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AN INTERVENTIONAL CLINICAL TRIAL TO MAKE COMPARISON OF ANTI-INFLAMMATORY EFFECTS OF GLIMEPIRIDE AND SITAGLIPTIN IN OBESE PATIENTS OF TYPE-2 DIABETES

Dr Hafza Hashmi[1], Dr Iqra Aslam[2], Dr Qurat ul Ain[3]

[1] Islamabad Medical and Dental College (IMDC), Islamabad

[2] Wah Medical College, Wah Cantt

[3] Rawalpindi Medical College, Rawalpindi

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Abstract:

Study Aim: *We conducted this study to make comparison of anti-inflammatory effects of glimepiride and sitagliptin in overweight patients of type-2 diabetes.*

Study design: *An Interventional Clinical Trial.*

Place and duration: *This study was carried out for the duration of six months starting from August, 2018 February, 2019 at Holy Family Hospital, Rawalpindi.*

Material and methodology: *We included a total of 110 overweight patients of type-2 diabetes. There were 70 (63.64%) males and 40 (36.36%) females. Randomly divided them into two groups as group-A and group-B. Sitagliptin 50mg was given to group-A while glimepiride 2mg was given to group-B for a time period of three months. Determined the dose corresponding to sugar level of blood. Measured the changes in C-reactive Protein (CRP) as primary results. Whereas, changes in lipid profile, HbA1C, blood sugar level and BMI were recorded as secondary results. Analysis of data was carried out through SPSS 20.*

Results: *All selected patients (110) were divided into two equal groups A and B. At the end of three months treatment HbA1C and blood sugar were found reduced but comparison results among both groups was non-significant with P value equal to 0.59 in group A and 0.17 in group B. Weight of body was slightly increased in group B using glimepiride. On the other hand, in group A using sitagliptin observed slight reduction in body mass. However, comparison of both groups was found non-significant with P value equal to 0.07. significant improvement observed in lipid profile of group A compared to group B that is) HDL-cholesterol (-2.6±6.2 A) vs (B 1.2±5.2) with P-value=0.03, LDL- cholesterol (-10±22.4 A) vs (B -0.8±18.7) with P-value=0.001, triglycerides (-19±44.6 A) vs (B -1.8±48.7) with P-value=0.001 and total cholesterol (-25±32.5 A) vs (B +1.5±45.4) with P-value=0.02. Significant reduction observed in CRP level during comparison of sitagliptin vs glimepiride as (-2.3±1.8 A) vs (B 0.8±1.5) with P-value=0.001.*

Conclusion: *In this study we observed that sitagliptin have strong anti-inflammatory effects as noticed via decrease in CRP levels in overweight patients of type 2 diabetes when compared with glimepiride. Sitagliptin also showed positive effects on lipid profiles and glycemic control.*

Key words: *C-reactive protein, Lipid profile, Glycemic index, Glimepiride, Sitagliptin, Type-2 Diabetes.*

Corresponding author:

Dr. Hafza Hashmi,

Islamabad Medical and Dental College (IMDC), Islamabad

QR code

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INTRODUCTION:

In patients of diabetes progression, complication of multiple cardiovascular disorders and initiation are dominated to have vital role of inflammation [1]. In various cardiovascular as well as non-cardiovascular disorders most studied and potential inflammatory marker is CRP. ongoing inflammation as an acute phase reactant is detected via CRP. Acuteness of inflammation in various cardiovascular diseases and inflammation in joints is also detectable through CRP which are measured to be one of the autonomous as well as collective risk factor in various cardiovascular disorders [2]. Because of CRP endothelial cells produce monocyte chemotactic protein-1, which may result in increased countenance of vascular adhesion molecule-1and intercellular adhesion molecule-1. Furthermore, CRP produces the monocyte cells to emancipate pro-inflammatory cytokines which have a main part in the pathogenesis of cardiovascular disease [3]

CRP is assessed in numerous vascular and cardiac diseases related with clinical and experimental studies. In response to dietary intake, calculation of fluctuations in lipid profile can be done through CRP assessment as revealed by various studies. These studies showed that changes in lipid profiles depend on baseline CRP concentration of patients. Patients with high baseline CRP have unbalanced serum lipid profile and vice versa. Likewise, after using diet of high fat, there is raise in the LDL-cholesterol, triglycerides, cholesterol and baseline CRP whereas, using diet with low fat has inverse influences. Overweight patients also have risen in baseline CRP as associated to their slim equivalents [4].

Sitagliptin also prevents enzyme DPP-4. Physiological concentration GIP and GLP in body is increased due to DPP-4. Such enzymes come up with Pleiotropic effects on body for instance silent inflammation, oxidative stress, hypertension, dyslipidemia and diabetes. It has been revealed in various studies that sitagliptin have anti-inflammatory effects by decreasing C-reactive Protein (CRP) in not only diabetic patients but also in non-diabetic patients [5,6]. Such results of studies produce the need that more thorough researches might be carried out to reveal more anti-inflammatory responses of sitagliptin. Therefore, we carried out this study to evaluate the effects of glimepiride and sitagliptin on C-reactive Protein (CRP) in obese patients of type 2 diabetes.

MATERIAL AND METHODOLOGY:

In the present study we screened out 110 diabetic patients out of 450 patients of type 2 diabetes who were using oral antidiabetic agents. We took the approval for the study from the ethical committee of the hospital. Took a written consent from all selected participants of the study. Explained all contents and perspectives of our study to the selected patients. Selection criteria was as patients of type 2 diabetic using glimepiride as an oral antidiabetic agent and having body mass index (BMI) more than 25 with HbA1C level less than 9. Excluded all those who were patients of type 1 diabetes, HbA1C more than or equal to 10, body mass index (BMI) more than 25, with history of pregnancy, smoking and alcohol users, having history of hypertension, ischemic heart disease, heart failure, renal and liver disorders. Furthermore, those patients were also not included in our study who were using any medicines or drugs such as statins, beta blockers, vitamin E, ACE inhibitors, DPP-4 inhibitors, pioglitazone, anti-platelets, NSAIDS, metformin, steroids, aspirin and other lipid lowering medicines. Randomly divided all selected patients (110) into two equal strength groups named as group A and group B. All patients were taking glimepiride 2mg to control diabetes. After a wash period of one-week group A was switched to sitagliptin 50mg whereas, group B was suggested to continue glimepiride 2mg. Both groups were advised to continue prescribed drugs for a duration of three months for group A and group B for whole duration of study.

Dosage of each tablet were as per drug titration according to level of blood sugar of the patients. Used the equation (kg/m^2) weight in kg divided by height in meter square for the calculation of body mass index (BMI). Cephalic vein puncture technique was used to take blood sample after 12 hours fasting. Used a standard assay kit for immunoturbidimetric method to examine CRP in all collected samples. Oxidase method was used to assess blood sugar level. Determined the HbA1C by liquid chromatography method and serum lipid profile by using enzymatic end point method. Used SPSS 20 for analysis of data. In the terms of gender, non-parametric data was compared via Fisher's exact test and expressed the disease duration in percentiles and numbers. Parametric data, from baseline, like lipid profiles, HbA1C, blood sugar and BMI were calculated as Mean ± standard deviation by means of paired T-test. Statistically significant P-value was less than 0.05. Comparison of group A and group B after 3 months was carried out through unpaired T-test.

RESULTS:

During the period of our study, tolerability and safety profiles of both tablets were fine. All selected patients (110) were divided into two equal groups A and B. Laboratory and demographic data of each group is displayed below in tabular form.

Table No 01: Gender distribution of patients

Gender	Quantity	Percentage
Male	70	63.64%
Female	40	36.36%

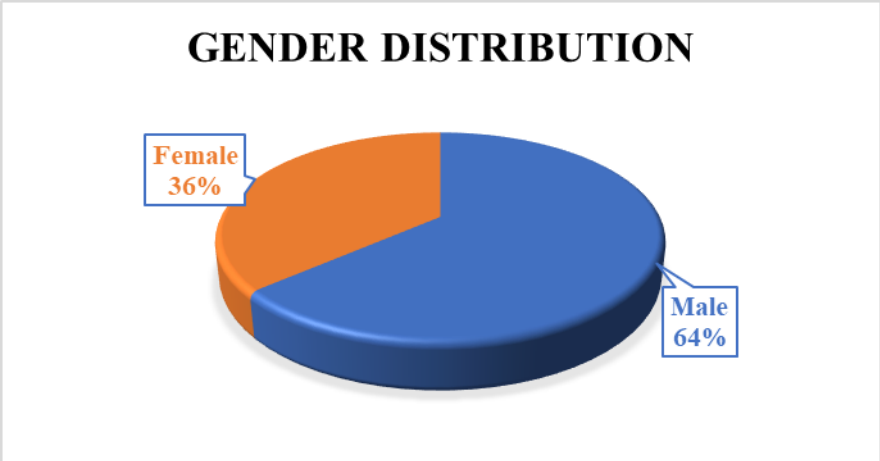

Table No 02: Baseline demographic characteristics of all patients

Demographic Characteristics	Mean±SD
Age (years)	54±8
BMI (kg/m2)	27±4
Duration of Tyupe-2 diabetes mellitus (years)	6.8±2.5
Laboratory parameters	
Fasting Blood glucose	156±10.5
Total Cholesterol	192±23.5
HbA1C	7.9±2.8
Hs CRP	5.8±6.7
HDL-Cholesterol	41.3±3.6
LDL-Cholesterol	120±12.4
Triglycerides	187±19.2

At the end of three months treatment HbA1C and blood sugar were found reduced but comparison results among both groups was non-significant with P value equal to 0.59 in group A and 0.17 in group B. Weight of body was slightly increased in group B using glimepiride. On the other hand, in group A using sitagliptin observed slight reduction in body mass. However, comparison of both groups was found non-significant with P value equal to 0.07. Significant improvement observed in lipid profile of group A compared to group B that is) HDL-cholesterol (-2.6±6.2 A) vs (B 1.2±5.2) with P-value=0.03, LDL- cholesterol (-10±22.4 A) vs (B -0.8±18.7) with P-value=0.001, triglycerides (-19±44.6 A) vs (B -1.8±48.7) with P-value=0.001 and total cholesterol (-25±32.5 A) vs (B +1.5±45.4) with P-

value=0.02. Significant reduction observed in CRP level during comparison of sitagliptin vs glimepiride as (-2.3±1.8 A) vs (B 0.8±1.5) with P-value=0.001. Tabular form of these results is shown below.

Table No 03: Average changes in baseline parameters of study in both groups

PARAMETERS	MEAN±SD		P-VALUE
	Group A	Group B	
BMI (KG/M2)	-0.02±0.7	+0.7±0.9	0.07
HBA1C (%)	-1.8±5.2	-2.4±4.8	0.17
FASTING BLOOD GLUCOSE (MG/DL)	-27±18.4	-35±14.2	0.59
TRIGLYCERIDES (MG/DL)	-19±44.6	-1.8±48.7	0.001
HS CRP (MG/L)	-2.3±1.8	0.8±1.5	0.001
TOTAL CHOLESTEROL (MG/DL)	-25±32.5	+1.5±45.4	0.02
HDL-CHOLESTEROL (MG/DL)	-2.6±6.2	1.2±5.2	0.03
LDL-CHOLESTEROL (MG/DL)	-10±22.4	-0.8±18.7	0.04

DISCUSSION:

Silent or subclinical inflammation is that inflammation which cannot be demonstrated clinically. Such silent inflammation can cause significant mortality and morbidity that is why it is crucial in overweight diabetic patients. On health system a huge economical and clinical burden is posed because of it [7]. There are various inflammatory markers to detect this inflammation but C-reactive protein (CRP), due to its long half-life, uniformity and stability, is considered one of the most studied inflammatory markers. It acts as a drug and disease monitoring tool and have a major role in detection of inflammation and in assessment of general population fitness level [8,9]. In this study we observed that after three months of treatment, sitagliptin showed strong anti-inflammatory effects as noticed via decrease in CRP levels in overweight patients of type 2 diabetes. Also noticed improvement in lipid profile and glycemic control with neutral effect on weight of body.

Several other studies showed similar results as compared to the results of our secondary study objective which were lipid profile, glycemic control and body weight. According to the findings of these studies, sitagliptin was considered as one of the safest oral antidiabetic medicines. It was accepted by patients of diabetes very well with enough glycemic control having no risk of hypoglycemia. It was found that sitagliptin neutrally reduces the weight. Furthermore, it has positive effects on serum lipid profile either alone or in combination. Our study got similar results as shown in these studies [10,11,12,13].

Asahara et al in his study observed improvement in lipid profiles and glycemic control of type 2 diabetic patients. He also observed reduction in inflammatory markers like TNF-α and C-reactive protein (CRP) with dosage of sitagliptin 50mg daily for the duration of 12 weeks [14]. Tremblay et al in his study concluded that sitagliptin has more distinct effect on increased cell adhesions and CRP levels as assessed with normal values in type 2 diabetic patients just after 06 weeks of treatment with it [15]. According to findings of another study, in addition to glycemic control effects of sitagliptin, significance improvement was observed in inflammation and endothelial dysfunction in patients with coronary artery disease and uncontrolled diabetes [16]. Makdissi et al in his study revealed that sitagliptin not only decreases IL-6 and CRP level but also has powerful properties of anti-atherogenic [6]. Sitagliptin prevents inflammation by decreasing TNF-α on mononuclear cells, nuclear factor Kappa-B kinase, chemokine receptor 2(CCR-2), mitogen-activated protein kinase (MAPK-8), toll like receptor (TLR-2 & TLR-R) and the expansion of CD-26. It also significantly decreases epicardial adipose tissue thickness (EAT), which is a marker of visceral fat in overweight patients of type 2 diabetes which were ineffectively controlled on metformin monotherapy [17].

It has been observed on few studies that even though sitagliptin considerably made better metabolic and hemodynamic parameters in patients of Type-2 diabetic but flunked to improved inflammation marked by reduction of CRP. It has been strongly indicated by all above mentioned studies that cardiovascular protection sitagliptin include several cellular and molecular procedures as like tissue repair, cell apoptosis, silent inflammation and oxidative stress reduction. But on the other hand, it was observed in some studies that although sitagliptin considerably improved metabolic and hemodynamic parameters in patients of type 2 diabetes but was unsuccessful to improve inflammation marked by CRP reduction

[18,19,20]. Possible reason observed in these studies was that some patients have acquiescent diseases like coronary artery disease, hypertension, obesity and dyslipidemia. Also observed dinking and smoking habits in some patients. All above mentioned conditions have huge effects on inflammation and its marker C-reactive protein (CRP). Hence this might be the reason of confound results in these researches. It is therefore recommended to conduct clinical studies with high sample size to resolve such ambiguities.

CONCLUSION:

In this study we observed that sitagliptin have strong anti-inflammatory effects as noticed via decrease in CRP levels in overweight patients of type 2 diabetes when compared with glimepiride. It also presented constructive effects on lipid profiles and glycemic control.

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