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"STUDY OF EFFICACY AND SAFETY OF SITAGLIPTIN IN PATIENTS WITH TYPE 2 DIABETES TREATED WITH COMBINATION OF INSULIN AND METFORMIN"

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ABSTRACT

Background: Diabetes mellitus is a public health concern that affects the global population. There are several treatment plans which manage the symptoms and complications of type 2 DM. In this research, a combination of insulin and metformin is analyzed along with the addition of sitagliptin for type 2 DM patients.

Objectives: The study aims to evaluate the safety, efficiency and efficacy of sitagliptin in patients with type 2 DM who are on a combination of insulin and metformin.

Methodology: The study is an observational retrospective study based on previously occurred follow-up. Over the course of 10-years treatment, around 20,000 patients with type 2 DM were screened, out of which 100 patients were randomly selected and assigned into two treatment groups with defined conditions and scenarios. Blood sugar, kidney and lipid profile of the patients were monitored.

Results: FBS, RBS, HbA1C among the participants who were taking sitagliptin as a therapy along with insulin and metformin were found to be lowered ($p<0.001$) than the participants not taking sitagliptin. CBC, serum electrolytes, Coagulation, lipid and kidney profile were also found to be supportive for enhanced safety and efficacy status among the patients along with lower number of reported ADRs. However, elevation in AST ($p <0.001$), ALT ($P<0.01$), serum creatinine ($p <0.01$) after the addition of sitagliptin need further investigation to rule out its hepatoprotective and nephroprotective status.

Conclusions: The study has evaluated the safety and efficacy of single or combination antidiabetic therapies needs to be considered while managing the diabetic condition.

Keywords: Type 2 DM, Sitagliptin, Metformin, Insulin, Safety and Efficacy

INTRODUCTION

Diabetes mellitus is a public health concern which affects the global population. It is estimated that for almost 90% of patients who are suffering from the disease which is type 2 diabetes (Ballav & Gough, 2013). Type 2 diabetes treatments and care put a heavy burden on healthcare budget and in many countries, allocation of healthcare budget for type 2 diabetes care is almost 10%. Due to changes in lifestyles and an increase in people with obesity, the international prevalence of diabetes has dramatically increased. In 2017, the global prevalence for this disease was found to be 425 million patients (Goyal & Jialal, 2020). Increase in age also raises the risk for diabetes so ultimately, the prevalence of diabetes mellitus also increases. It is estimated that about 1/4th of 25% of the population who are above 65 years of age has diabetes (Goyal & Jialal, 2020).

The risk factors for type 2 diabetes mellitus (DM) are lifestyle factors and genetics. It is a condition which leads to a state of hyperglycemia due to defective action of insulin and decreased level of secretion of insulin from pancreatic β- cells (Ozougwu et al., 2013).

Majority of the type 2 DM patients are found to be obese or overweight having a higher percentage of body fat, which is mainly distributed in the abdominal region (Stefan, 2020). It can be easily diagnosed either by plasma concentration of glucose (2-hour plasma glucose or fasting) or the haemoglobin A1C criteria. However, there are concerns associated with Hb A1C testing. It is not a completely treatable condition however; the situation gets better as the management and medication for the condition is appropriate and restricted. There are several treatment plans and therapies which manage the symptoms and complications of type 2 DM if taken appropriately with improved lifestyle behaviours and restricted diet as recommended to type 2 DM patients. Biguanides, Sulfonylureas, Meglitinides, SGLT2 inhibitors, DPP-4 inhibitors, Thiazolidinediones, GLP-1 receptor agonists, α-Glucosidase inhibitors and Insulin are the classes of drugs which are significantly used following the condition and situation of the patient and their response against of treatment plan (Chaudhury et al., 2017). The target is to achieve a good glycemic control together with risk factor modification for the anticipation of diabetes-related microvascular complications such as retinopathy, neuropathy, and nephropathy. The current research evaluates the efficacy and safety of Metformin (50 mg/1000 mg) along with insulin and sitagliptin (50 mg/500 mg) combination need to be evaluated and analyzed critically as a treatment therapy for type 2 DM patients.

METHODS

STUDY DESIGN

The study is an observational retrospective study based on previously occurred follow-up. The study is designed to compare the efficacy and safety of sitagliptin with other oral hypoglycemics and insulin. Total of 100 participants from Karachi Institute of Heart Disease (KIHD) were enrolled in the study and divided into following groups of treatment:

Group 1 and Group 2

Fifty of the participants diagnosed with type 2 diabetes and on combination therapy of metformin (1500 mg/day) and insulin (70/30 q12hr) (Vivek et al., 2015) therapy for 3 years or more were assigned group 1, while in group 2, same patients were added sitagliptin (100 mg/day) as an add-on therapy in addition to metformin and insulin.

SELECTION OF PATIENTS

Inclusion Criteria

Initially, patients who were diabetic i.e. T2 DM were included. As per the requirements, the patients

who were taking combination therapy of oral hypoglycemics and insulin were preferred for inclusion, along with this add-on of sitagliptin was the required condition. All the parameters such as age, gender, co-morbidities, and diagnoses were also taken into consideration.

Exclusion Criteria

Patients who were not having diabetes were excluded from the selection of participation. Similarly, patients with Type 1 diabetes were not included in this study. All the patients who have other serious diseases such as cancers, HIV, hepatitis patients with autoimmune disorders are excluded. It is also preferred not to include pregnant and lactating women in the research.

DATA COLLECTION

Patient data are purposively collected from the Karachi district's tertiary care hospitals and diabetic centers. Lab data of one and three months after treatment was collected. The data was collected on the prescribed format. The efficacy of the treatment was evaluated by monitoring the blood sugar profile of the patients such as FBS, RBS, and HbA1C. The safety of the treatment was assessed after monitoring of liver function test with its parameters like aspartate aminotransferase (AST) alanine transaminase (ALT) and alkaline phosphatase (ALP), coagulation profile with prothrombin time (PT) and international normalized ratio (INR), complete blood count (CBC) including red-blood cells (RBCs), white-blood cells (WBCs), haemoglobin (Hb) and platelets, lipid profile including low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TGs) and serum cholesterol, kidney profile with its parameters like serum urea and serum creatinine, serum electrolytes including levels of sodium (Na), potassium (K), magnesium (Mg) and chlorides (Cl).

Safety of sitagliptin as an add-on therapy was also evaluated by monitoring adverse effects reported by the patients such as hypoglycemia, nausea, vomiting, hypersensitivity and others (headache, diarrhea, weight loss, and muscle pain). Data regarding hypoglycaemia and other adverse events were collected by asking participants and checking prescriptions. Participants were asked about symptoms of hypoglycaemia, skin allergies, nausea and vomiting that required medical or non-medical assistance.

OUTCOME MEASURES

All the previously mentioned parameters considered for evaluation of efficacy and safety of sitagliptin were collected, examined and assessed.

DATA ANALYSIS AND STATISTICS

In our research, primary data is further analyzed using statistical tools such as SPSS and Microsoft Excel. Statistical Package for Social Sciences (SPSS) version 20.0 is used for evaluating the results. The data is analyzed by paired samples t-test. The results are presented in the form of mean ± standard deviation. The p value <0.05 is estimated to be considered significant.

RESULTS

3.1 PATIENTS' GENERAL CHARACTERISTICS

Throughout 10-year treatment, around 20,000 patients with type 2 DM are screened, out of which 100 patients are randomly selected and assigned one of the six treatment groups as shown in table 3.1. The number of patients assigned to each treatment includes 50 patients on metformin plus insulin alone, 50 on Metformin plus Insulin plus Sitagliptin. Concerning the gender of the patients, it is obtained that around 14% are male and 86% female in group 1 and group 2. From this data, it is anticipated that most of the cases of type 2 DM during ten years were reported among females in Karachi. Furthermore, type 2 diabetes mellitus patients belong to different age groups, mainly after 40 years. As shown in Table 3.1, most of the patients in groups 1 and 2 belong from the age group between 51 and 55 years. Moreover, all patients have been found with some types of co-morbidities along with the primary diagnosis of type 2 DM and Hyperglycemia. For instance, in groups 1 & 2 most patients are found with hypertension 36% and 88%, respectively. In comparison, the ratio of multiple co-

morbidities is higher among the patients in groups 1 & 2. It implies that patients, who received Metformin plus Insulin alone, and Metformin plus Insulin plus Sitagliptin are having previously determined higher risk of developing multiple co-morbidities.

Table 3.1: Characteristics of Patients with Different Treatments

	M+I (Group 1)	**S+M+I (Group 2)**
Gender		
Male	7 (14%)	7 (14%)
Female	43 (86%)	43 (86%)
Age		
31-35	0	0
36-40	0	0
41-45	4 (8%)	4 (8%)
46-50	11 (22%)	11 (22%)
51-55	18 (36%)	18 (36%)
56-60	12 (24%)	12 (24%)
61-65	5 (10%)	5 (10%)
Co-morbidities		
None	4 (8%)	4 (8%)
Hypertension	18 (36%)	18 (36%)
Hyperthyroidism	2 (4%)	2 (4%)
Spondylosis	1 (2%)	1 (2%)
Thrombocytosis	1 (2%)	1 (2%)
Multiple Co- Morbidities	24 (24%)	24 (24%)
Diagnosis		
Type 2 DM	50 (100%)	50 (100%)
Hyperglycemia	0	0

Where M= metformin; I= insulin; S= sitagliptin

3.2 EFFICACY AND SAFETY

To determine the efficiency and safety of sitagliptin among the patients with type-2 DM treated with insulin and metformin combination, a mean comparison is made by taking several parameters such as level of blood sugar (FBS, RBS, HbA1C), liver function test (AST,ALT, ALP), coagulation profile (PT, INR), complete blood count (WBCs, RBCs, Hb, Platelets), lipid profile (LDL, HDL, TGs, serum cholesterol), kidney profile (serum urea, serum creatinine), and serum electrolytes (Na, K, Mg, Cl). The results are presented below following the mentioned groups:

3.2.1: Efficacy and safety of sitagliptin with metformin and insulin in type-2 DM patients

3.2.1.1: Effect of treatment on blood sugar level of patients

Table 3.2 shows the comparative results of group 1 and group 2 patients who received the insulin and metformin alone and sitagliptin + metformin and insulin, respectively. It was first found that the blood sugar level has been changed significantly.

3.2.1.1.1: Effect on fasting blood sugar (FBS)

Data analyzed by Paired Samples t-Test show that FBS of group 1 and group 2 are weakly and positively correlated ($r = 0.225$, $p > 0.05$). However, the relationship between the two groups is statistically insignificant. There is a significant average difference between the FBS level of the two groups ($t_{49} = 18.45$, $p < 0.001$. (Graph 3.1).

3.2.1.1.2: Effect on random blood sugar (RBS)

Paired Samples t-Test analysis show that RBS of group 1 and group 2 are weakly and positively correlated ($r = 0.093$, $p > 0.05$). However, the relationship between the two groups is statistically insignificant. Likewise, there is a significant average difference between the RBS of the two groups ($t_{49} = 16.690$, $p < 0.001$). (Graph 3.2).

3.2.1.1.3: Effect on HbA1c

Paired Samples t-Test analysis shows that the correlation between HbA1c of groups 1 and 2 is weak and positive ($r = 0.257$, $p > 0.05$). However, the relationship between the two groups is statistically insignificant. Similarly, there is a significant average difference between the HbA1c of the two groups ($t_{49} = 28.386$, $p < 0.001$). (Graph 3.3).

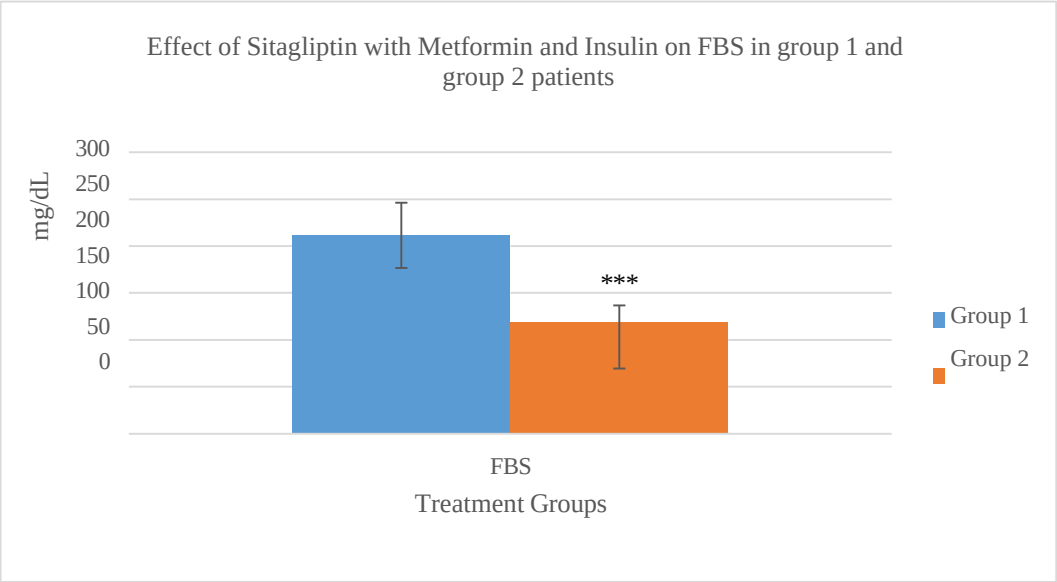
To summarize, it can be observed that all the parameters (FBS, RBS, and HbA1c) of group 2 were found lower than group 1, which indicates that combination of S with M and I are more effective in maintaining blood sugar profile in comparison to M and I combination.

Table 3.2: Effects of sitagliptin with metformin and insulin among type-2 DM patients of group 1 & 2

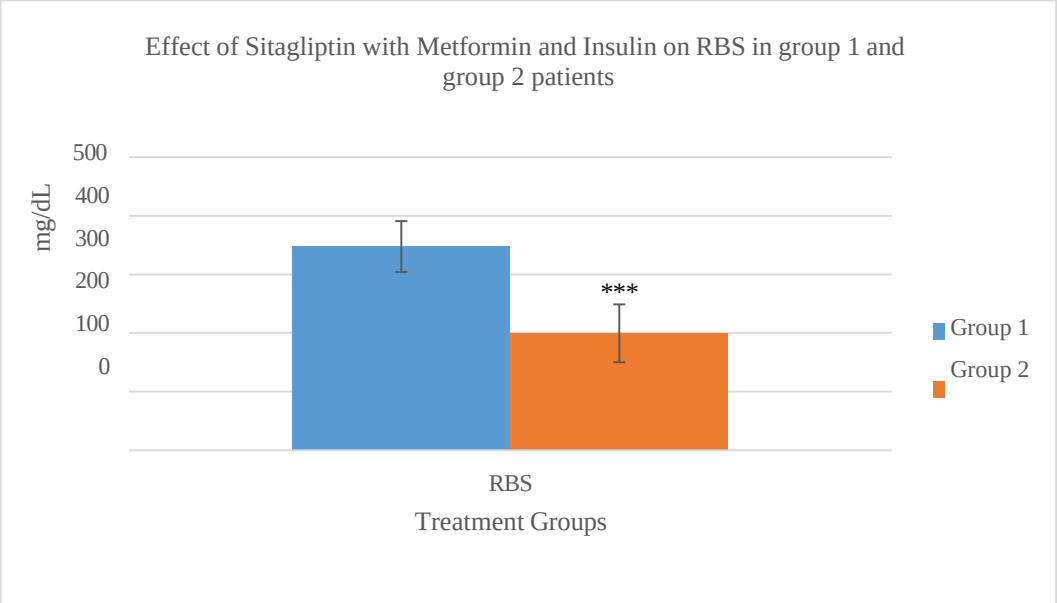
Estimated Treatment Differences (95% CI, df = 49) (N=50)						
Parameters	**Met + Ins**	**Sit + Met + Ins**	**Mean Diff.**	**r**	**T**	**P-Value**
	Mean ± S.D	**Mean ± S.D**				
Level of Blood Sugar						
FBS	211.54 ± 34.938	118.86 ± 17.927	92.68	0.225	18.457	0.000***
RBS	347.76 ± 43.661	199.46 ± 49.445	148.3	0.093	16.69	0.000***
HbA1c	13.572 ± 1.624	7.225 ± 0.602	6.347	0.257	28.386	0.000***
Lipid Profile						
Serum Cholesterol	181.12 ± 43.845	177.14 ± 45.238	3.98	0.505	0.635	0.528
HDL	44.84 ± 4.117	47.14 ± 8.526	-2.3	0.165	-1.84	0.072
LDL	111.56 ± 27.287	84.26 ± 12.841	27.3	0.356	7.514	0.000***
TGs	151.74 ± 31.424	135.3 ± 13.616	16.44	0.243	3.742	0.000***
Liver Function Test						
ALT	13.91 ± 4.213	17.24 ± 7.107	-3.33	-0.011	-2.836	0.007**
AST	14.5 ± 6.142	23.81 ± 12.865	-9.31	0.183	-4.986	0.000***
ALP	161.84 ± 64.373	165.32 ± 74.82	-3.48	0.665	-0.426	0.672
Kidney Profile						
Serum Urea	22.3 ± 4.791	21.82 ± 8.394	0.48	0.334	0.416	0.679
Serum Creatinine	1.03 ± 0.455	1.032 ± 0.367	-0.032	0.722	-0.723	0.473
Serum Electrolytes						
NA	140.52 ± 7.169	137.84 ± 5.281	2.68	0.426	2.764	0.008**
K	4.08 ± 0.308	4.19 ± 0.367	-0.11	0.675	-2.794	0.007**
CI	104.1 ± 2.485	102.3 ± 2.565	1.8	0.652	6.034	0.000***
Mg	32.414 ± 57.9	1.6 ± 0.551	30.814	-0.053	3.761	0.000***
Coagulation Profile						

PT	11.298 ± 0.436	10.908 ± 1.091	0.39	-0.082	2.284	0.027*
INR	1.023 ± 0.155	1.114 ± 0.344	-0.091	0.712	-2.493	0.016*
Complete Blood Count						
WBCs	10.186 ± 0.577	9.062 ± 2.117	1.125	0.448	4.123	0.000***
RBCs	4.748 ± 0.435	4.946 ± 0.521	-0.198	0.345	-2.543	0.014*
Hb	11.456 ± 1.558	12.084 ± 1.75	-0.628	0.471	-2.598	0.012*
Platelets	244.14 ± 44.543	258.86 ± 65.936	-14.72	0.38	-1.625	0.111

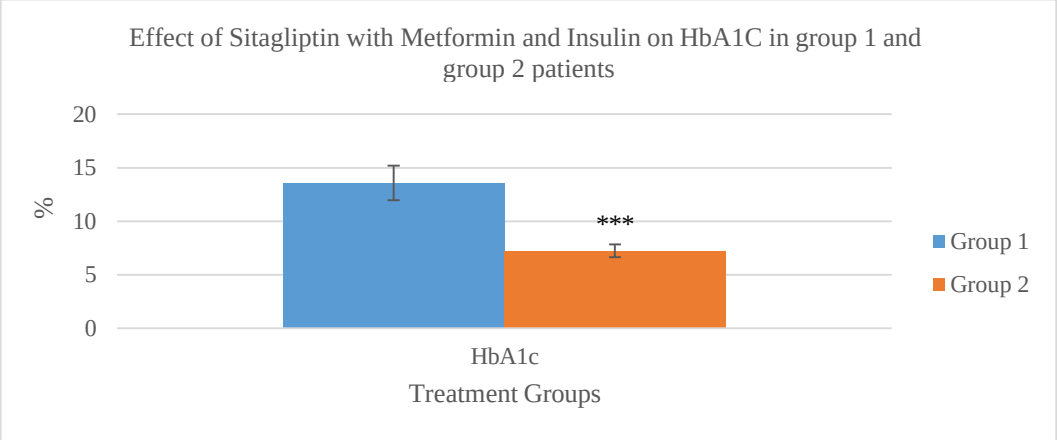
Values are mean ± SD. Data analyzed by paired sample t-test; n = 50. Significant at: *p<0.05; **p<0.01; ***p<0.001. Where Met= metformin; Ins = insulin; Sit= sitagliptin.



Graph 3.1: Effects of sitagliptin with metformin and insulin on FBS among group 1 & 2 patients



Graph 3.2: Effects of sitagliptin with metformin and insulin on RBS among group 1 & 2 patients



Graph 3.3: Effects of sitagliptin with metformin and insulin on HbA1C among group 1 & 2 patients

3.2.2: Effect of treatment on lipid profile of patients

The diversion in the results of the parameters of lipid profile of group 1 and group 2 is shown in Table 3.2:

3.2.2.1: Effects on serum cholesterol

Data analyzed by Paired Samples t-Test show that serum cholesterol of groups 1 and 2 are moderately and positively correlated ($r = 0.505$, $p < 0.05$). However, the relationship between the two groups is statistically significant. In the same way, there is not a significant average difference between the serum cholesterol of the two groups ($t49 = 0.635$, $p > 0.05$). (Graph 3.4).

3.2.2.2: Effects on HDL

Data analyzed by Paired Samples t-Test show that HDL of group 1 and group 2 are weakly and positively correlated ($r = 0.165$, $p > 0.05$). However, the relationship between the two groups is statistically insignificant. There is no significant average difference between the HDL of the two groups ($t49 = -1.84$, $p > 0.05$). (Graph 3.5).

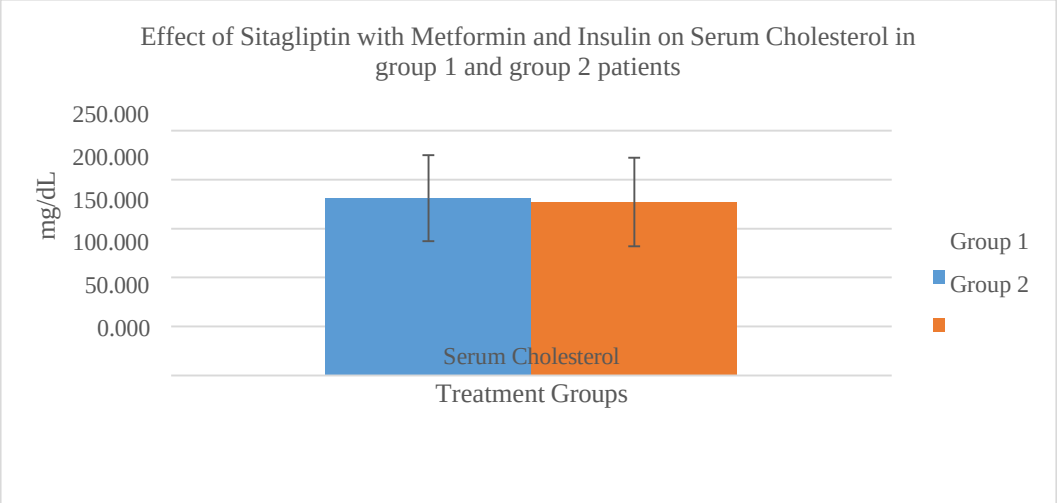
3.2.2.3: Effects on LDL

Data analyzed by Paired Samples t-Test show that LDL of group 1 and group 2 are weakly and positively correlated ($r = 0.356$, $p < 0.05$). However, the relationship between the two groups is statistically significant. Accordingly, there is a significant average difference between the LDL of the two groups ($t49 = 7.514$, $p < 0.001$). (Graph 3.6).

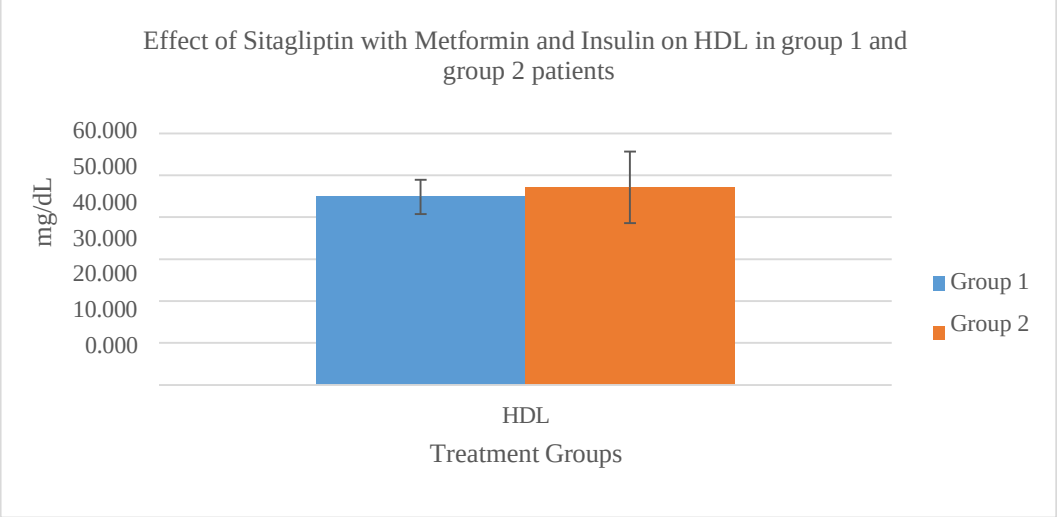
3.2.2.4: Effects on TGs

Data analyzed by Paired Samples t-Test show that TGs of group 1 and group 2 are weakly and positively correlated ($r = 0.243$, $p > 0.05$). However, the relationship between the two groups is statistically insignificant. Likewise, there is a significant average difference between the TGs of the two groups ($t49 = 3.742$, $p < 0.001$). (Graph 3.7).

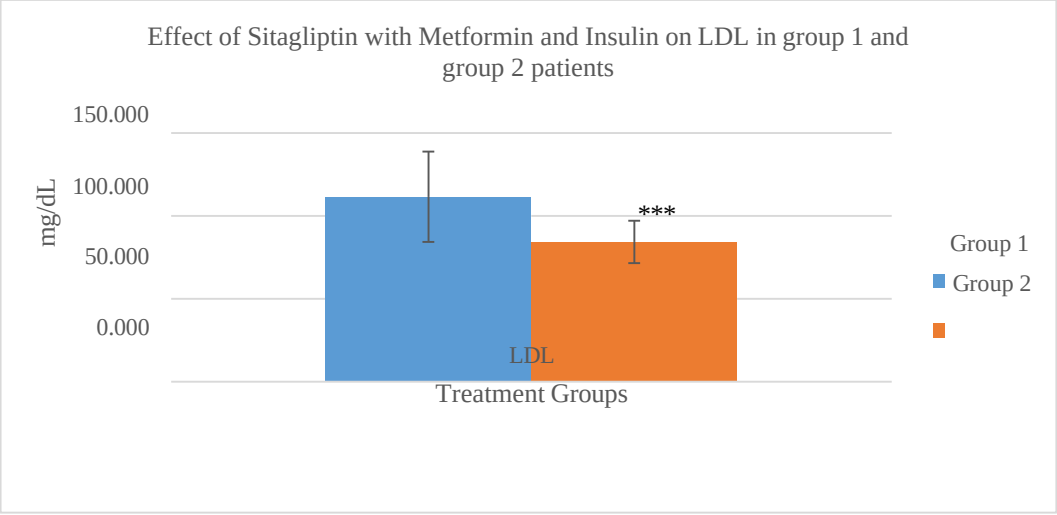
Lipid Profile mentioned that LDL, considered bad cholesterol, gets lowered when S is added with M and I (Group 2). Similarly, the TGs of Group 1 are higher than Group 2. Moreover, serum cholesterol of Group 1 is also found higher than Group 2. HDL increased in the same group of patients (S+M+I), showing that S has an excellent tendency to lower the cholesterol levels and work on the increase in good cholesterol levels. Finally, it seems that sitagliptin is safe enough for maintaining lipid profile towards normal in type 2 diabetics and does not deteriorate their lipids levels.



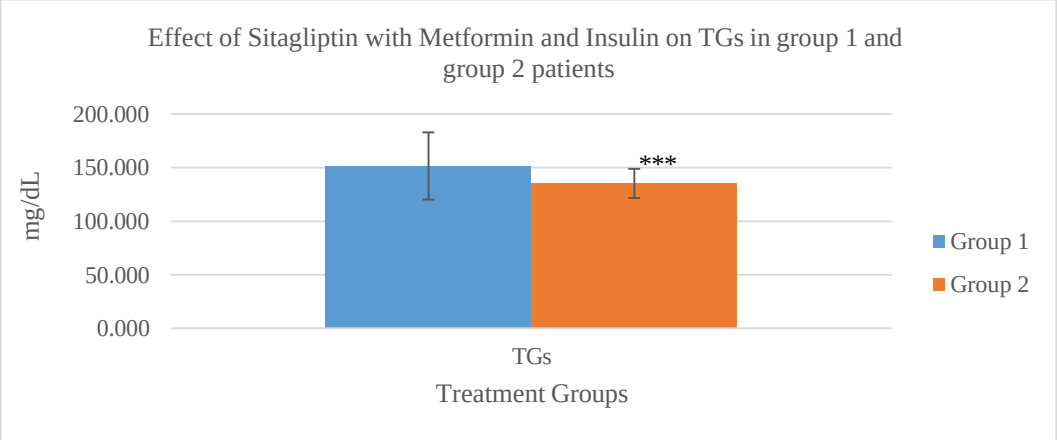
Graph 3.4: Effects of sitagliptin with metformin and insulin on serum cholesterol among group 1 & 2 patients



Graph 3.5: Effects of sitagliptin with metformin and insulin on HDL among group 1 & 2 patients



Graph 3.6: Effects of sitagliptin with metformin and insulin on LDL among group 1 & 2 patients



Graph 3.7: Effects of sitagliptin with metformin and insulin on TGs among group 1 & 2 patients

Values are mean ± SD. Data analyzed by paired sample t-test; n = 50. Significant at: *p<0.05; **p <0.01;
***p<0.001.

Effect of treatment on liver function test of patients

The effects of treatment on liver function test of group 1 and 2 are presented in Table 3.2.

Effects on ALT

Paired Samples t-Test show that ALT of group 1 and group 2 are weakly and negatively correlated (r = -0.011, p > 0.05). However, the relationship between the two groups is statistically insignificant. There is a significant average difference between the ALT of the two groups (t_{49} = -2.836, p <0.01). (Graph 3.8).

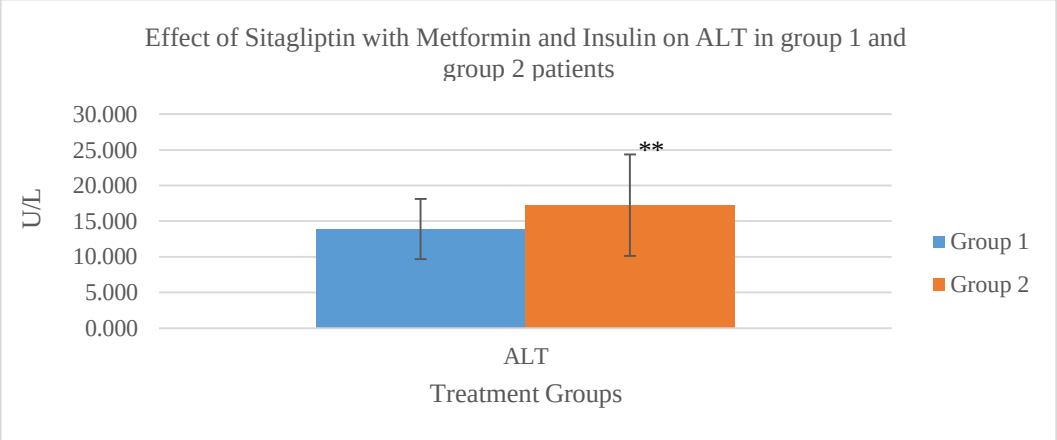
Effects on AST

Data analyzed by Paired Samples t-Test show that AST of group 1 and group 2 are weakly and positively correlated (r = 0.0.183, p > 0.05). However, the relationship between the two groups is statistically insignificant. In the same way, there is a significant average difference between the AST of the two groups (t_{49} = -4.986, p <0.001). (Graph 3.9).

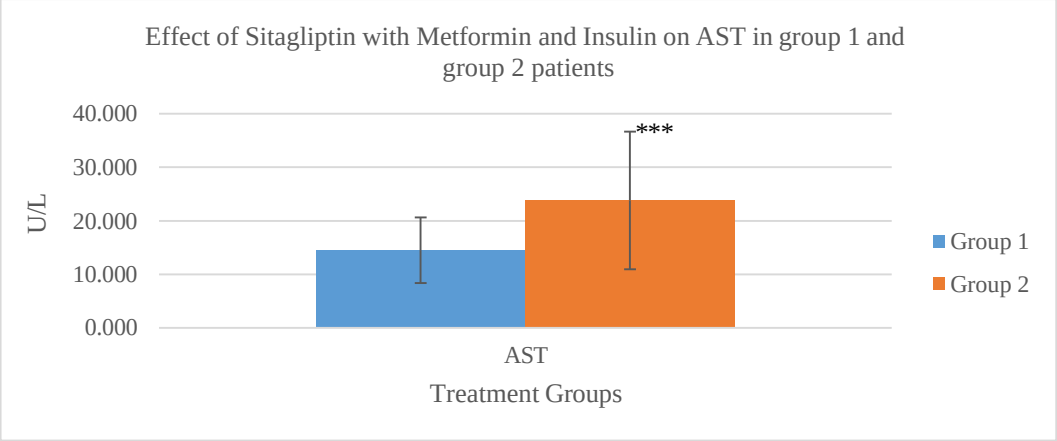
Effects on ALP

Data analyzed by Paired Samples t-Test show that ALP of group 1 and group 2 are moderately and positively correlated (r = 0.665, p <0.05). However, the relationship between the two groups is statistically significant. However, there is not a significant average difference between the ALP of the two groups (t_{49} = -0.426, p >0.05). (Graph 3.10).

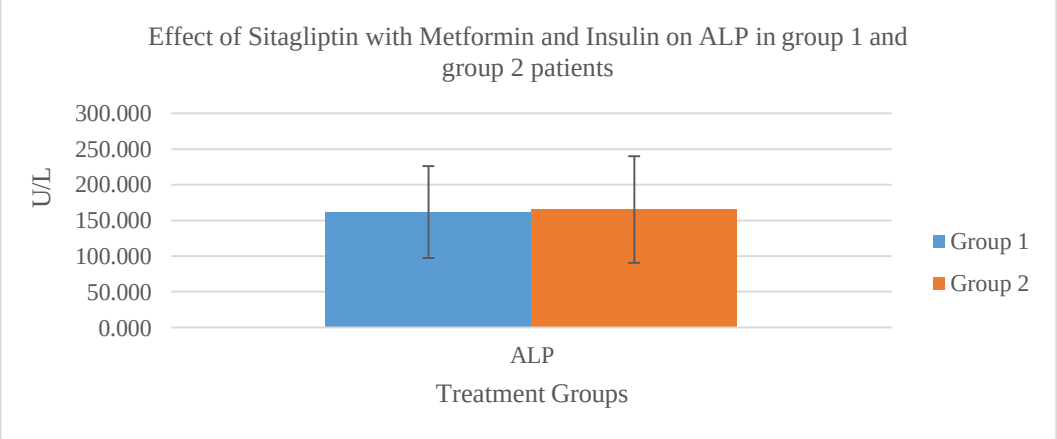
To summarize, the LFT profile also represents that ALT, AST, and ALP values were slightly lower in group 1, which is using M and I, while these parameters were on the higher side in group 2.



Graph 3.8: Effects of sitagliptin with metformin and insulin on ALT among group 1 & 2 patients



Graph 3.9: Effects of sitagliptin with metformin and insulin on AST among group 1 & 2 patients



Graph 3.10: Effects of sitagliptin with metformin and insulin on ALP among group 1 & 2 patients

Values are mean ± SD. Data analyzed by paired sample t-test; n = 50. Significant at: *p<0.05; ** p<0.01;
***p<0.001.

Effect of treatment on kidney profile of patients

The effects of treatment on kidney profile show no significant change in kidney functions of both groups as shown in Table 3.2:

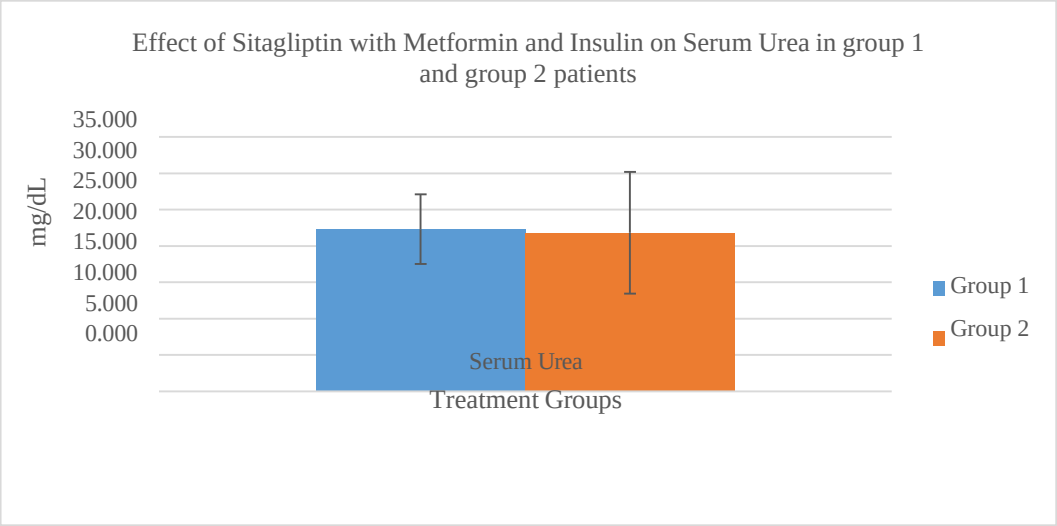
Effects on serum urea

Data analyzed by Paired Samples t-Test show that serum urea of group 1 and group 2 are weakly and positively correlated ($r = 0.334$, $p < 0.05$). However, the relationship between the two groups is statistically significant. There is no significant average difference between the serum urea of the two groups ($t49 = 0.416$, $p > 0.05$). (Graph 3.11).

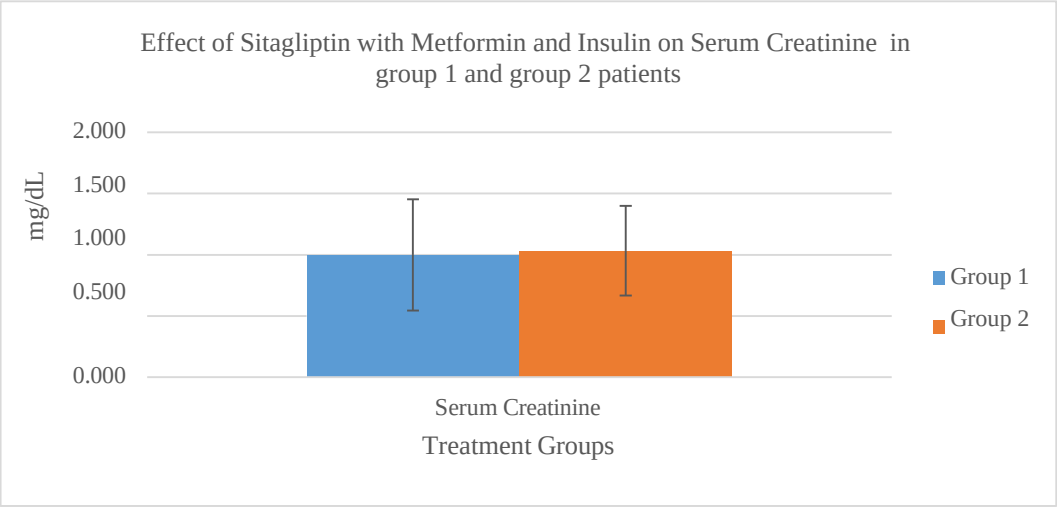
Effects on serum creatinine

Data analyzed by Paired Samples t-Test show that serum creatinine of group 1 and group 2 are strongly and positively correlated ($r = 0.722$, $p < 0.001$). However, the relationship between the two groups is statistically significant. Likewise, there is no significant average difference between the serum creatinine of the two groups ($t49 = -0.723$, $p > 0.05$). (Graph 3.12).

The kidney profile is critically analyzed when medicine's safety profile is being studied. Serum urea and serum creatinine, slightly altered compared to group 1 and group 2, showed that addition of sitagliptin with other antidiabetic agents maintains the safety outcomes with better efficacy.



Graph 3.11: Effects of sitagliptin with metformin & insulin on serum urea among group 1 & 2 patients



Graph 3.12: Effects of sitagliptin with metformin & insulin on serum creatinine among group 1 & 2 patients

Values are mean ± SD. Data analyzed by paired sample t-test; n = 50. Significant at: *p<0.05; **p <0.01;

***p<0.001.

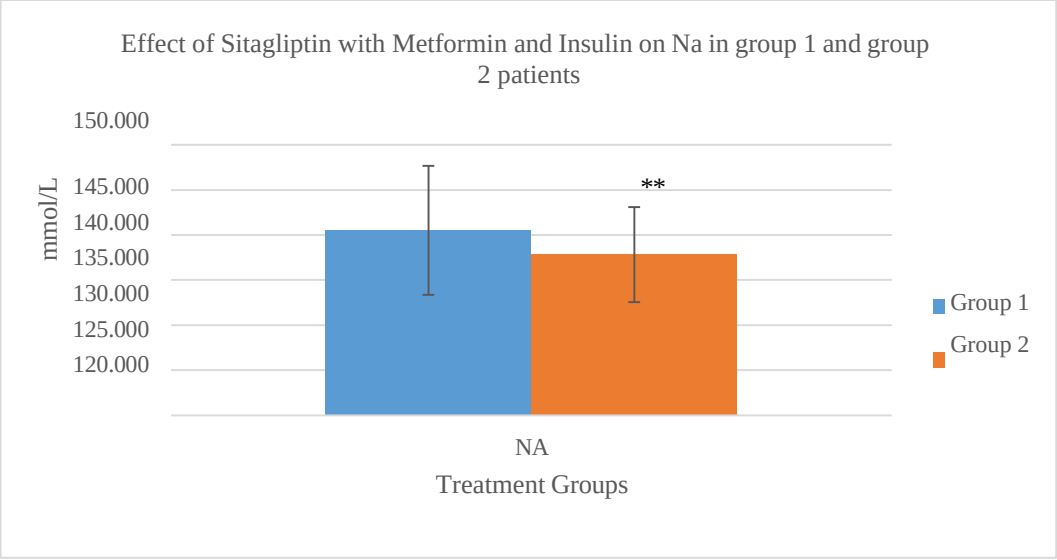
Effect of treatment on serum electrolytes of patients
The effect of treatment on serum electrolytes of group 1 and group 2 are shown in Table 3.2.

Effects on serum Na
Data analyzed by Paired Samples t-Test show that Na level of group 1 and group 2 are moderately and positively correlated ($r = 0.426$, $p < 0.01$). However, the relationship between the two groups is statistically significant. There is a significant average difference between the Na level of the two groups ($t_{49} = 2.764$, $p < 0.01$). (Graph 3.13).

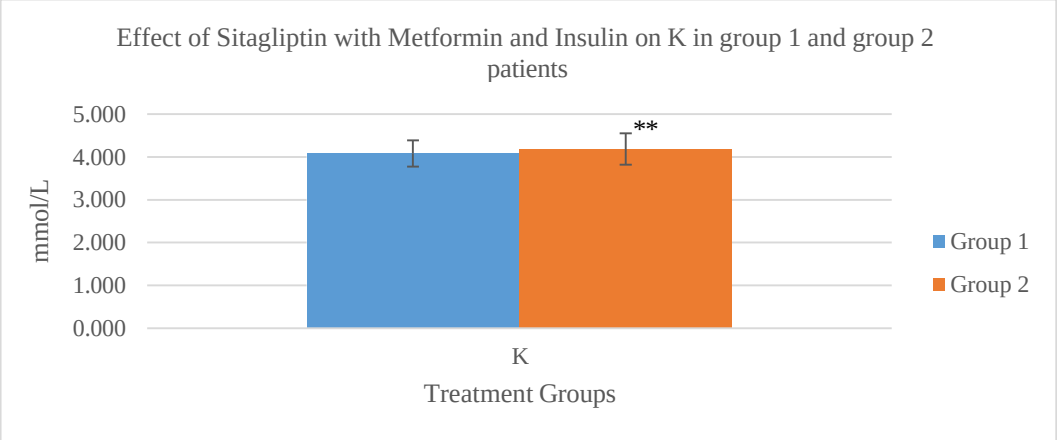
Effects on serum K
Data analyzed by Paired Samples t-Test show that K level of group 1 and group 2 are moderately and positively correlated ($r = 0.675$, $p < 0.001$). However, the relationship between the two groups is statistically significant. Likewise, there is a significant average difference between K level of the two groups ($t_{49} = -2.794$, $p < 0.01$). (Graph 3.14).

Effects on serum CI
Data analyzed by Paired Samples t-Test show that CI level of group 1 and group 2 are moderately and positively correlated ($r = 0.652$, $p < 0.001$). However, the relationship between the two groups is statistically significant. There is a significant average difference between Cl level of the two groups ($t_{49} = 6.034$, $p < 0.001$). (Graph 3.15).

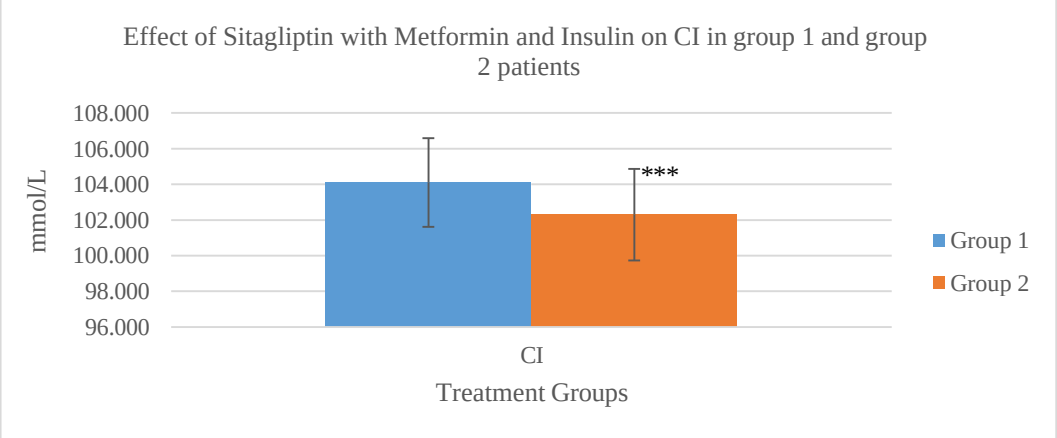
Effects on serum Mg
Data analyzed by Paired Samples t-Test show that Mg level of group 1 and group 2 are weakly and negatively correlated ($r = -0.053$, $p > 0.05$). However, the relationship between the two groups is statistically insignificant. Similarly, there is a significant average difference between the Mg level of the two groups ($t_{49} = 3.761$, $p < 0.001$). (Graph 3.16).



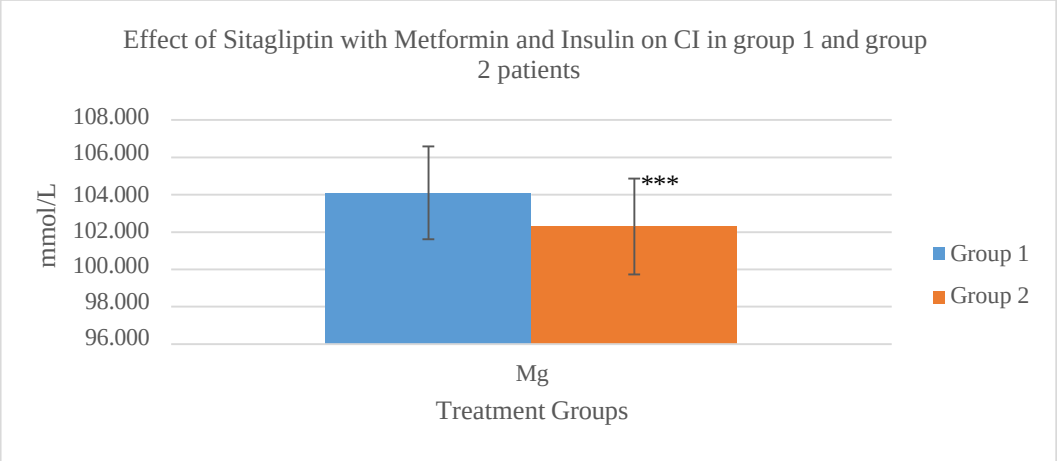
Graph 3.13: Effects of sitagliptin with metformin and insulin on Na among group 1 & 2 patients



Graph 3.14: Effects of sitagliptin with metformin and insulin on K among group 1 & 2 patients



Graph 3.15: Effects of sitagliptin with metformin and insulin on Cl among group 1 & 2 patients



Graph 3.16: Effects of sitagliptin with metformin and insulin on Mg among group 1 & 2 patients

Values are mean ± SD. Data analyzed by paired sample t-test; n = 50. Significant at: *p<0.05; **p <0.01;
***p<0.001.

Effect of treatment on coagulation profile of patients

The effect of treatment on the coagulation profile of group1 and group 2 are shown in Table 3.2.

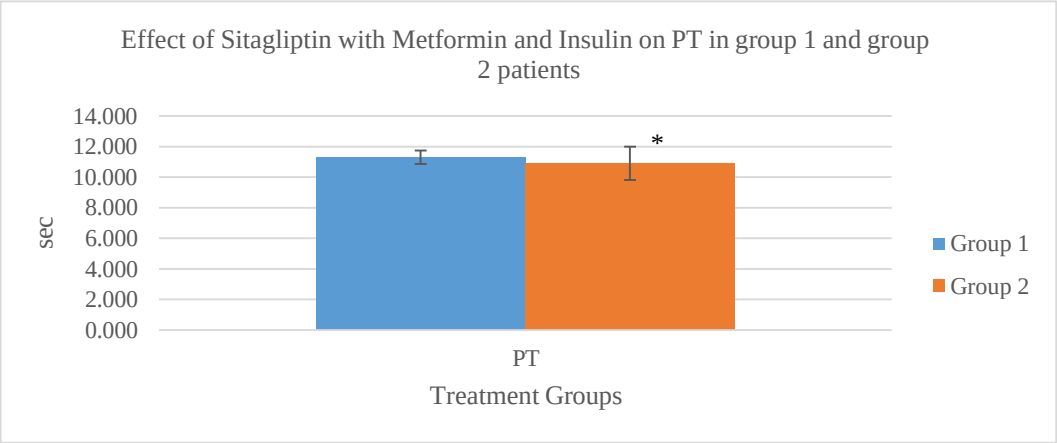
Effects on PT

Data analyzed by Paired Samples t-Test show that the PT of group 1 and group 2 are weakly and negatively correlated ($r = -0.082$, $p > 0.05$). However, the relationship between the two groups is statistically insignificant. There is a significant average difference between the PT of the two groups ($t49 = 2.284$, $p < 0.05$). (Graph 3.17).

Effects on INR

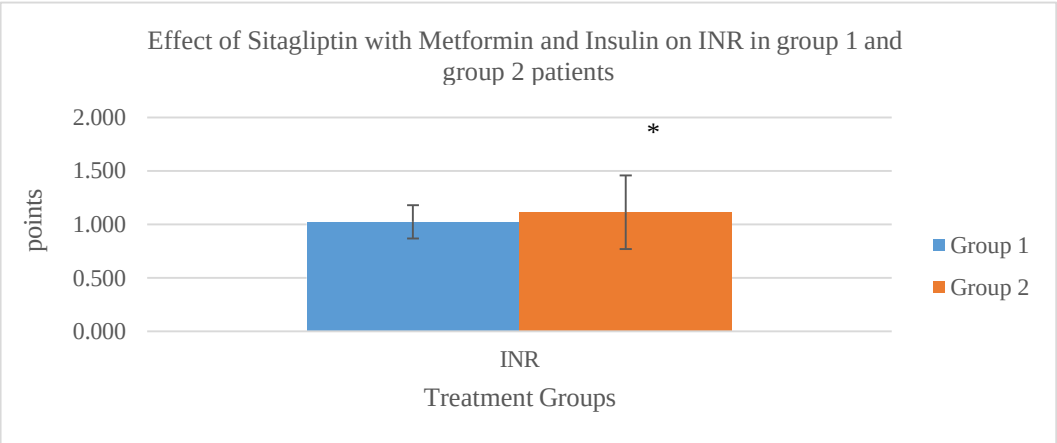
Data analyzed by Paired Samples t-Test show that INR of group 1 and group 2 are strongly and positively correlated ($r = 0.712$, $p < 0.05$). However, the relationship between the two groups is statistically significant. Similarly, there is a significant average difference between the INR of the two groups ($t49 = -2.493$, $p < 0.05$). (Graph 3.18).

The coagulation profile based on PT and INR shows that PT of group 1 is slightly higher than group 2, and INR of group 2 is slightly higher than group1. The addition of S does not affect these blood clotting parameters.



Graph 3.17: Effects of sitagliptin with metformin and insulin on PT among group 1 & 2 patients

Values are mean ± SD. Data analyzed by paired sample t-test; n = 50. Significant at: *p<0.05; **p <0.01; ***p<0.001.



Graph 3.18: Effects of sitagliptin with metformin and insulin on INR among group 1 & 2 patients

Values are mean ± SD. Data analyzed by paired sample t-test; n = 50. Significant at: *p<0.05; **p <0.01;
***p<0.001.

Effect of treatment on complete blood count parameters of patients

The effects of treatment on complete blood count's parameters of group 1 and 2 are presented in Table 3.2.

Effects on WBCs

Data analyzed by Paired Samples t-Test show that WBCs count of group 1 and group 2 are moderately and positively correlated ($r = 0.448$, $p < 0.01$). However, the relationship between the two groups is statistically significant. There is a significant average difference between WBCs count of the two groups ($t_{49} = 4.123$, $p < 0.001$). (Graph 3.19).

Effects on RBCs

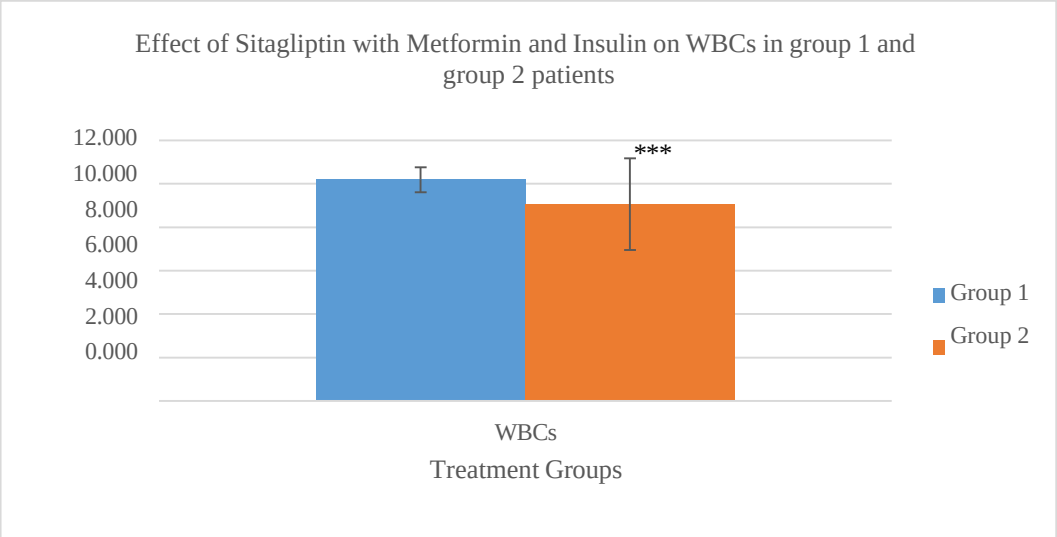
Data analyzed by Paired Samples t-Test show that RBCs count of group 1 and group 2 are weakly and positively correlated ($r = 0.345$, $p < 0.05$). However, the relationship between the two groups is statistically significant. Likewise, there is a significant average difference between RBCs of the two groups (S+M+I) ($t_{49} = -2.543$, $p < 0.05$). (Graph 3.20).

Effects on Hb

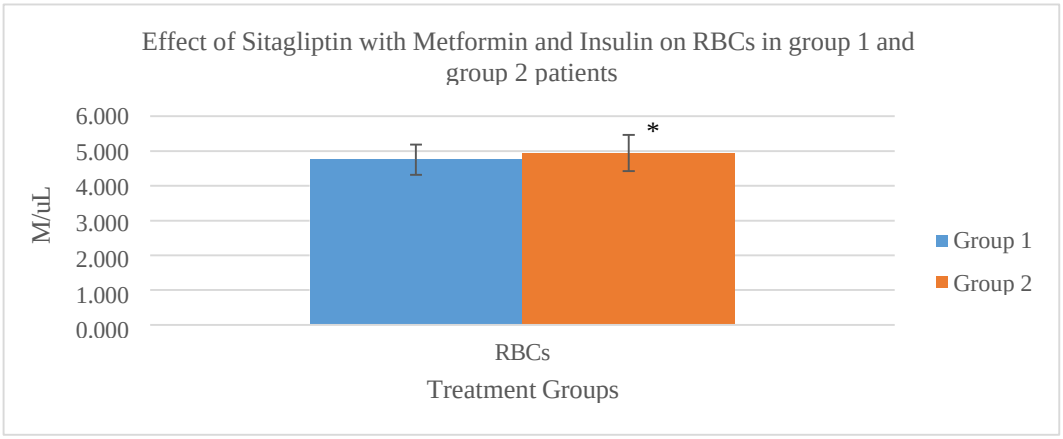
Data analyzed by Paired Samples t-Test show that Hb level of group 1 and group 2 are moderately and positively correlated ($r = 0.471$, $p < 0.01$). However, the relationship between the two groups is statistically significant. There is a significant average difference between Hb level of the two groups ($t_{49} = -2.598$, $p < 0.05$). (Graph 3.21).

Effects on platelets

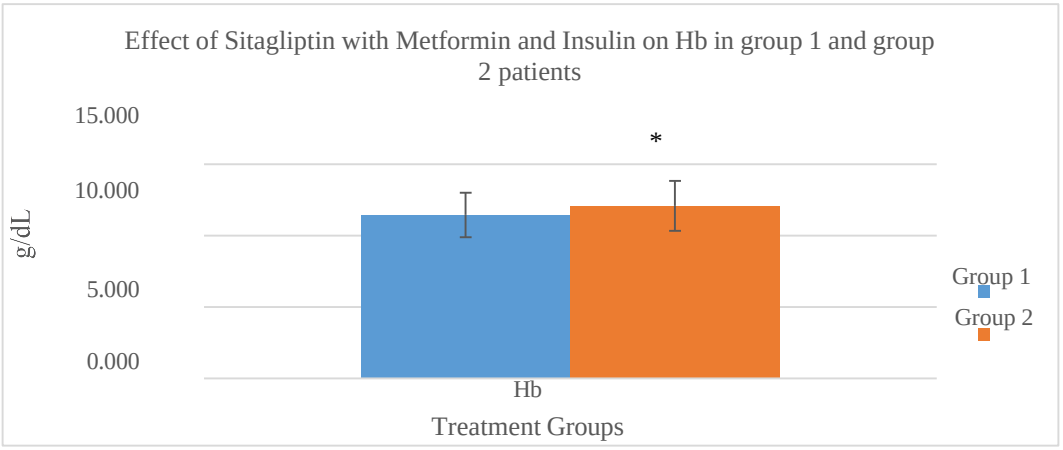
Data analyzed by Paired Samples t-Test show that platelets count of group 1 and group 2 are weakly and positively correlated ($r = 0.380$, $p < 0.01$). However, the relationship between the two groups is statistically significant. There is not a significant average difference between the platelets count of the two groups ($t_{49} = -1.625$, $p > 0.05$) found. (Graph 3.22).



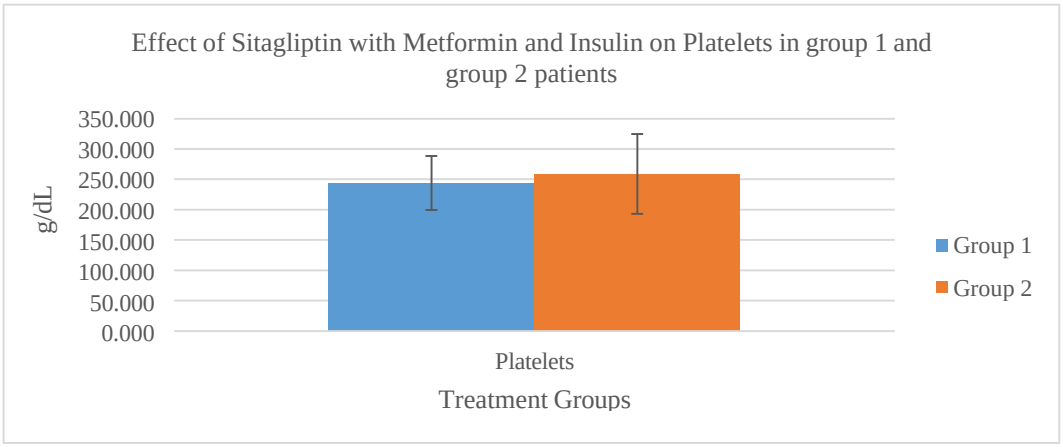
Graph 3.19: Effects of sitagliptin with metformin and insulin on WBCs among group 1 & 2 patients



Graph 3.20: Effects of sitagliptin with metformin and insulin on RBCs among group 1 & 2 patients



Graph 3.21: Effects of sitagliptin with metformin and insulin on Hb among group 1 & 2 patients



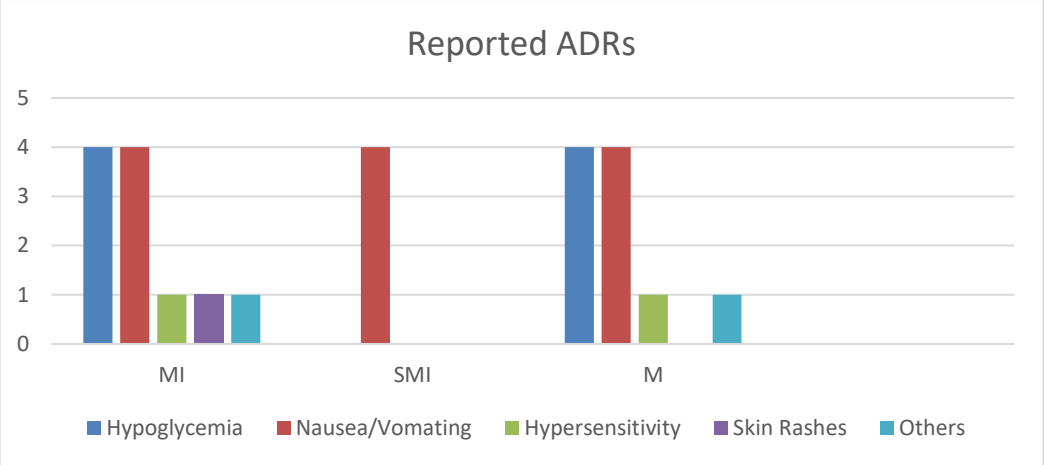
Graph 3.22: Effects of sitagliptin with metformin and insulin on platelets among group 1 & 2 patients

Values are mean ± SD. Data analyzed by paired sample t-test; n = 50. Significant at: *p<0.05; **p<0.01;
***p<0.001.

3.4 SAFETY EVALUATION OF SITAGLIPTIN FROM ADVERSE DRUG REACTIONS

Adverse Drug Reactions (ADRs) is the parameter that can be evaluated to analyze a drug's safety profile. For safety profile evaluation, ADRs of the medicaments given to the patients are studied by

selecting 24 patients from the 2 groups. The most-reported ADR of hypoglycemia is when the patients' blood sugar levels go below the average range of blood sugar levels or required levels. Four patients are from group 1, who suffered Hypoglycemia when using metformin and insulin. There is no patient-reported hypoglycemia in group 2, which are added with Sitagliptin and the previous therapy.
Similarly, four patients reported Nausea/Vomiting from group 1 and group 2. From group 1, 1 patient reported having hypersensitivity issues, one was told to have skin rashes, and 1 informed other than these ADRs. However, no patient from group 2 reported any of these ADRs. It shows that Sitagliptin is not only effective but safe, as the rate of producing ADRs is less than the other antidiabetic agents used in the study. (Graph 3.23)
The reported ADRs remained less reported once again, which is indicative of the good safety profile of sitagliptin as an antidiabetic agent. In both the groups where the sitagliptin is added, it can be seen that fewer ADRs are reported.



Graph 3.23: Safety Evaluation of Sitagliptin from ADRs Reported among Patients

DISCUSSION

Diabetes can be managed appropriately with antidiabetic agents and insulin along with adopting healthy lifestyle habits. Looking at the results, it can be stated that safety and efficacy levels of single or combination therapies are different which needs to be considered while treating a diabetic patient as per the diabetic condition, complications and comorbidities the patient is suffering from. When the group 1 and group 2 patients are compared who received the insulin and metformin combination therapy and metformin and insulin + sitagliptin respectively, the results of blood sugar levels were found better in the group 2 considering all the parameters. Such as, FBS and RBS were both lower in the group 2 than group 1 indicative of improved levels of efficacy when the sitagliptin added to the insulin and metformin treatment. In the similar manner, HbA1C which is highly considerable and reliable parameter when analyzing the situation of diabetes, the trend of the above was found that the HbA1C of group 1 was higher than the HbA1C levels of group 2. Marn-Pealver et al. (2016) also documented with the findings and demonstrated that sitagliptin reduces HbA1c levels considerably.
Moreover, the LFT represents that the addition of the sitagliptin to the metformin and insulin increased the ALT and AST notably. However, change in ALP level is not meaningful. Previous study showed safety and efficacy of sitagliptin in diabetic patients. However, drug-induced hepatotoxicity is reported by Shahbaz et al (2018) in only two cases of poorly controlled diabetic patients where sitagliptin was added for better glycemic control, therefore if drug-induced liver injuries are suspected it is suggested to monitor LFTs periodically in patients treated with sitagliptin and drug therapy to be stopped immediately if change in liver profile is noted.

CBC also represents that efficacy of the antidiabetic treatment get enhanced and safer when combined with sitagliptin. The increase in RBCs, Hb, and platelets count and decrease in the WBCs in group 2

are all good indications in this regard (Aono et al., 2016).
Similarly, lipid profile of patients also indicated that the LDL levels get lowered when sitagliptin was added to metformin and insulin therapy. Elhini et al., (2021) reported improvement in lipid metabolism and concluded that increase in HDL levels and lowering of LDL, total cholesterol, serum result in weight-loss and lowering in blood pressure (Elhini et al., 2021). (Xu et al., (2017) studied the effect of sitagliptin on lipid metabolism in animal model of fatty liver and reported hepato-protection and modulation in lipid metabolism which is due to increased expression of lipid metabolizing enzymes and up regulation of peroxisome-proliferative activated receptor alpha. The outcomes of our research also proved that when sitagliptin was added to metformin and insulin therapy, it seems to be hepato-protective and having favorably lipid metabolism.

Kidney profile is one of the main parameters for analyzing safety profile of a drug treatment in type 2 diabetic patients because diabetes itself is a risk factor for chronic kidney disease in those patients. Results of the present study are also in accordance to the previous findings and a meaningful decrease in FBS, RBS, and HbA1c levels when sitagliptin is added to the therapy (metformin and insulin) was observed. These findings suggest that addition of sitagliptin not only improved the status of blood glucose control but could be another reason for reducing the progression of diabetic nephropathy.

Diabetes is associated with disturbance in serum level of sodium, potassium, magnesium etc. (Liamis et al. 2014). In the present study, addition of sitagliptin to metformin and insulin therapy resulted in lowering of Na, Mg, and Cl which is suggestive of good excretion of Na and Cl. Based on these findings it could be concluded that fluid is not being retained in excess amount in those patients therefore, risk of hypertension could be minimized in those patients' taking insulin and metformin in combination with sitagliptin.

In the present study, treatment with sitagliptin was found to be well tolerated with low incidence of hypoglycemia in those patients who were added with sitagliptin i.e. group 2. Glucose-dependent mechanism of action of sitagliptin could be the reason of this low incidence rate of hypoglycemia (Ballav & Gough, 2013) Moreover, only ADR reported from group 2 were nausea and vomiting. Previous studies reported GI adverse effects with different antidiabetic, including metformin, α-glucosidase inhibitors and GLP-1 analogues (Mehanna, 2013).

Since sitagliptin increases intact GLP-1 and GIP levels (Kelly et al., 2021), therefore in the current study, the incidence rates of nausea and vomiting were increased in sitagliptin add- on group (i.e. group 2). The GI adverse effects profile of the sitagliptin co-administered groups was similar to that of metformin alone and metformin co- administered groups. However, in group 1 there were several ADRs which were reported by the patients such as skin rashes, hypersensitivity issues and others, whereas, incidence of such ADRs is low in groups where sitagliptin is administered in combination.

Hypoglycemia is the most significant impediment to insulin-dependent type 2 diabetes patients meeting their glycemic objectives (Donner & Sarkar, 2019). However, from above findings it can be observed that hypoglycemic effects are not observed in group 2 where patients were added sitagliptin in their therapy.

As per research objective, sitagliptin is effective as well as safe when used in combination with other antidiabetic agents but care should be taken while monitoring the liver and kidney parameters while giving therapy.

Lastly, in accordance the research questions which are investigative about the level of safety and efficacy of sitagliptin in type 2 DM patients treated with insulin and/or other oral hypoglycemic

combination, results can be considered as favorable and optimistic. The findings are suggestive good levels of efficacy as all the levels of the blood sugar are reduced which were elevated due to diabetes. The levels of the HbA1C were also found reduced and with satisfied results in the parameters checked and evaluated for analyzing the safety profile of sitagliptin such as coagulation profile, CBC, and serum electrolytes levels. The addition of the sitagliptin has found satisfactory and enhancing in all the combination where it was added. Another fact which positively impacts the safety level of sitagliptin for using it in combination with insulin and/or other oral hypoglycemic combination is it has improved the situation of the ADRs as well when used in combination.

CONCLUSIONS

In this study safety and efficacy of sitagliptin was checked in patient with type-2 diabetes treated with insulin and metformin combination. Results considered as favorable and idealistic. The discoveries are suggestive great levels of adequacy as all the levels of the blood sugar are diminished which were elevated due to diabetes. The levels of the HbA1C were too found diminished and with fulfilled results within the parameters checked and assessed for analyzing the safety profile of sitagliptin such as coagulation profile, CBC and serum electrolytes levels. The addition of the sitagliptin has found satisfactory. Another fact which emphatically impacts the safety level of sitagliptin with metformin and insulin combination is the lowering down the ADRs.

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