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Research Article

Comparative evaluation of effects of combined oral anti-diabetic drugs (sulfonylurea plus pioglitazone and sulfonylurea plus metformin) over lipid parameters in type 2 diabetic patients

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ABSTRACT

Background: Type 2 diabetes is associated with significant cardiovascular morbidity and mortality. Dyslipidemia, which affects almost 50% of patients with type 2 diabetes, is a cardiovascular risk factor characterized by elevated triglyceride levels, low high-density lipoprotein (HDL) cholesterol levels, and a preponderance of small, dense, low-density lipoprotein (LDL) particles. In addition to their glucose-lowering properties, oral anti-diabetic agents may have effects on lipid levels, especially triglycerides (TGs), HDL-C, LDL-C and total cholesterol levels.
Methods: A prospective, open-labeled, randomized, parallel-group study was carried out in sizable number of patients (n=40) of established type 2 diabetes on combined oral anti-diabetic drugs, to investigate the effects of combined oral anti-diabetic on lipid parameters who was not receiving any hypolipidemic agent in addition.
Results: Statistically significant mean reduction of triglycerides (TGs) of 25.1mg/dl (a 15.30% reduction from baseline value) and by 13.5 mg/dl (a 8.94% reduction from baseline value) in the SU (sulfonylurea) plus PIO (pioglitazone) and SU plus MET (metformin) group respectively. Present study also shows improvement in HDL cholesterol with SU plus PIO group by 13.18% which is almost twice that observed in SU plus MET group (8.06%). Present study also shows increase in LDL cholesterol with SU plus PIO group by 2.10%, is just opposite to SU plus MET group (4.92 % decrease). With SU plus PIO group, a statistically significant mean reduction of total cholesterol (TC) of 8.33mg/dl (5.14 % decrease) and by 7.62 mg/dl (4.28% decrease) in the SU plus MET group.
Conclusions: Pioglitazone, a thiazolidinedione, has been shown to improve the lipid profile in patients with type 2 diabetes by increasing HDL-C levels and by decreasing triglyceride and total cholesterol levels in monotherapy or combination regimens with sulfonylurea. Metformin also has been shown to reduce LDL-C, TC, and TG levels and increase HDL-C levels in monotherapy and in combination regimens with sulfonylurea. In contrast, LDL cholesterol levels mild increase with pioglitazone monotherapy or with SU combination therapy. Thus the results of this study have demonstrated that SU plus pioglitazone is an effective combination regimen for patients insufficiently treated with SU monotherapy and may provide possible positive effects on other coronary risk factors/ dyslipidemias associated with the type 2 diabetes.

Keywords: Type 2 diabetes, Sulfonylureas, Metformin, Pioglitazone, Serum lipid parameters

INTRODUCTION

With an increasing incidence worldwide, diabetes mellitus (DM) will be a leading cause of morbidity and mortality for the foreseeable future.[1] Currently the number of cases of diabetes worldwide is estimated to be around 366 million in 2011; by 2030 this will have risen to 552 million. In India, 61.3 million persons effected with diabetes in 2011 and it will be 101.2 million by 2030.[2] The number of people with type 2 diabetes is increasing in every country and is associated with

significant morbidity and mortality due to cardiovascular complications.[3]

The hallmarks of type 2 diabetes are hyperglycemia, insulin resistance, and insulin deficiency, and it is increasingly recognized that insulin resistance contributes to the characteristic dyslipidemia associated with type 2 diabetes.[4] Diabetic dyslipidemia is characterized by low high density lipoprotein (HDL), increased triglycerides, and postprandial lipemia. Defects in insulin action and hyperglycemia could lead to changes in plasma lipoproteins in patients with diabetes.[5] Hyperglycemia increases the risk of microvascular complications[6], while dyslipidemia is a major risk factor for macrovascular complications in patients with type 2 diabetes. Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for CVD.[7,8]

Today varieties of agents of different modes of action are available to improve glycaemic control. Sulfonylurea (SU) drugs (e.g., glyburide, glipizide, and glimepiride) improve glucose levels by stimulating insulin secretion by the pancreatic β-cell. Glimepiride, a member of sulfonylurea class, appears to have a useful secondary action in increasing insulin sensitivity in peripheral cells. Biguanides (principally metformin), reduces glucose levels primarily by decreasing hepatic glucose production and by increasing insulin action in muscle and fat.[9] Recent in vitro and in vivo evidence has shown that metformin activates the AMP-activated protein kinase (AMPK), a major cellular regulator of lipid and glucose metabolism.[10] Thiazolidinediones (pioglitazone) have emerged as novel, effective glucose-lowering agents by stimulating peroxisome proliferator-activated receptor gamma (PPARγ) which increase the peripheral action of insulin.[11]

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. The thiazolidinediones protect β-cell structural and functional integrity and functionality and metformin by reducing gluconeogenesis and AMPK mediated action complement the actions of sulfonylureas (if administered in combination) by inducing and maintaining improvements in insulin resistance, the abnormal lipid profile associated with type 2 diabetes and other cardiovascular risk factors.[12] Thus, there is a strong rationale to support the addition of thiazolidinediones or biguanides (metformin) to sulfonylureas as a treatment option for type 2 diabetes. This combination may be particularly effective in the early stages of the disease when β-cell function is at its highest[12], allowing maximal benefit to be obtained from the insulin secretion-promoting abilities of the sulfonylureas and the β-cell-protective effects of the thiazolidinediones. Study has shown that lipid and glucose homeostasis is interrelated. So by controlling glycemic level these drugs in combination also may affect plasma lipid parameters.[13] Present work was conducted to investigate the effects of combined oral hypoglycemic on lipid profile in type 2 diabetic patients who was not receiving any hypolipidemic agent in addition.

METHODS

A prospective, open-labeled, randomized, parallel-group study was carried out in sizable number of patients (n=40) of either sex of established type 2 DM on combined oral anti-diabetic drugs, attending OPD of Department of Endocrinology, a tertiary care teaching hospital, Meerut, Uttar Pradesh. Study was approved from institutional ethical committee. Informed written consent was sought and obtained from each subject before recruitment into the study. Their medical history and personal data were obtained via comprehensive and structured questionnaires. Patients were screened for inclusion /exclusion criteria.

Inclusion criteria

Male & Female patients with type 2 DM aged 30-75 yrs on combined oral anti-diabetics, having no serious physical or biochemical abnormalities other than those generally associated with type2 diabetes were included in the study. Patients of type 2 diabetes with mean duration of disease of (7.0±5.7) years.

Exclusion criteria

Patients with type 1 diabetes or ketoacidosis, a history of myocardial infarction, transient ischemic attacks, or stroke in previous 6 months, symptomatic heart failure, liver dysfunction, renal impairment, chronic hypoxic lung disease, septicemia, malabsorption, history of lactic acidosis, pregnant or breast feeding women, patients requiring insulin, substance abuse. Patients receiving any concomitant hypolipidemic medication, which may affect lipid homeostasis and any previous treatment with metformin, pioglitazone or other thiazolidinediones were not permitted. Patients using lipid lowering drugs were excluded from the study.

Subjects who passed the screening were randomized into two groups. Group1 [SU (sulfonylurea) plus PIO (pioglitazone)] included 40 patients (29 male and 11 female), their ages range between 40-69 years (49.3 ± 5.8) treated with PIO 15 mg to 45 mg/day before meal. Group2 [SU plus MET (metformin)] included 40 patients (26 male and 14 female), theirs ages range between 45 – 65 years (51.2± 7.6) treated with MET 850 mg to maximum 2500 mg/day before meal. A SU, preferably glimepiride (1-2mg daily) was started in both the groups.

Dose levels were increased at 4, 8 and12 weeks according to patient's blood sugar levels & tolerability of drugs. Lipid parameters (mg/dl) were assessed at baseline, 3 monthly for 12 months and at the end of study. The total duration of the study was 12 months. All the adverse events, if any, in each treatment group were noted periodically. Glimepiride, a sulfonylurea, 1 or 2mg tab

was available as Glucoryl tab, Alkem Laboratories Ltd. Metformin 850 mg tab and Pioglitazone 15 mg Tab were available as Glyciphage tab and Pozitiv tab, Franco-Indian Pharmaceuticals Pvt. Ltd.

Collection of blood samples

After an overnight fast, venous blood samples were drawn from the subjects with venepuncture with metal free, stainless steel needles into appropriately coated tubes.8 ml of blood was collected in fasting condition into three vials with all aseptic precautions. Serum was separated by centrifugation at 3000 rpm for 5 minutes, which was collected in plain tube and kept frozen unless analyzed immediately. The serum was utilized for determination of total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C).

Lipid parameters were studied by the following mechanisms

1. Total cholesterol (TC) by enzymatic end point CHOD-POD method[14]
2. Triacylglycerol (Triglyceride) by enzymatic glycerol phosphate oxidase / peroxidase method[15]
3. HDL- Cholesterol (HDL-C) by direct enzymatic end point method[16]
4. LDL – cholesterol (LDL-C) by direct enzymatic end point method[17]
5. VLDL- cholesterol (VLDL-C) by Friedewald's formula[18]

Commercial kits and equipments for biochemical analysis

The measurements of the triglycerides, HDL Cholesterol and total cholesterol were performed with the kits manufactured by Transasia Biomedicals Ltd (In technical collaboration with ERBA diagnostics Mannheim, Germany). The LDL-C measurement with the homogeneous method was performed with the kits manufactured by Transasia Biomedicals Ltd. The tests were done on ERBA Chem 5 semi autoanalyser. The data obtained were statistically analyzed by using paired t-test between pre-treatment and post-treatment parameters of each variable. Then the treatment outcomes of both the groups were statistically analyzed by using unpaired t-test.

RESULTS

Table 1: General Patient's demographic profile.

S. No	Characteristics			SU plus PIO group or (group 1) (n=40)	SU plus MET group or (group 2) (n=40)
1	Gender		Male Female	29 (62.5%) 11 (27.5%)	26 (65%) 14 (35%)
2	Age (years)		Mean ± SD	55 ± 9.80	53 ± 8.70
3	Weight (kg)	Mean ± SD	Baseline 12 month	62.4 ± 14.2 65.2 ± 15.3	65 ± 15.7 63.9 ± 13.8
4	Duration of Disease (years)	Mean ± SD		7.0 ± 5.6	6.7 ± 5.8

This study was conducted in total 80 patients (55 males and 25 females) in the age group of 30-75 years with type 2 diabetes mellitus who were attending Out Patients Department of Endocrinology & Human Metabolism of tertiary care teaching hospital. SU plus PIO group (n=40) consists of 29 males and 11 females with mean age of 55.9±9.8 years (30-75 years).The mean duration of disease was 7.0±5.8 years (table-1). SUM group (n=40) consists of 26 males and 14 females with the mean age 52.45±7.8 (30-75 years). The mean duration of disease was 8.3±6.2 years (Table 1).

Statistically significant mean reduction of triglycerides (TGs) of 25.1mg/dl (a 15.30% reduction from baseline value) and by 13.5 mg/dl (a 8.94% reduction from baseline value) in the SU plus PIO and SU plus MET group respectively.

Present study also shows statistically significant improvement in HDL cholesterol with SU plus PIO group by13.18% which is almost twice that observed in SU plus MET group (8.06%).

Present study also shows increase in LDL cholesterol with SU plus PIO group by 2.10%, is just opposite to SU plus MET group (4.92 % decrease).

Table 2: Comparative evaluation of triglycerides levels in group 1 & group 2.

Duration Months	SU plus PIO group or (group 1) (n=40) Mean ± SD (mg/dl)	SU plus MET group or (group 2) (n=40) Mean ± SD (mg/dl)
0 (baseline)	164 ± 55.5	151 ± 42.3
12	139 ± 41.3**	138 ± 37.3*

*p(<0.05) as compared to the baseline values.
**p(<0.01) as compared to the baseline values.

Table 3: Comparative evaluation of high density lipoprotein (HDL) levels in group 1 & group 2.

Duration Months	SU plus PIO group or (group 1) (n=40) Mean ± SD (mg/dl)	SU plus MET group or (group 2) (n=40) Mean ± SD (mg/dl)
0 (baseline)	41.5 ± 8.67	43.3 ± 9.43
12	46.9 ± 8.34**	46.8 ± 9.87*

*p (<0.05) as compared to baseline values.
**p (<0.01) as compared to baseline values.

Table 4: Comparative evaluation of low density lipoprotein (LDL) levels in group 1 & group 2.

Duration Months	SU plus PIO group or (group 1) (n=40) Mean ± SD (mg/dl)	SU plus MET group or (group 2) (n=40) Mean ± SD (mg/dl)
0 (baseline)	104 ± 35.7	115 ± 31.1
12	106 ± 35.8*	109 ± 28.5**

*p (<0.05) as compared to baseline values.
**p (<0.01) as compared to baseline values.

Table 5: Comparative evaluation of total cholesterol levels in group 1 & group 2.

Duration Months	SU plus PIO group or (group 1) (n=40) Mean ± SD (mg/dl)	SU plus MET group or (group 2) (n=40) Mean ± SD (mg/dl)
0 (baseline)	162 ± 37.5	178 ± 36.5
12	154 ± 33.6*	170 ± 33.6*

*p (<0.05) as compared to baseline values.

With SU plus PIO group, a statistically significant mean reduction of total cholesterol (TC) of 8.33mg/dl (5.14 % decrease) and by 7.62 mg/dl (4.28% decrease) in the SU plus MET group.

DISCUSSION

Present prospective, randomized, open parallel study was conducted with an aim to compare the superiority of combination therapy on lipid parameters in addition to glycaemic control in patients with type 2 diabetes. Study was conducted on patients with type 2 diabetes mellitus those were attending Out Patients Department of Endocrinology of a tertiary care teaching hospital, Meerut for a period of 12 months. 80 patients of either sex in age range 30-75 years of type 2 diabetes who passed the screening were randomly enrolled in the study and equally divided in two groups (n=40). The major therapeutic goal in patients with type2 diabetes is to optimize glycaemic control by controlling blood pressure

and lipid levels, in order to reduce the development and or the severity of long term diabetic complications.

Improving lipid parameters in patients with type 2 diabetes with combined oral hypoglycemic: Statistically significant mean reduction of triglycerides (TGs) of 25.1mg/dl (a 15.30% reduction from baseline value) and by 13.5 mg/dl (a 8.94% reduction from baseline value) in the SU plus PIO and SU plus MET group respectively (Table 2). These findings are in line with the observations made by Kipnes, M.S et al.,(2001)[19] and Hanefeld, M et al.,(2004)[20] who reported mean reduction of 0.42 mmol/l (16% reduction) in the SU plus pioglitazone group and by 0.28mmol/l (reduction of 9%) in the SU plus metformin group. Glitazones exert a hypotriglyceridemic action via PPAR-γ-mediated induction of lipoprotein lipase expression in adipose tissue. PPARs play also a role in intracellular lipid metabolism by up-regulating the expression of enzymes involved in conversion of fatty acids in acyl-coenzyme A esters, fatty acid entry into mitochondria and peroxisomal and mitochondrial fatty acid catabolism (Gervois, P, 2000)[21]. Study had shown that TZDs significantly reduced plasma FFA levels, fasting serum TGs levels and increased fasting HDL cholesterol levels in 20 patients with type 2 diabetes over 6 month study (Yamasaki,Y et al.,1997).[22]

In the SU plus PIO group of present study, high-density lipoprotein (HDL) cholesterol was increased by 5.47mg/dl (13.18% increase) and by 3.49 mg/dl (8.06% increase) in the SU plus MET group (table-3). These findings are consistent with the observations made by Kipnes, M.S et al.,(2001) and Hanefeld, M et al.,(2004) who reported mean increase of 12% HDL in SU plus PIO group in the Kipnes, M.S et al 52 week study; and mean increase of 0.16 mmol/l (correlating with a 14% increase) in the SU plus PIO group and by 0.09 mmol/l (8% increase) in the SU plus MET group in the Hanefeld, M et al 52 week study. In type diabetes, the increased secretion of apo-B containing lipoprotein may be the result of increased FFA flux to the liver. Because of increased endogenous secretion of apoB-containing lipoprotein particles, the increased plasma levels of TG can drive a metabolic process that results in reduced HDL cholesterol levels. In a substrate driven reaction, cholesterol ester transfer protein (CETP) exchanges VLDL-TG for HDL cholesterol.TG rich HDL particles are hydrolysed by hepatic lipase, as a result, are rapidly catabolized and cleared from plasma (Hopkins, GJ and Barter, PJ, 1986).[23] HDL functions in cellular cholesterol efflux and has direct anti-oxidative as well as anti-inflammatory properties (Kontush, A and Chapman, M.J, 2006).[24] The association between reduced HDL cholesterol levels and increased risk of heart disease is well established (Gordon, DJ et al., 1989).[25] Plasma HDL cholesterol levels are generally increased with pioglitazone therapy (Henry RR, 1997).[26] Present study also shows improvement in HDL cholesterol with group1 by13.18% which is almost twice that observed in group 2 (8.06%) (Table 3).

There was a small statistically significant increase of 2.19 mg/dl in LDL cholesterol in the SU plus PIO group (2.10 % increase) compared with a small decrease of 5.66mg/dl (4.92 % decrease) in the SU plus MET group (Table 4). These findings fall in line with the observations made by Hanefeld, M et al.,(2004) who reported mean increase of 0.08 mmol/l (2% increase from baseline value) in the SU plus PIO group and a small but significant decrease of 0.16 mmol/l(5%decrease)in the SU plus MET group. Kipnes , M.S et al.,(2001) report which showed a mean increase of LDL by 6.6% in the SU plus pioglitazone group also are in same direction but different magnitude. The effects of the TZDs on LDL cholesterol are more complex. Small, dense LDL particles may confer increased atherogenecity by virtue of their intrinsic physiochemical and metabolic properties, including reduced LDL receptor affinity, greater propensity for transport into the subendothelial space, increased binding to arterial wall proteoglycans , and susceptibility to oxidative modifications (Chait, A et al., 1993).[27] Oxidative modification confers atherogenic properties on LDL cholesterol particles; and is a measurable risk factor (Steinberg, D et al., 1989).[28] Evidence suggests that PPAR-γ may be important regulator of foam-cell gene expression and that oxidized LDL cholesterol regulates macrophage gene expression through activation of PPAR-γ. Furthermore, PPAR-γ promotes uptake of oxidized LDL cholesterol by macrophages. Thus, an interaction between PPAR-γ and oxidized LDL cholesterol may be important in the development of atherosclerosis in diabetes (Tontonoz, P et al., 1998).[29] Metformin activate AMPK (AMP-activated protein kinase), which then inactivates other critical enzymes that regulate lipid and glucose metabolism. The net effect is: (1) increased fatty acid oxidation, (2) decreased fatty acid synthesis, with the resulting effects of (3) lowered blood glucose following a reduction of glucose synthesis in liver and increased metabolism in muscle (Wood, P.A, 2006).[30] Present study also shows increase in LDL cholesterol with SU plus PIO group by 2.10%, is just opposite to SU plus MET group (4.92 % decrease). Further studies are needed to assess if this increase in LDL cholesterol level has any effect on the long-term outcomes of these patients.

With SU plus PIO group, a statistically significant mean reduction of total cholesterol (TC) of 8.33mg/dl (5.14% decrease) and by 7.62 mg/dl (4.28% decrease) in the SU plus MET group (Table 5). These findings are in contrast to those observed by Kipnes, M.S et al., 2001 who reported mean increase of 1.4-2.3% in the SU plus pioglitazone group. Observations made by Rendella, M.S et al., (2003)[31] who reported mean reduction of 5% in the pioglitazone arm and 4.5% in the metformin arm are similar to present study. Similar observations were also made by Derosa, G et al.,(2004)[32] who reported mean reduction of 11% in TC levels with SU plus PIO group. Giugliano, D et al., (1993)[33] also reported that metformin decrease serum cholesterol level during 12 week study period. According to Wood, P.A, (2006) glitazones can

increase or decrease but metformin only decrease the TC levels in dyslipidemic diabetic patients. Interestingly present study also shows decreasing trends of total cholesterol level in SU plus PIO group though many studies have shown that TZDs substantially increase the levels of total cholesterol.

No patient withdrew from the study because of hypoglycemia. A mean weight gain of 2.7kg was observed in SU plus PIO group compared with a reduction of 0.9 kg in the SU plus MET group over 12 months. The weight gain with the use of TZDs could be due to improvement in glycemic control with decreased glycosuria and caloric retention. Several studies have shown that the weight gain with TZDs may be associated with an increase in subcutaneous adipose tissue and a concomitant decrease in visceral fat (Kelly, IE et al., 1999[34] and Miyazaki, Y et al., 2001). Except for aspartate aminotransferase (SGOT), which remained unchanged, liver function tests (LFT) were reduced over time in both the groups. Mean reductions in alanine aminotransferase (SGPT) and γ-glutamyl transpeptidase (GGT) were greater in SU plus PIO group (- 5 units/l vs -2.33 units/l and -12units/l vs -7 units/l, respectively) than SU plus MET group. The reduction in alkaline phosphatase was greater in the SU plus MET group (-14 units/l vs. -8 units/l) than SU plus PIO group. Gastrointestinal disorders occurred more frequently in SU plus MET group (22.5% vs. 12.5%) with diarrhea, in particular more frequently in the SU plus MET group (12.5% vs. 2.5%). There was no significant difference in the incidence of cardiac disorders between two groups. Mild –to-moderate edema was commonly reported adverse events in the SU plus PIO group (7.5% vs. 2.5%).

CONCLUSIONS

Thus the results of the present study have demonstrated that the addition of pioglitazone or metformin with sulfonylureas in type 2 diabetes have complementary effects on lipid profiles in addition to improved glycemic control throughout the one year study period.

Importantly, the significant improvements in lipid profile with pioglitazone or metformin were seen in the setting of add-on therapy to sulfonylureas, thus providing an additive benefit, and the effects were sustained over 1 year.

Compared with metformin plus SU, addition of pioglitazone to SU resulted in significantly greater improvements in triglycerides, HDL cholesterol and total cholesterol levels. Thus the results of this study have demonstrated that SU plus pioglitazone is an effective combination regimen for patients insufficiently treated with SU monotherapy and may provide possible positive effects on other coronary risk factors/ dyslipidemias associated with the type 2 diabetes.

In light of above:

- Both are useful combinations.
- Selection should be based on patient's anticipated benefit.
- Much wider and elaborate study is required to correlate the findings of present study.
- Further studies will help to determine whether the improvements in the metabolic control obtained by adding pioglitazone or metformin to the sulfonylurea therapy can be sustained.

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