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Saxagliptin versus Glimepiride Combination with Metformin in Type 2 Diabeted Mellitus

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Abstract: Various groups of oral hypoglycemic agents (OHAs) are recently available, but there is a need for agents with different mechanisms of action that achieve better efficacy and can be used either as monotherapy or in combination with treatment regimens**.** Dipeptidyl peptidase-4 inhibitors improve glycemic control in patients with type 2 diabetes mellitus (T2DM) when used as monotherapy or in combination with other OHAs. The main aim of the present study is to compare the effects of Saxagliptin versus Glimepiride on efficacy of treatment in patients with T2DM in combination with metformin. A retrospective observational study will be performed on patients each in (Saxagliptin+Metformin) and (Glimepiride+Metformin) group, who are receiving treatment for at least 12 weeks. Glycated hemoglobin (HBA1c) will be the chief parameter of efficacy. At 12 weeks both groups (Saxagliptin and Glimepiride) produced significant ($P < 0.05$) reduction in HbA1C, with 51.4% of patients in saxagliptin group and 25.7% of patients in glimepiride group achieving target HbA1C. Reduction was also significant ($P < 0.05$) in both groups in fasting blood glucose (FPG). Saxagliptin group showed insignificant decrease in body weight by whereas glimepiride group showed significant increase in body weight. The addition of Saxagliptin to ongoing Metformin monotherapy provided significant HbA1c-lowering efficacy after at least 12 weeks of treatment compared with the addition of Glimepiride.
Keywords: Type2DM, Saxagliptin, Metformin, Glimepiride, Efficacy.

INTRODUCTION

Diabetes mellitus (DM) is a chronic, lifelong disease caused by deficiency or resistance of the hormone insulin which regulates the level of glucose in the blood [1]. The American Diabetic Association defines DM as a "group of metabolic diseases of several etiologies characterized by chronic hyperglycemia resulting from disturbances of carbohydrate, fat and protein metabolism, resulting from defects in insulin secretion, insulin action, or both" [2]. Table 1 summarizes the diagnostic criteria for diagnosing DM as recommended by the World Health Organization (WHO, 2006).

Table-1: WHO diagnostic criteria of diabetes and intermediate hyperglycemia

Diabetes mellitus	
Fasting plasma glucose Or 2–h plasma glucose	≥7.0mmol/l (126mg/dl) ≥11.1mmol/l (200mg/dl)
Impaired Glucose Tolerance (IGT)	
Fasting plasma glucose and 2–h plasma glucose	< 7.0mmol/l (126mg/dl) ≥7.8 and <11.1mmol/l (140mg/dl to 200mg/dl)
Impaired Fasting Glucose (IFG)	
Fasting plasma glucose and (if measured) 2–h plasma glucose	6.1 to 6.9mmol/l (110mg/dl to 125mg/dl) <7.8mmol/l (140mg/dl)

Type 1 DM (T1DM) is the end result of absolute or relative insulin deficiency (TA, 2014). Type 2 DM (T2DM) is a heterogeneous group of disorders manifested by variable ranges of insulin resistance,

inadequate insulin secretion, and increased glucose production [3].

Goals of Treatment

Apparently, individualization glycemic targets and the drugs used to reach them are needed for each patient in order to maximize benefits and minimize risks [4]. The glycemic goal recommended by the American Diabetes Association (ADA) is at HbA1C level of <7%, while the International Diabetes Federation (IDF) advocate a recent glycemic goal at HbA1C level of <6.5% [5]. Implementing adequate treatment goals is necessary to slow the occurrence of, or reduce the progress of microvascular complication. Ensuring adequate glycemic control through efficient disease management will significantly improve the patient's quality of life and reduce rates of morbidity and mortality [6].

Pharmacological Therapy

When choosing the pharmacologic treatment plan, a chief element is to recognize whether the patient is insulin deficient, insulin resistant, or both. Pharmacological choices can be allocated into insulin sensitizers, secretagogues, alpha glucosidase inhibitors, incretins, pramlintide, SGLT-2 inhibitors, insulin and insulin analogs. Monotherapy with metformin is the first treatment option of T2DM. However, combination therapy should be considered as initial choice if HbA_1C is greater than 7.5% [7]. Table 2 summarizes the different OHAs available.

Table-2: Common Oral Hypoglycemic Agents

Subgroup	Generic Name	Class	Route	Comments
Biguanides	Metformin	Sensitizer	Oral	Weight loss, No hypoglycemia GI upset
Thiazolidinediones	Rosiglitazon, Pioglitazone	Sensitizer	Oral	Weight gain, Peripheral edema
Alpha glucosidase inhibitors	Acarbose, Miglitol		Oral	GI upset
Sulfonylureas	Chlorpropamide, Glibenclamide, Glimepiride, Glipizide	Secretagogue	Oral	Hypoglycemia, Weight gain
Exenatide	Liraglutide	GLP-1 analog	Subcutane-ous	Weight loss GI upset
Glinides	Nateglinide, Repaglinide	Secretagogue	Oral	Weight gain
Extended release exenatide	Pramlintide	GLP-1 analog	Subcutaneous	Weight loss
Dipeptidyl peptidase-4 inhibitors (DPP-4s)	Sitagliptin, Saxagliptin Linagliptin	DPP-4 inhibitors	Oral	No hypoglycemia, Nasopharyngitis, Weight neutral
SGLT-2 inhibitors	Canagliflozin Dapagliflozin	Renal glycosuria	Oral	Polyuria, UTIs

GI, gastrointestinal; GLP-1, glucagon-like peptide type 1; UTIs, urinary tract infections

Sulfonylureas (SUs), Biguanides, and Thiazolidinediones (TZDs) are the common used oral hypoglycemic agents (OHAs) in the management of T2DM. Recent treatment guidelines recommend metformin as the initial drug to be used along with diet and lifestyle changes for the larger part of patients unless there is a contraindication. Incretin effect is accountable for up to 70% of insulin secretion after oral glucose administration and targeting incretin mimetic hormones appears to be hopeful in the management of T2DM [8]. Dipeptidylpeptidase-4 (DPP-4) inhibitors are novel oral OHAs, which may be used as monotherapy or in combination with other OHAs such as metformin, thiazolidinediones or even sulfonylureas. Four different DPP-4 inhibitors are available in the market: sitagliptin, vildagliptin, saxagliptin and linagliptin. They may be as single agents or in fixed-dose combined formulations with metformin. Now available DPP-4 inhibitors vary obviously in their pharmacologic features, and this may have consequences on their clinical efficacy and safety profiles. Saxagliptin is a potent, reversible, competitive DPP-4 inhibitor with high selectivity for human DPP-4 and potency around tenfold more than that of vildagliptin or sitagliptin [9]. Saxagliptin has been available in Europe as monotherapy (Onglyza®) and in a fixed-dose combination with metformin (Komboglyze®).

The aim of this study is to compare the effects of Saxagliptin versus Glimepiride on efficacy of

treatment in patients with T2DM mellitus in combination with metformin.

MATERIALS AND METHODS

This is a retrospective observational study conducted in outpatient department of medicine in King Hussein Medical Center (KHMC) at The Royal Medical Services (RMS) in Amman/Jordan. Ethical approval has been obtained from the IRB committees at the RMS. The patient's baseline characteristics were noted medical records. Patients more than 18 years of age, with T2DM while on a stable dose of metformin (>1500 mg/day) and saxagliptin (2.5-5 mg/day) or glimepiride (2-8 mg/ day) for at least 12 weeks prior to the last clinic appointment were eligible for this study. Fifty patients each were recruited in saxagliptin and glimepiride group. Results of blood chemistry and complete blood count were accessed through revision of patient's medical profiles. Patient were excluded from the study if they did not meet screening criteria which includes having records of patient about HbA_1c, weight, height, and fasting blood glucose. Those patients were also excluded from the study if they had a history of T1DM, used any other OHAs besides metformin and saxagliptin or glimepiride within 12 weeks of the screening visit or had impaired renal function. The primary efficacy outcome was change from baseline in HbA1c at 12 weeks. Secondary outcome was change from baseline in body weight. Laboratory data which were compared are fasting lipid parameters i.e. total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and serum creatinine was compared depending upon availability. The sample size derived was 72 per group.

STATISTICAL ANALYSIS

The data were analyzed using the Statistical Package for the Social Sciences, version 22 (SPSS). The comparison of qualitative data was done by using Student's t-test. Within-group pre and post-treatment comparisons were performed by applying a paired t-test separately in each group. The data were expressed as mean± SD. A p-value <0.05 was considered statistically significant.

RESULTS

Base line parameter

As shown in (Table1), the baseline parameters of both groups are almost similar and there is no statistically significant difference among them. Weight and BMI in saxagliptin group was lower compared to glimepiride group.

Table-1: Comparison of baseline parameter in saxagliptin and glimepiride group

Parameter	Metformin + Saxagliptin	Metformin + Glimepiride	p-value
Age	66.4±11.1	65.9±11.9	0.58
Female (%)	41(58.5)	43 (61.4)	0.49
Weight	71.9±10.9	73.1±11.8	0.072
BMI	31.2±4.9	31.9±7.6	0.068
HbA1C(%)	7.38±1.71	7.41±1.58	0.51
FPG	124.6±31.2	129.6±29.8	0. 15

BMI- Body Mass Index, HbA1c- Glycated hemoglobin, FPG- fasting plasma glucose, • Values indicates Mean±SD
• Unpaired t test was used for statistical analysis.
• p<0.05 was considered significant

Efficacy

As shown in (Table 2), there was a statistically significant difference in between the groups in efficacy parameters i.e. HbA1c and FPG are concerned. Furthermore, compared to baseline both groups showed significant reduction in FPG (p <0.05) (Table 3). However, the glimepiride group was associated with weight gain whereas the saxagliptin group was associated with weight loss (P<0,05), (Table 2). This resulted in a statistically meaningful difference between-groups after at least 12 weeks of treatment (p<0.05), (Table 3).

Table-2: Efficacy parameters after 3 months of treatment

Parameter	Metformin + Sitagliptin	Metformin + Glimepiride	p-value
HbA1C (%)	7.09±1.11	7.31±1.19	0.037
FPG	117.31±26.42	119.63±30.48	0.0388
Weight	71.43±10.78	75.3±12.66	0.023

HbA1c- Glycated haemoglobin, FPG- fasting plasma glucose
• Values indicates Mean±SD
• Unpaired t test was used for statistical analysis
• p<0.05 was considered significant

Table-3: Change in parameters before and after treatment for 12 weeks in saxagliptin and glimepiride group

Parameter	Metformin+ Saxagliptin		p-value	Metformin+Glimepiride		p-value
	Before	After		Before	After	
HbA1c (%)	7.38±1.71	7.09±1.11	0.039	7.41±1.58	7.31±1.19	0.072
FPG	124.6±31.2	117.31±26.42	0.022	129.6±29.8	119.63±30.48	0.01
Weight(kg)	71.9±10.9	71.43±10.78	0.21	73.1±11.8	75.3±12.66	0.049
Lab values*						
TC	199.23±31.03	197.38±30.99	0.51	186.36±33.28	184±36.39	0.51
LDL	123.71±28.66	118.97±19.15	0.53	128.72±22.37	127.73±21.81	0.35
TG	143.66±41.59	139.93±36.69	0.84	141.68±42.76	140.36±41.39	0.66
HDL	44.53±6.01	46.68±6.15	0.41	44.54±6.35	43.91±6.72	0.31
SrCr	0.89±0.12	0.88±0.15	0.39	0.91±0.18	0.92±0.19	0.84

• HbA1c- Glycated haemoglobin, FPG- Fasting plasma glucose, TC- Total cholesterol, LDL- low density lipoprotein, TG- Triglycerides, HDL- High density lipoprotein, SrCr-Serum creatinine

• Values are Mean ± SD.

• Statistical analysis was done using paired t test. ($p<0.05$ considered significant)

DISCUSSION

In the present study, patients with T2DM on a stable dose of metformin in addition to treatment with the DPP-4 inhibitor, saxagliptin, or the sulfonylurea agent, glimepiride were included. The result revealed that efficacy of lowering HbA1c is statistically significant for saxagliptin in comparison with glimepiride group. When comparing both groups, number of patients in saxagliptin group achieved the therapeutic target of HbA1c ≤7% was greater, (36 pt in saxagliptin group vs 18 pt in glimepiride group). The reduction in fasting blood sugar level was found to be statistically significant in both study groups.

Treatment with saxagliptin was associated with weight loss whereas weight gain was observed in glimepirde group. The result of this study is consistent with previous studies where DPP-4 inhibitors were found to be more efficacious when compared with sulphonylureas such as glipizide and glimepiride [10-13].

The increase in body weight associated with certain OHAs is an undesired effect in patients with T2DM [14], nevertheless glimepiride has been associated with less weight gain compared to other sulphonylureas [15]. In the current study, adding of saxagliptin to ongoing metformin monotherapy was associated with weight loss, whereas the addition of glimepiride was associated with weight gain. No significant differences were observed in laboratory safety assessments between two groups. A study by winter. (2018) had similar finding with DPP-4 inhibitors showing better glycemic control over sulfonylureas as add-on diabetes [16]. This may be explained by the fact that DPP-4 inhibitors improve glycemic control by increasing the concentration of incretins gut derived peptides which stimulate insulin secretion in a glucose-dependent manner.

In a study by Rosenstock *et al*. [17] included a main treatment cohort (MTC) with 401 patients (HbA(1c) > or = 7% and < or =10%) randomized and treated with oral saxagliptin 2.5, 5, or 10 mg once daily or placebo for 24 weeks and a separate open-label cohort (OLC) with 66 patients (HbA(1c) > 10% and < or =12%) who received saxagliptin 10 mg once daily for 24 weeks revealed that in the MTC, saxagliptin demonstrated statistically significant decreases in adjusted mean HbA(1c) changes from baseline (mean, 7.9%) to week 24 (-0.43%, -0.46%, -0.54%) for saxagliptin 2.5, 5, and 10 mg, respectively, vs. +0.19% for placebo (all $p < 0.0001$). Adjusted mean FPG was significantly reduced from baseline (-15, -9, -17 mg/dL) for saxagliptin 2.5, 5, and 10 mg, respectively, vs. +6 mg/dL for placebo ($p = 0.0002$, $p = 0.0074$, $p < 0.0001$, respectively). More saxagliptin-treated patients achieved HbA(1c) < 7% at week 24 (35% (p = NS), 38% [$p = 0.0443$], 41% [$p = 0.0133$]) for saxagliptin 2.5, 5, and 10 mg, respectively, than placebo (24%). This study concluded that once-daily saxagliptin monotherapy was in general well tolerated and revealed clinically significant drops in main parameters of glycemic control vs. placebo [17].

In an Indian study by Muthukrishnan *et al*. [18], also showed consistency with our finding as it found that the DPP-4 inhibitor (Sitagliptin) with metfromin and metfromin alone group fared better than the glimepiride group for glycemic control, lesser treatment failures, and less weight gain [18]. The findings showed that 73.3% of the patients receiving sitagliptin reached pre-specified glycemic target in comparison with 30% patients in glimepiride group ($p<0.001$). Sitagliptin group also had less weight gain (mean wt. change in kg. 1.9 vs 3.5, $p<0.05$).

CONCLUSION

The addition of saxagliptin to ongoing metformin monotherapy provided significant HbA1c-lowering efficacy after at least 12 weeks of treatment compared with the addition of glimepiride.

Saxagliptin users had modest weight loss compared to gain with glimepirde. Similar results were observed across most other efficacy outcomes reported. Further researches are required to address longer-term efficacy outcomes for saxagliptin compared to glimepirde as add-on to metformin.

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