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Half of Three Oral Antidiabetic Drugs as a Regimen for Treatment of Type 2 Diabetes Mellitus Patients in Low-income Populations

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Authors' contributions

This work was carried out in collaboration between all authors. Author MAM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors EME and AAH managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

There is a progressive increase in the number of patients developing type 2 diabetes mellitus (T2DM), worldwide. Several classes of antidiabetic drugs are available. Metformin is a biguanide with many pleiotropic effects in addition to decreasing hyperglycemia. Dipeptidyl-peptidase 4 (DPP4) inhibitors are a group of medications used as glucose-lowering agents in T2DM.The combination of metformin plus DPP4 inhibitors have an additive effect on improving HbA1c level but of high cost, especially in low-income countries like Egypt. So, the aim of this study is to assess the efficacy and safety of adding sulphonylureas (e.g, glimepiride or gliclazide) to half the dose of a DPP4 inhibitor /metformin combinations compared to using the full dose of this DPP4 inhibitor /metformin combination in T2DM.

Materials and Methods: This prospective study was conducted on186 patients with type 2 diabetes mellitus (T2DM), who achieved glycemic targets on DPP4 inhibitor (sitagliptin or

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vildagliptin) 50 m /metformin 1000 mg, twice daily fixed-dose combination. The enrolled subjects were then divided into 2 groups. Group1 were 92 patients continued on the same regimen. Group 2 (patient who could not afford the high cost of the DPP4 inhibitors) shifted to half the dose of the DPP4 inhibitor / metformin plus a dose of sulphonylureas (SU) either Glimepiride (4 mg) or Gliclazide (60 mg slow release form) once daily. For both groups: weight, fasting blood glucose (FBG), 2 hours postprandial glucose (2 hrs PPG), and glycated hemoglobin (HbA1c), were measured at the start and after 12 weeks of the study.

Results: There were a decrease in FBG, 2hs PPG, and HA1c with an increase in weight and in the mean number of hypoglycemic episodes per patient among participants shifted to half the dose of DPP4 inhibitor /metformin with an added dose of SU compared to the other group of patients continued on the full dose of the same DPP4 inhibitor /metformin combination.

Conclusion: Adding sulphonylureas (either glimepiride or gliclazide) to half the dose of a DPP4 inhibitor/metformin combination is non-inferior to using the full dose of this DDP 4 inhibitor/metformin combination twice daily in T2DM patients with low risk of hypoglycemia. This regimen may be effective and safe for low-income populations like Egypt.

Keywords: DPP4 inhibitors; hypoglycemia; sulphonylureas; type 2 diabetes mellitus; low-income; Egypt.

1. INTRODUCTION

The estimated number of diabetes mellitus (DM) patients in 2015, were over 412 million worldwide. With 1 in every 11 adults currently diagnosed, the ratio is expected to increase to 1 in 10 by 2040 [1]. More than 90% of them are Type 2 diabetes mellitus (T2DM) [1]. The guidelines recommended metformin as the initial treatment for T2DM [2]. Metformin is a biguanide, with many pleiotropic effects in addition to decreasing hyperglycemia as hypoinsulinemia, reduction of hepatic glyconeogenesis, improving lipid profile and decreasing hypercoagulability [3,4,5,6]. Moreover, several studies [7,8] emphasized its beneficial effects on the cardiovascular system, so it is widely used worldwide. Dipeptidyl-peptidase 4 (DPP4) inhibitors are a group of medications used as glucose-lowering agents in T2DM [9]. They act by inhibition of DPP4 enzyme activity to prevent the inactivation of the incretin hormone glucagon-like peptide (GLP)-1 in the peripheral circulation. Increased circulating GLP-1 levels, result in an increment in insulin secretion and inhibition of glucagon secretion leading to increasing glucose utilization and a reduction in hepatic glucose production. So a reduction of postprandial and fasting blood glucose occurs, which in turn reduces HbA1c [10]. In addition to their efficacy as antihyperglycemic agents, they have several other beneficial effects. They cause lower rates of hypoglycemia in comparison to other antidiabetic medications, less cardiovascular risks and weight neutral effects [11,12,13,14]. Sitagliptin has a blood pressure, low-density lipoprotein- cholesterol (LDL-C) and triglyceride lowering effects [15]. Vildagliptin demonstrated an increment in high-density lipoprotein-cholesterol (HDL-C) observed even at a dose of 50 mg/day [16], and a reduction in insulin resistance documented by a reduction in insulin and glucagon levels [17].

The combination of metformin plus DPP4 inhibitors showed an additive effect on improving HbA1c levels [18,19,20,21]. But these medications may be unaffordable especially in low-income countries like Egypt. Egypt is present in the top ten countries for the number of adults with diabetes in the 8th place [1]. We think that many of our T2DM patients may be unable to maintain these combinations. So, we aimed in this study to assess the efficacy and safety of adding sulphonylurea (e.g, glimepiride or gliclazide) to half the dose of DPP4 inhibitor/metformin combination compared to using the full dose of this DPP4 inhibitor/metformin combination in patients with T2DM.

2. MATERIALS AND METHODS

This prospective study was conducted on 186 patients with type 2 diabetes mellitus (T2DM), who achieved glycemic targets on DPP4 inhibitor (sitagliptin or vildagliptin) 50 mg /metformin1000 mg, fixed-dose combination twice daily. The enrolled subjects were then divided into 2 groups. Group 1 were 92 patients continued on the same regimen, Group 2 patient (who could not afford the high cost of the DPP4 inhibitors) shifted to half the dose of the DPP4/metformin plus a dose of sulphonylureas (SU) either Glimepiride (4mg) or Gliclazide (60 mg slow release form) once

daily. Selected patients were recruited from the outpatient clinic of internal medicine at Alfayum University Hospital during the period from January 2016 to July 2016, after the approval of the local ethics committee. Written informed consent was obtained from the participants.

Inclusion criteria included patients with T2DM older than 18 years, who achieved glycemic targets (HbA1C <7%), on DPP4 inhibitor 50 /metformin1000, fixed-dose combination twice daily. Exclusion criteria were patients older than 60 years old, pregnant or lactating females, with a history of cardiovascular disease within 6 months prior to the study, uncontrolled severe hypertension, patients with impaired liver or kidney functions, current or previous history of malignancy or on chemotherapy.

All the participants were subjected to a thorough history and medical examination including weight. Fasting blood glucose (FBG), 2 hours postprandial blood glucose (2hrsPPG), and glycated hemoglobin (HbA1c), were measured at the start and after 12 weeks of the study. Self-monitoring of blood glucose was advised, especially if any symptoms of hypoglycemia developed. All through the study, any hypoglycemic episodes were reported. Confirmed hypoglycemic episodes were defined as glucose value of ≤ 70 mg/dL (with or without symptoms) based on the American Diabetes Association (ADA) and Endocrine Society Consensus report definition [1] or severe hypoglycemia (severe episodes requiring assistance). Also, the monthly costs of the used antidiabetic medications were calculated.

2.1 Statistical Analysis

Data were collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using SPSS software version 18 in windows 7. A simple descriptive analysis in the form of numbers and percentages for qualitative data and arithmetic means as central tendency measurement, standard deviations as a measure of dispersion for quantitative parametric data, and inferential statistic test. For quantitative parametric data: One way ANOVA test was used in comparing more than two independent groups of quantitative data. Paired t-test was used in comparing two dependent quantitative data. For qualitative data: Chi-square test to compare two or more than two qualitative groups. The P-value ≤ 0.05 was considered the cut-off value for significance.

3. RESULTS

A total number of 186 type 2 DM patients (52.2% males and 47.8% females) participated in our study. There were 92 participants in group 1, 46 of whom were male (50%) and 4 6(50%) were females, with a mean age of 42.2±7.5, mean diabetes duration of 8.9±2.1 months. There were 94 participants in group 2, 51 of whom (54.3%) were males & 43(45.7%) were females, with a mean age of 40.6±7.2 and mean diabetes duration of 8.8±2.2 months.

There were a decrease in FBG, 2hs PPG and HA1c (115±17.6 vs 113.5±18.5, 163.1±31.6 vs 159.9±31.1 and 6.72±0.4 vs 6.68±0.6 respectively) and an increase in weight (92.6±8.7 vs 93.3±12.4) among patients on half the dose of DPP4 inhibitor /metformin with an added dose of SU compared to the other group of patients continued on full dose DPP4 inhibitor /metformin combination twice daily but these differences were statistically nonsignificant as shown in Table 1.

Table 1. Comparison of different variables between patients continued on full dose DPP4 inhibitor /metformin combination with those shifted to half the dose DPP4 inhibitor /metformin with an added dose of SU

Variables	Group 1 (n=92) Mean ± SD	Group 2 (n=94) Mean ± SD	p-value
Weight	92.6±8.7	93.3±12.4	0.7
FBG	115±17.6	113.5±18.5	0.54
2HPPG	163.1±31.6	159.9±31.1	0.49
HbA1c	6.72±0.4	6.68±0.6	0.67

This decline in FBG, 2 hs PPG, and HA1c among group 2 patients on half the dose of DPP4 inhibitor /metformin with an added dose of SU revealed that this regimen provided better control or at least was not inferior to the regimen of full dose DPP4 inhibitor /metformin combination twice daily in our study.

There was a statistically significant difference with p-value =0.01 as regard the number of hypoglycemic episodes per patient with a low mean of attacks per patient (0.2± 0.4) during the period of this study among group I patients treated with full dose DPP4 inhibitor /metformin and higher number of attacks per patient (0.39 ±0.7) among group 2 patients treated with half the dose of DPP4 inhibitor /metformin with an added-on SU, as shown in Fig. 1.

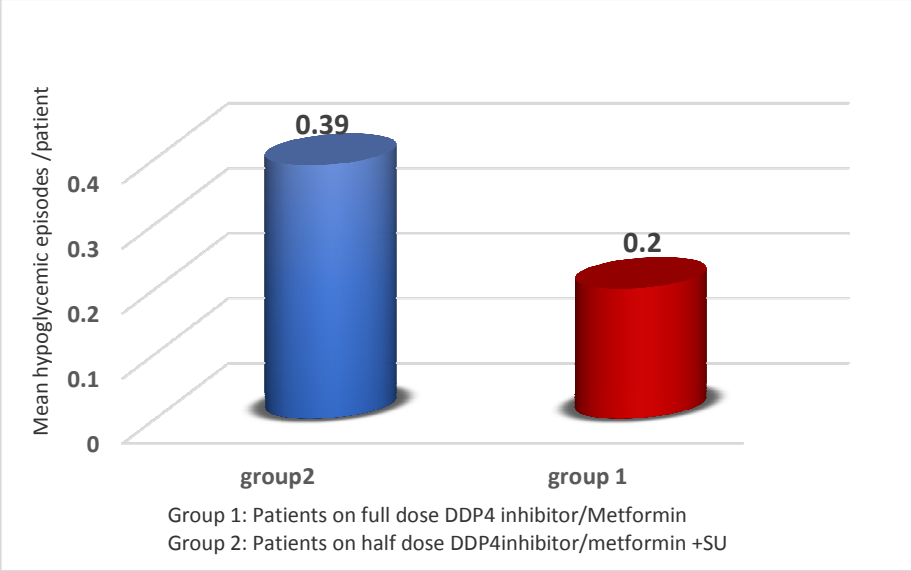

Fig. 1. Comparison between the 2 studied groups regarding the mean of hypoglycemic episodes per patient

Hypoglycemic episodes were more frequent [26 patients (27.7%)] among patients on added SU to half the dose of DPP4 inhibitor /metformin combination as compared to those on full dose DPP4 inhibitor /metformin combination twice daily [15 patients (16.3%)] as shown in Fig. 2.

There was a higher risk of developing a hypoglycemic episode on half dose DDP4/metformin regimen with an added SU relative to the full dose regimen with a calculated relative risk 1.7. In addition, we reported one episode of severe hypoglycemia in patients on three antidiabetic drugs with an added SU, while we did not report any of such episodes in patients on full dose DPP4 inhibitor /metformin combination.

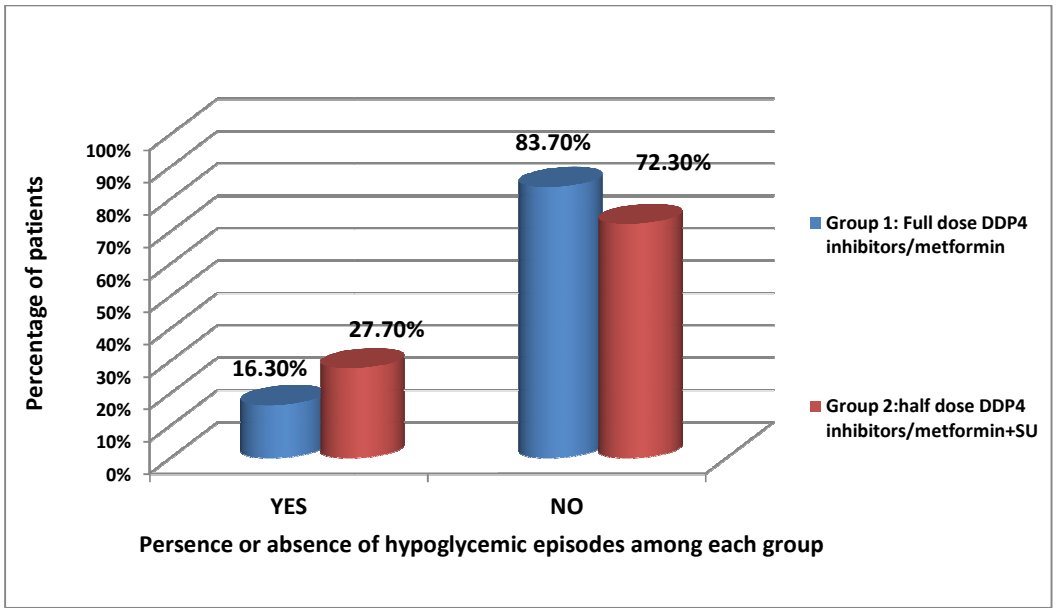

Fig. 2. Comparison between the 2 studied groups as regard hypoglycemia frequency

Calculation of the total 3 months cost of treatment per patient at the time of our study was in group 1 (full dose DPP4 inhibitor/metformin) about 660 L.E while it was about 375 L.E in group 2 (half dose DPP4 inhibitor/metformin plus SU).

4. DISCUSSION

In this study, we found that using half the dose of DPP4 inhibitor/metformin plus SU were non-inferior to full dose DPP4 inhibitor/metformin as regard their efficacy in achieving the glycemic targets assessed by HbA1c but with a significant increase in hypoglycemic episodes frequency and a modest increase in weight. Our results were consistent with Yang et al. [22], who reported in Chinese patients a meaningful drop in HbA1c after adding vildagliptin 50 mg once daily to glimepiride without an increase in weight or risk of hypoglycemia which can be explained by the use of variable doses of glimepiride in their study. These results also came in agreement with Lukashevich et al. [23], but with higher SU doses as the patients enrolled in their study were poorly controlled and in agreement with Kikuchi et al. [24], reporting the same results in Japanese patients with any dose of glimepiride. Several studies [25,26,27,28] reported similar results with sitagliptin 100 mg once daily when was added to SU plus metformin therapy.

Moreover, SU alone although their efficacy, are characterized by high secondary failure rates and β-cell function deterioration so, add-on antidiabetic medications are frequently needed [29,30,31].

Although SU are known to be associated with a significant risk of hypoglycemia and a mild weight gain, glibenclamide and glyburide have the highest risk, glimepiride and glipizide pose an intermediate risk and the least risk is with gliclazide [32]. In this study, the added SU were gliclazide and glimepiride because gliclazide is a preferred SU in our country as it is a cost-effective drug, of affordable price, with lower hypoglycemic risk, and with lower mortality and morbidity rates compared to other SU [33,34].

In our study we tried upon adding SU, to use average doses to avoid hypoglycemic events assumed to occur with maximal doses, in addition to avoidance of low drug efficacy which may occur with small doses when we used half the dose of DDP4 inhibitors and metformin.

We reassessed the patients after 12 weeks in agreement with several studies that presumed that 3 months is a sufficient period for sitagliptin to assess its clinical effect [35,36].

Regarding compliance with the medications, there was no issue of concern to be mentioned.

In this study, we estimated the total cost of 3 months of treatment per patient when SU were added to half the dose of DDP4 inhibitors/metformin combination to be about 375 LE which represented about half of the estimated costs for a full dose DDP4 inhibitors/metformin. This is the main purpose for which this study was performed. Egypt is one of the low-income countries with most of our populations are not under health insurance coverage, so using affordable regimens is a prerequisite on prescribing any medications especially for those with chronic diseases with multiple comorbid conditions.

There are several limitations of our study. First, we did not measure markers of insulin secretion capacity, β-cell function nor glucagon level to assess the reflection of this regimen on them. Second, the enrolled patients were relatively of young age ≤ 60 years, with a low-risk of hypoglycemia, so this regimen may be applicable on some selected patients. Third, we did this study on a small sample size with fixed doses of SU so we advise further studies with larger sample size and lower SU doses.

5. CONCLUSION AND RECOMMENDATIONS

Adding a sulphonylurea (either glimepiride or gliclazide) to half the dose of a Dipeptidyl-peptidase 4 (DPP4) inhibitor/metformin combinations is non-inferior to using the full dose of this Dipeptidyl-peptidase 4 inhibitor/metformin combination twice daily in T2DM patients with a low-risk of hypoglycemia. This regimen may be effective and safe for low-income populations like Egypt. Further studies of this regimen with a larger scale of patient's selection to involve older patients with using lower doses of SU are recommended.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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