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COMPARATIVE STUDY OF THE EFFICACY OF METFORMIN-GLIMEPIRIDE AND METFORMIN-SITAGLIPTIN COMBINATION AS AN ANTI-INFLAMMATORY THERAPY IN DIABETIC PATIENTS

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ABSTRACT **Background-** Type 2 diabetes is a major health problem worldwide requires proper management that included education, dietary control, and therapeutic approaches. Several novel drugs have been developed that are either used as monotherapy or as a combination therapy

Aim- This study aimed to compare the efficacy of drug combination Metformin-Glimepiride and Metformin-Sitagliptin in reducing blood glucose triad (FBS, PPBS, HbA1C) and inflammatory markers in diabetic patients.

Materials And Methods-40 type 2 diabetic patients were taken and categorized into two groups for those receiving Metformin-Glimperide combination as Group 1 and for those receiving Metformin-Sitagliptin combination as Group 2. Blood levels of FBS, PPBS, HbA1C, CRP, and IL-6 were estimated and compared at baselines after 3 months and after 6 months.

Results- In groups 1 and 2, both drug combinations significantly, lowered FBS, PPBS, HbA1c while in the case of inflammatory markers metformin-Siitagliptin significantly reduced the level of CRP and IL-6 compared to Metformin-Glimperide combination.

Conclusion- Metformin when given in combination with Sitagliptin lowers the inflammatory responses more effectively. This property can be applied to prevent inflammation-induced atherogenesis and cardiovascular complications in diabetes.

KEYWORDS : Diabetes, Inflammation, Metformin, Sitagliptin, Glimepiride

INTRODUCTION

The precipitation of diabetes as a global health burden has been tremendously increased in the past few decades. In 2010, the prevalence was reported to be 285 million worldwide which is supposed to reach 438 million by 2030 that will be largely contributed by countries like China and India where there is a trend of sedentary lifestyle urbanization and consumption of high-calorie diet. [1]

Insulin resistance is a key factor that results in diabetes. It is associated with obesity and endothelial dysfunction through multiple signaling pathways that lead to glucotoxicity and inflammation. [2] Inflammation markers such as IL-6 TNF-α and CRP are involved in the development and progression of atherosclerosis a major risk factor for diabetic vascular mortality. Hence there is a necessity for therapeutic intervention in addition to dietary control and exercise to prevent both microvascular and macrovascular complications.

Though no complete cure has yet been discovered for diabetes, different modalities has been set up for the management such as lifestyle modifications, dietary control, and use of oral hypoglycemic agents like biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase-IV inhibitors, insulin, etc. [3]

Few oral hypoglycemic agents (OHA) have been proved to lower the level of inflammatory markers in addition to blood glucose, thereby exhibiting cardioprotective functions. The first-line drug of choice and the most commonly used OHA in diabetes is metformin. Newer agents like DPP-inhibitors (Sitagliptin, Linagliptin, etc.) are also recommended for therapeutic interventions. Similarly, gliptins also reduce blood glucose levels by increasing the level of incretin and decreasing that of glycogen. [4] Studies have shown that these OHA have anti-inflammatory actions also. Thus, in his study, an effect was made to evaluate the anti-inflammatory effect of metformin therapy in combination with glimepiride and sitagliptin in the diabetic patients who were inadequately controlled with metformin monotherapy.

MATERIALS AND METHOD

The study was conducted in the Department of Pharmacology, JNU Medical College and Hospital, Jaipur. 40 patients attending the medical outpatient department of the hospital were randomly selected. With the approval of the institutional ethical committee and consent of the patient, the study was commenced and conducted for a 6-month duration from Feb 2020 to July 2020. The patients who were initially on metformin treatment but failed to achieve adequate glycemic control were included in the study.

Patients with Type 1 Diabetic, cardiac problems, renal or hepatic disorders, and other terminal complications were excluded.

The patients included in this study were categorized into two groups namely Group 1 and Group 2 depending upon the combination drug therapy they received. Patients in group 1 were given Metformin-Glimepiride combination while the patient in Group 2 received Metformin-Sitagliptin combination. The dose of Metformin, Sitagliptin, and Glimepiride were 500 mg, 50 mg, and 1mg respectively. Before the administration of the drugs, the baseline value of fasting sugars (FBS), postprandial blood sugars (PPBS), HbA1C, IL-6, and CRP were estimated by using standard protocols. The patients were strictly observed for 6 months. The biochemical investigations were conducted at the end of 3 months and 6 months and results were compared with that of baseline values.

Statistical Analysis

The values were recorded as mean and standard deviation analyzed using student t-test (paired). The p-value of <0.05 is considered as statistically significant.

RESULT

Figure 1 shows the distribution of patients based on gender while figure 2 shows the distribution of patients based on age in both the groups of patients

Table-1: Comparison Of The Biochemical Variable At A Baseline Level, 3 Months And 6 Months In Group 1 (metformin-glimepiride Group)

Parameters	Metformin-Glimepiride (Group 1)				
	Baseline (A)	3 months (B)	6 months (C)	p (A-B)	p (A-C)

FBS	205.05±57.39	171.1±47.84	151.5±44.79	0.049*	0.002**
PPBS	262±58	215.2±55.47	190.32±42.88	0.014*	<0.001**
HbA1c	9.6±1.2	8.22±0.81	7.32±0.6	<0.001**	<0.001**
CRP	6.56±2.08	5.28±1.84	4.58±1.79	0.004**	0.003**
IL-6	9.26±2.33	7.85±1.95	6.95±1.91	0.044*	0.002**

*→Significant (p<0.05), **→Highly significant (p<0.01)

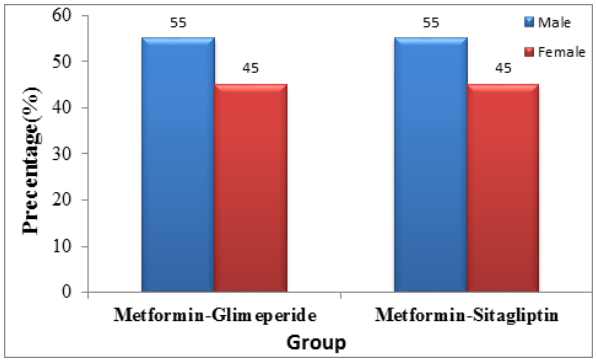

Figure 1: Distribution Of Patients Based On Gender

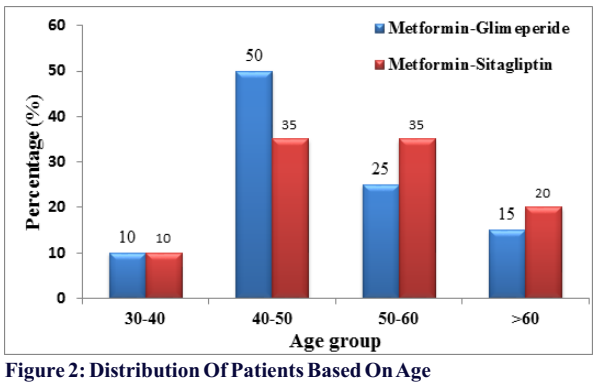

Figure 2: Distribution Of Patients Based On Age

Table-2: Comparison Of The Biochemical Variable At A Baseline Level, 3 Months And 6 Months In Group 2 (metformin-sitagliptin Group)

Parameters	Metformin-Sitagliptin (Group 2)				
	Baseline (A)	3 months (B)	6 months (C)	p (A-B)	p (A-C)
FBS	199.4±547.6	166.31±40.17	142.39±33.81	0.043*	<0.001**
PPBS	264.73±47.95	220.14±44.44	184.71±37.36	0.004**	<0.001**
HbA1c	9.25±1.36	7.85±0.83	7.07±0.67	<0.001**	<0.001**
CRP	6.52±1.35	5.05±1.45	3.73±1.57	0.002**	<0.001**
IL-6	8.85±2.37	6.68±2.36	5.46±2.04	0.006**	<0.001**

*→Significant (p<0.05), **→Highly significant (p<0.01)

Table-3: Comparison Of Mean Of Difference Of Biochemical Variable Before And At The End Of 6 Months In Group 1 And Group 2

Parameters	Mean difference (Baseline to 6 months)		
	Metformin-Glimepiride	Metformin-Sitagliptin	p
FBS	53.56±17.66	53.01±21.16	0.928
PPBS	71.36±33.69	80.02±27.64	0.38
HbA1c	2.28±0.8	2.18±0.79	0.695
CRP	1.97±0.67	2.79±0.94	0.003**
IL-6	2.3±0.86	3.39±1.08	0.001**

*→Significant (p<0.05), **→Highly significant (p<0.01)

DISCUSSION

Inflammation mediated by insulin résistance is the main mechanism that leads to endothelial dysfunction and cardiovascular disorders in diabetic patients via the activation of several signaling pathways involving NF-KB. Therapeutic management is a convenient reassure to intervene the inflammatory process and atherogenesis. Drugs like metformin, sitagliptin have been shown to have anti-inflammatory properties.

In the study of Andrew *et al*, the diabetic patient receiving metformin showed a lower level of CRP, TNF-α, and TLR2/4. Metformin is a biguanide, decreases hepatic synthesis by activating AMP-dependent protein kinase. It also reduces intestinal glucose absorption and decreases glycogen levels via stimulation of serine-threonine kinase II. The signals generated cause suppression of glycogenic and lipogenic enzymes and increase fatty acid oxidation. [5]

In this study, inflammatory markers like CRP and IL-6 were estimated in diabetic patients' before and after the combination during therapy Metformin-Sitagliptin and Metformin Glimiperide). The reduction in blood glucose and HbA1C level was also compared. In the patients receiving Metformin-Sitagliptin combination, the FBS, PPBS, and HbA1C decreased to 142.39±33.81, 184.71±37.36, and 7.07±0.67 from 199.4±547.6, 264.73±47.95, and 9.25±1.36 after 6 months of therapy while among the patients receiving metformin-Glimiperide combinations the FBS, PPBS, and HbA1C reduced to 151.5±44.79, 190.32±42.88 and 7.32±0.6 from 205.05±57.39, 262±58 and 9.6±1.2 respectively. The decrease in the level of blood sugar triad (FBS, PPBS, HbA1c) was significant in both groups of patients. A significant difference was not observed which indicated that both the drug combinations Metformin-Glimepiride and Metformin-Sitagliptin have equal efficacy in blood sugar management. In contrast, Devrajant et al reported glimepiride to more effectively reduce HbA1c level than sitagliptin. [6]

The result of this was in line with that of IGPP *et al* [7]. Similarly, Sharma M *et al* in their study too conducted a comparative analysis of the efficacy of Metformin-Glimiperide and Metformin-Sitagliptin during combination therapy in diabetes. They showed a significant reduction in triad after the therapy. As per them, sitagliptin combination caused greater reduction compared to glimepiride combinations. Their result was in accordance with that of Singh *et al* and thus studies. [8]

Similarly, Devarajant V *et al* also studied the efficacy of metformin, sitagliptin, and glimepiride in diabetic patients. In their study of 12 weeks duration, they administered sitagliptin at a dose of 50 per 500 of metformin mg twice daily in one group of patients and glimepiride at a dose of 1 or 2 mg per 1000 mg metformin once daily. The authors reported that at the end of 12 weeks, GBS, PPBS, HbA1C significantly improved from baseline value in both the groups. [9]

Regarding CRP and IL-6 level significant reduction in its level was observed in both the patient groups (group 1 and 2). However, the Metformin-Sitagliptin combination caused a greater reduction in the level of inflammatory markers CRP and IL-6 than the Metformin-Glimepiride combination. When the mean difference of CRP and IL-6 at baseline and after 6 months was compared in both the patient groups, a significant difference was observed indicating sitagliptin to a more effective anti-inflammatory agent. Sitagliptin is also known to be anti-inflammatory in previous studies. Sitagliptin not only activates AMPK but also inhibits MAPK along with P38-ERR77-00 which further causes suppression of NF-Kb-associated inflammatory signaling pathways. [10]

Sitagliptin is a type of DDP-4 (dipeptidyl peptidase-4) inhibitors that increase the level of incretin hormone-induced cAMP thereby hindering the translocation of NF-KB-65 nuclear protein causing suppression of pro-inflammatory signals. [11] DPP-4 inhibitors are given as monotherapy in the cases that are not controlled with diet and exercise. [12] Many studies have shown the safety and superior efficacy of DPP-4 inhibitors. In Japan Sitagliptin was among the first DPP-4 inhibitors to gain approval in 2009 [12]. Intake of Sitagliptin once-daily, at a dose of ≥100 mg potentially inhibit plasma DPP-4 activity by ≥80%. [13]

Incretin significantly contributes to insulin sensitivity in a healthy person while its function is impaired in diabetic patients. [14] After a meal incretin like glucose-dependent insulinotropic peptide (GIP) and glycogen like peptide -1 (GLP-1) are released that stimulated insulin-secreting. These incretins undergo rapid degradation by DPP-4, thus DPP-4 inhibitors can effectively increase GLP- levels and stimulate incretin action. [15]

Glimepiride is a sulfonylurea that decreased insulin resistance and

glycemia by causing active utilization of glucose through GLUT-4 protein. [16] Sulfonylureas shut the ATP-sensitive potassium channels in islets of the pancreas thus stimulating insulin secretion. [17] Glimeperidine, a second-generation sulfonylurea is frequently used along with metformin for the reduction of blood sugar. Metformin is most commonly given with sulfonylurea combination. [18] Studies have shown that sulfonylureas inhibit NLRP3 and reduce inflammatory responses. [18,19] Studies reporting no significant effect of sulfonylureas on levels of inflammatory markers are also available. [20,21]

Theoretically, there occurs a synergetic action between metformin and sitagliptin in reducing blood. Since both the drugs have a potential effect on reducing the inflammatory responses, the combination therapy can be more helpful in reducing microvascular ad microvascular complications. A study of Makdissi A *et al* reported a significant reduction n CRP and IL-6 level after 3 months of sitagliptin therapy. [22]

CONCLUSION

In this study, the efficacy of drug combination Metformin-Glimepiride and Metformin-Sitagliptin in reducing inflammatory markers in diabetic patients were compared. Both the combinations therapy significantly reduced plasma sugar triad (FBS, PPBS, and HbA1C) while regarding the inflammatory markers CRP and IL-6, Metformin-Sitagliptin combination showed more significant reduction their levels compared to Metformin-Glimepiride combination. Though metformin is widely known to have anti-inflammatory properties, the Metformin-Sitagliptin combination showed superior improvement in glycemic status and reduction in inflammatory markers. Thus the finding of this study suggests that both glimepiride and sitagliptin significantly improves glycemic status when given in combination with metformin. However for control of inflammatory mechanisms, the Metformin-Sitagliptin combination is more potent, thus a fixed those of these drugs combination may be fruitful in delaying or preventing the inflammatory reactions that can lead to atherosclerosis thereby exhibiting cardio-protective actions when administered as initial therapy for the management of diabetes.

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