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# Comparative study to evaluate safety and efficacy of Metformin versus sitagliptin alone and combination in type 2 diabetes mellitus

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**Abstract**--Type 2 Diabetes mellitus (Type 2DM) is chronic, lifelong progressive metabolic disease characterized by hyperglycaemia due to absolute or relative insulinopaenia. The metabolic dysregulation that contributes to hyperglycaemia includes diminished insulin secretion, impaired glucose utilization or increased glucose production, and eventually causes pathophysiological changes in multiple organs and organ systems. Our study showed Sitagliptin was superior in reducing HOMA-IR when compared with metformin. If combination of Sitagliptin and metformin is used far superior reduction will be achieved on HOMA- IR. Limitation of our study was short duration of study and small sample size.

**Keywords**---Sitagliptin, Metformin, Hyperglycaemia.

**Introduction**

Type 2 Diabetes mellitus (Type 2DM) is chronic, lifelong progressive metabolic disease characterized by hyperglycaemia due to absolute or relative insulinopaenia. The metabolic dysregulation that contributes to hyperglycaemia includes diminished insulin secretion, impaired glucose utilization or increased glucose production, and eventually causes pathophysiological changes in multiple

organs and organ systems.[1] The prevalence of DM has shown a dramatic rise over the past 200 years. It is estimated that in 2017, there were 451 million people (ages 18-99 years) with diabetes worldwide, and this number is expected to rise, mostly due to type 2 DM. Prevalence of Diabetes in India according to International Diabetes Federation (IDF) in 2017, more than 61.3 million Indians are currently suffering from diabetes i.e. more than 8 %. [2]

Monotherapy with Metformin, a biguanide agent acts primarily as an insulin sensitizer. Its primary clinical site of action is in the liver, improving hepatic insulin sensitivity and as a result, decreasing hepatic gluconeogenesis. Metformin may also increase both hepatic and splanchnic glucose utilization[3]. Metformin also has significant effects on peripheral insulin sensitivity, primarily at muscle and modestly at adipocyte by phosphorylation and activation of AMP-activated protein kinase[4].

Sitagliptin is an oral, highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of patients with Type 2 Diabetes Mellitus. Sitagliptin inhibits the enzymatic degradation and inactivation of glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) by DPP-4 the major incretins involved in glucose homeostasis, thereby increasing insulin release and lowering glucagon secretion in a glucose-dependent manner.[5] Treatment with sitagliptin 100 mg once daily leads to improvements in glycaemic control in patients with Type 2 Diabetes Mellitus, including reductions in fasting and postprandial glucose concentrations. Sitagliptin has not been associated with an increased risk of hypoglycaemia when administered as either monotherapy or in combination with agents not known to cause hypoglycaemia.[6] The combined use of sitagliptin and metformin is an effective method of lowering glucose levels in Type 2 Diabetes Mellitus and this combination had been approved by US Food and Drug Administration.[7]

As with all antihyperglycaemic agent, monotherapy with metformin is often unsuccessful in achieving or maintaining adequate glycaemic control. Furthermore, patients who initially get to goal with monotherapy frequently require additional agents over time in order to maintain glycaemic control due to the progressive decline in pancreatic beta cell mass. Initial combination therapy offers an alternative approach to single-agent therapy for the treatment of Type 2 Diabetes Mellitus, especially in patients with moderate-to high HbA1c levels for which the use of initial combination therapy is considered a potential treatment option supported by practice guidelines.[8]

So, the purpose of this study was to assess the safety/tolerability and efficacy of initial therapy with the Fixed Dosed Combination of Metformin/Sitagliptin compared with Metformin and Sitagliptin monotherapy in drug-naive patients with Type 2 Diabetes Mellitus not controlled on a diet/exercise regimen.[9]

## **Material and Methods**

Study Design: Open label, Randomized, Parallel group, Comparative and Prospective clinical study.

- 1) 90 Diagnosed naive cases of patients of Type II DM.

- 2) They were randomly allocated into 3 groups of 30 each by chit method.
- 3) Group I received Metformin 500 mg BD for 3 months,
- 4) Group II received Sitagliptin 50 mg BD for 3 months
- 5) Group III Metformin 500 mg BD and Sitagliptin 50mg BD for 3 months

**Study center**

Study will be conducted in Type 2DM patients attending the outpatient department of Medicine in tertiary care center.

**Inclusion criteria**

Patients of either sex having age group between 30 -60 years, Patients willing to participate and willing to give written informed consent prior to any study-related procedures and to comply with the requirements of the study protocol. Patients having newly diagnosed Type II DM with prandial blood glucose levels >180 mg% and <250 mg%. HbA1c in the range of 6.5 to 8.5 % at screening and BMI >27 kg/m<sup>2</sup>

**Exclusion criteria**

Presence of Type I DM, Known allergy to study drugs, Deranged liver function test or kidney function test, History of myocardial infarction or anemia. Pregnant and lactating women. Presence of gastrointestinal diseases like inflammatory bowel disease, large hernias, intestinal obstruction, active ulcers, chronic pancreatitis. Taking any other concomitant medication effecting glucose homeostasis like corticosteroids.

**Ethics, consent and permissions:**

- The study will be conducted after approval from Institutional Ethics Committee for Medical Research.
- Study will be conducted as per Declaration of Helsinki, ICH good Clinical Practice (GCP) guidelines and the ICMR guidelines for Biomedical Research on Human Subjects, 2006.

**Methodology****Subjects:**

- All the Type 2DM patients attending outpatient department (OPD) of Medicine.
- Permission from treating consultant was be obtained for subjects to participate in the study.
- Subjects were screened for selection criteria. Baseline evaluation included recording of demographic details, BMI, medical history, general and systemic examination and laboratory investigations, which included complete haemogram, hepatic and renal function tests and routine urine analysis. The eligible patients will be enrolled as randomization.

**Investigations:****Blood sugar**

Fasting and Postprandial Blood Sugar were done on semi auto analyzer by glucose oxidase /peroxidase [GOD / POD] method.

**Adverse Event (AE):** Patients withdrawn due to an AE were supposed to be followed until the AE has abated, or until a stable situation had been reached. All tests/examinations/ scheduled at study completion were supposed to be performed at premature termination/dropout. Drop outs were supposed to be replaced. All premature discontinuations, reasons and their causes were documented.

### Statistical analysis

Paired, unpaired t-tests and ANOVA were used to measure the differences among the group.

### Results

#### Base line Characteristics

A total of 120 subjects were enrolled in this study. Patients were randomly divided into two groups of 60 each

Table No. 1: Age and sex wise distribution of the subjects under study

Age in years	Group I (MET)		Group II (PIO)	
Gender	M	F	M	F
18-40	24	36	18	42
Total	60		60	
p-value	P=0.0466			

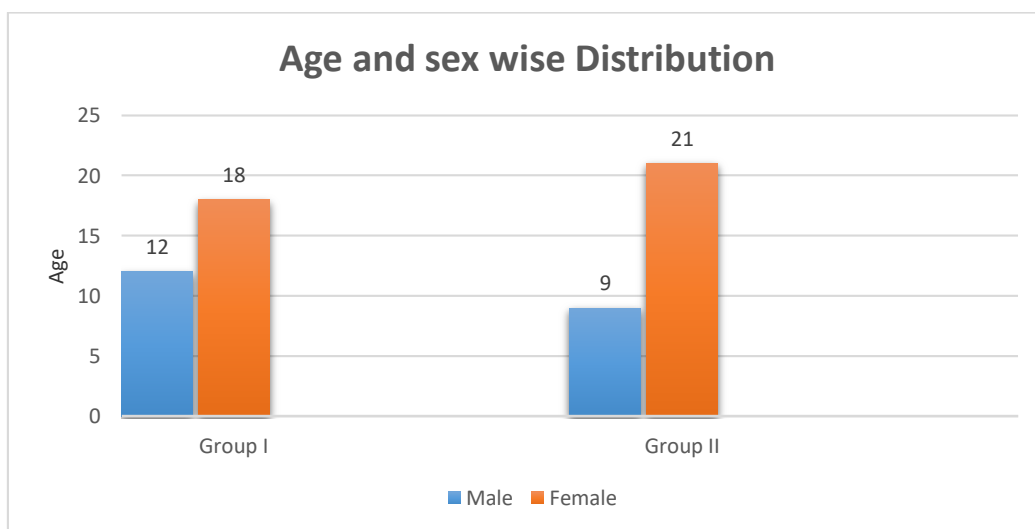


Figure 1: Age and sex wise distribution of the subjects under study

Table no. 1 shows the age and sex wise distribution of the subjects in 2 groups under study. Two groups consisted of 60 subjects each. Group I consisted of 40% male and 60% female patients. Male patients in Group II were 30% and female were 70%.

Table 2: Comparison of Fasting Blood Glucose in both groups at baseline and after 3<sup>rd</sup> and 6<sup>th</sup> months using unpaired t-test

FBG	Group I Mean±SD	Group II Mean±SD	p-value
Baseline	119.38± 9.20	120.05±5.10	P=0.322 NS
After 3 Months	95.50±3.93	89.60±3.40	P<0.0001 HS
After 6 Months	88.20±2.70	74.58±4.73	P<0.0001 HS

If  $p > 0.05$  Not Significant,  $p < 0.05$  Significant, NS= Not significant, HS= Highly Significant

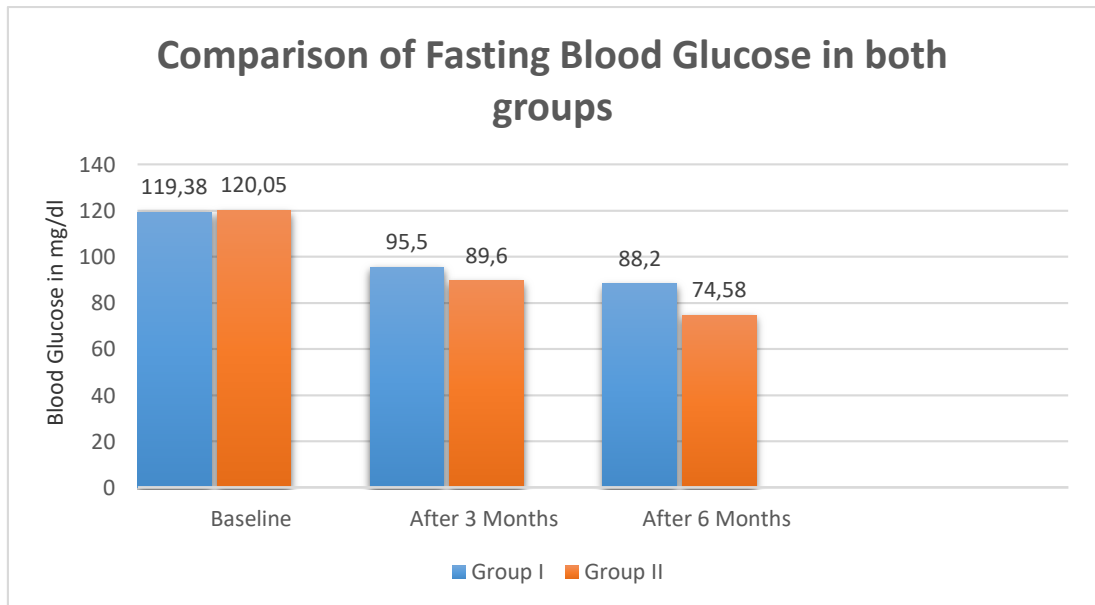


Figure 2: Comparison of Fasting Blood Glucose in both groups at baseline and after 3<sup>rd</sup> and 6<sup>th</sup> months

There was a statistically HIGHLY significant decrease in Fasting Blood Glucose levels in Group I and II, after 3<sup>rd</sup> and 6<sup>th</sup> months of treatment as compared to baseline.

Table 3: Comparison of Mean Differences of Fasting Blood Glucose at baseline Vs After 6 months in Groups analyzed by paired "t" test

FBG	Mean Difference	P-value
Baseline Vs After 6 months in Group I	31.18	P<0.0001 S
Baseline Vs After 6 months in Group II	45.47	P<0.0001 S

P value < 0.05 is significant & P value > 0.05 is not significant

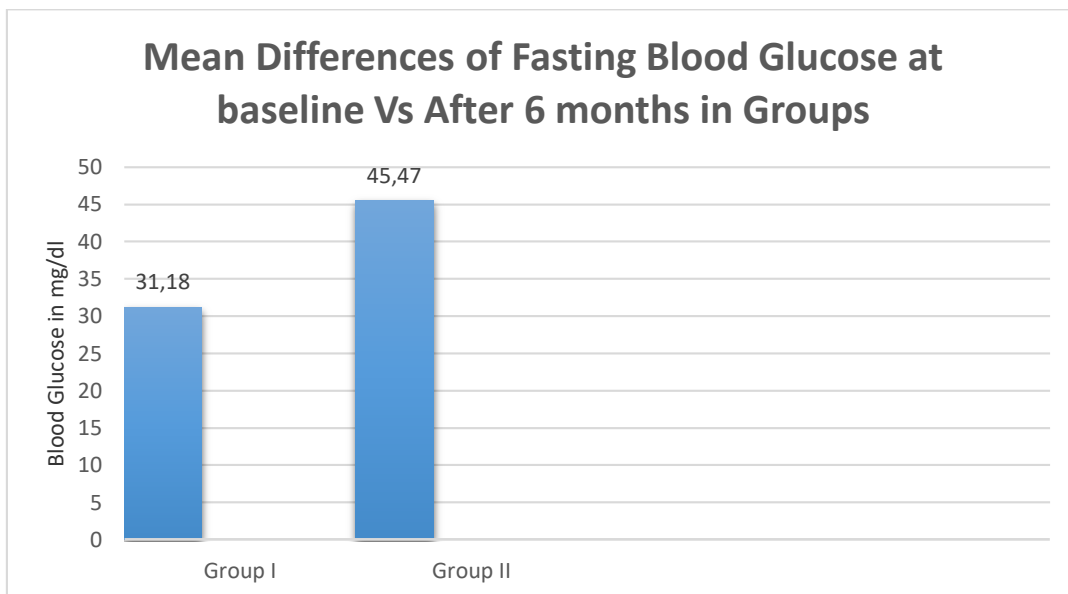


Figure 3: Comparison of Mean Differences of Fasting Blood Glucose at baseline Vs After 6 months in Groups

Table 4: Comparison of HOMA-IR in both groups at baseline and after 6<sup>th</sup> months using unpaired t-test

HOMA-IR	Group I Mean±SD	Group II Mean±SD	p-value
Baseline	3.44 ± 0.46	3.30 ± 0.45	P=0.062 NS
After 6 Months	2.21 ± 0.30	1.91 ± 0.32	P<0.0001 HS

If  $p > 0.05$  Not Significant,  $p < 0.05$  Significant

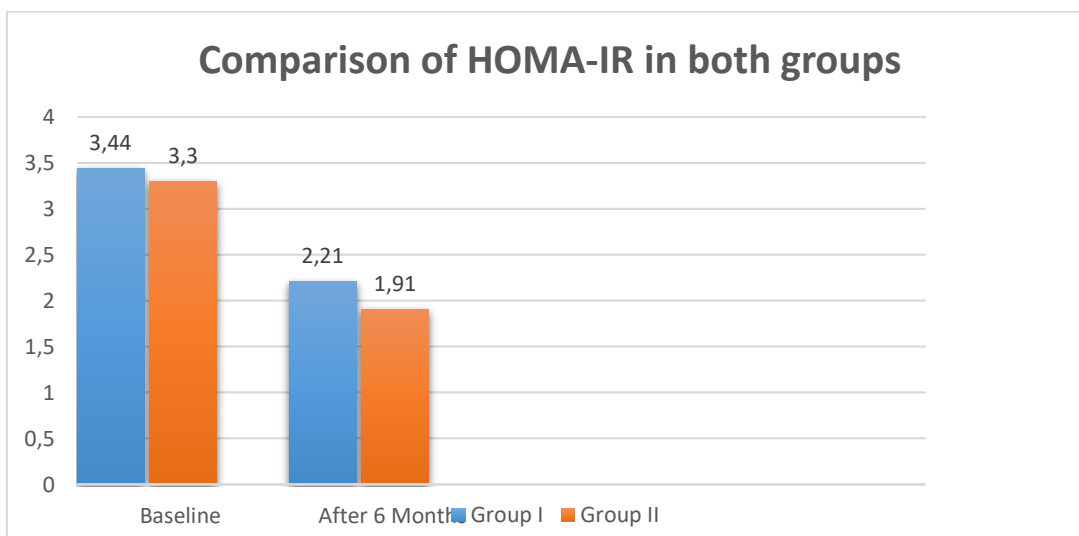


Figure 4: Comparison of HOMA-IR in both groups at baseline and after 6<sup>th</sup> months

There was a statistically HIGHLY significant decrease in HOMA-IR in Group I and II, after 6<sup>th</sup> months of treatment as compared to baseline

Table 5: Comparison of Mean Differences of HOMA-IR at baseline Vs After 6 months in Groups analyzed by paired “t” test

HOMA-IR	Mean Difference	P-value
Baseline Vs After 6 months in Group I	1.22	P<0.0001 S
Baseline Vs After 6 months in Group II	1.36	P<0.0001 S

P value < 0.05 is significant & P value > 0.05 is not significant

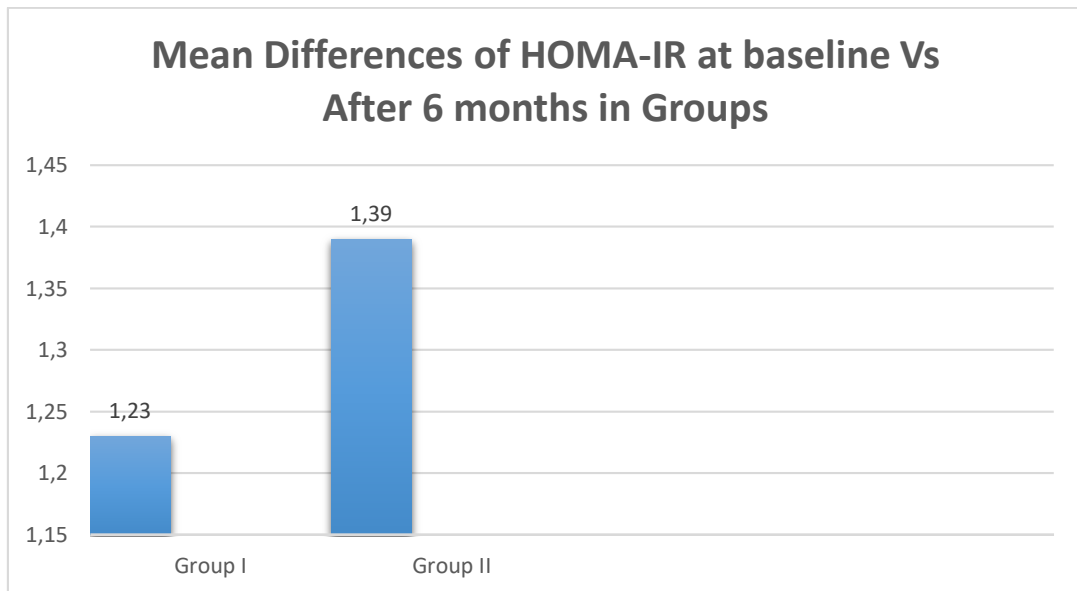


Figure 5: Comparison of Mean Differences of HOMA-IR at baseline Vs After 6 months in Groups

Table 6: Comparison of HbA1c in both groups at baseline and after 6<sup>th</sup> months using unpaired t-test: -

HbA1c	Group I Mean±SD	Group II Mean±SD	p-value
Baseline	5.17 ± 0.31	5.13 ± 0.42	P=0.310 NS
After 6 Months	4.47 ± 0.25	5.95 ± 0.20	P<0.0001 HS

If p > 0.05 Not Significant, p < 0.05 Significant

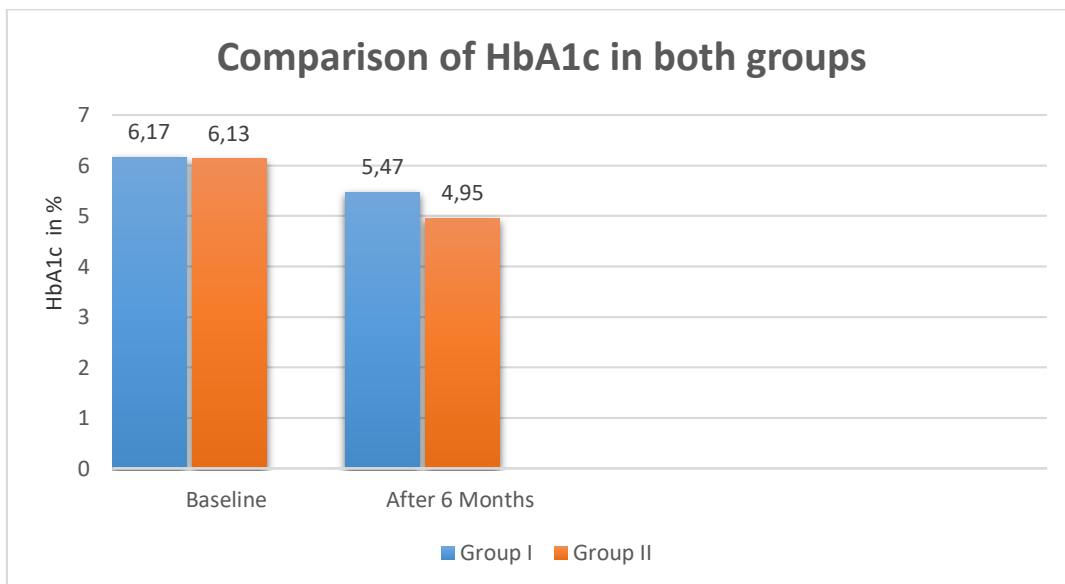


Figure 6: Comparison of HbA1c in both groups at baseline and after 6<sup>th</sup> months

There was a statistically HIGHLY significant decrease in HbA1c in Group I and II, after 6<sup>th</sup> months of treatment as compared to baseline.

Table 7: Comparison of Mean Differences of HbA1c at baseline Vs After 6 months in Groups analyzed by paired “t” test

HbA1c	Mean Difference	P-value
Baseline Vs After 6 months in Group I	0.5	P<0.0001 S
Baseline Vs After 6 months in Group II	1.2	P<0.0001 S

P value < 0.05 is significant & P value > 0.05 is not significant

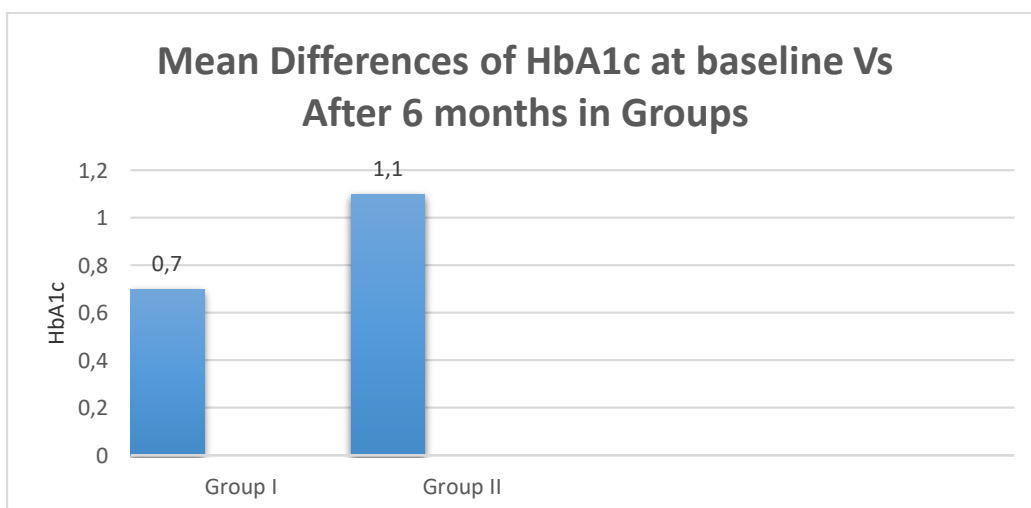


Figure 7: Comparison of Mean Differences of HbA1c at baseline Vs After 6 months in Groups



Table 8: Comparison of Serum insulin in both groups at baseline and after 6<sup>th</sup> months using unpaired t-test

Serum Insulin	Group I Mean±SD	Group II Mean±SD	p-value
Baseline	32.58 ± 3.49	31.13 ± 2.85	P=0.441 NS
After 6 Months	23.73 ± 3.21	26.77 ± 2.52	P<0.0001 HS

If  $p > 0.05$  Not Significant,  $p < 0.05$  Significant

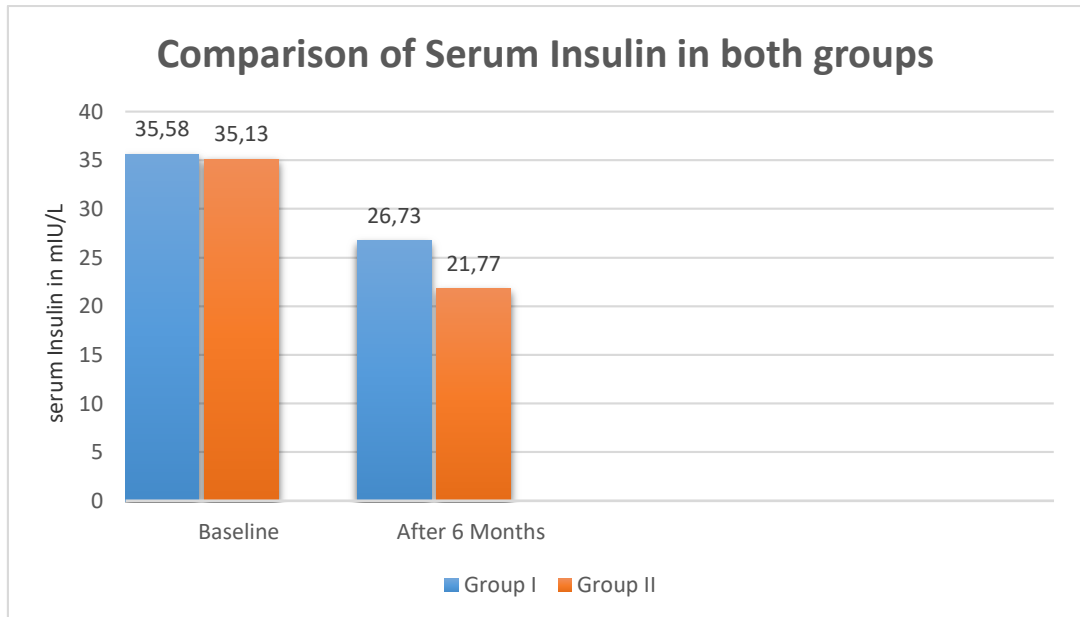


Figure 8: Comparison of Serum insulin in both groups at baseline and after 6<sup>th</sup> months

There was a statistically HIGHLY significant decrease in Serum insulin in Group I and II, after 6<sup>th</sup> months of treatment as compared to baseline.

Table 9: Comparison of Mean Differences of Serum insulin at baseline Vs After 6 months in Groups analyzed by paired “t” test

Serum Insulin	Mean Difference	P-value
Baseline Vs After 6 months in Group I	7.85	P<0.0001 S
Baseline Vs After 6 months in Group II	11.36	P<0.0001 S

P value < 0.05 is significant & P value > 0.05 is not significant

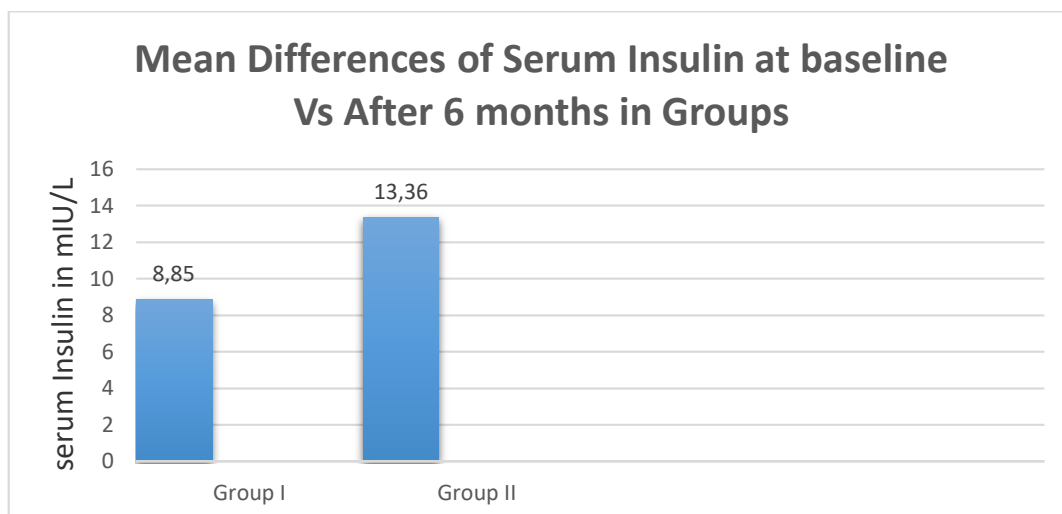


Figure 9: Comparison of Mean Differences of Serum insulin at baseline Vs After 6 months in Groups

Table 10: Adverse Drug Reaction

Groups	Weight gain	Diarrhea	Nausea/ vomiting	Abdominal Pain
Group I (MET)		2	2	2
Group II (PIO)	1			
Total	1	2	2	2

Weight gain was reported in group II in one patient only while diarrhea and abdominal pain was seen in two patients in group I nausea/vomiting was reported by two patients in group I.

## Discussion

Presently, objectives for treatment of prediabetes include not only normalization of hyperglycemia, but also reduction of complication associated with insulin resistance. Directly targeting underlying insulin resistance in the periphery is a relatively new approach for treating prediabetes and type 2 diabetes. Both Sitagliptin and metformin are first-line therapeutic interventions in the management of type 2 diabetes patients, but their mechanisms of action are different and there are no data that directly compare their antihyperglycemic efficacy, their effects on insulin resistance, or their tolerability on recently diagnosed prediabetes Oral Antidiabetic Medication naive patients. Therefore, we compared the efficacy and tolerability of monotherapy with Sitagliptin to metformin in this population. The primary objective of the study was to compare the effect of each treatment on HOMA IR and hemoglobin A1C (A1C).

## Effects on HOMA IR

Both groups showed significant reduction in HOMA-IR level at the end of study period. After six months of treatment mean HOMA-IR was reduced from 3.44 to

2.21 from baseline which was statistically highly significant [ -1.23,  $p < 0.0001$ ] in metformin group L **MP van der Aa et al** [16] showed mean HOMA IR reduction from baseline. (-1.0,  $p < 0.02$ ) with metformin which is comparable with our study. On the other hand, mean HOMA-IR was reduced from 3.30 to 1.91 from baseline which was statistically highly significant [-1.39,  $p < 0.0001$ ] in Sitagliptin group. **Silvio E. Inzucchi et al** [17] showed mean HOMA IR reduction from baseline. (-1.3,  $p < 0.0001$ ) with Sitagliptin. However, mean difference change from baseline was greater with Sitagliptin treated group when compared with metformin group (-1.39 vs -1.23). Our finding is similar to the study done by **IMRE PAVO et al** [18] which showed statistically significant reduction in mean HOMA-IR (4.9,  $p < 0.002$ ) with Sitagliptin when compared with metformin. (-0.9,  $p < 0.003$ ).

### Effects on HbA1c

There was statistically significant difference between the treatment groups in HbA1c change from baseline. Metformin group had significant decreases from baseline in HbA1c (-0.7,  $p < 0.001$ ) after six months of treatment. Our result matches with the study done by **BARRY J. GOLDSTEIN et al** [19] who showed reduction of HbA1c with metformin (-0.82,  $p < 0.005$ ). Similarly, in Sitagliptin group there was a significant mean decrease in HbA1c from baseline (-1.1,  $p < 0.0001$ ). Ours finding correlate with study done by **Aronoff S et al** [20] which showed significant mean decrease in HbA1c (-1.0,  $p < 0.05$ ). Mean difference change from baseline was greater with Sitagliptin treated group when compared with metformin group (-0.8 vs -0.5). Our finding is similar to the study done by **IMRE PAVO et al** [18] which showed statistically significant reduction in HbA1c (-1.3,  $p < 0.001$ ) with Sitagliptin when compared with metformin. (-1.2,  $p < 0.001$ ).

Both treatments were generally well tolerated. In our study, most common adverse effects reported were weight gain with Sitagliptin and nausea, vomiting and diarrhea with metformin. **IMRE PAVO et al** [18] reported weight gain with Sitagliptin and nausea, diarrhea with metformin in his study. No treatment was needed for these adverse effects. There was no drop out in our study. The present study clearly shows a difference in HOMA-IR and HbA1c between treatment groups (in favor of Sitagliptin). Furthermore, the significant difference between HOMA-IR and HbA1c results for the two drugs in the current study is in accordance with a glucose disposal rate for Sitagliptin that is two to four times higher than that observed with metformin, as measured by clamp techniques used in the previously cited studies. [21,22] Both metformin and Sitagliptin have been shown to improve glycemic control as well as insulin resistance; therefore, a direct comparison of these two drugs is of particular clinical interest. This is an innovative head-to-head comparison of the effects of Sitagliptin and metformin, and, together with the recent publication of **Hallsten et al**. [23] is one of the first trials to compare the effects of TZD and metformin monotherapy both in general and specifically in patients of prediabetes who are also naive to glucose-lowering medication.

Whereas, insulin resistance prevails in these patients, insulin-sensitizing agents represent viable treatment options. Hepatic function in prediabetes is of particular interest. In addition to different effects on insulin sensitivity, Sitagliptin and metformin had different effects on body weight; Sitagliptin treatment resulted

in weight gain, whereas metformin treatment resulted in weight loss. Weight reduction in patients treated with metformin has been shown in a vast majority of previous studies. [24] Because obesity often contributes to the etiology of prediabetes, weight reduction with metformin therapy may be an additional benefit. Weight loss in patients who are obese may be particularly beneficial in terms of the associated risk reduction of both microvascular and macrovascular complications.

More consistently, increased body weight has been reported after treatment with PPAR-  $\gamma$  agonists. Previous studies have shown a shift of fat distribution from visceral to subcutaneous adipose tissue during treatment with thiazolidinedione, including Sitagliptin suggesting this shift as a potential explanation for the seemingly paradoxical simultaneous improvement in glycaemia and insulin resistance observed with increase in body weight. [25] Because visceral adiposity was not assessed in the present study, we could not determine whether relationships existed between body fat distribution and the differential effects of Sitagliptin and metformin on glycemic control and insulin sensitivity.

Limitations of this study include the use of indirect measures of insulin sensitivity as indicators of insulin resistance, instead of more invasive and logistically challenging techniques, such as the hyperinsulinemic-euglycemic clamp, or a frequently sampled i.v glucose tolerance test. **Quon et al** [26] has emphasized greater clinical utility of HOMA as compared with less predictive indirect measures of insulin sensitivity such as the fasting glucose to insulin ratio, especially when glucose levels are abnormal. Based on the ability of HOMA to accurately mimic the results of glucose clamp techniques, **Bonora et al** [27] have concluded that HOMA is a reliable indicator of insulin sensitivity in large-scale studies in which procedures such as clamp techniques may be impractical. Thus, the indirect measures of insulin sensitivity used in this study are considered as surrogates for insulin resistance measured using the diagnostic gold standard of clamp studies.

Results of our study confirm that both Sitagliptin and metformin represent effective and safe first-line pharmacological treatment options in recently diagnosed, Oral Antidiabetic Medication -naive patients of prediabetes. The present study demonstrates that Sitagliptin and metformin monotherapies are equally effective in lowering A 1C and HOMA-IR, but improvements were more pronounced in patients on Sitagliptin therapy. Further clinical investigations are indicated to clarify to what degree insulin sensitivity contributes to the efficacy of Sitagliptin or metformin monotherapy in the early stages of prediabetes.

### **Conclusion**

Our study showed Sitagliptin was superior in reducing HOMA-IR when compared with metformin. If combination of Sitagliptin and metformin is used far superior reduction will be achieved on HOMA- IR. Limitation of our study was short duration of study and small sample size.

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