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Original Research Article

Comparative study: Efficacy and tolerability of vildagliptin vs. pioglitazone as an add-on therapy to metformin in poorly controlled type 2 diabetes mellitus patients in Punjab

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Abstract

Introduction: The incidence of diabetes in urban Punjab is on the rise and the number of diabetics is increasing year by year.

Material and methods: This 24 week study was designed to compare vildagliptin versus pioglitazone as an add-on therapy in patients of type 2 diabetes mellitus inadequately controlled with metformin alone in Punjabi population. Sixty patients were randomized in two groups to receive either vildagliptin 100 mg (group 1) or pioglitazone 30 mg (group 2) in addition to metformin 1000 mg. The primary efficacy end point was change in FBG, PPG and HbA1c. Secondary end point included lipid profile, body weight and peripheral edema.

Results: There was no significant difference between mean reduction in FBG, PPG and HbA1c in both groups. There was significant decrease in mean body weight in group 1 in contrast to significant increase in group 2. Both the treatment groups reported a significant decrease in TG, TC, LDL and increase in HDL.

Conclusion: Vildagliptin displays robust efficacy with the added benefits of a much lower risk of peripheral edema, hypoglycemia and no weight gain, making it a promising alternative to pioglitazone as an add-on therapy to metformin in Punjabi population.

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Key words

Diabetes mellitus, Vildagliptin, Pioglitazone.

Introduction

Type 2 diabetes mellitus (T2DM) is a global epidemic with an estimated worldwide prevalence of 6% (246 million people) in 2007 and forecast to rise to 7.3% (380 million) by 2025 (IDF, 2006). The prevalence of diabetes is steadily increasing in the developing countries like India [1]. India had 40.9 million diabetics in 2006 and it is expected to increase to 69.9 million by 2025 [2]. The incidence of diabetes in urban Punjab is on the rise and the number of diabetics is increasing year by year [3].

In addition to diet and exercise, the majority of people with diabetes need drug therapy to achieve optimal blood glucose levels. Monotherapy with oral antidiabetic agents is the first line pharmacologic treatment option. However, patients with more severe diabetes are managed with dual therapy [4, 5]. Metformin is the most commonly prescribed first line antidiabetic drug worldwide, but due to the progressive worsening of blood glucose control during the natural history of type 2 diabetes, combination therapy usually becomes necessary [6].

Adding a sulfonylurea to metformin has been the conventional and the gold standard combination therapy for decades. However, this combination substantially increases the risk of hypoglycemia resulting in symptoms or increased food intake to avoid or treat them. Therefore, the need for alternative combination therapies was warranted.

Recently, newer agents which induce a glucose-dependent stimulation of insulin secretion (dipeptidyl peptidase-4 inhibitors) and which increase insulin sensitivity (thiazoloidinediones) become available and can provide an attractive alternative for use in combination with metformin [7].

Pioglitazone is an insulin sensitizer or a thiazolidinedione which acts by improving insulin sensitivity at the cellular level. It reduces insulin resistance by binding to PPAR γ which results in change of expression of genes involved in regulating glucose and lipid metabolism, insulin signal transduction and other tissue differentiation.

Vildagliptin is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor that prevents the rapid degradation of endogenous glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) and increases plasma levels of their intact, active form. By stabilizing endogenous incretin hormones at physiological concentrations, DPP-4 inhibitors increase the sensitivity to glucose of both insulin and glucagon secretion (i.e., increase insulin secretion and suppress glucagon secretion in a glucose-dependent manner), thereby lowering glucose levels. DPP-4 inhibitors are thus the first oral agents addressing the dual α- and β- islet cells dysfunction present in T2DM [8, 9, 10, 11].

The potential effects of various antidiabetic drug classes on weight balance are well recognized. Both insulin and insulin secretagogues (sulfonylureas and glinides) promote weight gain, especially in regimens designed to achieve intensive glycemic control. Thiazolidinediones (TZDs) are associated with weight gain, while metformin is generally associated with weight neutrality or weight loss. Incretin-based therapies, including glucagon-like peptide (GLP)-1 receptor agonists and dipeptidyl peptidase

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(DPP)-4 inhibitors, are associated with weight loss or weight neutrality [5].

Present study examined the efficacy and tolerability, with a special focus on the weight neutrality of the DPP-4 inhibitor vildagliptin as compared to TZDs pioglitazone (vildaglitin plus metformin versus pioglitazone plus metformin) in the diabetic patients inadequately controlled with metformin alone. As Punjabi population on high risk of weight gain during their diabetes medication, a rational drug combination (dual or triple therapy) is required to achieve better efficacy and tolerability.

Material and methods

Study design and settings

This was multi centered, open, randomized parallel study evaluating the comparative effect of vildagliptin and pioglitazone in combination with metformin (1000 mg BD) on glycaemic and lipid profile in diabetic patients over a period of 24 weeks in punjab. Written informed consent was obtained from all the patients prior to their enrollment. Flow of the participants through the study including randomization, medications and drop outs were as per **Chart - 1**.

Inclusion criteria

Previously diagnosed type 2 diabetes mellitus (DM) patients in the age group of 30-70 years of either sex, on metformin (1000 mg BD) for a minimum of ≥ 4 weeks and whose FBG >126 mg/dl, PPBG >200 mg/dl and HbA1C between 7-9%.

Exclusion criteria

Patients with history of Type 1 DM, those who had experience acute metabolic diabetic complications in past 6 months, with renal failure, liver failure, cardiac failure, who are likely to undergo surgery during the study period, with chronic intestinal disease, with history of hypersensitivity to the test drug, pregnant and lactating women were excluded from the study.

Intervention drugs

After meeting the inclusion criteria, patients were randomized into two groups of 30 each on the basis of additional anti hyperglycemic drugs to be given. To group 1, Tab. Vlidagliptin 50 mg BD orally was given for 24 weeks and to group 2, Tab. Pioglitazone 15 mg BD orally for 24 weeks was given and the patients were directly started at this dose. To check compliance and ensure regular medication by the patient, a log book was checked regularly which was given to each patient.

On the start of the study, (Day 0), after taking the history of the patients and doing the clinical examination, routine investigations were sent. The baseline FBG, PPBG, HbA1C and lipid profile were obtained after 12 hour overnight fasting. Initially patients were followed after 15 days and subsequently every month up to 24 weeks. FBG and PPBG were recorded at interval of 4 weeks while HbA1C and lipid profile were recorded at 12 weeks intervals.

Statistical analysis

The results were tabulated as mean ± standard deviation (SD) and analyzed using student's t test. The level of significance was determined as its 'p' value with $p > 0.05$ taken as not significant, $p < 0.05$ taken as significant at 5% significance level, $p < 0.01$ taken as significant at 1% significance level and $p < 0.001$ taken as highly significant.

Results

Demographics and baseline characteristics

Sixty patients (33 females and 27 males) who were randomized (by random number tables)

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and completed the study were included in the analysis. In both the groups, maximum number of patients was in the age group of 50-60 years and least number of patients was within 30-40 years of age. Mean age in group 1 was 56 ± 3 years and in group 2 was 57 ± 4 years. There was no statistically significant difference in age distribution between the two groups.

Baseline mean Body mass index (BMI) of patients in group 1 was 28.1±1.4 kg/m^2 and in group 2 was 28.6±1.2 kg/m^2 indicating that majority of the patients in both the groups were in the overweight range and there was no statistically significant difference in BMI between the two groups at the start of study as per **Table – 1**.

Efficacy

Time course of the mean FPG and PPBG during 24-week treatment with the vildagliptin and pioglitazone as add on therapy to metformin was as per **Chart - 2**. There was a statistically significant decrease of FPG and PPBG after 4, 8, 12, 16, 20 and 24 weeks (P < 0.001) compared with baseline in both groups, and we did not observe any significant differences between the 2 groups.

Time course of the mean HbA1c during 24-week treatment was as per **Chart - 3**. The adjusted mean reduction in HbA1c from baseline to endpoint was statistically significant after 12 and 24 weeks (P <0.001) in both groups, without any significant differences between the 2 groups.

Changes in fasting lipid parameters observed during 24-week treatment with vildagliptin and pioglitazone as add on therapy to metformin was as per **Chart – 4** and **Chart - 5**. There was a statistically significant decrease of serum TC, TG and LDL after 12 and 24 weeks (P < 0.001) compared with baseline in both groups, and no statistically significant difference between the 2 groups was observed.

Fasting HDL level during 24-week treatment was as per **Chart - 5**. A statistically significant increase of serum HDL was observed after 12 and 24 weeks (P < 0.001) compared with baseline in both groups but no statistically significant difference was noticed between the 2 groups.

Tolerability

During the 24-week study, all the treatments appeared to be well tolerated. Vildagliptin added to metformin was generally well tolerated, the frequency of any specific adverse effect was generally low and most adverse events were considered to be mild and unrelated to study medication. Adverse events like weight gain, headache and peripheral edema were reported in the patients on pioglitazone and metformin dual therapy.

Body weight did not change from a mean baseline to endpoint in patients receiving vildagliptin, but increased similarly in patients receiving pioglitazone. 13 patients (43%) out of 30 in pioglitazone group showed a mean weight gain of 1.2± 0.5 kg after 24 weeks of therapy whereas no weight gain was observed in patients receiving vildagliptin therapy.

Peripheral edema was reported in 3 patients (10%) out of 30 in pioglitazone group but there was no such case reported in vildagliptin group.

Hypoglycemia was limited to one mild event in patient receiving vildagliptin and pioglitazone as an add-on therapy to metformin. No severe hypoglycemic events were reported in both the groups.

No major changes or consistent trends over time were observed for any hematological,

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biochemical, urinalysis parameter or vital signs, and the frequency of treatment-emergent ECG abnormalities was low and comparable in all treatment groups.

Discussion

The present work represents the first report on the effects of a vildagliptin added to metformin versus pioglitazone added to metformin in Punjab population. The main findings of this study were that in patients with T2DM inadequately controlled by metformin monotherapy, addition of the DPP-4 inhibitor vildagliptin produced statistically significant and clinically meaningful reductions in HbA_{1c} level; the combination had a good overall tolerability profile and was associated with a very low incidence of hypoglycemia.

In our study there was significant reduction in FBG, PPG and HbA1c levels of T2DM patients on vildagliptin and pioglitazone as add on therapy to metformin. These findings were similarly reported in various studies.

In a 40 week study conducted by Ahren on 279 T2DM patients significant HbA1c ($p \leq 0.001$), FBG ($p \leq 0.0057$) and PPG ($p \leq 0.0001$) reduction was found with combination of vildagliptin and metformin [8]. Similarly 24 week study conducted by Bosi on 544 T2DM patients significant HbA1c ($p \leq 0.001$), FBG ($p \leq 0.003$) reduction was found with combination of vildagliptin and metformin [12].

24 week study conducted by Goodman and 52 week study conducted by Ferrannini on T2DM patients on combination therapy of vildagliptin and metformin , there was significant reduction in HbA1c ($p \leq 0.001$), in both study [13, 14].

Bolli (24 week study) on 576 T2DM patients reported simillar significant reduction in HbA1c ($p \leq 0.001$), with both vildagliptin and pioglitazone as add on to metformin [15].

In a 58 week study conducted by Derosa and 26 month study conducted by Saufert on T2DM patients with combination of pioglitazone and metformin FBG reduced by 21 mg/dl and 32 mg/dl, PPG reduced by 29 mg/dl and 63 mg/dl, HbA1c reduced by 1.4% and 0.9% respectively [16, 17].

Regarding fasting lipid parameters both vildagliptin and pioglitazone had a similar impact on each of the parameters, with an increase in HDL and decrease in TC, TG and LDL levels. However the extent to which lipid parameters affected favorably with pioglitazone was greater than that with vildagliptin.

Various studies reported significant reduction in TC, TG and LDL with pioglitazone [18, 19, 20] and increase in HDL [18]. Various studies has shown similar effect of viladagliptin on lipid profile [11, 14, 21].

DPP-4 inhibitors are body weight-neutral as shown in many studies. This body weight neutrality is different from the increase in body weight which is associated with treatment with thiazolidinediones, sulphonylureas and insulin [12, 15, 22, 23, 24, 25, 26, 27].

Various authors in their study reported increased in body weight with pioglitazone add on to metformin [15, 17, 28, 29] whereas there is no significant change in the body weight with vildagliptin add on therapy with metformin [8, 14, 26, 30, 31, 32].

The incidence of peripheral edema was found in 5.9% [33], 9.3% [34], of the patient with pioglitazone and metformin combination

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whereas there is no such case of peripheral edema was reported with vildagliptine as add on therapy to metformin [25, 30, 32].

In summary, the multi centered, open, randomized parallel study evaluating combination therapy with vildagliptin and metformin showed statistically significant and clinically meaningful reductions in HbA1c when vildagliptin was added to metformin, that were evident across all demographic and disease subgroups. In patients with T2DM inadequately controlled with metformin, the addition of vildagliptin (100 mg daily) was equally effective as that of pioglitazone (30 mg daily). Efficacy was well preserved over 24 weeks. Fasting and post prandial plasma glucose were significantly reduced; and the beneficial effects on glucose control was clearly accompanied by consistent improvements of parameters for β-cell function. The effects on fasting lipids were neutral and, in contrast to the pioglitazone/metformin combination there was weight gain. Overall the tolerability profile was good, with in particular no risk of hypoglycemia, peripheral edema and weight gain with vildagliptin and metformin combination therapy.

Conclusion

T2DM is often accompanied by other conditions (i.e. overweight/obesity with associated metabolic syndrome, high residual CV risk), which are considered as risk factors and thereby, could further affect both morbidity and mortality. DPP-4 inhibitors provide effective and consistent glycemic control. Compared to other oral hypoglycemic agents, DPP-4 inhibitors produce similar reductions in blood glucose glycated hemoglobin (HbA1c) levels, but they offer several attractive clinical advantages. A negligible risk of hypoglycemia, especially much lower than that observed with sulfonylureas, weight neutrality, contrasting favorably with the weight gain generally observed with sulfonylureas and thiazolidinediones (TZDs) are the key points, which make the DPP-4 inhibitors stand out. Therefore, it is no surprise that this pharmacological class is expected to play an increasing role in the management of T2DM.

Vildagliptin and pioglitazone when added to metformin treatment are effective in improving glycemic control for 24 weeks in patients with type 2 diabetes. In this study, the efficacy and tolerability of vildagliptin was comparable to pioglitazone on the main parameters HbA1c, FPG, PPG, lipid profile, and adverse events like peripheral edema and weight gain.

The combination of vildagliptin and metformin, two oral anti-diabetic agents with complementary mechanisms of action, provides superior efficacy and allows more patients to reach their glycemic targets compared to continuing metformin monotherapy, without increasing the risk of hypoglycemia, without exposing to weight gain and without altering common cardiovascular risk factors (hypertension and lipid profile).

Vildagliptin displays robust efficacy with the added benefits of a much lower risk of hypoglycemia and no weight gain, making it a promising alternative to pioglitazone as add-on therapy to metformin in Punjab population.

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Table - 1: Demographics and baseline characteristics of the study groups.

Demographic	Vildagliptin + metformin (Group 1)	Pioglitazone + metformin (Group 2)
No. of patients	30	30
Sex ratio (male/female)	14/16	13/17
Age (years), mean±SD	56.50±3.06	57.43±4.21
Body weight (kg), mean±SD	80.4±0.2	80.1±0.3
BMI (kg/m^2), mean±SD	28.1±1.4	28.6±1.2

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Chart – 1: Flow of study.

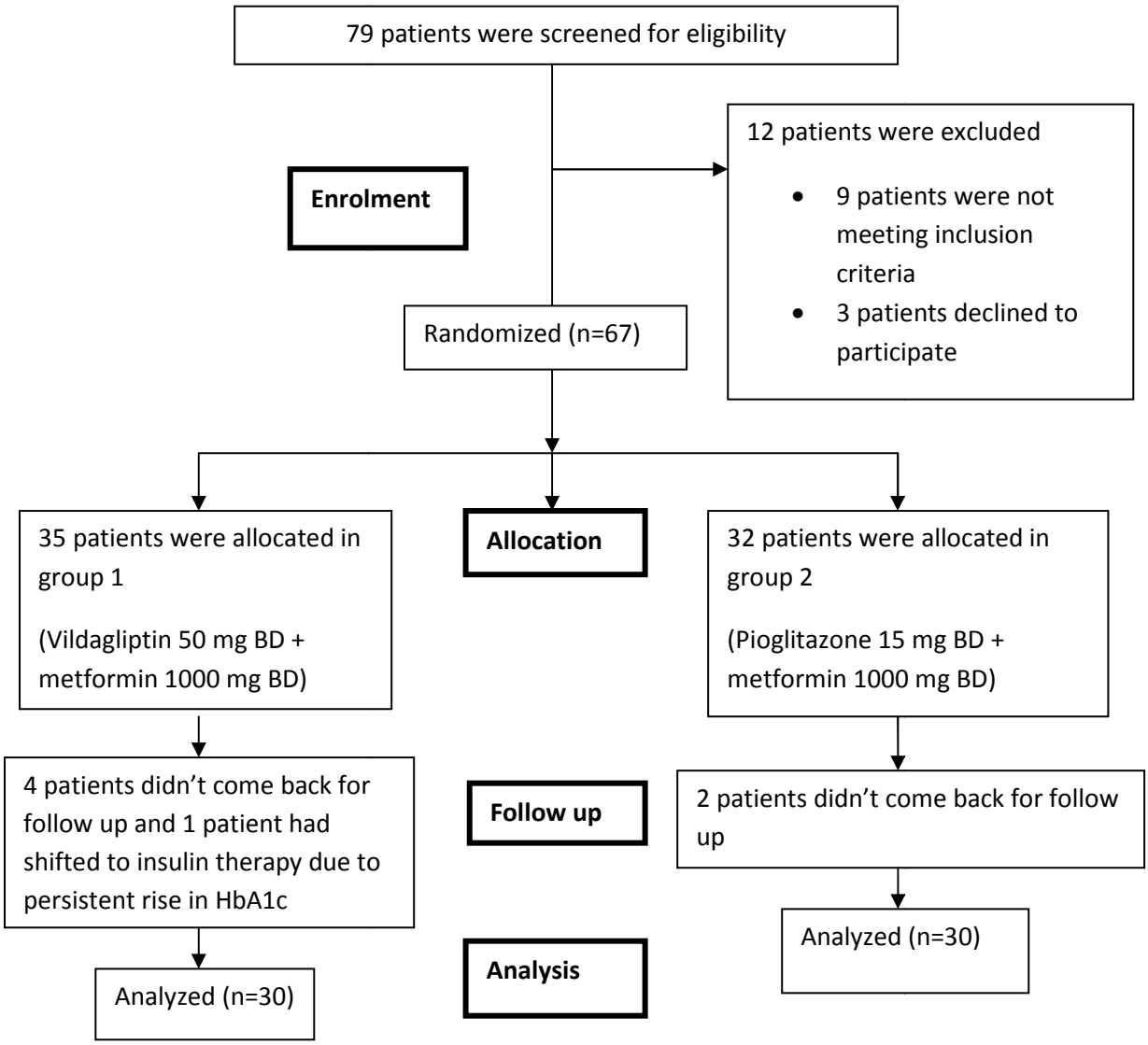

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Chart - 2: FBG and PPBG levels during treatment with vildagliptin + metformin (group 1) and pioglitazone + metformin (group 2) over a period of 24 weeks.

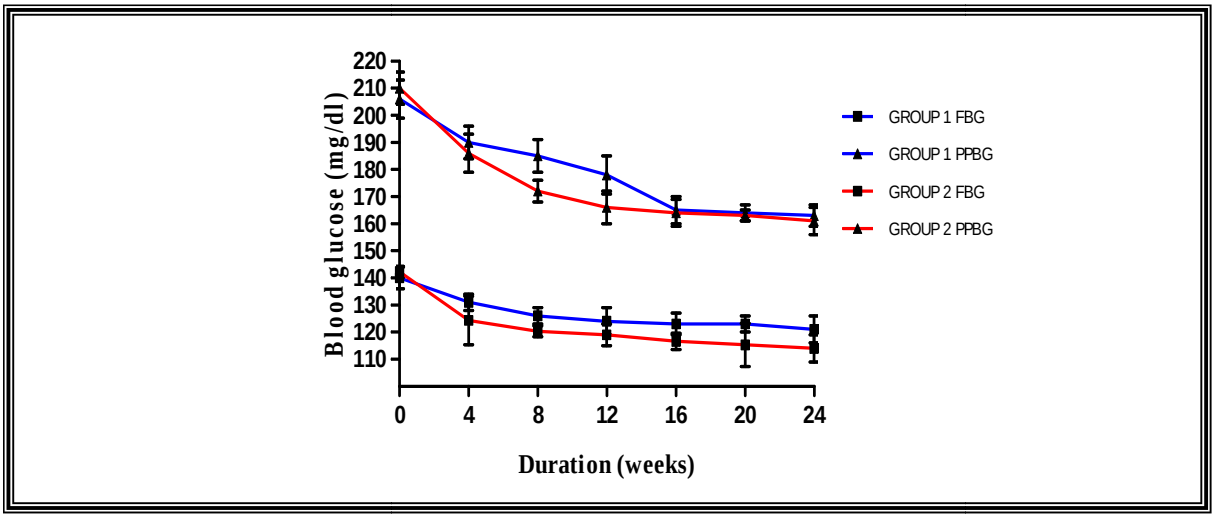

Chart - 3: Glycosylated hemoglobin levels (HbA1c) during treatment with vildagliptin + metformin (group 1) and pioglitazone + metformin (group 2) over a period of 24 weeks.

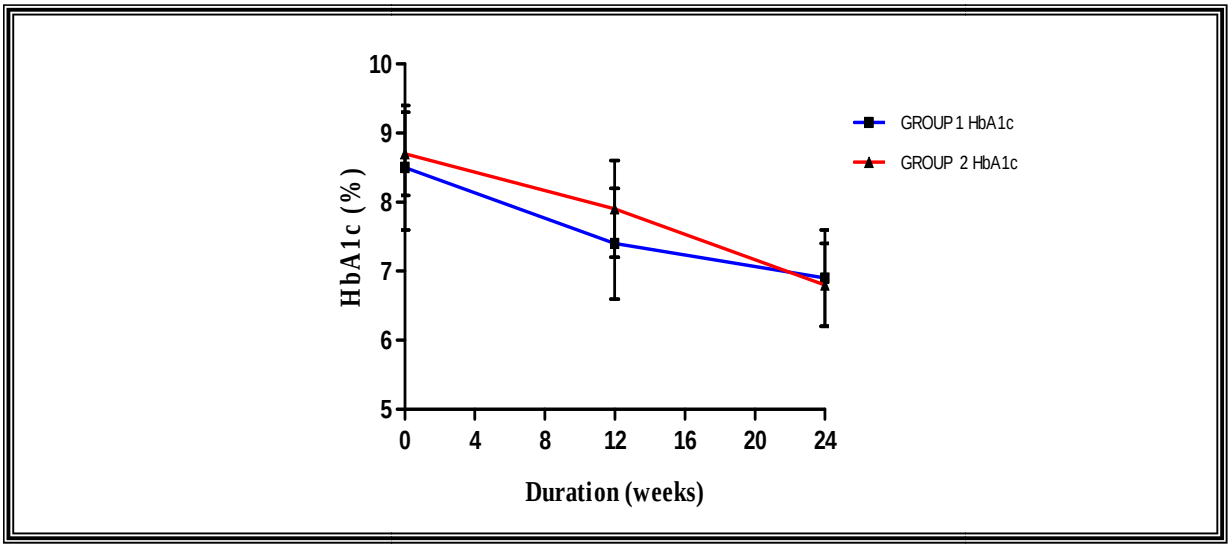

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Chart - 4: Serum total cholesterol (TC) and TG levels during treatment with vildagliptin + metformin (group 1) and pioglitazone + metformin (group 2) over a period of 24 weeks.

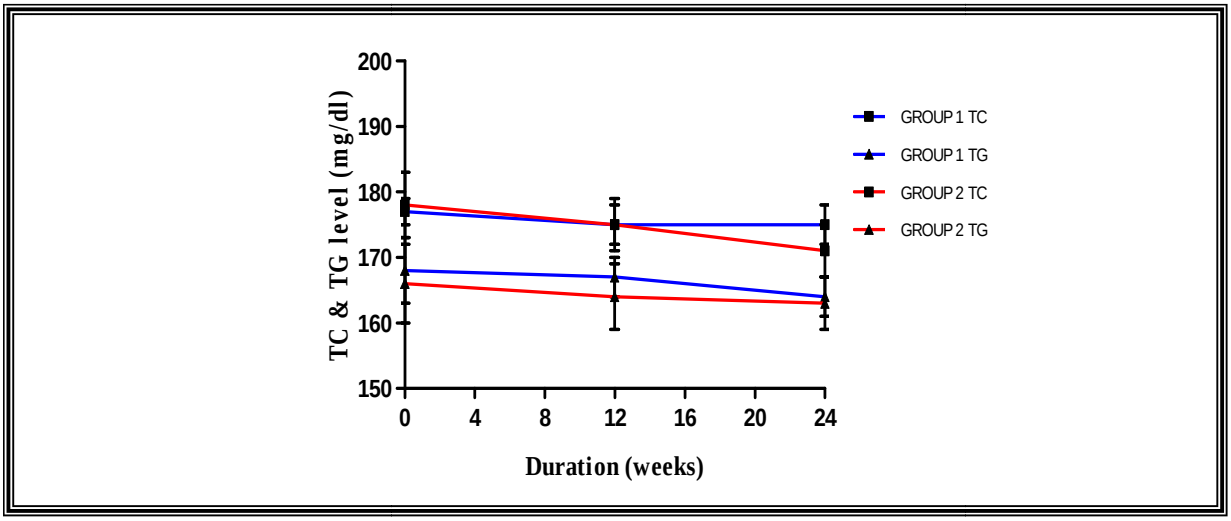

Chart - 5: Serum LDL and HDL levels during treatment with vildagliptin + metformin (group 1) and pioglitazone + metformin (group 2) over a period of 24 weeks.