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Original Research Article

A STUDY TO EVALUATE EFFECT OF SITAGLIPTIN + METFORMIN COMBINATION ON BODY MASS INDEX, SERUM HDL CHOLESTEROL LEVEL & SERUM TRIGLYCERIDE LEVELS IN RECENTLY DIAGNOSED PATIENTS WITH TYPE 2 DIABETES MELLITUS.

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ABSTRACT

Objectives: To evaluate the effect of combination of Metformin along with Sitagliptin on Body mass index, HDL-C & Triglyceride levels in recently diagnosed patients of type 2 Diabetes mellitus.

Methods: This cross-sectional study includes analysis of total 25 patients receiving Metformin alongwith Sitagliptin as. Their body weight (BMI) & biochemical parameters namely HDL & Triglycerides were recorded at time of enrollment of paticipants and upon subsequent follow-ups.

Results: After 24 week in patients receiving Sitagliptin 50 mg + Metformin 1000 mg in tablet form reduction in BMI was observed as compared to baseline values. Also the elevation in levels of serum HDL cholesterol was observed. The serum triglyceride levels showed variation as evident by observations recorded on 12^{th} , 24^{th} , and 36^{th} week.

Conclusions: Effects Sitagliptin 50 mg + Metformin 1000 mg taken twice a day as initial treatment in patients recently diagnosed with type 2 Diabetes mellitus was apparent as decrease BMI values, a rise serum HDL cholesterol which is considered good cholesterol whereas serum Triglyceride levels showed variations.

Key Words: DPP4 Inhibitors, Sitagliptin , Metformin, Combination,BMI,HDL,Lipid profile.

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1. INTRODUCTION

Diabetes mellitus (DM), a widespread endocrine metabolic disorder, is an important cause of morbidity and mortality worldwide. Development of diabetes includes several pathogenic processes ranging from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that causes resistance to insulin action.[1]
Diabetic dyslipidemia is commonly diagnosed in diabetes mellitus, which is characterized by increased plasma levels of triglycerides, low-density lipoprotein cholesterol (LDL-C) and decreased levels of high-density lipoprotein cholesterol (HDL-C). Diabetic dyslipidemia complicates the management of diabetes mellitus and its complications such as cardiovascular, renal disorders, etc.[1]
Post meal hyperglycemia in type 2 diabetics is in part due to high post meal glucagon levels. Incretin-based treatments control post meal rise in glucose by targeting this mechanism.
The incretin based medicines are available in two group of drugs: DPP-4 Inhibitors and GLP-1 analogs. Incretin-based therapies comprise DPP-IV(Dipeptidyl peptidase) inhibitors. E.g. Sitagliptin, vildagliptin, saxagliptin etc and GLP-1 analogs like IV Exenatide ,Semaglutide, liraglutide and oral semaglutide. The risk of hypoglycemia is minimal with these class of drugs[19]
Metformin drug which belongs biguanide class of drugs. It is an oral anti diabetic drug . It is indicated in treatment of T2DM as an initial therapy. It has long been used in clinical practice to for treatment of type 2 diabetes mellitus, and exhibits acceptable therapeutic efficacy. It's role has been suggested in overcoming insulin resistance (hyperinsulinemia), which is considered as one of the most important factors in pathogenesis of T2DM.[18]
Thus a combination therapy of Sitagliptin along with metformin would target two different mechanism of pathogenesis of type 2 diabetes mellitus. Moreover combination of sitagliptin and metformin may be good initial treatment option for patients as an alternative to insulin injection.[18]
The aim of this study is to evaluate effect of sitagliptin + metformin combination on body mass index, serum hdl cholesterol level & serum triglyceride levels in recently diagnosed patients with type 2 diabetes mellitus.

2. MATERIALS AND METHODS

This study included subjects with recently diagnosed Type 2 Diabetes mellitus. The study was conducted at tertiary level teaching hospital in North- Eastern part of Uttar Pradesh.
Informed consent was obtained from subjects enrolled in the study. The subjects was given a choice of leaving the study in between. Enrolment of subjects in the study was initiated after ethical clearance from ethical committee of BRD Medical College, Gorakhpur.
A total of 25 subjects were studied who were regular in follow-ups. The period of study was three years. The included subjects were enrolled at different points in time during the entire phase of the study. All investigations were carried out in these subjects at the baseline(0^{th} week) i.e at the time of enrollment, and upon subsequent follow-ups at 12^{th} week , 24^{th} week and 36^{th} week.
Body mass index was calculated as a function of body weight and body height. Body weight in kgs and height in meters were recorded subsequent to which body mass index was calculated as **BMI = weight (kg) / [height (m)]^2**. FBS was recorded at baseline for the diagnosis of Type 2 DM as per WHO guidelines.

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Random venous blood sample was taken and analyzed for lipid profile i.e serum High density lipid(HDL) cholesterol and seum Triglycerides in a total 25 subjects.
Thus a total of three Parameters were observed

A) BODY MASS INDEX – BMI
B) SERUM HDL CHOLESTEROL
C) SERUM TRIGLYCERIDES

Inclusion criteria
The Patients with raised FFBS level >= 126mg/dl as per WHO guidelines for diagnosis of Diabetes Mellitus (recorded for the very first time) and confirmed by medical history were classified as recently diagnosed type 2 diabetics for the purpose of this study and included in the study.
Out of all the enrolled those patients who completed all the follow ups on designated time and from whom investigation were obtained as per set criteria were finally included in this study.
Exclusion criteria
Patients with type 1 diabetes mellitus, Individuals with type 2 diabetes mellitus taking other oral hypoglycemic agents since many years & who are on insulin therapy or having drug induced hyperglycemia & Pregnant females were excluded from the study.

Statistical analysis
Data collected was entered into a spreadsheet computer program (Excel 2010; Microsoft, US). All Values are expressed as mean ± SD.
Z test is used for statistical analysis. Various values of p were obtained. If $p>0.05$ was considered insignificant, whereas $p<0.05$ was considered significant $p<0.01$ was considered as more significant and $p<0.001$ was considered to be most significant. All the comparasions were made from the baseline values. As the same group was compared for follow up values with baseline values of the parameters so sample size for baseline values was designated as n1 and sample size for follow up values was taken as n2 since no loss to follow up was noted therefore n1=n2 and total sample size was n1+n2 therefore Z test was employed for sample size was >30.

3. RESULTS

Different parameters namely a) body mass index, b) serum hdl cholesterol and c) serum triglycerides were calculated and evaluated in patients receiving :
Tab Sitagliptin 50 mg + Metformin 1000 mg in combination twice a day(BD).
Results are observed and tabulated and test of significance was applied.
Where p values denoted are indicative of comparison between baseline group and one of the three follow up group (either 12^{th} week ,24^{th} week or 36^{th} week)
A) BMI
Table 1 demonstrates statistically significant reduction in BMI in after 24 week onwards(pvalue <0.01 at 24 weeks), and the reduction in BMI at 36^{th} week is highly significant $p<0.001$.
The fact that there's significant reduction in BMI on or after 24 weeks (6 months) onwards indicates that weight loss in treated is observed post commencement of the medications.

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Table 1: **Mean± S.D. of BMI in patients treated with Tab Sitagliptin 50 mg + Metformin 1000 mg**

DURATION	0 WEEK (BASELINE)	12TH WEEK	24TH WEEK	36TH WEEK
BMI	26.54±2.05	25.58±1.99 **(p>0.05)**	24.62±1.79 **(p<0.01)**	23.98±1.29 **(p<0.001)**

B) SERUM HDL-CHOLESTEROL

HDL-Cholesterol level showed a significant rise from 12th week hence further it is observed that the difference from baseline becomes highly significant at 24th week and 36th week.

Table 2: **Mean± S.D. of serum HDL-cholesterol in patients treated with Tab Sitagliptin 50 mg + Metformin 1000 mg**

DURATION	0 WEEK (BASELINE)	12TH WEEK	24TH WEEK	36TH WEEK
HDL	33.8±5.05	36.04±6.12 **(p<0.01)**	39.56±4.36 **(p<0.001)**	40.84±5.12 **(p<0.001)**

C) SERUM TRIGLYCERIDES

The levels of serum triglycerides are observed as fluctuating : at 12th week the values were more or less comparable with no significant difference, the levels are observed as increased at 24th week as compared to baseline, whereas at 36th week the values showed a decrease in levels of triglycerides when copared to the levels at 24th week but still were higher than those of the baseline values, and the difference was significant when compared to baseline values.

Table 3: **Mean± S.D. of serum Triglycerides in patients treated with Tab Sitagliptin 50 mg + Metformin 1000 mg BD**

DURATION	0 WEEK (BASELINE)	12TH WEEK	24TH WEEK	36TH WEEK
TRIGLYCERIDES	205.0±46.51	205.3±61.43 **(p>0.05)**	232.34±59.72 **(p<0.001)**	219.56±54.08 **(p<0.001)**

4. DISCUSSION

This study was conducted in total of 25 patients to assess the effects of Metformin + Siatgliptin Combination in reduction in Body weight & improvement in Lipid profile. i.e. HDL-C & Triglyceride levels. A group of 25 patients were evaluated where each individual served as one's own control . Patients were recalled in 3 follow-ups. i.e. 12 weeks, 24 weeks, 36 weeks. On their 1st visit and upon subsequent follow ups, BMI was calculated & their blood investigations such as serum HDL & Serum Triglycerides level were carried out & findings were noted in specially prepared case history proforma.

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The Results of our study is comparable to the studies conducted by Katsuyama et al.[2] which reported that Body weight and BMI in obese were significantly greater as compared to non-obese at baseline. After 6 months of initiating Sitagliptin use, significant reduction in body weight in obese group, whereas no change was noted in non-obese group, on the similar lines Yanai et al.[3] found a significant reduction in body weight and body mass index from the baseline after 6 months ($p<0.01$).

Also Seck et al.[4] reported that administration of oral Sitagliptin was associated with significant weight loss ($p<0.05$) (-1.6 kg) as against weight gain (+0.7 kg) with glipizide. Study conducted by Yang et al.[5] in 2012 revealed a small decrease from baseline body weight in the placebo group compared with no change in the Sitagliptin group (between-group difference 0.5kg; $p<0.01$).

Lim S et al.[6] obsereved, through multivariate regression analysis that after 52 weeks reduction in HbA1c was significantly associated with body mass index & other parameters. In another study, Amjad et al.[7] revealed significant difference in weight as well as other parameters for glycemic control in the two groups, of Sitagliptin+ Metformin & of Glimiperide group. In glimepiride group there was slight increase in weight (-2.7±2.23kg vs. +2.45±0.55kg, $p<0.01$). It was concluded that Sitagliptin, a DDP-4 antagonist which is well tolerated.is as efficacious as glimepiride in reducing HbA1C and fasting blood sugar. It also causes reduction in weight.

A study conducted by Demir S. et al.[8] had concluded that in patients exhibiting inadequate glycemic control, addition of a DPP-4 inhibitor as a second oral anti diabetic agent to Metformin monotherapy provides better glycemic control and does not cause weight gain. Also Weinstain et al.[9] had observed that Sitagliptin/Metformin led to weight loss (-1.4 kg), while pioglitazone led to weight gain (3.0 kg) ($p<0.001$).

Many other comparative studies such as one performed by Chawla S. et al.[12] revealed a significant ($p<0.01$) decrease in High density lipoprotein (HDL‑C) & a significant ($p<0.01$) decrease in Triglyceride, whereas Katsuyama et al.[2] had also established that significant differences was seen in effects of Sitagliptin treatment on body weight and lipid metabolism between obese and non-obese patients with type 2 diabetes.

Contrary to findings of our study, a conducted by Shigematsu E. el al.[10] had shown that changes in the lipid profile after Sitagliptin treatment, the HDL level & Triglyceride level were not significantly ($p>0.05$) reduced after 12 weeks of Sitagliptin treatment from baseline.

Garimella S. et al.[14] had reported significant ($p<0.05$) reduction in triglycerides. Their results clearly indicate the beneficial effect of Metformin on lipid profile in type II diabetes patients. Fan M et.al.[15] had concluded that Sitagliptin alone or in combination significantly ($p<0.001$) improved serum HDL-C levels & serum triglycerides (TGs) in patients with type 2 diabetes mellitus. Pavithra N.et al.[1] had assessed the lipid lowering effect of antidiabetic drugs such as Metformin & combination of Metformin & Glimepiride in type 2 diabetes mellitus patients. The results showed the efficacy of the administration of combination of Metformin and glimepiride simultaneously and Metformin as monotherapy. There were significant changes in triglycerides during the study period. The results of the present study have demonstrated that the addition of glimepiride to Metformin in type 2 diabetes have

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beneficial effects on lipid profiles in addition to improved glycemic control throughout the study period. Whereas as Mervat M. et al.[16] had demonstrated the effect of Sitagliptin monotherapy on lipid profile and Results of their study revealed that Sitagliptin significantly ($p<0.01$) reduces TG. It was further stated that Sitagliptin as monotherapy is effective in treatment of dyslipidemia in newly diagnosed T2DM.

5. Conclusion

Tab Sitagliptin 50 mg + Metformin 1000 mg taken twice as initial treatment in patients recently diagnosed with type 2 Diabetes mellitus resulted in a decrease in BMI values.
There's also observed a rise in serum HDL cholesterol (high density lipid cholesterol) which is considered to be good cholesterol, this suggests a positive role of given treatment in counteracting dyslipidemia in patients of type 2 DM.
Serum triglycerides showed a variation in values as compared to baseline values and the values recorded at follow ups. This according to us suggests that serum triglycerides might not be a good indication of lipid profile control in the patients of type 2 DM.

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