International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Original Research Article

To Compare the Effect of Oral Hypoglycaemic Drugs Glibenclamide and Pioglitazone on Blood Sugar, Lipid Abnormalities in Type 2 Diabetes Mellitus

Vitthal S. Shinde[1], M. G. Kalekar[2], B.D.Samant[3], D.R.Chaudhari[3],Vijay P. More[4], Rasika D. Yadav[1]

[1]Department of Biochemistry, Dr. Ulhas Patil Medical College & Hospital Jalgaon-Maharashtra.
[2]Department of Biochemistry, Grant Medical College & Sir J. J. Hospital Mumbai.
[3]Department of Pharmacology, Dr. Ulhas Patil Medical College & Hospital Jalgaon-Maharashtra
[4]Department of Community Medicine, Dr. Ulhas Patil Medical College & Hospital Jalgaon- Maharashtra.

Corresponding Author: Vitthal S. Shinde

Received: 06/02//2014 *Revised: 27/02/2014* *Accepted: 04/03/2014*

ABSTRACT

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 150 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) and Pioglitazone (insulin sensitizer) 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), group 2, (75patients) were subjected to treatment with Pioglitazone (15mg twice 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 effect than Pioglitazone. In addition the hypoglycemic episode and weight gain were less in patients treated Glibenclamide with than those treated with Pioglitazone. Glibenclamide produces greater percent reduction with respect to fasting blood glucose levels, postprandial blood glucose levels compared to Pioglitazone.

Key words: Oral hypoglycemic drugs, Glibenclamide, Pioglitazone, Type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM exist and are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a

tremendous burden on the individual with diabetes and on the health care system. In the United States, DM is the leading cause of end-stage renal disease (ESRD), nontraumatic lower extremity amputations, and adult blindness. [1] The prevalence of diabetes mellitus has been increasing worldwide with an expected doubling of diabetic population from 171 million to 366 million between 2000-2030. The greatest relative increase will occur in Middle Eastern Crescent, Sub Saharan Africa and India. [2]

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, abnormal lipid and protein metabolism along with specific long term complication affecting the retina, kidney and nervous system. [3] Diabetes mellitus may be categorized into several types, but the two major types are type I (Insulin dependent diabetes mellitus) and type 2(Non insulin dependent diabetes mellitus).

Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and secretion give rise to the common phenotype of hyperglycemia in type 2 DM and have important potential therapeutic implications now that pharmacologic agents are available to target specific metabolic derangements. Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

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. [4] 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 [5] and, therefore, TG measurements exhibit a high intra- and inter-individual variability [6] 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) [5] 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). [6] Also elevated triglycerides levels are commonly seen in type II diabetic subjects. [7] 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[7]. 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. [8]

Type 2 diabetes is the commonest form of diabetes and is characterized by disorder of insulin secretion and/ or insulin resistance. [9] Oral hypoglycemic agent, glibenclamide is a second generation which is more potent than first generation sulfonylureas. [10] It is valuable in the treatment of non obese patient with type 2 diabetes, who fails to respond to dietary measures alone. It stimulates the secretion and enhances the utilization of insulin by

appropriate tissues Pioglitazone (thiozolidinediones) is introduced in 1999 and widely used as monotherapy or in fixed dose combination with either metformin or glimepiride. [10] It is a potent hypoglycemic agent. [11, 12] The present study was conducted to investigate the effects of Glibenclamide and Pioglitazone 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 and Pioglitazone separately were also conducted.

The current study with Glibenclamide and Pioglitazone drug therapy was undertaken to see their effects in glycemic control in patients of type 2 diabetes mellitus.

MATERIALS AND METHODS

Patients : 150 consecutive type 2 diabetes patients (mean age, 50.15 years) in Mumbai, out of these 75 were treated with drug of Glibenclamide 5 mg, and another 75 treated with drug Pioglitazone 15 mg , if 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. One hundred and fifty patients who met the inclusion criteria had their baseline, fasting and postprandial blood sugars, and lipid profiles were done. They were then treated with Pioglitazone 15 mg/day and 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 a19 and very-low-density lipoprotein cholesterol according to formula proposed by Wilson, cited by DeLong et al10. VLDL - cholesterol (mg/dl) = 0.20 x triglycerides

RESULT

In the present study they compare effect of oral hypoglycemic drugs Glibenclamide and Pioglitazone on the group of 150 patients in type 2 diabetic mellitus. The mean age of the group was 50.15±5.14. Out of these 150 patients, 75 (Group 1) treated with Glibenclamide and remaining 75 (Group 2) with Pioglitazone.

Table 1: Effect of Glibenclamide treatment on Group 1.

Parameters	At day 0	At day 90	P value
Fasting blood glucose(mg/dl)	222.11±9.59	137.12±9.66	<0.05
2 hr post prandial glucose (mg/dl)	257.34±3.49	201.54±5.19	<0.05
Serum total cholesterol(mg/dl)	217.44±8.31	201.77±6.06	N.S
Serum Triglycerides (mg/dl)	188.69±5.64	168.31±5.61	<0.05
High density lipoprotein (mg/dl)	33.37±1.90	41.61±1.44	<0.05
Low density lipoproteins(mg/dl)	141.97±3.96	125.75±4.19	N.S.
Very low density lioprotiens(mg/dl)	37.04±3.10	33.15±1.41	N.S.

Table 2: Effect of Pioglitazone treatment on Group 2.

Parameters	At day 0	At day 90	P value
Fasting blood glucose(mg/dl)	219.93±10.45	165.16±8.36	<0.05
2 hr post prandial glucose(mg/dl)	260.25±5.31	195.67±6.12	<0.05
Serum Total cholesterol(mg/dl)	215.84±7.85	210.48±4.66	N.S
Serum Triglycerides (mg/dl)	188.87±5.94	176.80±4.73	<0.05
High density lipoprotein (mg/dl)	33.70±1.78	35.28±2.80	<0.05
Low density lipoproteins(mg/dl)	140.20±4.18	135.16±5.92	N.S.
Very low density lipoproteins(mg/dl)	36.17±3.35	34.64±2.36	N.S.

Table 3: Percentage decrease of fasting and post prandial blood glucose in diabetic Patients treated with Glibenclamide and Pioglitazone after 90 days of treatment.

Drugs	Decrease of fasting blood glucose (Mg/dl) after 90 days	Decrease of post prandial blood glucose (Mg/dl) after 90 days
Glibenclamide	38.26 %	21.68 %
Pioglitazone	24.58 %	15.36 %

- P<0.05 indicates the significance of parameter after 90 days of Glibenclamide treatment.
- N.S. indicates insignificance of parameter after 90 days of Glibenclamide treatment.

The table 1 showed the effect of Glibenclamide on fasting and 2 hr post prandial blood glucose level in diabetic patient treated with Glibenclamide group 1 at 90 days of treatment. 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). 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.

- P<0.05 indicates the significance of parameter after 90 days of Glibenclamide treatment.
- N.S. indicates insignificance of parameter after 90 days of Glibenclamide treatment.

The table 2 showed the effect of Pioglitazone on fasting and 2 hr post prandial blood glucose level in diabetic patient treated with Pioglitazone group 2 at 90 days of treatment. 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). The same table also showed that Pioglitazone significantly increases HDL-C after 90 days of treatment at 5 % level of significance. The insignificant decrease was observed with Pioglitazone therapy in Serum total cholesterol, LDL-C and VLDL –cholesterol concentration.

It is obvious from the table that Glibenclamide produces higher percentage decrease in fasting and post prandial blood glucose level after 90 days of treatment when compared to Pioglitazone.

Table 4: Adverse effects of Glibenclamide compared to Pioglitazone.

Adverse effect	Group I (Glibenclamide)	Group II (Pioglitazone)
Hypoglycemia (mild) Hypersensitivity	10 %	15 %
Tolerability	Good	Good
Headache	2.5 %	5 %

The table 4 showed high percent of adverse effects (Hypoglycemia and Headache) in Glibenclamide treated patients compared to Pioglitazone treated patients

DISCUSSION

Diabetic patients have many complications which include elevated of LDL-C and triglycerols, low levels of HDL-C level a known risk factor for cardiovascular disease and a preponderance of abnormalities in the composition of the smaller, dense particles. [14] The result of Jenkins et al suggested that HDL is more important than the other lipoprotein in influencing atherosclerosis; this finding needs to be interpreted since there is closer metabolic interrelation between lipoprotein species.

Recent epidemiological studies have elucidated the importance of individual lipoprotein in predicting future clinical coronary heart disease. High density lipoproteins (HDLs) appear to exert the greatest influence independently of other lipoprotiens, with low density lipoproteins (LDLs) having a weaker, though still significant, independent relation with coronary heart disease.

Glibenclamide showed significant reduction in fasting and postprandial blood glucose after 4 and 8 weeks of treatment. This result is in agreement with the observation of Kolterman et.al 1984 [13] and Rosak et.al 2002 [14] who found that glibenclamide significantly reduced blood glucose levels. Glibenclamide have the mechanism of action in lowering blood glucose. Like Sulfonylureas, acts by linide stimulating the release of insulin from the B-cell of the pancreas by inhibiting ATP-sensitive K channels, thereby activating the Ca++ channel with increase in intracellular calcium to release insulin. [15] Therefore glibenclamide is a novel and superior to rosiglitazone in controlling postprandial glucose profile in type 2 diabetic complications. Regarding lipid profile in type 2 diabetic patients treated with glibenclamide, these results were supported by Ykijarvinan 2004 [15] study, where lipid profile changes as a result of improved glycaemic control are uniform findings associated with anti- diabetic therapy. Epidemiologic studies have shown a positive relation between serum TG levels and coronary artery disease [16] whereas

there is an inverse relationship between HDL-C levels and cardiovascular risk at any level of LDL-C. In an overview of studies conducted in the Asia-Pacific region, Woodward et al. [17] found evidence of potential benefit for coronary heart disease with increases in HDL-C as well as decreases in the cholesterol/HDL ratio.

This study showed that edema was related to dose of pioglitazone which confirmed the findings in previous studies. [17, 18, 19] Prevalence of edema other studies reported 5.9 -33.0 % [20, 21] depending on whether patients received pioglitazone monotherapy or combination therapy and concurrent drugs related to edema.

However, we attempted to study of the effect of Glibenclamide on lipids and NIDDM (type 2) patients with Glibenclamide significantly ($P<0.05$) increased the HDL cholesterol concentration. Again in no case was there any tendency for low-density lipoprotein level to rise during Glibenclamide therapy. [22-23] Similarly Tamai et al. [24] found no significant change in very low density lipoprotein cholesterol during Glibenclamide therapy. Although we observed a non significant reduction in low density lipoprotein in NIDDM patients. Clinically Glibenclamide was well tolerated. No gastrointestinal complains and no skin rashes or other side effects were noted or reported in the present study over 90 days treatment.

The purpose of present study was to provide the importance of effect of Glibenclamide drug in their mediation of biologic effect or on lipid and lipoprotein metabolism. However, in view of these observations, we do fell that we can safely say that Glibenclamide treatment did not have an adverse effect on either LDL or HDL cholesterol metabolism.

CONCLUSION

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 than Pioglitazone. Assessment of blood glucose levels was performed on the 1st day and at the end of therapy (90th day). The current study additionally evaluated change in blood sugar levels. The therapy of Glibenclamide showed a significant drop in the blood sugar level when compared between days 1 to day 90 and was found more effective than the group which received Pioglitazone. In the light study of discussion it is obvious the Glibenclamide was more effective tolerable and safer than Pioglitazone 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 without dr.'s prescription because pharmacist and patient both of knowledge disease. Just like dispirin as analgesic. Glibenclamide is famous anti-diabetic drug in our state as compared of other antidiabetic drugs.

REFERENCES

1. Harrison's principles of internal medicine 16 th edition page 2152
2. Sarah Wild, Gojka Roglic, Anders Green, Richard Sicree. Global Prevalence of Diabetes Estimates for the year 2000 and projections for 2030 .Diabetes Care 2004, 27 (5):1047– 1053.
3. David, M.N., James M, Daniel E. The epidemiology of cardiovascular disease in type 2 diabetes mellitus. Lancet; (1997), 350: 514-519.
4. Zimmet P, Cowie C, Ekoe JM, et al. Classification of diabetes mellitus and other categories of glucose intolerance. International text book of diabetes mellitus chapter 1, 3rd Ed, (2004), pp 3 14.

5. Taskinen MR. Diabetic dyslipidaemia. From basic research to clinical practice. Diabetologia 2003; 46: 733–749.
6. Howard By. Lipoprotein metabolism in diabetes mellitus. J. Lipid. Res. 1987; 28:61 3-28.
7. Saltiel AR, Olefsky JM. Perspective in diabetes. Thiazolidinediones in the treatment of insulin resistance and type II diabetes. Diabetes, 1996; 45:169.
8. Pietzsch J, Julin U, Henefeld M. In vivo evidence for increased apolipoprotein A-I catabolism in subejcts with impaired glucose tolerance. Diabetes 1998; 47:1928-34.
9. Packard CJ, Shepherd J. Lipoprotein heterogeneity and apolipoprotein B metabolism. Arterioscler Thromb Vasc Biol 1997; 17: 3542–3556.
10. Bookstein L, Gidding SS, Donovan M, Smith FA. Day-to-day variability of serum cholesterol, triglyceride, and high-density lipoprotein cholesterol levels. Impact on the assessment of risk according to the National Cholesterol Education Program Guidelines. Arch Intern Med 1990; 150: 1653–1657.
11. Lebovitz. E, Feinglos MN. The oral hypoglycemic agents. In: diabetes mellitus, Theory and Practice, 3rd ED. (M. Ellenberg and H. Rifkin eds.) medical Examination Publication, New Hyde Park, New York, (1993), pp. 591-610.
12. DeFranzo RA. Bondonna RC, Ferrannini E. Pathogenesis of NIDDM. In Albert KGMN, Zimmet P, Defronzo RA (eds). International Text book of Diabetes Mellitus 2nd Ed. Chichester: wiley, (1997), pp, 635-712.
13. Lebovitz. E, Feinglos MN. The oral hypoglycemic agents. In: diabetes mellitus, Theory and Practice, 3rd ED. (M. Ellenberg and H. Rifkin eds.) medical Examination Publication, New Hyde Park, New York, (1993), pp. 591-610.
14. Haffner SM. Management of dyslipidemia in adults with diabetes. Diabetes Care 1998; 21:9(1):1600-78
15. Kolterman OG, Gray RS, Shapiro G et al. The acute and chronic effects of sulfonylurea therapy in type II diabetic subjects. Diabetes; (1984), 33 (4): 346-354.
16. Rosak C, Haupt E, Walter T et al. The effect of combination treatment with acarbose and glibenclamide on postprandial glucose and insulin profiles: Additive blood glucose lowering effect and decreased gypoglycaemia. Diabet nutr metab; (2002), 15: 143-151.
17. Gromada J, Dissing S, et al. Effects of the hypoglycaemic drugl repaglinide and glibencamide on ATP-sensitive potassium –channels and cytosolic calcium levels in Beta TC3 cells and rat beta pancreatic cells. Diabetologia; (1995), 38: 1025-32.
18. YKi-Jarvinen H. Thiazolidinediones. N Engl J Med; (2004), 351: 1106-18.
19. Assmann G, Schulte H, Funke H, von Eckardstein A. The emergence of triglycerides as a significant risk factor in coronary artery disease. Eur Heart J. 1998:19(Suppl):M8 14.
20. Woodward M, Barzi F, Feigin V, et al. Associations between high-density lipoprotein cholesterol and both stroke and coronary heart disease in the Asia-Pacific region. Eur Heart J. 2007; 28:2653–2660.
21. Majima T. Komatsu Y, Doi K. Shigemoto M, Takagi C, Fukao A, et.al. Sagely and efficacy of low-dose pioglitazone (7.5 mg/day) vsstandard – dose pioglitazone (15 mg/day) in Japanese women with type 2 diabetes mellitus. Endocr. J., 2006; 53(3):325-30.
22. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen A, Schneider RL, et.al Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes : a 6-month randomized placebo-controlled dose respoooonse study. Diabetes Care, 2000; 23:1605-11.
23. Miyazaki Y, Matsude M, Defronzo RA. Dose response effect of pioglitazone on

insulin sensitivity and insulin secretion in type 2 diabetes. Diabetes Care, 2002; 25:517-23.
24. Hussein Z, Wentworth JM, Nankervis AJ, Proietto J, Colman PG. Effectiveness and side effect of thiazolidinediones for type 2 diabetes: real life experience from a tertiary hospital. MJA, 2004; 181(10):536-9.
25. Waugh J, Keating GM,Plosker GL, Lasthope S, Robinson DM. Pioglitazone : a review of its use in type 2 diabetes mellitus. Drugs, 2006;66(1):85-109.
26. Howard By, Xiaoren P, Harper I, et al. Effect of sulfonyurea therapy on plasma lipids and high density lipoprotein composition in non-insulin dependent diabetes mellitus. Am J.Med., 1985:79(suppl.3B):78-85.
27. Falko JM,Osei K. Combination insulin/glyburide therapy in type 2 diabetes mellitus. Effect on lipoprotein metabolism and glucoregulation. Am. J. Med., 1985: 79 (suppl.2B) 92-101.
28. Hughes TA. Kramer JO, Segrest JP. Effect of glyburide therapy on lipoprotein in non-insulin dependent diabetes mellitus. Am. J. Med. 1985; 79(suppl.3B) 86-91.
29. Tamai T, Nakai T, Yarnada S, et al. The effect of Glibenclamide and insulin on plasma high density lipoprotein in diabetes. Artery, (abstract):1982; 9:477-93.

How to cite this article: Shinde VS, Kalekar MG, Samant BD et. al. To compare the effect of oral hypoglycaemic drugs glibenclamide and pioglitazone on blood sugar, lipid abnormalities in type 2 diabetes mellitus. Int J Health Sci Res. 2014;4(4):53-60.

****