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To determine the pharmacokinetic effects of combination therapy of gliclazide and metformin HCL Tablets in the management of Diabetes

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Background: Diabetes type 2 is a chronic disease that has to be treated with medication. Gliclazide and metformin are two commonly used medications in monotherapy. However, the use of these medications in combination was an interesting strategy due to their complimentary activity.

Aim: Based on the following variables: oxidative stress, lipid profile, and hepatorenal functioning, the study examined the principal therapeutic potentials of combination metformin/gliclazide treatment over metformin monotherapy.

Subjects and methods: A comparison research was done between March 2021 and March 2022. In the trial, 40 type 2 diabetes patients got combination metformin and gliclazide medication (500 mg BD and 80 mg OD, respectively). There were 80 type 2 diabetic individuals assessed. The remaining 40 got metformin monotherapy (500 mg BD) and were matched with the first group in terms of age and length of diabetes mellitus. According to established protocols, measurements were made for fasting blood sugar (FBG), total glycated haemoglobin (HbA1c), lipid peroxidation, total antioxidant capacity, serum creatinine, aspartate and alanine transaminases, total cholesterol, triglycerides, high-density lipoproteins, and low-density lipoproteins.

Results: Oxidative stress, lipid profiles, and hepatocellular functions were equivalent in the patients of the two groups. Patients on metformin had substantially lower levels of FBG and HBA1c than those receiving combined therapy (7.61 (6.70-8.89) mmol/L vs. 9.00 (7.30-10.68) mmol/L; P =.022 and 7.00 (6.40-7.65) % vs. 8.20 (7.20-9.75) %, respectively.

Conclusion: Patients receiving metformin and gliclazide together did not vary from those receiving metformin alone in terms of oxidative stress, lipid profile, or hepatocellular function. In contrast, the diabetic individuals receiving combination treatment had poor glucose control.

Keywords: Diabetes mellitus, Gliclazide, Glucose, Lipids, Metformin, Oxidative stress

I. INTRODUCTION

Diabetes mellitus (DM) impairs liver, renal, and cardiovascular (Chawla et al., 2016, Narres et al., 2016, and Morling et al., 2015) functioning as well as the body's ability to produce antioxidants (Grindel et al., 2016). According to recent research (Asmat et al., 2016), dyslipidemia and altered oxidative stress in several bodily organs are the main causes of diabetes complications (de Souza Bastos et al., 2016). The cornerstone of evaluating pharmacological regimens used to treat DM is understanding the aetiology underlying diabetic complications (Zhang et al., 2013). Potential therapeutic advantages of anti-diabetic medications are often evaluated by assessing their effects on glycemic control, oxidative stress, lipid profile, and hepatorenal functions (Goldstein et al., 2003; Sun et al., 2014; Manik et al., 2013). (Ahad et al., 2014).

Metformin and gliclazide are used in clinical practise to treat type 2 diabetes, either singly or in combination (T2DM). Diabetes patients with metabolic abnormalities have been shown to benefit from metformin monotherapy (Chakraborty et al., 2011, Esteghamati et al., 2013) and reduce oxidative stress (Kim et al., 2013). Gliclazide has recently been shown to synergistically enhance fasting blood glucose (FBG) and reduce levels of glycosylated haemoglobin (HbA1c) in type 2 diabetes patients receiving metformin treatment (Al-Gareeb et al., 2016). The therapeutic effects of metformin/gliclazide treatment on oxidative stress, lipid profiles, and hepatocellular functions haven't received enough attention, nevertheless (Hong et al., 2013). Additionally, there is a dearth of studies on the combined therapy of metformin and gliclazide for the treatment of T2DM.

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II. SUBJECTS AND METHODS

Subjects

The study recruited 80 T2DM patients from Al Basam Diabetes Center – Unaiza – Qassim – KSA during the period from March 2015 to March 2016. The control group consisted of 40 T2DM patients on metformin treatment (500 mg BD). The metformin monotherapy group was matched for age and duration of DM with a test group of 40 patients on combined metformin/gliclazide therapy (combined therapy group) (500 mg BD + 80 mg OD, respectively). The patients with other systemic diseases, major diabetic complications, treatment with beta blocker, steroids, thiazides, and/or insulin were excluded from the study.

Methods

Five ml of venous blood were taken from each patient during their regular follow-up in the general diabetes clinic. To determine HbA1c level, 1.5 ml of the blood sample was added to EDTA tube. The blood serum was separated from the remaining 3.5 ml to determine oxidative stress status, FBG level, hepatorenal function, and lipid profile.

HbA1c level was determined according to the standard technique (Bunn et al., 1976) using a specific glycated hemoglobin kit (Sigma–Aldrich, St. Louis, MO, USA). FBG level was determined in mmol/L with the standard oxidase methods (Barham and Trinder, 1972). The extent of lipid peroxidation was determined colorimetrically (Ohkawa et al., 1979) using lipid peroxide (LPD) kit (GenWay Biotech, Inc, USA). Total antioxidant capacity (TAC) was measured colorimetrically (Koracevic et al., 2001) using TAC kit (GenWay Biotech, Inc, USA). Total cholesterol was measured using enzymatic, liquid, colorimetric test – CHOD/PAP method with UDI diagnostics kits (CAT.NO EL24-1200, KSA) (Allain et al., 1974). Serum triglycerides were measured through enzymatic colorimetric GPO method with UDI diagnostics kits (CAT.NO EL59L-1000, KSA) (Fossati and Prencipe, 1982). Serum HDL was measured by enzymatic, colorimetric test – HDL precipitating reagent phosphotungstate method with UDI diagnostics kits (CAT.NO EL41-360, KSA) (Warnick and Albers, 1978). LDL was indirectly measured using the Friedewald equation (Nauck et al., 2002) based on the presence of total cholesterol, HDL, and triglyceride levels [LDL = total cholesterol – HDL – (triglycerides/5)]. Serum creatinine was determined according to the standard colorimetric method (Fabiny and Ertingshausen, 1971). Aspartate (AST) and alanine (ALT) transaminase (IU) were assessed colorimetrically (Reitman and Frankel, 1957). Statistical analysis

Data were analyzed using SPSS for Windows (version 16.0, Chicago, SPSS Inc. USA). Normal distribution of variables was examined using Shapiro-Wilk test. The studied variables were described with median and 25–75 interquartile (Q1–Q3) and Boxplot charts. Significant statistical differences of studied variables were assessed among diabetic groups using Mann-Whitney U test. A P value of <.05 was considered significant.

III. RESULTS

The duration of T2DM and age at the time of diagnosis of the diabetic patients undergoing metformin treatment (Median (Q1–Q3) = 50.00 (45.00–57.75) and 2.00 (1.00–5.00) years, respectively) were not significantly different as compared to those in the combined therapy group [Median (Q1–Q3) = 53.00 (45.25–60.00) and 4.00 (2.00–6.75) years, respectively; P > .05]. Patients on metformin treatment exhibited significantly lower levels of FBG [7.61 (6.70–8.89) mmol/L vs. 9.00 (7.30–10.68) mmol/L, P = .022] and HBA1c [7.00 (6.40–7.65) % vs. 8.20 (7.20–9.75)%, P < .001] compared to those on combined therapy

IV. DISCUSSION

The combined metformin/gliclazide therapy is commonly used for treating T2DM; however, the therapeutic benefits of this combination on oxidative stress, lipid profile, and hepatorenal functions have not been thoroughly studied before. In the present study, it is evident that the above-mentioned parameters were comparable in both studied groups. Glycemic control was poor in the diabetic patients undergoing combined therapy compared to those on metformin monotherapy.

Nowadays, oxidative stress in diabetic patients is the cornerstone for the pathogenesis of all complications in diabetes (Asmat et al., 2016). Increased free radical production greatly affects glycemic control, lipid profile, and hepatorenal function in diabetic patients. The observed insignificant differences between monotherapy and combined therapy groups in this study is consistent with the results of previous studies (Meişoğullari and Tuerkeli, 2008), which demonstrated that separate (not combined) administration of metformin or gliclazide greatly improved oxidative

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stress status in diabetic patients. Previous reports proved that administration of gliclazide or metformin decreased oxidative stress as evidenced by decreased catalase (CAT), glutathione S-transferase (GST), erythrocytes glutathione peroxidase (Gpx) levels, and malondialdehyde (MDA) levels with no significant differences between gliclazide or metformin-treated groups (Meişoğullari and Tuerkeli, 2008). Moreover, Chen and his colleagues also recommended the use of combined gliclazide/metformin therapy over metformin monotherapy for better oxidative stress status in T2DM patients as evidenced by improved MDA and superoxide dismutase (SOD) levels (Chen et al., 2010). Contrary to the results of this study, Hassan and Abd-Allah demonstrated that combined metformin/gliclazide treatment greatly improved lipid profile as evidenced by decreased total cholesterol and significantly increased HDL level compared with the control group (Hassan and Abd-Allah, 2015). The comparable effects of mono vs. combined therapies regarding lipid profile as proved in this study is parallel with a previous study that similar efficacy of both drugs on lipid profile (Tessier et al., 1999).

With respect to the hepatorenal function, this study revealed no significant differences in both studied groups. Our results were consistent with a large study involving 600 T2DM patients conducted by Su et al. They concluded that no statistical differences were observed before and after 24 weeks of metformin treatment (Su et al., 2014). The present results regarding glycemic control contradict to the findings of at least two recent reports that proved better glycemic control in patients with combined gliclazide/metformin therapy {FormattingCitation}. In clinical practice, diabetic patients are offered combined therapy only when monotherapy fails. This indicates that patients on combined therapy are likely to suffer from a higher degree of insulin resistance and are expected to respond poorly to anti-diabetic treatment. It should be noted that some studies revealed no significant differences on glycemic control between mono and combined therapy (Chen et al., 2010), and so further investigations are recommended to clarify this point.

In conclusion, the combined metformin/gliclazide treatment seems to be beneficial to safeguarde against important complications of DM. This is because oxidative stress, lipids profile, and hepatorenal functions of poorly controlled diabetic subjects on combined therapy are still comparable with that of the patients on monotherapy.

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