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Comparison of Efficacy, safety and treatment outcome of metformin alone vs metformin and sitagliptin combination in patient with type II Diabetes mellitus: A prospective study.

Vishal Chudasama, MeghaPatel, Kiran Suthar, Bharat Rajpurohit
Shri M N College of Pharmacy, Khambhat

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ABSTRACT:
Background: Type 2 diabetes is often referred to as non–insulin-dependent diabetes mellitus (NIDDM). In type 2 diabetes, the insulin secretory response is impaired—increasingly so as the disease progresses with time, but in most cases, a comorbid defect is the failure of many cells of the body to properly respond to circulating insulin, particularly certain cells in the liver and skeletal muscles having a primary glucose storage role, and certain cells in adipose tissue. Yet no cure is available, education of populace is still the key to control this emerging epidemic.Type 2 diabetes has most often been treated with various drugs as monotherapy or in combination of either drugs acting by other mechanism or Insulin effective glycemic control. Biguanides monotherapy or its combination with dipeptidyl peptidase-4 inhibitor is a preferred therapy due to better efficacy and safety.
Objective: The study was carried out to compare the clinical efficacy and adverse effects of combination therapy over monotherapy for oral anti-diabetics in patient with type II Diabetes mellitus.
Methodology: Present observational, prospective, single centric and cross-sectional study was conducted over a period of 3 months on patients who met the inclusion and exclusion criteria. Patients They were divided in 2 groups based on treatment plan Group A (Metformin 500 mgb.i.d.) and Group B (Metformin/Sitagliptin 500 mg/50 mg b.i.d.). From Group Atwo patient withdraw consent and three lost to follow up, while From Group B three patient withdraw consent and one lost to follow up. So HbA1c, FPG, 2Hr-PPG, RPG were evaluated and compared with base line data for total patients Group A n = 35 and Group B n = 36 Demographic pattern and all over safety was assessed.
Result: At the end of 12 weeks of designed study Group B (Metformin/Sitagliptin 500 mg/50 b.i.d.) showed men significant differencefrom baseline in HbA1c over Group A (Metformin 500 mg b.i.d.). There was also significant difference in FPG, 2Hr-PPG, RPG and BMI in group B over Group A. The adverse events presented by patients were those expected for each component monotherapy independently.
Conclusion: Combination therapy showed better outcome in controlling blood sugar levels compared to monotherapy. Combination therapy is a better choice for producing hypoglycemic effect in diabetes mellitus type 2 patients. No unexpected drug-related adverse effects and better tolerability with combination of treatment regimen rule out any drug drug interaction.
KEY WORDS: Type II Diabetes mellitus, metformin, sitagliptin, Blood glucose, HbA1c

I. INTRODUCTION:

A large and growing number of medicinal substances act onendocrine systems. The endocrine pancreas and related hormones orchestrate the delivery of fuel substrates for use and storage during fed (absorptive) periods, as well as mobilization of fuel stores during fasting (post absorptive) periods.[1]

Diabetes mellitus (DM) is a disease affecting human being since long era. It was first reported in Egyptian manuscript about 3000 years ago[2]Diabetes is a condition that happens when your blood glucose, likewise called glucose, is as well high. Blood glucose is our primary wellspring of vitality and originates from the food that we eat. Insulin, a hormone which is normally discharged by pancreas, helps glucose from food get into the cells to be utilized for vitality. Some of the time your body doesn't make enough or any insulin or doesn't utilize insulin well. Glucose at that point remains in the blood and doesn't reach to the cells. Diabetes is a chronic condition wherein the body can't direct the measure of sugar in the blood.[3]

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Over the long term, hyperglycaemia, contribute to the development of complications such as retinopathy, nephropathy and neuropathy. There is considerable evidence that, clinically and genetically, diabetes is heterogeneous group of disorders.[4]DM is characterized by chronic hyperglycaemia and impaired carbohydrates, lipids, and proteins metabolism caused by complete or partial insufficiency of insulin secretion and/or insulin action.[5]

Diabetes mellitus, a common chronic disease, affected an estimated population of 415 million in 2015. India, an epicentre of diabetes, had 69.2 million diabetic patients in 2015. This is projected to increase to 123.5 million in 2040.[6]

Diabetes mellitus is classified according to its aetiology and clinical presentation. As such, there are four types or classes of diabetes mellitus viz; type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types.[7]

Type 2 is most common of all four which accounts for more than 90% of all cases. Type 1 diabetes mellitus is a syndrome of absolute insulin deficiency. The high prevalence of type 2 diabetes mellitus, and the proven efficacy of diabetic therapy in reducing disease-related complications, warrants an active approach to case finding and adherence to evidence based therapeutic guidelines. The development of clinical symptoms in type 2 diabetes (polyuria, polydipsia, unexplained weight loss) often occurs after the onset of micro vascular complications.

When acceptable metabolic control is not achieved, either because the patient does not adapt to changes in life style or because, in spite of complying with the diet and exercising regularly, therapeutic objectives are not attained, pharmacological treatment must begin. The treatment strategy of diabetes has to be based on the knowledge of its pathophysiology. Thus, insulin is essential for treatment of type 1 diabetic patients because there is a defect in insulin secretion. However, treatment of type 2 diabetic patients is more complex because a defect in both insulin secretion and insulin action exists. Therefore, the treatment selection will depend on the stage of the disease and the individual characteristics of the patient. [8]

Early inception of pharmacologic treatment is related with improved glycaemic control and decreased long haul complexities in type 2 diabetes. Medication classes like Biguanides Sulfonylureas, Meglitinide subordinates, Alpha-glucosidase inhibitors, Thiazolidinediones (TZDs), Glucagonlike peptide–1 (GLP-1) agonists, Dipeptidyl peptidase IV (DPP-4) inhibitors, Specific sodium-glucose transporter–2 (SGLT-2) inhibitors and Insulin are for the treatment of type 2 diabetes incorporate the accompanying:[9] Although T2DM patients are generally independent of exogenous insulin, they may need it when blood glucose levels are not well controlled with diet alone or with oral hypoglycaemic drugs.[5]

Between 1957 and 1960, the biguanides were introduced on the market (phenformin, buformin, and metformin) and became very popular.[10] Because of its effectiveness and safety, metformin is one of the drugs most used in the treatment of type 2 diabetes. [11,12] Their main mechanism of action of Metformin is to reduce hepatic glucose production by decreasing both gluconeogenesis and glycogenolysis. It also increase glucose uptake by the skeletal muscle.

Sitagliptin is utilized alone or together with different medications (eg, insulin, glimepiride, metformin, or pioglitazone) and with appropriate exercises and diet to treat high glucose levels brought about by type 2 diabetes. Sitagliptin controls glucose levels by expanding substances in the body that make the pancreas discharge more insulin. It likewise induces the liver to stop delivering sugar (glucose) when there is an excessive amount of sugar in the blood.[13]

II. AIM OF WORK:

A combination of antidiabetic agents of different drug classes in a fixed-dose combination (FDC) may offer advantages in terms of efficacy, tolerability, and treatment compliance. To evaluate efficacy and safety of sitagliptin and metformin combination over metformin monotherapy and to find out clinical advantage of sitagliptin over metformin monotherapy.

III. MATERIALS AND METHODS:

The observational, prospective, single centric and cross-sectional study was conductedover a period of 12 weeks in the Department of General Medicine of a Hospital. The institutional ethical committee clearance was obtained before initiation of the study. Using a standard proforma, the details of patients such as demographic data were collected and analysed.

A total of 80 patients fitting into the subject selection criteria were included in the study. They were broadly divided into two treatment groups that included monotherapy and combination therapy groups. Subject selection criteria were as follows:

International Journal of Pharmaceutical Research and Applications
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Inclusion Criteria
Patients with history of diabetes
Patients with inadequate glycaemic control glycated haemoglobin ≥7 and ≤ 10.
Men and Women (30-65 years) with newly diagnosed with type 2 diabetes or diagnosed within past one year. and who were not currently on OHA or were taking metformin as monotherapy.

Exclusion Criteria
Patients with Type 1 diabetes.
Pregnant and lactating mother.
Patients with the history of acute pancreatitis.
Patients with coexisting conditions such as sepsis, dehydration, hepatic insufficiency, renal impairment, and acute congestive heart failure.

Patients satisfying inclusion and exclusion criteria were randomized in two treatment groups as following:
Group A: In this group, patients were put on mono-therapy of metformin 500 mg, orally b.i.d. for twelve weeks.
Group B: In this group, patients had fixed dose combination of metformin 500 mg and Sitagliptin 50 mg, b.i.d. for twelve weeks. (dual therapy)

Safety Assessment:

The safety assessment in this study was included monitoring of adverse effects (Whether it was detected by the investigator or experienced by patient) at each scheduled visit.A safety report card was given to each subject for recording the adverse events at home. Safety was assessed in terms of both subjective and objective systemic adverse-effects.

Outcome Measures:
Primary Outcome Measures:
The changes in HbA1c, FPG, 2Hr-PPG, RPG were recorded at baseline and at the end of 12 weeks.
Secondary Outcome Measures:
The adverse events like diarrhoea, nausea, abdominal pain, nasopharyngitis, arthralgia, back pain, cough was recorded.

Data Handling:
Data were collected in Case Report Form from Hospital and converted into spread sheet.

Statistical analysis:

Demographic data and adverse effect were analyzed using descriptive statistics. For efficacy parameter, the mean percentage reduction in plasma sugar from baseline to the end of the study was calculated for both groups. FPG, 2Hr-PPG, HbA1c and RPG before and after treatment within each group was compared and Data were expressed as the mean value ± SD, number and percentage.
Data was analyzed by using t-test and ANOVA model.

IV. RESULT

Primary analysis focused on the comparison of the two- drug combination versus monotherapy.
Patients who met selection criteria were enrolled in the study. Total 80 patients were enrolled in the study. Among them up Four patient withdraw consent and five lost to follow up during study so 35 patients were enrolled in metformin group (group A) and 836patients were enrolled in metformin+sitagliptin group (group B).
The patients were advised to take same brand of the medication throughout the study.
The demographic data and clinical outcome in both the groups i.e., group A and B of randomized patients is presented below.

Demographic Characteristics of the Study Subjects:

Table 1.Patient demographics and Baseline characteristics data

Sr. No	Characteristics	Metforminn =35 Group A (Mean± SD)	Metformin+Sitagliptin Group Bn = 36 (Mean ± SD)
1	Age	52.24 ± 7.36	52.02 ± 8.33
2	Male	22 (62.85%)	24 (66.67 %)
3	Female	13 (37.14 %)	12 (33.33%)
4	BMI (kg/m²)	26.75 ± 2.92	26.91 ± 2.84
5	Baseline – FPG	146.34 ± 10.89	146.97 ± 10.62
6	Baseline – 2 Hr-PPG	204.06 ± 17.80	213.08 ±11.67
7	Baseline- HbA1c	8.14 ± 0.44	8.26 ± 0.48
8	Baseline – RPG	183.52 ± 17.27	191.89 ± 20.41

International Journal of Pharmaceutical Research and Applications
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Baseline characteristics of the study population are summarized in Table 1.
The two groups were comparable in terms of age, sex, BMI, gender.

Efficacy parameter:

Table 2 Blood Glucose at baseline and week 12:

week 12	Treatment	At Baseline	week 12	% Reduction
FPG	Metformin	146.34 ± 10.89	135.23 ± 10.67	7.61%
	Metformin+sitagliptin	146.97 ± 10.62	128.61 ± 9.18	12.49%
2-Hr PPG	Metformin	204.06 ± 17.80	178.12 ± 18.57	12.71%
	Metformin+sitagliptin	213.08 ±11.67	173.98 ± 12.91	18.36%
HbA1c	Metformin	8.14 ± 0.44	7.27 ± 0.41	10.70%
	Metformin+sitagliptin	8.26 ± 0.48	7.11 ± 0.51	13.92%
RPG	Metformin	183.52 ± 17.27	163.97 ± 17.43	10.78%
	Metformin+sitagliptin	191.89 ± 20.41	161.66 ± 15.75	15.76%

As shown in the Table 2 Analysis of glycemic efficacy end point data after 12 weeks revealed significant decrease in FPG,2-Hr PPG, HbA1c and RPG in two treatment groups from baseline. In Metformin + sitagliptin treated group FPG was decreased from 146.34 ± 10.89 to 128.61 ± 9.18(12.49 % reduction) at 12 weeks, 2- Hr PMG was decreased from 213.08 ±11.67 to 173.98 ± 12.91(18.36 % reduction) at 12 weeks, HbA1c was decreased from 8.26 ± 0.48 to 7.11 ± 0.51(13.92 % reduction) at 12 weeks and RPG was decreased from 191.89 ± 20.41 to 161.66 ± 15.75(15.76 % reduction) at 12 weeks. In Metformin treated group FPG was decreased from 146.34 ± 10.89 to 135.23 ± 10.67(7.61 % reduction) at 12 weeks, 2-Hr PMG was decreased from 204.06 ± 17.80 to 178.12 ± 18.57(12.17% reduction) at 12 weeks, HbA1c was decreased from 8.14 ± 0.44 to 7.27 ± 0.41(10.7 % reduction) at 12 weeks and RPG was decreased from 183.52 ± 17.27 to 163.97 ± 17.43(10.78 % reduction) at 12 weeks.

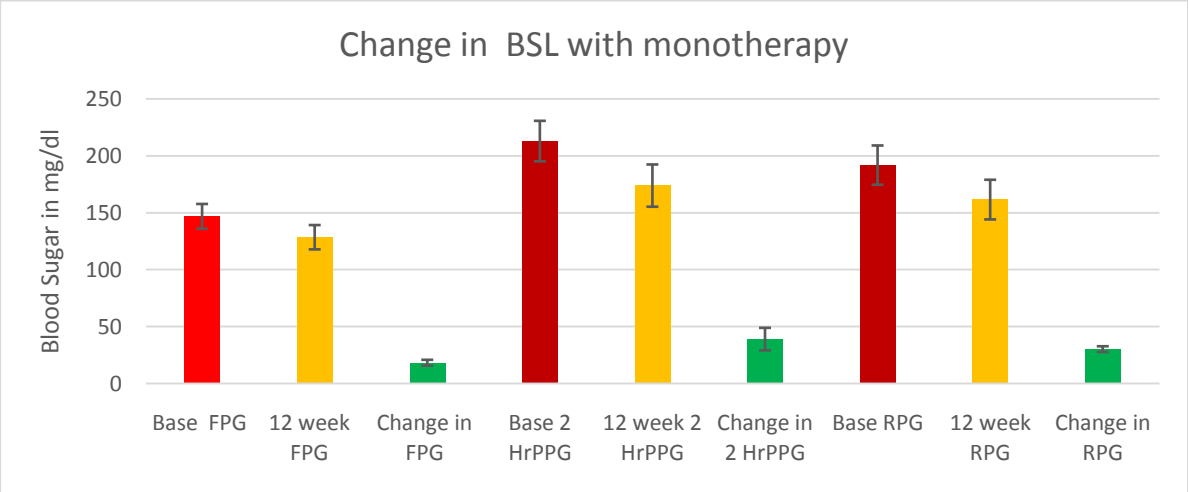

Figure: 1 Change in FPG, 2Hr PPG and RPG with monotherapy at end of 12 week.

International Journal of Pharmaceutical Research and Applications
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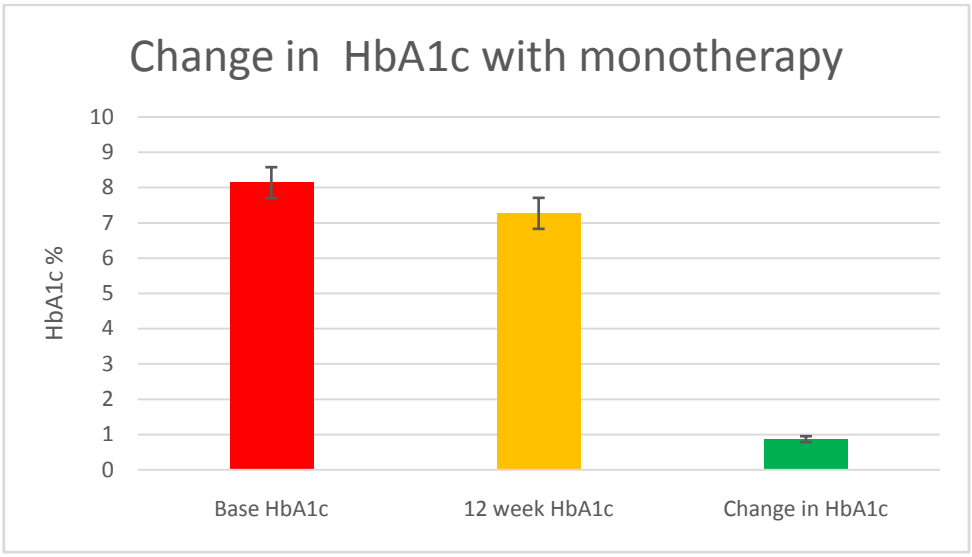

Figure: 2 Change in HbA1c with monotherapy at end of 12 week.

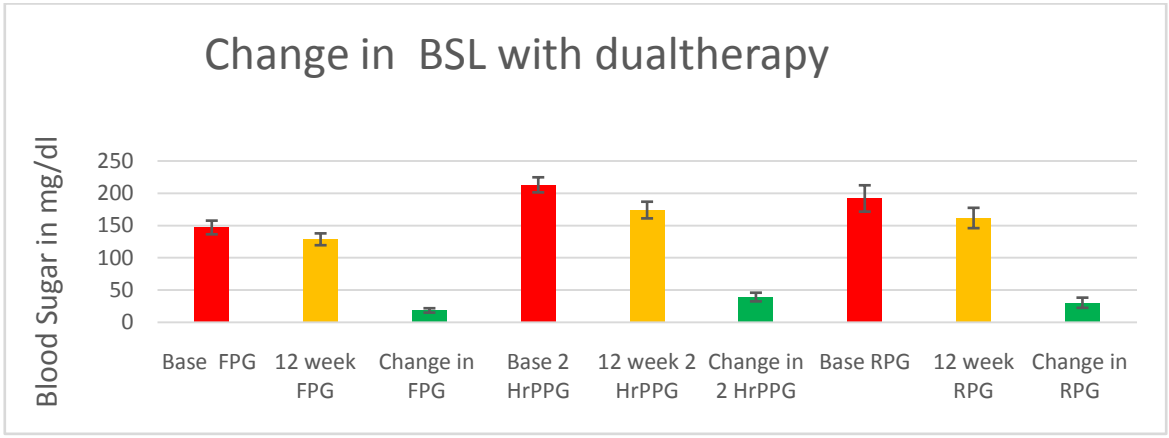

Figure 3: Change in FPG, 2Hr PPG and RPG with dualtherapy at end of 12 week.

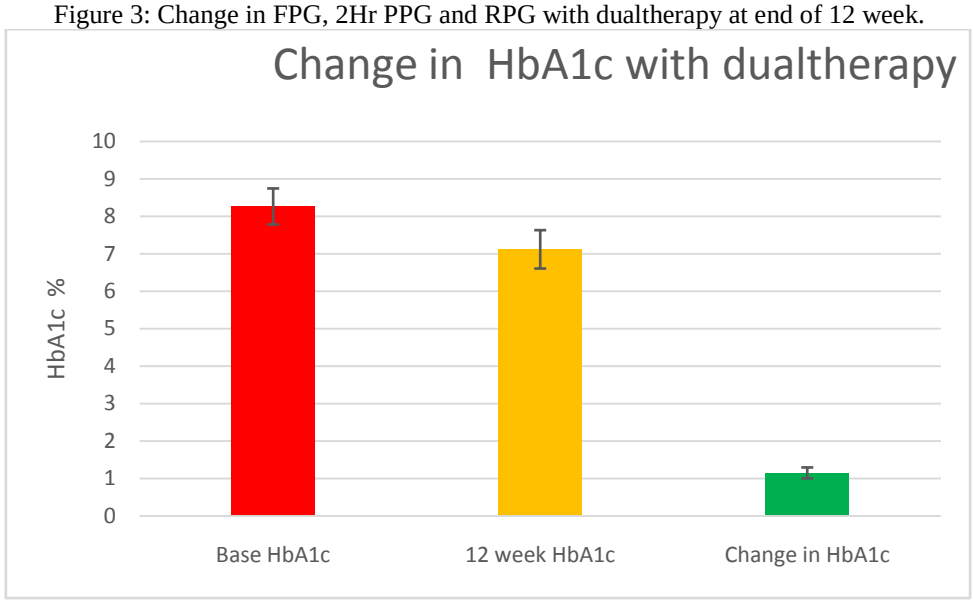

Figure: 4 Change in HbA1c with dualtherapy at end of 12 week.

International Journal of Pharmaceutical Research and Applications
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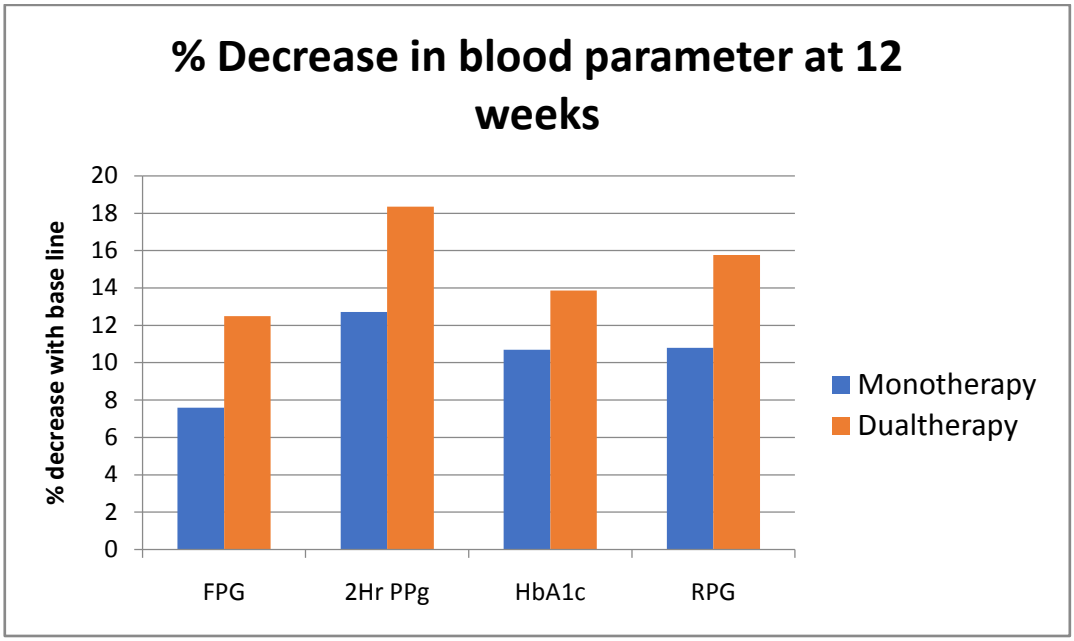

Fig 5: Comparison of decrease in Plasma glucose level & HbA1c between Monotherapy &Dualtherapy at end of 12 weeks.

Treatment Safety Assessment:
Adverse event related to two medications shown in table no. and in figure no

Table: adverse events related to different treatment

Adverse Event	Metformin Groupn = 35	Metformin + Sitagliptin Groupn = 36
Abdominal pain	5 (14.28 %)	4 (11.11%)
Diarrhea	4 (11.42 %)	3 (8.33 %)
Nausea	2 (5.2671 %)	1 (2.77 %)
Vomiting	1 (2.63 %)	1 (2.77 %)
Nasopharyngitis	0	4 (11.11%)
Arthralgia	2 (5.26 %)	3 (8.33 %)
Back Pain	0	3 (8.33 %)
Cough	0	2 (5.56 %)

V. DISCUSSION:

The finding of this study demonstrated that metformin + sitaglitptin combination was very well tolerated and effective and allow achievement of adequate blood glucose control in the majority of patients using a simple treatment strategy. Combination treatment has been shown to increase the efficacy of treatment and reduce adverse effects. Early commencement of combination treatment has been proposed as a way to deal with accomplishglycemic objectives prior and postpone the decay of glycemic control and with conceivable better protection of β-cell work. Beginning combination treatment is proposed to prompt better and quicker accomplishment of glycemic targets versus monotherapy and to obstruct clinical inactivity and may perhaps slow the decay of β-cell work.[14]

Our study found that dual combination of metformin 500 mg + sitagliptin 50 mg were associated with greater reduction inHbA1c, FPG 2-Hr PPG compared with metformin monotherapy at 12 weeks follow up. Dual combination therapy was also associated with a high percentage of patients reaching the HbA1c Goal and blood sugar targets compared with metformin treatment. Treatment with metformin/sitagliptin combination led to a significant increase in the proportion of patients achieving an HbA1C < 7% compared with metformin alone.(20 of 36 patients [55.56%] in the

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metformin + sitagliptin group versus 13 of 35 patients [42.85 %] in the metformin group alone.

Both treatment groups had same safety profiles. In our study safety report card was analyzed at every follow up for the adverse events experienced by patients. Overall, Abdominal pain, diarrhoea, Nausea, vomiting, arthralgiawere reported with approximately the same frequency. Nasopharyngitis, Back pain, cough were reported more in metformin/sitagliptin treated group than metformin alone group. Patients didn't report any signs of low blood sugar levels, no significant weight changes and same occurrence of the gastrointestinal side effects.[15]

Sitagliptin, The DPP-4 Inhibitor, has a unique advantage of oral administration. It is well tolerated and is considered neutral on weight. Combination of sitagliptin and metformin helped in achieving the HbA1c goal in patients. More patients achieved their target HbA1c in the combination group than in monotherapy during the study.

In summary, ADA guidelines for the management of diabetes recognize that most patients will eventually require combination therapy to achieve the target HbA1c in early setting.Since diabetes is a progressive condition, monotherapy didn't help to achieve target HbA1c. The present study adds to the existing evidence important new data showing that metformin and sitagliptin combination are superior to metformin monotherapy in terms of reducing the blood glucose level and achieving HbA1c targets.

Limitation of the study:
It is a single centric study with small sample size
The current study enrolled only patients who HbA1c was between 7 to 10 %, the study results may not be generalized to the overall Diabetic patients

VI. CONCLUSION:

The results of present study demonstrated that combination therapy of metformin and sitaglitpin were associated with significant blood glucose reductions and achieving HbA1c targets compared to metformin monotherapy.

No major adverse effects had been reported in this study and the combination therapy have similar side effects as that metformin monotherapy.

Thus the combination of sitagliptin 50 mg + metformin 500 mg have demonstrated superior efficacy than metformin monotherapy in achieving HbA1c target in type 2 diabetic patients.

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