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Original article

Effectiveness Treatment for Diabetes Prevention: 6-Months Results from the Prediabetes

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Abstract

ADA has the same cut-off value for IGT (140-200 mg/dL) but has a lower cut-off value for IFG (100-125 mg/dL) and has additional hemoglobin A1c (HbA1c) based criteria of a level of 5.7% to 6.4% for the definition of prediabetes. Due to progressive nature of prediabetes to diabetes, dual drug therapy produces additive effects, allows the use of submaximal doses, and less side effects of individual agents. Therefore, the present study was designed to study the effect of FDC of Metformin with Pioglitazone Versus FDC of Metformin with Voglibose on Lipid levels as an add-on drug in obese with prediabetes patients whose dyslipidemia status was uncontrolled with metformin alone. ***Material and Methods:*** The present study was open, randomized parallel group comparison of two active treatment groups over a period of six months. Sixty-seven patients of either sex in the age group of 30-60 years, suffering from obese with prediabetes, with FBG: 100-125 mg/dl and PPBG: 140-200 mg/dl as per ADA were selected at randomly. The effect of FDC of Metformin with Pioglitazone and FDC of Metformin with Voglibose were observed on various parameters of FBG, PPBG, Serum Adiponectin and Serum ghrelin levels. ***Results:*** At the end of 3rd and 6th months it was observed that though both FDC of Metformin with Pioglitazone and FDC of Metformin with Voglibose reduced Blood Glucose significantly but FDC of Metformin with Pioglitazone caused a statistically significantly greater amount change in FBG, Serum Adiponectin and Serum ghrelin levels as compared with FDC of Metformin with Voglibose. ***Conclusions:*** Though FDC of Metformin with Pioglitazone and Metformin with Voglibose were equally effective in lowering FBG, Serum Adiponectin and Serum ghrelin levels yet Metformin with Pioglitazone showed better results in improving Glycemia, as compared with FDC of Metformin with Voglibose.

Keywords: ***Prediabetes, Metformin, Pioglitazone, Voglibose, Adiponectin and ghrelin***

Introduction

The World Health Organization (WHO) has defined prediabetes as a state of intermediate hyperglycemia using two specific parameters, impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110 to 125 mg/dL) and impaired glucose tolerance (IGT) defined as 2-hours plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dL) after ingestion of 75 g of oral glucose load or a combination of the two based on a 2 hrs oral glucose tolerance test (OGTT).[1] On the other hand, the American Diabetes Association (ADA), has the same cut-off value for IGT (140-200 mg/dL) but has a lower cut-off value for IFG (100-125 mg/dL) and has additional hemoglobin A1c (HbA1c) based criteria of a level of 5.7% to 6.4% for the definition of prediabetes.[2]

The overall prevalence of prediabetes in all 15 states of India was 10.3%.[3] The world-wide prevalence of IGT in 2010 was estimated to be 343 million (7.8%) ranging from 5.8% in South East Asia to 11.4% in North American and Caribbean Countries of the nation's population. International Diabetes Federation projects an increase in prevalence of prediabetes to 471 million globally by 2035.[4] Several studies have shown an association of increased risk of chronic kidney disease and early nephropathy with prediabetes.[5] While prediabetes has been associated with an increased risk of diabetic retinopathy, macrovascular disease but whether this elevated risk is due to prediabetes itself or due to development of diabetes remains unclear.[6]

Metformin, a biguanide class of Antidiabetic agents, is the first line drug for the treatment of type 2 diabetes mellitus.[7] Metformin is used clinically for the treatment of obesity and diabetes, and its mechanism of actions include the following: (1) lowers plasma glucose levels by inhibiting gluconeogenesis in liver, (2) decreasing the intestinal absorption of glucose, and (3) improving insulin sensitivity by increasing peripheral glucose uptake and utilization.[8] Additionally, metformin has a variety of pleiotropic effects including improved lipid and cholesterol metabolism, decreased inflammation and inhibition of cell growth.[9] (4) Increases plasma levels of glucagon-like peptide 1 (GLP-1) is a member of the incretin family of peptide hormones release incretin from the gut in response to ingested glucose. It induces insulin release from pancreatic β-cells, retards gastric emptying, inhibits glucagon release from α cell and produces a feeling of satiety.[10]

Pioglitazone, an insulin-sensitizing Thiazolidinedione (TZDs), is widely used for the treatment of type 2 diabetes. TZDs are known to activate peroxisome proliferator-activated Receptor-γ (PPAR- γ) which are ligand activated transcription factors which belong to the nuclear receptor superfamily.[11] PPAR- γ activation by pioglitazone lead to increases insulin sensitivity in liver, fat and skeletal muscle cells, increases peripheral and splanchnic glucose uptake and decreases hepatic glucose output.[12] Pioglitazone is dependent on the presence of insulin in order to exert its beneficial effects and may help preserve β-cells of the islets of Langerhans, but does not act as an insulin secretagogue.[13]

Voglibose is an alpha-glucosidase inhibitor used for lowering post-prandial blood glucose levels in people with type-2 DM. It reduces intestinal absorption of starch, dextrin, and disaccharides by inhibiting the action of α-glucosidase in the intestinal brush border.[14] Inhibition of this enzyme catalyzes the decomposition of disaccharides into monosaccharides and slows the digestion and absorption of carbohydrates. α - Glucosidase inhibitors do not stimulate insulin release and therefore do not result in hypoglycemia. Voglibose is most effective α - glucosidase inhibitor among its class.[15]

Adiponectin is an adipose-derived hormone with a variety of beneficial biological functions on glucose and lipid metabolism.[16] Adiponectin levels are inversely correlated with visceral obesity; therefore, high levels of adiponectin are negative correlated with obesity whereas low adiponectin levels exhibit a positive correlation. Serum levels of adiponectin are associated with metabolic syndrome and therefore metabolic syndrome development may be associated with obesity, adipose tissue content and hormonal levels.[17] Low level of adiponectin has been found in patients with type 2 diabetes, prediabetes, dyslipidemic and obese.[18]

Ghrelin is synthesized as a pre-prohormone, in the epithelial cells lining the fundus of the stomach, with smaller amounts produced in the placenta, kidney, pituitary and hypothalamus.[19] Ghrelin is an appetite-stimulating hormone that increases growth hormone secretion and food intake in humans.[20] Furthermore, ghrelin regulates several physiological processes, including glucose metabolism, insulin secretion, gastric emptying, cell proliferation, learning and memory, stress and anxiety.[21] Ghrelin contributes to long- term energy homeostasis by increasing body weight and adiposity, presumably through a reduction of lipid oxidation.[22] Blood concentrations of ghrelin are lowest shortly after consumption of a food, and then gradually rise during the fast and reach the peak just prior to the next meal.[23] Ghrelin concentrations in blood are reduced in prediabetes humans as compared to Type 2 DM.[24]

Material and Methods

Study design and settings

The present study was Prospective, Randomized, Open-label, Single Centre and Parallel-group, evaluating comparative effect of Fixed Dose Combination (FDC) of Metformin with Pioglitazone versus FDC of Metformin with Voglibose in Prediabetes patients over a period of six months in outpatient department of Medicine in MGM Hospitals and College, Aurangabad. The study was conducted after Approval of institutional ethical committee, informed consent was taken, regulations as per Declaration of Helsinki, ICH good Clinical Practice (GCP) guidelines and the ICMR guidelines for Biomedical Research on Human Subjects, 2006 were followed.

Inclusion criteria

Patients with Prediabetes diagnose according to ADA criteria (FBG: 100-125 mg/dl and 2hrs PPBG 140-200 mg/dl) in the age group of 30-65 years of either sex, all patients provided written, vernacular, witnessed, informed consent to participate in the study, Patients willing to take medications as directed & willing to come for the follow-ups.

Exclusion criteria

Patients with history of Type I and Type II DM, with acute medical emergencies like diabetic ketoacidosis, polycystic ovarian disease, liver disease, kidneys disease, cardiovascular disease, any microvascular complication, with chronic GIT disease, concomitant with steroid therapy and history of hypersensitivity to test drug, pregnant and lactating women also excluded from the study.

Intervention drugs

After meeting the inclusion criteria, patients were randomized by a Chit method into two groups, each consist of 67 patients. In group A: Tab. Metformin 500 mg + Tab. Pioglitazone 7.5 mg combination BD orally was given for 6 months and group B: Tab. Metformin 500 mg + Tab. Voglibose 0.2 mg combination BD orally for 6 months 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 medical history, demographic details, physical measures (waist circumference, body mass index (BMI)), general and systemic examination of the patients, routine laboratory investigations were sent. The baseline fasting Blood glucose (FBG), post-prandial blood glucose (PPBG), Serum Adiponectin, Serum Ghrelin, urea and creatinine were measured.

Patients were given a 15 days' supply of either drug with proper directions and asked to report back after 15 days. Initially patients were followed after 15 days and subsequently every month up to 6 months. FBG and PPBG were recorded monthly while Serum Adiponectin, Serum Ghrelin, Blood Urea and Serum Creatinine recorded at 3 and 6 months' intervals.

Statistical Analysis

The collected data was compiled in MS Excel sheet for analysis in Statistical Package for the Social Sciences (SPSS) 24th version was applied. The qualitative data was represented in the form of frequencies and percentage also represented in visual impression like bar diagram, pie diagram etc. Quantitative data was represented in the form of mean and standard deviation. To check significance difference between baseline and after three months and after six months effect of Group A Versus Group B in Prediabetes patient. A paired 't' test was applied and also quantitative data was represented in the form of pie diagram and bar diagram. The level of significance was determined as its 'p' value with $p < 0.05$ was taken as significant at 5% significance level, $p < 0.01$ was taken as significant at 1% significance level and $p < 0.001$ was taken as highly significant, $p > 0.05$ was taken as insignificant. Drop outs were not considered in the analysis.

Results

Total 150 patients with Prediabetes were screened out of 144 eligible patients were randomized equally into two treatment groups who were randomized in the study. In group A: 5 patients

and in group B: 5 patients were lost from trial. Both the groups were similar in demographic profile at baseline as shown in Figure 1.

In both the groups, maximum number of patients was in the age group of 51-60 years and least number of patients was within ≤40 years of age. Mean age in group A was 52.29 ± 6.55 and in group B was 51.10 ± 6.62. There was no statistically significant difference in age distribution between the two groups.

Table 1: Comparison of Mean Age in Groups:

Age-Group	Group A [Met + Pio]		Group B [Met + Vog]	
	No	Percentage	No	Percentage
≤40 year	04	5.9%	02	2.9%
41—50	26	38.8%	26	38.8%
51—60	37	55.2%	39	58.2%
Total	67	100	67	100
Mean±SD	52.29 ± 6.55 years		51.10±6.62 years	
z-value	1.04			

Table 2: Gender difference between Group A and Group B

	Group A		Group B		Chi-Square test p=value
	n=67	(%)	n=67	(%)	
Male	43	64.17	46	68.65	0.112
Female	24	35.83	21	31.35	
Total	67	100	67	100	

The table 2 reflects that 134 prediabetic patients selected, in Group A: 43 were male (64.17%) while 24 were female patients (35.83%). In Group B consisted of 46 male patients (68.65%) and 21 female patients (31.35%). There was no statistically significant difference in number of patient from Group A and Group B patients (0.112).

Table 3: Comparison of Mean Fasting Blood Glucose level between Group A and Group B at baseline, after 3 months and after 6months (Z- test):

		Group A Mean±SD	Group B Mean±SD	z-value	p-value
FBS (mg /dl)	Baseline	104.15± 4.38	103.14±3. 38	0.07	P= 0.150 ns
	After 3 Months	89.92± 6.70	92.41±5.4 2	2.72	P= 0.016 *
	After 6 Months	78.47± 7.20	80.85±7.5 1	3.01	P= 0.029 *

*Mean ± SD in mg/dl, SD: Standard deviation, NS: Not significant, * p<0.05 significant, ** p<0.001 highly significant*

In Table 3, in Group 'A' the mean of FBG level was 104.15±4.38 mg/dl at baseline followed by 89.92±6.70 mg/dl after 3rd month, and 78.47±7.20 mg/dl after 6th month. In Group 'B' the mean of FBG level was 103.14±3.38 mg/dl at baseline, followed by 92.41±5.42 mg/dl after 3rd month, and 80.85±7.51 mg/dl after 6th month.

FBG levels within both the groups showed significant reduction over a period of 6 months. But on comparison between group A versus group B patients, there was a statistically highly significant difference in mean percentage change in PPBG levels at the end of 3rdand 6th month of study period (P=0.029 and p< 0.05 respectively).

The major changes in mean difference of baseline to after 6 months has occurred in group A as compared with group B.

Table 4: Comparison of Mean Post Prandial Blood Glucose level between Group A and Group B at baseline, after 3 months and after 6months (Z- test):

		Group A Mean±SD	Group B Mean±SD	Z-value	p-value
PPBG (mg/dl)	Baseline	174.44± 16.62	174.85± 15.22	0.14	P= 0.892 ns
	After 3 Months	161.11± 15.68	153.76± 15.75	2.70	P= 0.017 *
	After 6 Months	146.59± 16.83	124.08± 9.96	9.42	P<0.0001 **

Mean ± SD in mg/dl, SD: Standard deviation, NS: Not significant, * p<0.05 significant, ** p<0.001 highly significant

In Table 4, in Group 'A' the mean of PPBG level was 174.44±16.62 mg/dl at baseline followed by 161.11±15.68 mg/dl after 3rd month, and 146.59±16.83 mg/dl after 6th month. In Group 'B' the mean of PPBG level was 174.85±15.22 mg/dl at baseline, followed by 153.76±15.75 mg/dl after 3rd month, and 124.08±9.96 mg/dl after 6th month.

PPBG levels within both the groups showed significant reduction over a period of 6 months. But on comparison between group A versus group B patients, there was a statistically highly significant difference in mean percentage change in PPBG levels at the end of 3rdand 6th month of study period (P=0.017 and p< 0.0001 respectively).

The major changes in mean difference of baseline to after 6 months has occurred in group B as compared with group A.

Table 5: Comparison of Serum Adiponectin level between Group A and Group B at baseline and after 6months (Unpaired- test):

		Group A Mean±SD	Group B Mean±SD	p-value
Adiponectin (µg/ml)	Baseline	8.76 ± 4.69	8.31 ± 5.41	P= 0.892 ns
	After 6 Months	12.59± 7.83	11.08±8.96	P<0.0001 **

In Table 5, in Group 'A' the mean of Serum Adiponectin level was 8.76 ± 4.69 µg/ml at baseline followed by 12.59±7.83 mg/dl after 6th month. In Group 'B' the mean of Serum Adiponectin level was 8.31±5.41 mg/dl at baseline, followed by 11.08±8.96 mg/dl after 6th month.

Serum Adiponectin levels within both the groups showed significant increased over a period of 6 months. But on comparison between group A versus group B patients, there was a statistically highly significant difference in mean percentage change in Serum Adiponectin levels at the end of 6th month of study period (p< 0.0001).

The major changes in mean difference of baseline to after 6 months has occurred in group B as compared with group A.

Table 6: Comparison of Serum Ghrelin level between Group A and Group B at baseline and after 6months (Unpaired- test):

		Group A Mean±SD	Group B Mean±SD	p-value
Ghrelin (pg/ml)	Baseline	44.89 ± 5.32	45.01 ± 6.33	P=0.681 ns
	After 6 Months	61.59± 8.93	56.08± 9.12	P<0.0001 **

In **Table 6,** in **Group 'A'** the mean of Serum Ghrelin level was 44.89 ± 5.32 pg/ml at baseline followed by 12.59±7.83 mg/dl after 6th month. In **Group 'B'** the mean of Serum Ghrelin level was 8.31±5.41 mg/dl at baseline, followed by 11.08±8.96 mg/dl after 6th month.

Serum Ghrelin levels within both the groups showed significant increased over a period of 6 months. But on comparison between group A versus group B patients, there was a statistically highly significant difference in mean percentage change in Ghrelin levels at the end of 6th month of study period ($p< 0.0001$).

The major changes in mean difference of baseline to after 6 months has occurred in group B as compared with group A.

Discussion

The controlling of Prediabetes consists of diet control, exercise and pharmacological therapy. In the present study 67 Prediabetes patients were given FDC of Metformin with Pioglitazone and FDC of Metformin with Voglibose in group A and group B respectively. The result of add on therapy with Pioglitazone or Voglibose as a secoond agent was detected on various parameters.

In our study, significant decrease in FBG and PPBG in both FDC of Metformin with Pioglitazone and FDC of Metformin with Voglibose. The reduction in various parameters was perceived in consecutive sequence commiserating with duration of study i.e. at baseline, 3rd and 6th months. But on contrast, arrangement of FDC of Pioglitazone with Metformin resulted in greater decline in FBG than FDC of Metformin with Voglibose. Whereas, PPBG was significantly reduced in FDC of FDC of Metformin with Voglibose than FDC of Metformin with Pioglitazone with metformin. Similarly, study conducted by Amita Jindal et al. supports with our study.[25]

Moreover, FDC of Metformin with Pioglitazone and FDC of Metformin with Voglibose have an impact on serum Adiponectin and Serum Ghrelin Level and these were increased significantly from baseline to after 6 months. Several previous cross-sectional and longitudinal studies have established that low Adiponectin and Ghrelin levels are associated with increased risk of T2DM.[26] In the prospective Diabetes Prevention Programme (DPP), which enrolled participants with prediabetes, an approximately 3 μg/mL higher baseline adiponectin level predicted a 20–40% lower risk of progression to T2DM during approximately 3 years of follow-up.[27] Cross-sectional and longitudinal studies have previously reported a consistent association between low Adiponectin and Ghrelin levels prevalent prediabetes and T2DM.[28]

In the present study, interventions that have been increases Adiponectin and Ghrelin levels with treatment of Metformin, Pioglitazone and Voglibose. We found that lower baseline Adiponectin and Ghrelin levels predicted a risk of progression from prediabetes to Type 2 DM. The latter finding indicates that the association of Adiponectin and Ghrelin with diabetes risk is evident at a much earlier stage in the pathogenesis of dysglycemia. Thus, the ability to maintain high Adiponectin and Ghrelin production might be protective of dysglycemia in persons at high risk for T2DM, whereas hypoadiponectinemia could be a risk factor for the initiation of early glucose abnormalities leading to diabetes from prediabetes.

Moreover, the present report has several strengths, by extending the previous observations in important directions. First, we demonstrate in a prospective study that the previously reported association of lower Adiponectin and Ghrelin levels with increased risk of T2DM manifests at a more proximal stage, and is evident during transition from prediabetes to Type 2 DM. Second, our findings suggest that the putative mechanisms whereby adiponectinemia interacts with glucose homeostasis to confer protection against dysglycemia are operative even in persons who are among the highest risk groups for diabetes, namely, offspring of parents with T2DM. Third, our findings were obtained from our study was consistent in men and women, indicating that the known gender and ethnic differences in Adiponectin and Ghrelin expression do not abrogate the interaction between adiponectinemia and glucose homeostasis. Finally, we have used Various methods (including FBG and PPBG) to acquire data on the associations between adiponectinemia and insulin action, insulin secretion and dyslipidemia in prediabtes patients.

Our data indicate that the association of Adiponectin and Ghrelin with insulin sensitivity is particularly healthy among Indian, which suggests that interventions that increase Adiponectin and Ghrelin secretion may have enhanced insulin-sensitizing potency in Indian. Also, our analyses focused on baseline Adiponectin and Ghrelin levels and after 6 months; thus, our assessment include the potential effects of changes in adiponectin and Ghrelin secretion that occurred during the course of the FDC of Metfromin and Pioglitazone and FDC of Metformin and Voglibose.

The present report has some limitations related to the population studied: our findings were obtained from prediabetes patients. As these participants represent a selected group at high risk for developing diabetes, the strong association between baseline Adiponectin and Ghrelin levels followed by 6 months and incident prediabetes may be applicable to individuals without a family history of diabetes, or the general population.

Conclusion

Thus, among prediabetes patients enrolled in our study, baseline Adiponectin levels and Ghrelin were inversely related to the risk of incident prediabetes to Type 2DM. This predictive relationship was evident, despite gender and ethnic differences between baseline Adiponectin and Ghrelin levels and after 6 months. Based on our finding, it can be predicted that interventions with FDC of Metformin and Pioglitazone and FDC of Metformin and Voglibose that boost Adiponectin and Ghrelin levels may offer protection against the risk of dysglycemia, regardless of gender or ethnicity. Though, FDC of Metformin and Pioglitazone showed better results in controlling glycemic profile (FBG) and increases Serum Adiponectin and Serum Ghrelin levels as compared with FDC of Metformin with Voglibose.

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