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Original Article

Comparison of sitagliptin, glimepiride, and metformin group with glimepiride and metformin group in treatment of diabetes mellitus type 2 patients

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ABSTRACT

Objective: To compare glycaemia control between glimepiride and metformin group with sitagliptin, glimepiride and metformin group in uncontrolled type 2 diabetic patient.
Methods: This retrospective, randomized, clinical study was done in the diabetes research center. The number of the patient in this study was thirty-five patients. The patients examined individually in detail to check their general health in addition to the physical state. For all the patients, data had been collected and fasting plasma glucose level had been measured. Participants have been chosen by unresponsiveness of diabetic patient to single therapy of metformin or glimepiride in this trial. The patients were allocated into 2 groups. Group I include 14 patient given glimepiride, metformin and sitagliptin, while group II include 21 patients given glimepiride and metformin. Both groups continue treatment for thirty days and statistical analyses include data collection was done.
Results: A statistical significant decrease was found in fasting plasma glucose level when compare before and after treatment regimen of sitagliptin, Glimepiride and Metformin group while no significant difference in fasting plasma glucose when comparing the triple therapy group (Sitagliptin, Glimepiride and Metformin) with the double therapy group (Glimepiride and Metformin) after thirty days of treatment.
Conclusion: No significant difference was found between glimepiride and metformin therapy with sitagliptin, glimepiride and metformin therapy in uncontrolled type 2 diabetic patient.

Keywords: Glycaemia, biguanides, sulfonyl urea, glucagon.

INTRODUCTION

Type two diabetes mellitus (T2DM) is a multi-factorial disease caused by unresponsiveness of tissue to insulin with inability of pancreas to secret enough insulin [1]. Diabetes mellitus increases, as developing life causes decrease physical activity and increase number of obese subjects, [2] where dietary fatty acids is considered the main cause of skeletal muscle insulin resistance [3].

Insulin resistance and systemic inflammation have shown by many human studies [4] lead to abnormal increase in insulin signaling by adipocytes and then an increase lipolysis of adipocyte and insulin resistance [5]. Interleukin-1ß (IL-1ß) has a major role in activation of inflammation in ß-cells islet of pancreas directly [6].

Metformin became the most widely used drug for diabetes type 2 because of its wide safety margin and its good ability to manage blood glucose profile of the patients [7].

Metformin's mechanism of action includes lowering blood glucose level mainly via an inhibition of release of glucose from the liver [8]. In addition to increase the uptake of glucose from blood by skeletal muscle, adipocytes and enterocytes [9-11].

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A minor mechanism includes possibly a delay in gastrointestinal absorption of glucose and decrease food intake [12].

Sulfonyl urea drugs occupied a specific sulfonyl urea receptor in pancreas Beta –cells and its binding not related to blood glucose level then inhibition of K+ channel ATP-dependent type and enhancement of insulin secretion occur [13].

Glimepiride, which is one of sulfonyl urea differ from all others. It has a unique property in increasing insulin sensitivity in addition to its ability to enhance first and second phase secretion of insulin. The hypoglycemic side effect of sulfonyl urea glimepiride metabolites is absent, giving additional benefit to prescribe glimepiride to T2DM patients [14].

Sitagliptin control glucose level in blood by inhibiting DPP-4 enzyme, inactivation of the glucose-dependent insulin tropic polypeptide (GIP) and incretin hormones glucagon- like peptide 1 (GLP-1), and both are gut incretins that increase the glucose-dependent insulin uptake. In addition to that, GLP-1 also stopping the glucagon response hormones after a meal uptake [15-17].

The function of DPP-4 enzyme biologically suggests that blocking of the DPP-4 will lead to active GLP-1 increment in the serum and at the same time, the antagonistic metabolites will be reduced. The net result is decrease diabetogenic effect [18].

The target for DPP- 4 inhibitor drugs, therefore, is to inhibit the action of DPP- 4 by using a different molecule. This new molecule will compete for attaching the binding site as a substrate on the DPP-4 enzyme. The inhibition of enzyme inactivation for active endogenous GLP-1promot that GLP-1original substrate will stay for prolong time in the serum [19].

The aim of study comparing glycaemia control between glimepiride and metformin group with sitagliptin, glimepiride and metformin group in uncontrolled type 2 diabetic patient.

Materials And Methods

This retrospective, randomized, clinical study was done in the diabetes research center. The patient's number was thirty five. All persons included have assent to be subjected in the study and agreed of the study by College of Pharmacy /Al-Nahrain University, order number 1129 in 23/12/2020.

The patients were checked for their general health and physical state in details. The diagnosis done by a physician. Data had been collected for all patients, include sex and age, weight, patient medical history, allergy, social state and occupation. The baseline data of fasting plasma glucose level had been measured.

Participants have been chosen by un-responsiveness of diabetic patient to single therapy of metformin or glimepiride. When treatment is started, for every patient should make up thirty days from the baseline time to monitor again for fasting plasma glucose level.

Two groups of patient used. Group I include 14 patient (8 male and 6 female) given glimepiride (4 mg daily), metformin (850 mg three times daily) and sitagliptin (50 mg daily). While group II include 21 diabetic patients (13 male and 8 female) given glimepiride (4 mg daily) and metformin (850 mg three times daily).Both groups continue treatment for thirty days.

Statistical method includes result collection then analysis aiding with SPSS-25 in addition to Microsoft excel 2020. Mean with standard deviation, in addition to unpaired t-test was done. The difference was significant statistically when the $P \leq 0.05$ and significantly high when the $P \leq 0.001$ [20].

Results

All groups are comparable in relation to age, weight and fasting plasma glucose at the beginning of the study (Table 1). A Statistical significant decrease was found in fasting plasma glucose level when compare before and after treatment regimen of Sitagliptin, Glimepiride and Metformin group, while high significant decrease was found in fasting plasma glucose level when compare before and after treatment regimen of Glimepiride and Metformin group .

It was found that no significant difference in fasting plasma glucose when comparing the triple therapy group (Sitagliptin, Glimepiride and Metformin) with the double therapy group (Glimepiride and Metformin) after four week of treatment. (Table 2 and Figure 1).

Table 1. Demographic data for the studied groups (Data are present as mean ± SD).

Parameters	Sitagliptin, Glimepiride and Metformin	Glimepiride and Metformin
Number	14	21
Gender (male, female)	(8,6)	(13,8)
Age (year)	55.5±7.85	56.43±8.21
Weight (kg)	96.64±15.93	89.48±11.35

Table 2. Fasting plasma glucose and glycemic index before and after treatment for the studied groups.

Parameters	Sitagliptin, Glimepiride and Metformin	Glimepiride and Metformin
FPG mg/dl (before treatment)	218.71+58.31	223.67+51.51
FPG mg/dl (after treatment)	171.21+43.15 *	171.81+35.04 **
HbA1c % (before treatment)	9.2± 2.01	9.4± 1.87
HbA1c % (after treatment)	7 .6± 0.96 *	7.5± 0.67 **

Data are present as mean ± SD, (*): high significant difference P< 0.004 versus before treatment for group 1, (**): high significant difference P< 0.001 versus before treatment for group 2, FPG: fasting plasma glucose, HbA1c %: glycated hemoglobin percentage.

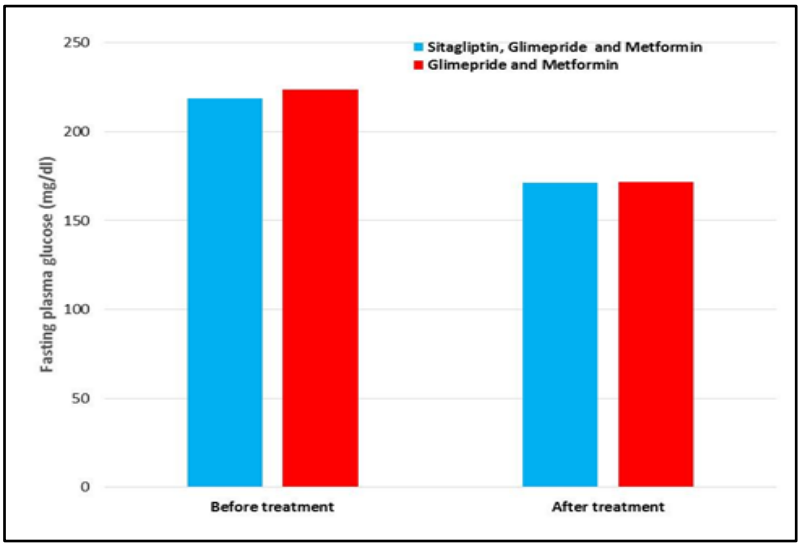

Figure 1. Fasting plasma glucose before and after treatment in the studied groups

DISCUSSION

The investigated drugs in this study has many uses in medicine and the combination therapy is highly used and successful in different clinical areas such as infectious disease and cancer [21]. The main idea of using Low dose regimen in the combination treatment, to decreasing side effects [22]. Another rational benefit presents in fixed dose combination of metformin and a DPP-4 enzyme inhibitors that the latter drugs are causing high HbA1c reduction, and used in not

well-tolerated patients [23].

A Statistical significant decrease was found in fasting plasma glucose level when Sitagliptin is added as triple therapy to Glimepiride and Metformin, this result was identical with a study in T2DM Chinese patients have hyperglycemia on a sulfonylurea drug alone or, with or without metformin and when sitagliptin added, significantly greater control in blood sugar occur when compared to the addition of placebo [24].This complementary action of metformin with sitagliptin to increasing the intact GLP-1 concentrations could explain the increased control of sugar when triple therapy used [25].

Although the mode of action of sulphonylureas and sitagliptin to employ their effects are different, both drugs have the same final mechanism of action which enhances insulin secretion from the pancreas [26, 27]. This different mode of action of sulphonylurea and sitagliptin drugs give the rational brilliant idea of the combination therapy to control glycaemia.

The high significant decrease that was found in fasting plasma glucose level when compare before and after treatment regimen of Glimepiride and Metformin group in this study were identical with the significant better control in HbA1c concentration which shown after addition of glimepiride [28].

It is supposed that in cases of increased insulin resistance, an insulin sensitizer drugs would be more effective in T2DM patients than from cases of less insulin resistance [29] with the notice that insulin secretagogues drugs may be more suitable in cases of T2DM patients having low beta cell activity from those that have high beta cell activity.

This is lead to an overall benefit by preventing hypoglycemia side effect. This is occurring because glimepiride response well to the load of sugar by improves the first and second phases of insulin production [30].

The unexpected result of no significant difference between Sitagliptin, Glimepiride and Metformin group when compared with the Glimepiride and Metformin may be due to the short duration of the study. Longer duration trails suggested in the future with increased number of cases enrolled in similar studies.

Conclusion

No significant difference was found between glimepiride and metformin dual therapy when compared to sitagliptin, glimepiride and metformin triple therapy in uncontrolled type 2 diabetic patient. A high statistical difference was found for dual therapy and statistically difference also found for triple therapy before and after trail.

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Conflicts of Interest

There are no conflicts of interest

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