Cihan University-Erbil Scientific Journal (CUESJ)

Research Article

A comparative Study of Efficacy and Safety among Metformin, Sitagliptin, and Glimepiride Monotherapies in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Effective management of Type 2 diabetes mellitus (T2DM) requires lifestyle changes and suitable medications to enhance quality of life and prevent complications. Choosing the right treatment involves considering the patient's clinical profile, drug efficacy, side effects, and cost. This study compares the safety and efficacy of sitagliptin, glimepiride, and metformin in T2DM patients. A prospective cross-sectional study was conducted at the Diabetes Center of Layla Qasim, Erbil, Iraq, that included 143 diabetic patients. They were divided into three groups: Group A received glimepiride (n = 50), Group B metformin (n = 48), and Group C sitagliptin (n = 45). Drug costs, therapeutic outcomes, and side effects were analyzed.

Patients aged 30–78 participated, with a female-to-male ratio of 83:60. All groups showed statistically significant differences in hemoglobin A1c (HbA1c) levels (P = 0.001). Total cholesterol and low-density lipoprotein levels were also significantly different (P = 0.047 and P = 0.010, respectively). Sitagliptin group had higher triglycerides and high-density lipoprotein-cholesterol. Gastrointestinal side effects were prominent in the metformin group. When selecting medication for T2DM, factors such as age, HbA1c, glucose levels, obesity, metabolic syndrome, insulin secretion, and hypoglycemia risk should be considered. Both sitagliptin and glimepiride were well tolerated, with minimal hypoglycemia risk and no significant weight differences between groups. Glimepiride is an effective, safe, and weight-neutral adjunct to metformin, offering extrapancreatic benefits and remains a viable second-line treatment option for T2DM patients.

Keywords: Diabetes, hemoglobin A1c, metformin, glimepiride, sitagliptin

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the most prevalent form of the chronic metabolic disease known as diabetes mellitus.[1] Diabetes is a chronic condition; thus, patients frequently require long-term care. T2DM is a global epidemic that is expected to impact more than 550 million people by 2035.[2] Despite receiving medication and making lifestyle changes patients with T2DM show increasing glucose levels over time, which is probably due to deteriorating β-cell activity. The defining features of Type 2 diabetes include insulin resistance in peripheral tissues and insufficient insulin production.[3] According to one study, an even higher percentage of people with Type 2 diabetes do not adequately regulate their blood sugar levels in emerging nations, particularly China, and about two-thirds of patients in wealthy countries.[4] A study conducted in the Kurdistan region of Iraq, which included patients from the diabetes centers in the provinces of Erbil, Duhok, and Suleimania, showed that 92% of patients had hemoglobin A1c (HbA1c) levels at and above 7%, indicating non-optimal glycemic control.[5]

In every country in the globe, obesity continues to be a serious threat to public health.[6] Diabetes rates have quadrupled globally since 1980 due to obesity.[7] Assessing the effectiveness of diabetes treatment often relies on HbA1c;

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Received: June 25, 2024
Accepted: September 20, 2024
Published: October 30, 2024

DOI: 10.24086/cuesj.v8n2y2024.pp104-109

however, this measurement does not provide information on how the treatment affects insulin secretion or insulin resistance.[8] Oral hypoglycemic medications come in a wide variety of forms, and there are significant variations among them in terms of their effects and price. Most patients need to choose medications with a curative effect and at a reasonable cost if they want to take them for a long time.[9]

Metformin, which is the first line and primary medication used in the treatment of Type 2 diabetes, is a biguanide insulin-sensitizing agent that works by preventing the production of glucose in the liver, improving insulin's effect on glucose uptake in peripheral tissues, and lowering the absorption of glucose from the intestine. The decrease in liver energy generation triggers adenosine monophosphate-activated protein kinase, which is a cellular metabolic sensor.[10] Metformin is effective on its own and also when used in conjunction with other medications that reduce blood glucose levels. It is generally considered a first-line treatment of T2DM well-tolerated, has minimal adverse effects, and is inexpensive.[11]

The incretin effect is explained by hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both of which are produced in the intestine. This effect produces a greater insulin secretory response when glucose is taken orally compared to when it is administered intravenously to maintain the same blood sugar levels.

Incretin action is impaired in Type 2 diabetic patients due to the lack of response of diabetic β-cells to GIP.[12] After eating a meal, the incretin hormones that are released from the gut encourage the release of insulin.

Evidence shows that GLP-1 and GIP are the two most important incretins. Both hormones significantly increase the release of insulin. The availability of endogenous GLP-1 is increased by oral dipeptidyl peptidase-4 (DPP4) inhibitors, which improves glucose-induced insulin secretion and reduces glucagon release. Both body weight and stomach emptying are unaffected by these substances.[13] The first drugs in this class to get Food and Drug Administration (FDA) approval are vildagliptin and sitagliptin. Sitagliptin achieves its anti-hyperglycemic action by reducing the inactivation of incretin hormones. Sitagliptin is a potent, highly specific, reversible, and competitive inhibitor of the DPP-4 enzyme. Sitagliptin has been associated with a twofold increase in postprandial GLP-1 plasma levels in both healthy individuals and patients with T2DM compared to a placebo.[14]

Sulfonylureas, such as glimepiride or Glipizide, either alone or in combination with metformin, are one of the oral anti-hyperglycemic agents that are frequently recommended in low- and middle-income nations of Asia and Africa. This family of medications lowers hyperglycemia and glycated HbA1c levels in persons with T2DM by increasing the release of insulin from beta cells.[15]

This study aimed to examine the impact of a variety of antidiabetic medications (metformin, glimepiride, and sitagliptin) on the serum levels of HbA1c and other specific analytical parameters.

METHODOLOGY

Study Design

A cross-sectional prospective study was performed at the Diabetes Center of Layla Qasim/Erbil/Iraq to compare the safety profile and efficacy of sitagliptin, glimepiride, and metformin among individuals suffering from T2DM. The study was approved by Hawler Medical University, Ethics Committee College of Pharmacy. In this study, patients who were taking metformin 500 mg, sitagliptin 100 mg, and glimepiride 2 mg in fixed dosage forms as monotherapies were recruited and divided into three treatment groups. The duration of treatment varied for each patient ranging from 3 months to 1 year.

In this study, the Medonic hematology analyzer was used for hemoglobin measurement, along with the lyse reagent. For the tests of HbA1c, fasting blood sugar (FBS), lipid profile, kidney function, and bilirubin, cobas® c 111 analyzer was used, conducted using the corresponding test kits designed for each of these tests for the cobas® system.

Study Setting

The patients were recruited from the Diabetic Center of Layla Qasim in the city of Erbil in the Kurdistan region of Iraq from November 2022 to February 2023.

Study Population

Eligible individuals included both sexes, regardless of age, with different anti-diabetic pharmacological modalities taken as monotherapy. Patients with a history of connective tissue disease, terminal illness, liver disease, kidney disease, or pregnancy were excluded from the study. A total number of 143 patients with diabetes were included in this study.

Statistical Analysis

Statistical Package for the Social Sciences version 23 was used in conjunction with Microsoft Excel 2010 to conduct

Table 1: Baseline traits of study participants

Variable	Frequency	Percentage
Gender		
Female	83	58
Male	60	42
Education		
Primary school	18	12.6
High school	32	22.4
University	13	9.1
Illiterate	80	55.9
Smoker		
Yes	66	46.2
No	77	53.8
Exercise		
Yes	73	51
No	70	49

the statistical study. The mean and standard deviation were used to characterize the quantitative data. One-way analysis of variance was used to determine the statistical significance of the differences between the three groups, and a descriptive statistic was deemed significant at $P \leq 0.05$.

RESULTS

The age of studied subjects ranged between ages 30 and 78, in a gender ratio of (83:60) female to male. The majority of the patients in the study were illiterate, in an illiterate to literate ratio of (80:63). The majority of the patients were non-smokers in a ratio of (77:66) non-smoker to smoker presented in Table 1.

In Table 2 biochemical analysis has shown statistically significant differences between the treatment groups in terms of HbA1c, total cholesterol (TC), and low-density lipoprotein (LDL), with the Group II (glimepiride) recording the lowest HbA1c level (6.35), and Group I (metformin) the lowest triglycerides (TG) (167) and LDL (126.5) levels among the three treatment groups.

Table 3 shows in Group II (glimepiride), hypoglycemia was more prevalent. As for Group I (Metformin), patients experienced gastrointestinal (GI) disturbances such as diarrhea, flatulence, and nausea most.

Moreover, finally, the majority of skin sensitivity symptoms such as pruritis, angioedema, rash, and urticaria were observed among Group II (glimepiride) and Group III (sitagliptin) participants.

DISCUSSION

This study was carried out to determine, in terms of various parameters, the effects of metformin, sitagliptin, and

Table 2: Post-treatment comparison of physical and chemical parameters in the full analysis set

Groups	Group I (metformin)	Group II (glimepiride)	Group III (sitagliptin)	*P*-value
Age	57.40±8.97	54.62±10.16	54.49±10.74	0.278
BMI	23.95±3.27	24.30±3.77	23.99±3.64	0.868
WC	35.50±3.85	37±4.88	36.49±4.60	0.245
HbA1c	6.43±0.95	6.35±1.14	7.11±0.93	0.001*
FBS	178.58±56.59	155.28±38.69	165±57.00	0.081
SBP	135.84±9.47	140.93±12.57	137.46±10.39	0.080
DBP	85.98±4.77	88.93±16.27	86.54±5.73	0.372
TC	167±31.14	196.47±76.98	179.48±39.72	0.047*
TG	178.71±67.31	168.63±50.06	181.11±68.75	0.593
LDL	126.50±34.03	159.58±60.88	164.32±73.59	0.010*
HDL	46.59±7.93	43.17±6.81	47.02±13.81	0.141
Creatinine	0.71±0.42	0.74±0.38	0.65±0.33	0.544
Bilirubin	8.78±14.62	4.20±6.59	4.79±12.61	0.176
Urea	21.21±12.65	22.87±11.40	23.83±12.73	0.627
Hb	16.58±14.92	14.18±1.40	13.99±1.20	0.310

The results were expressed as number and mean±standard deviation. *P*-value was calculated by using one-way analysis of variance test for category data. Non-significant (N.S) difference ($P>0.05$). *Significant difference (S) ($P\leq0.05$). BMI: Body mass index, HbA1c: Hemoglobin A1c, FBS: Fasting blood sugar, TC: Total cholesterol, TG: Triglyceride, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Table 3: Safety parameters observed in the three study groups

Safety parameters	Group I (metformin)	Group II (glimepiride)	Group III (sitagliptin)
Hypoglycemia	14	18	14
Pruritis	20	29	26
Angioedema	1	8	11
Rash	22	32	32
Urticaria	2	15	13
Diarrhea	33	28	15
Nausea	32	22	26
Flatulence	28	16	13
Constipation	8	11	21
Arthralgia	27	22	32
Myalgia	24	22	23

glimepiride (taken respectively in fixed dosages of 500 mg, 100 mg, and 2 mg) on recently diagnosed Type 2 diabetic patients.

Our results show that glimepiride as an initial treatment is superior to others in reducing HbA1c and FBS levels. The current research indicates that T2DM is more frequent in females (Male: Female = 60:83), due to their more inactive and diabetes-promoting lifestyle in our community, which is akin to prior researches.[16,17] The age at which the disease most commonly starts is in between (30 and 77) years of age. Conventionally, thought of as an ailment that affects middle age and older people Type 2 diabetes is now being diagnosed at a younger age.[18] Almost half of the participants (46.2%) in this study were smokers; other research has shown that cigarette smoking is an important modifiable risk factor for T2DM.[19]

The total study period of 12 weeks showed HbA1c for all three groups to be significantly different ($P < 0.001$) and significant differences in TC and LDL with *P*-values (0.047) and (0.010), respectively. The antidiabetic medicines being studied have several mechanisms of action. Metformin monotherapy has been shown to reduce mean HbA1c by 1.3% after 29 weeks, compared to a 0.4% increase in the placebo group.[20] To suggest the mechanism of action of metformin, 131 fasting blood metabolites were studied by Xu *et al*.[20] in three separate cross-sectional cohort studies. When Type 2 diabetes patients using metformin were compared to control groups, the amounts of three metabolites (acyl-alkyl phosphatidylcholines) were shown to be lower in the metformin-treated patients. Lower plasma amounts of LDL cholesterol were associated with the lowering of these metabolites.

One of the most effective oral antidiabetic medications, sulfonylureas, has been used to treat T2DM since 1950.[21]

In Indian clinical settings, sulfonylureas, especially modern ones such as glimepiride, are commonly used as the initial complementary treatment to metformin because of its superior effectiveness, safety, and low cost.[23]

Glimepiride exhibits distinctive binding properties with the sulfonylurea receptor 1 (SUR1), leading to rapid attachment and detachment. Glimepiride increases insulin sensitivity and enhances glucose consumption through glucose transporter four due to its extrapancreatic effects.[24] Our study showed that HbA1c was 6.35 ± 1.14, which means it was well controlled by the glimepiride monotherapy.

As for LDL levels, the results showed a significant difference between the three treatment groups. A meta-analysis, incorporating trial sequence analysis of randomized clinical trials, concluded that second and third-generation sulfonylureas, such as glimepiride, did not show an association with higher general and cardiovascular mortality, myocardial infarction, or stroke.[25] In contrast to studies by Salpeter and Kim, which found that newly diagnosed Type 2 diabetic patients on metformin had statistically significant differences in lipid profiles at baseline, the current study supported this research and showed that metformin, decreased TC, LDL-C, and TG levels in a non-significant way.[26,27]

DPP-4 antagonists promote insulin secretion by deactivating incretins such as GLP-1 and gastric inhibitory polypeptide which is a different mechanism than traditional hypoglycemic drugs.[28] According to one research, sitagliptin, used as a single medication, reduced both HbA1c level and fasting blood glucose levels.[29] Certain clinical studies have shown a 5% drop in LDL-C and fasting TC post-sitagliptin treatment. Although a different trial did not find a significant drop in fasting TG, postprandial TG was lowered by around 9.5%.[30]

Oral hypoglycemic drugs were found to be a common cause of side effects, particularly GI side effects; however, the mechanism underlying these side effects remained controversial, and conflicting study results were reported; additionally, these symptoms were common in both diabetic patients and normal community members, making the relationship difficult to establish; and even in patients with diabetes, there was a significant interindividual variation in the frequency and severity of these side effects, which may have prevented a genetic predisposition.[31] Patients taking metformin tablets commonly report GI side effects as their biggest issue. Metformin is commonly linked to GI side effects such as diarrhea, nausea, and vomiting. It was noted, meanwhile, that some patients would stop their treatment since the cost of their medications is increasing.[32]

In our study, metformin drug used had GI side effects in a frequency of (Diarrhea, $n = 33$ and Nausea, $n = 32$ cases). Study done by McCreight has shown that patients using metformin tablets typically complain about GI adverse effects.[33] According to current literature, the most prevalent GI side effects of metformin include diarrhea, nausea, and vomiting (with a prevalence of 2–63%).

Sulfonylureas function on the ATP-K channel in the pancreatic beta cells to promote the release of insulin, hence lowering hyperglycemia associated with diabetes. Hypoglycemia is a frequent adverse effect of sulfonylureas that, if ignored, can result in altered mental state, convulsions, coma, or even death. Within 6 months of starting sulfonylurea therapy, 20% of patients are thought to develop hypoglycemia.[34]

Hypoglycemia was one of the common side effects of glimepiride in this study which accounts as ($n = 18$) of using this antidiabetic drug as monotherapy. The fact that glimepiride has two mechanisms of action leads to a dramatic decrease in blood sugar levels while posing little risk of hypoglycemia or increased body weight.[23] Study done by Pranarka had shown that the KIR channel gets blocked when the ligand sulfonylurea binds to SUR1, causing membrane depolarization. This opens voltage-dependent calcium channels and allows calcium to enter the cell. The release of insulin is triggered by the increased intracellular calcium levels. It acts as a direct secretagogue, but it also enhances secretion of insulin indirectly in response to fuels like glucose.[35]

In this study, pruritis side effect was mostly induced by glimepiride ($n = 29$). The antidiabetic sulfonylurea drug glimepiride generally is well tolerated. Glimepiride-related skin side effects are uncommon and might include rash, pruritis, photosensitivity, and lichenoid eruption. According

to a number of studies, it is doubtful that sulfonamide antimicrobials (such as sulfamethoxazole-trimethoprim [SMX-TMP]) and sulfonamide non-antimicrobials, including the antidiabetic sulfonylurea drug; glimepiride, will work in harmony. Here, this research describes a case of neonatal toxic epidermal necrolysis in a patient who had a medical history of SMX-TMP hypersensitivity, most likely due to glimepiride.[36]

This case emphasizes an uncommon adverse reaction associated with the administration of the DPP-4 inhibitor sitagliptin. Thirty-three instances of joint pain associated with DPP-4 inhibitors were found by the U.S. FDA. Sitagliptin is widely used in type 2 D.M.; the side effect rash ($n = 32$) cases have been reported in this study.

Study done by Sargın, describe a case there have been reports of hypersensitivity reactions and widespread skin eruptions associated with sitagliptin and its metabolites are extremely rare.[37]

Finally, the present study had some limitations, the most protuberant one being the rather small number of patients, which was due to restrictions on resources and financing.

CONCLUSION

Despite the study being brief, both glimepiride and sitagliptin were well received with no significant variations in weight across groups and a low likelihood of hypoglycemia.

Considering the good efficacy, safe profile, low risk of hypoglycemia, lack of weight change, additional extrapancreatic action, and low cost, glimepiride remains a sensible choice as a supplement to metformin in patients with Type 2 diabetes.

Contemporary sulfonylureas such as glimepiride remain a significant choice as a second-line treatment following metformin among the latest antidiabetic medications.

ACKNOWLEDGMENT

We would like to express our deep gratitude to the Layla Qasim Diabetes Center in Erbil for their cooperation; without them, this research would not have been possible.

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