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Research Article

Effects of Metformin, Glimepiride and their Combination on Glycemia and Lipid Profile of NIDDM Patients- A study in Iraqis

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ABSTRACT

To compare the effects of an insulin sensitizer, metformin, with an insulinsecretagogue, glimepiride, on blood glucose level and lipid profile in newly diagnosed type 2 diabetes.This is an open-label, randomized study carried out on 50 newly diagnosed type 2 diabetic patients and 20 healthy subjects. Patients were randomly divided into three groups and assigned for treatment with either metformin (n=20) or glimepiride (n=10) or both (n=20) for 12 weeks. We observed the level of fasting blood glucose (FBG), glycated hemoglobin (HbA_{1c}) and lipid profile before and after 12weeks of treatment.after 12 weeks, FBG and HbA_{1c} significantly decreased in all treated groups. The level of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c) were significantly decreased, whereas high-density lipoprotein (HDL-c) was increased markedly only in metformin treated group as monotherapy and as combination with glimepiride, while no significant changes were observed in triglyceride (TG) level in any group. Metformin improve lipid profile when used in type 2 diabetic patients and reduce the risk of cardiovascular complications.

Keywords: Type 2 DM, lipid profile, metformin, glimepiride.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a glucose metabolismdisorder caused by insulin deficiency and/or insulinresistance[1]. T2DM patients are more prone to cardiovascularcomplications (CVD), which can occur earlier and more frequently ascompared to non-diabetic patients[2].

Dyslipidemia, an established risk factor for CVD, is strikingly common in patients with type 2 diabetes, affecting almost 50% of this population [3]. In addition to hyperglycemia and hypertension, dyslipidemia is a modifiable CVD risk factor that remains largely uncontrolled in patients with T2DM[3].

Hyperglycemia increases the risk of microvascular complications[4], while dyslipidemia is a major risk factor for macrovascular complications in patients with type 2 diabetes[5,6]. Elevated low-density lipoprotein cholesterol (LDL-c) is a major risk factor for CVD[5]. As such, management of LDL-c is the primary goal of therapy for diabetic dyslipidemia[7-9]. Furthermore, type 2 diabetes increases the risk of CVD mortality independent of LDL-c levels, adding to the greater overall cardiovascular risk in this population[10]. Therefore, aggressive lipid treatment goals have been recommended for patients with type 2 diabetes[7-9,11].

As the prevalence of type 2 diabetes increases, prevention of CVD is becoming an increasingly urgent public health concern, requiring aggressive management of the entire lipid profile 7. Numerous evidence suggested that improving glycemic control, in patients with type 2 diabetes, have a substantial potential to reduce the risk of long term complications[12].

In present study, wesought to clarify the effects of 2 classes of antidiabetic drugs on lipid profile, glimepiride, an insulinsecretagogue, and metformin, an insulinsensitizer, 2 diametrically

oppositestrategies for management of hyperglycemia.

MATERIALS AND METHODS

Patient Selection

50 male patients with newly diagnosed T2DM were participated in the present study. They are randomly selected and assigned either to metformin, glimepiride or combination treated groups. All subjects were recruited from the National Diabetes Center for Treatment and Research/Baghdad; age 30–69 years, body mass index (BMI) 25-35. All subjects have been treated for 12 months. All subjects were diagnosed with T2DM in accordance with the WHO diabetes diagnostic criteria of 1999 and had never been treated before.

METHOD

After 12 hours overnight fasting, blood samples were analyzed for FBG, HbA_{1c}, TC, TG, LDL-c, VLDL-c and HDL-c levels. All subjects were orally administered with either 1–2 mg Glimepiride once a day before meal and/or 500-850 mg metformin twice a day. After 12 weeks of the treatment, we observed the changes in these parameters. FBG measured using enzymatic colorimetric method (Spinreact, Spain), HbA_{1c} determined by high-performance liquid chromatography (HPLC)(Bio-Rad Variant, Italy). Plasma TG and TC were determined by enzymatic techniques(Randox, UK) and (Spinreact, Spain) respectively.HDL-c levels weremeasured after precipitation of plasma apoB-containinglipoproteins with phosphotungstic acid; LDL-c level wascalculated using the Friedewald formula [13].LDL-c = Total cholesterol – (HDL-c + (0.20 TG)) and VLDL-c = 0.20 TG (mg/dL).

Statistical Analysis

Data are expressed as means ± SE. Statistics were performed using SPSS (version 19). Differences from baseline were assessed by the paired Student's *t* test. A P-value of <0.05 was considered significant.

RESULTS

Patients

Of 50 patients randomized to treatment, 20 in the metformin group, 10 in the glimepiride group and 20 in the glimepiride + metformin group, all patients received at least one dose of the study drug. There were no apparent differences between the three groups with respect to demographic and baseline characteristics (Table 1).

Glycaemic Control

Changes from baseline to the end of the study are summarized in Table 2. FBG and HbA_{1c} were progressively decreased in all groups. Combination of metformin and glimepiride was superior in reducing FBG and HbA_{1c} levels than monotherapy of each one alone;there was no significant difference between metformin or glimepiride monotherapy with respect to the change in FBG or HbA_{1c}.

Lipid Profile Control

Treatment with metformin alone or in combination with glimepiride produced a significant decrease in serum TC and LDL-c levels, and significance increase in HDL-c levels.While treatment with glimepiride alone produced non-significant changes. All treatment groups show non-significant changes in serum TG and VLDL-c levels.

DISCUSSION

In consistent with many studies,significant improvement in glycemic parameters (FBG and HbA1c) was seen over a short period of 8-12 weeks in moderately severe, newly diagnosed diabetic patients treated with either glimepiride, metformin or combination, when compared with pre-treatment[14-16]. The improvements in glycemic parameters with glimepiride and metformin were similar, while combination produced a lower degree of reduction with respect to the change in FBG and HbA_{1c}[17,18,19].A previous studies approved that glimepiride increases insulin sensitivity at peripheral target sites and improve glycemic control in newly diagnosed diabetic subjects[20], The extra-pancreatic effects of glimepiride made its combination with metformin more effective in improving glycemic control (synergistic effect) by reducing glucose level and HbA_{1c} more than monotherapy of each[21,22].

Newly diagnosed type 2 diabetic patients, at baseline, show varying features with respect to lipid profile, present study agreed with previous studies; demonstrated that metformin as monotherapy and as combination with glimepiride reduced TC, LDL-c,non-significant decrease in TG levels[23,24,25] and increase serum HDL-c level[23], there was no significant difference between metformin monotherapy and the combination therapy with respect to these parameters[26]. However, these studies and ours note that the lipid-lowering effects of metformin were observed in the patients with pre-existing dyslipidemia (have elevated TC, LDL-c, TG levels at baseline according to The United States' National Cholesterol Education Program (NCEP)) not in patients who had normal serum lipid levels before treatment[27]. Therefore, our results demonstrate that metformin used in diabetic treatment improves lipid profile in agreement with previous studies[28].

The present study reported that glimepiride has no significant effect on serum TC, LDL-c and HDL-c levels, the small sample size and limited duration may lack some of data and cause some of the

conclusions to be drawn. However, although we gota non-significant reduction with LDL-c, other workers attributed the reductionto the increased production of LDL-c receptors by insulin, which's seen stimulated by glimepiride[29], and we expect to get more tangible results with larger sample size and longer duration.Non-significant change in HDL-c levels with glimepiride treatment consistent with previous studies[30,31, 32].

Conflicting results about the effect of glimepiride on TG level, in some studies glimepiride decrease TG level[33], in others not affected[30]. Our result supported by Steven *et al*., showed an increase in TG level with glimepiride treatment although it is statistically non-significant but the values were far above normal range[32]. This effect may be due to an external source, since our study did not include carbohydrate restriction or special diet program, TG elevated in most patients treated with glimepiride which is appetite inducer. Studies approved that increases in fasting plasma triglyceride concentrations are commonly observed during the consumption of low-fat, high-carbohydrate (LF/HC) diets[34,35, 36].

CONCLUSION

Metformin improve lipid profile when used in type 2 diabetic patients and reduce the risk of CVD.

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Table 1: Patient characteristic at baseline

Characteristic	Metformin (M)	Glimepiride (G)	M + G
n=50	20	10	20
Age; years	52.63± 2.23	48.80± 2.99	47.95± 1.55
FSG mg/dl	213.47 ± 13.14	218 ± 13.97	249.05 ± 12.15
HbA_{1c}; %	9.47 ± 0.58	8.75 ± 0.36	11.65 ± 0.39
TC mg/dl	196.42 ± 13.58	210.60 ± 14.51	201.35 ± 15.11
TG mg/dl	128.37 ± 10.06	231 ± 49.15	153.10 ± 14.62
LDL-c mg/dl	129.05 ± 13.00	138.10 ± 12.80	119.70 ± 15.63
VLDL-c mg/dl	25.63 ± 2.03	46.20 ± 9.83	32.00 ± 3.05
HDL-c mg/dl	43.26 ± 1.69	38.60 ± 1.11	43.65 ± 1.70

Table 2: Changes from baseline and after 12 weeks in glycemia and lipid profile

Variable/time point	Metformin	Glimepiride	Metformin + Glimepiride
FPG (%) Baseline Week 12 Change from baseline	213.47 ± 13.14 132.95 ± 3.99*[b] -37.72 %	218 ± 13.97 132.60 ± 1.45*[b] -39.17 %	249.05 ± 12.15 145.15 ± 3.41*[a] -41.72 %
HbA1c (%) Baseline Week 12 Change from baseline	9.47 ± 0.58 6.04 ± 0.32*[a] -36.27 %	8.75 ± 0.36 5.71 ± 0.21*[b] -34.74 %	11.65 ± 0.39 6.91 ± 0.31*[a] -40.70%
TC (%) Baseline Week 12 Change from baseline	196.42 ± 13.58 152.68 ± 11.26*[a] -22.27 %	210.60 ± 14.51 196.80 ± 8.47[b] -6.55 %	201.35 ± 15.11 158.40 ± 7.93*[a] -21.33 %
TG (%) Baseline Week 12 Change from baseline	128.37 ± 10.06 118.47 ± 9.47[b] -7.71 %	231 ± 49.15 302.50 ± 45.70[a] 30.95 %	153.10 ± 14.62 141.20 ± 16.41[b] -7.77 %
LDL-c (%) Baseline Week 12 Change from baseline	129.05 ± 13.00 81.26 ± 11.00*[a] -37.03 %	138.10 ± 12.80 105.10 ± 10.06[a] -23.90 %	119.70 ± 15.63 85.95 ± 9.99*[a] -28.20 %
VLDL-c (%) Baseline Week 12 Change from baseline	25.63 ± 2.03 24.07 ± 1.91[b] -8.42 %	46.20 ± 9.83 60.50 ± 9.14[a] 30.95 %	32.00 ± 3.05 28.10 ± 3.28[b] -12.19 %
HDL-c (%)			

Baseline	43.26 ± 1.69	38.60 ± 1.11	43.65 ± 1.70
Week 12	47.42 ± 1.71*[a]	39.60 ±1.05[b]	48.60 ± 1.63*[a]
Change from baseline	9.61 %	2.59 %	11.34 %

Data are given as mean ± SE for baseline and end of study values for change from baseline; * significantly different compared to pre-treatment level (P<0.05); values with non-identical superscripts (a,b) among different groups are considered significantly different (P<0.05).

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