibenclamide possibly has anti atherogenic activity by inhibiting platelet aggregation via suppression of arachidonic acid metabolism. A lowering effect of TC, TG, LDL, VLDL, is favouring cardioprotective measure against atherogenesis. Besides this, more important is slight rise HDL also accounts for

cardioprotection. A low level of HDL is unfavourable feature for cardioprotection. These parameters mean values are represented in the tubular forms and evaluated.

Finally Glibenclamide is found to have a significant cardioprotective inference in relation to lipid profile features comparatively with Pioglitazone. A reasonable rational use of the drugs for antilipidemic purpose is always necessary, to prevent cardiovascular riskfactor. It appears that the Glibenclamide is not a competent substitute for antilipidemic agents, but in Diabetes Mellitus patients from the beginning of the glycaemic control, the Glibenclamide itself precludes the onset of the hyperlipidemia measures comparatively as a cardioprotection.

SUMMARY AND CONCLUSION

Type 2 diabetes is characterised by a gradual decline in glycaemic control and progression from oral glucose-lowering monotherapy to combination therapy and exogenous insulin therapy. Functional decline of the insulin-secreting b-cells is largely responsible for the deterioration in glycaemic control. Preservation of b-cell functionality, in addition to maintaining glycaemic control and reducing insulin resistance, is now regarded as a key target for long-term management strategies. Early, aggressive intervention with combination therapy is emerging as a valid approach to optimise long-term outcomes and combining agents with differing modes of action and secondary effect profiles should prove valuable. Sulfonylureas exert their glucose-lowering effect through differing mechanisms of action – the sulfonylureas by stimulating insulin secretion. This agents offer excellent improvements in glycaemic control when given as monotherapy or in combination. The thiazolidinediones protect b-cell structural and functional integrity and functionality and complement the sulfonylureas by inducing and maintaining improvements in insulin resistance, the abnormal lipid profile associated with type 2 diabetes and other cardiovascular risk factors. This combination may be particularly effective in the early stages of the disease when b-cell function is at its highest, allowing maximal benefit to be obtained from the insulin secretion-promoting abilities of the

sulfonylureas and the b-cell protective effects of the thiazolidinediones.

The present study, the Glibenclamide was found more effective in lowering both fasting and post prandial blood glucose levels in the patients of type 2 diabetes mellitus

Seventy five patients of Diabetes Mellitus were observed for lipid profile fluctuation in relation to Glibenclamide. The changes in the lipoprotein levels noted before and after 90 days of drug administration. After the study of therapy and investigation, it is understood that the patients who were treated with Glibenclamide group there is a significant fall in the levels of total cholesterol, Triglycerides and LDL levels comparatively. And there is rise, in the level of HDL.

Type 2 diabetes manifests in an insulin-resistant individual when pancreatic b-cells are unable to produce sufficient insulin to overcome insulin resistance in the muscles and liver. Intervening early to attain glycaemic control and protect b-cell function is now regarded as central to improving long-term outcomes for patients with type 2 diabetes. The insulin secretagogues sulfonylureas and biguanides represented the mainstay of oral glucose-lowering therapy from their development in the 1940s to the 1990s. Today, these agents are still used and are proving especially useful in early combination therapy regimens with agents that improve glycaemic control by different molecular mechanisms. In patients treated with a sulfonylurea, there is a strong rationale to support the early combination with thiazolidinediones in type 2 diabetes. In addition to improving and maintaining glycaemic control, the thiazolidinediones reduce b-cell stress, improve insulin resistance and modify a variety of cardiovascular risk factors, including the abnormal lipid profile and increased low-grade inflammation activity associated with type 2 diabetes. The combined benefits of thiazolidinediones and sulfonylureas may delay the progression of type 2 diabetes and the need for exogenous insulin therapy, and may also offer benefits in terms of reduced risk of CVD.

In the light study of discussion it is obvious the glibenclamide was more effective tolerable and

safer in short duration. Diabetes mellitus is chronic prolong disease for whole life. Poor community can afford it easily on base of marketing of this drug. Patient easily go and purchase economically in fact mostly people buy it from pharmacy because pharmacist and patient both of knowledge disease. Glibenclamide is famous anti-diabetic drug in our state as compared of other antidiabetic drugs.

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