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Improving the Glimepiride Efficacy in Type 2 Diabetes Treatment: A Review of the Potential Advantages and Disadvantages of Glimepiride as Hypoglycemic Oral Medication.

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ABSTRACT

Type 2diabetes(T2DM) is a major health problem that affects the majority of advanced and developing countries at the same limit, T2DM is a common metabolic disorder which caused by primary two factors :inability of pancreatic beta cells to secrete enough insulin to counteract hyperglycemia and insulin resistance due to dyslipidemia, obesity and low physical activity, also there are unmodifiable factors like genetic predisposition ,family history ,age, ethnicity and race . The major concern of T2DM is its microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular, peripheral vascular, and cerebrovascular diseases) complications which act as a burden on health and economic organizations so finding proper, available and safe medications is a great concern to many countries to reduce the load on economic and health organizations. There are many oral drug classes introduced for treating T2DM, one of them is sulphonylurea. The most commonly used drug of this class is glimepiride which is considered as the most effective and the safest one of sulphonylureas but it has some side effects like weight gain, hypoglycemia, and destruction of beta-cell after a short duration of reaching the maximal dose so many experimental and clinical trials are done to improve its safety profile. In this review, we provided a general view of experimental and clinical trials that were done to avoid glimepiride side effects through combination with other oral hypoglycemic drugs, drug supplements, and natural products. Additionally, clarification if natural products combination with glimepiride had better safety profile and efficacy rather than other drug categories.

1. Introduction

Diabetes is the ninth leading cause of mortality all over the world [1]. Globally, from 100,000 individuals about 7079 will have T2DM by 2030[2]. Diabetes prevalence in the Arab world increased

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largely during the past 20 years, due to poor dietary choices and Western lifestyle adaptation. In 2035, Diabetes is estimated to double in the Arab world [3]. About 15.2% of Egyptian population are suffering from diabetes, these huge number of diabetic patients in Egypt acts as a socioeconomic burden [4]. About half of patients with diabetes are unaware of their condition and are susceptible to diabetic complications. Diabetes is characterized by high morbidity and mortality rates among patients in the Arab world [5]. Type 2 diabetes(T2DM) is characterized by insulin resistance which generated after metabolic syndrome induction due to dyslipidemia ,obesity and low physical activity [6],also characterized by insufficiency of pancreatic beta cells and progressive destruction of these cells due to oxidative stress produced by permanent hyperglycemia and hyperlipidemia [7].T2DM complications are microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular, peripheral vascular, and cerebrovascular diseases)[8]. The majority of socioeconomic costs associated with T2DM are related to its complications [9]. So, through the last decades many experimental and clinical trials were done to discover proper, safe, available medications, and can reduce diabetic complications [10]. There are many classes of oral antidiabetic drugs such as sulfonylureas (SUs), alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, sodium-glucose cotransporter inhibitors and biguanides [11]. Sulphonylureas are divided into first generation (chlorpropamide,acetohexamide, tolbutamide, and tolazamide),second generation (glyburide, gliclazide,and glipizide) and glimepiride which is considered as the third generation of sulphonylureas[12].First generation sulphonylureas are not used any more due to high cardiovascular risks and severe hypoglycemia , First generation sulphonylureas are replaced by second generation sulphonylureas [13].Second generation SUs are potent and used once daily but it is a must to be used in parallel with exercise and diet management ,second generation SUs can be used in combination with other oral hypoglycemic drugs like metformin, alpha glucosidase inhibitors ,and pioglitazone. Second generation SUs are totally prohibited to be used with the metiglinides [14]. According to food and drugs administration website (FDA): glyburide, glipizide, and glimepiride are the only available sulphonylureas for T2DM treatment prescriptions but are totally prohibited in case of lactation and pregnancy [15]. Also, glyburide is totally prohibited for elderly patients due to severe hypoglycemia risk factors [16]. Sulfonylureas in general are not recommended for old patients and those with hepatic or renal impairment [17, 18]. Sulphonylureas are accused of increasing cardiovascular risks and sudden death due to Ventricular Arrhythmia [19]. Glimepiride has many advantages such as low cost, available, orally administrated,rapid hypoglycemic action, and up to 24 hours duration of action[20].Also, it has many advantages over other sulphonylureas ,it is the only sulfonylurea approved by the FDA for combination therapy with insulin[21],also in comparison with other sulfonylurea, glimepiride has lower incidence of cardiovascular risks[22] . Secretion of insulin is controlled by glimepiride's secretagogue activity, glimepiride binds to its specific receptors (SUR) to cause cell depolarization and stimulation of insulin release [23]. Furthermore, Glimepiride enhances the sensitivity of peripheral tissues to insulin, increasing peripheral glucose uptake, thus reducing plasma blood glucose levels and glycated hemoglobin levels (HbA1C) [24]. In other hand ,glimepiride has many disadvantages which limited its use as oral hypoglycemic agent such as hypoglycemia due to increasing endogenous insulin secretion; hypoglycemic unawareness can lead to autonomic symptoms, leading to neuroglycopenia symptoms and potential hypoglycemic coma[25], Weight gain[26],and pancreatic beta cell destruction after receiving the maximal dose of glimepiride by few weeks which called secondary sulphonylurea failure [27, 28]. There are many experimental and clinical

trials were performed to improve glimepiride safety profile through add-on therapy with other oral hypoglycemic categories, drug supplements or with natural products after glimepiride dose adjustment.

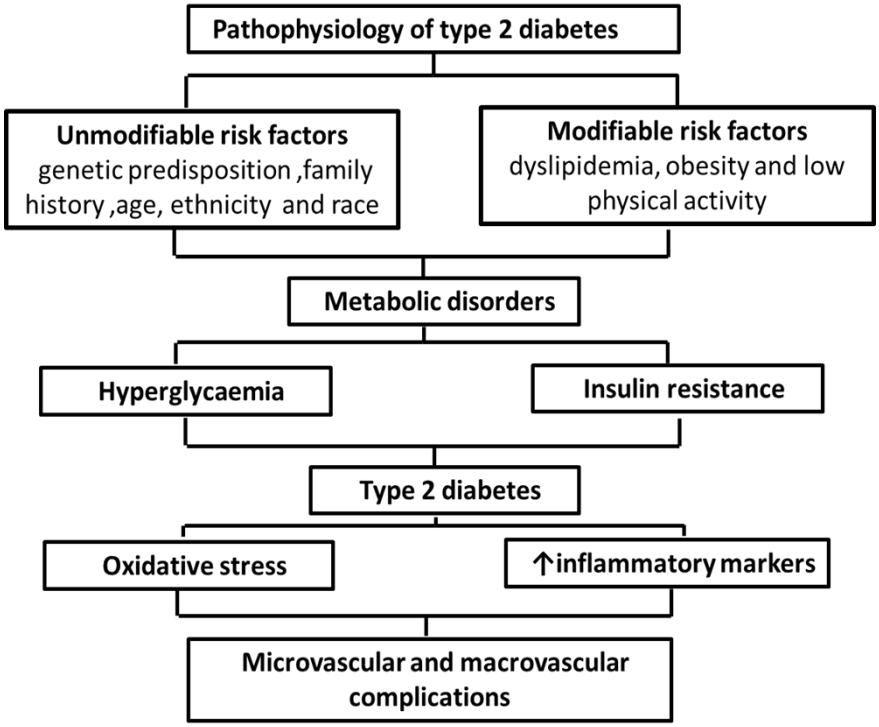

Figure 1. Pathophysiology of type 2 diabetes mellitus.

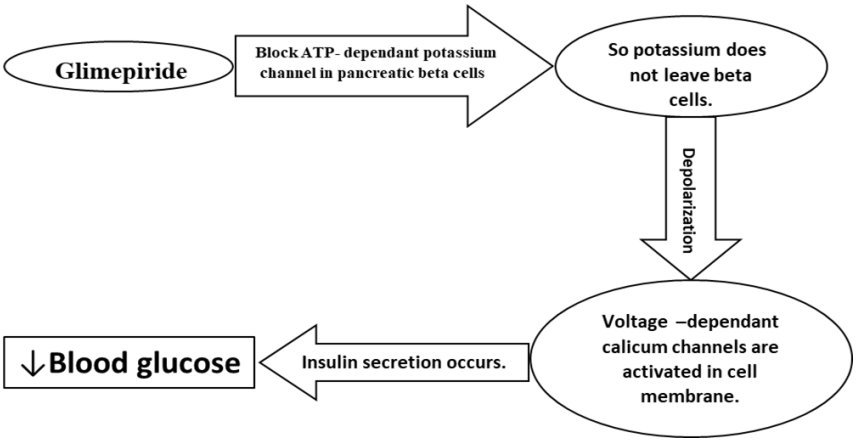

Figure 2. Glimepiride mechanism of action.

2. Clinical and experimental trials to improve glimepiride efficacy and overcome its side effects.

There are many trials were done to improve the safety profile of glimepiride through combination therapy with other oral hypoglycemic drugs like dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, thiazolidinediones, and human glucagon-like peptide-1 (GLP-1) analog. Also, combination with other drug supplements and combination with natural products.

According to the previous studies, glimepiride had clinically significant improvements in glycemic control as monotherapy. However, patients face severe side effects like hypoglycemia, weight gain, and beta-cell destruction. So, using the minimal dose of glimepiride in combination with the proper dose of other oral hypoglycemic drug is a necessity to avoid glimepiride side effects [28, 39]**, table 1**.

Table 1: Add -on therapy to other oral hypoglycemic drugs:

Combination regimen	Type of study	Results	Country	Ref.
Glimepiride (1.44 ± 0.90 mg/day) + Sitagliptin (73.1 ± 25.4 mg/day)	Clinical study was performed on 82 T2DM Japanese patients for 52-week.	The combination therapy resulted in low dose of both drugs. The combination drug regimen showed a significant decrease in blood glucose, blood pressure, albumin excretion and hypoglycemia incidence with no effect on weight.	Japan	[29]
Glimepiride (less than 4 mg/day) + Metformin (≥1500 mg/day) + Vidaglipitin (50 mg/day).	Clinical study was performed on 246 T2DM patients uncontrolled by glimepiride and metformin combination for 24 weeks.	Adding vildagliptin to glimepiride and metformin combination introduced a hopeful triple drug therapy for patients falling on glimepiride and metformin combination and cannot take insulin. This triple combination significantly controlled glycemic parameters with no weight gain or hypoglycemia risks.	USA	[30]
Glimepiride (1-4 mg/day) + Alogliptin (12.5 or 25 mg/day)	Clinical study was performed on 312 T2DM Japanese patients who did not achieve required glycemic control with exercise and diet plus	The combination regimen showed a significant decrease in blood glucose. With no reported hypoglycemia.	Japan	[31]

	glimepiride for 24 weeks.			
Glimepiride (2mg or less mg/day) + Sitagliptin (50 mg/day)	Clinical study was performed on 41 T2DM patients were divided into two groups, the first group was taking up titrated dose of glimepiride to 6 mg and the second group was taking the combination therapy for 24 weeks.	The combination regimen showed a significant glycemic control with low hypoglycemia incidence and produced a protective effect on pancreatic beta cells when compared to high dose of glimepiride.	Japan	[32]
Glimepiride (4 mg/day) + Dapagliflozin (2.5, 5 or 10 mg/day)	Clinical study was performed on 519 T2DM patients uncontrolled by glimepiride monotherapy for 48 weeks.	Dapagliflozin combination with glimepiride received required glycemic control, reduced weight, and was generally well-tolerated, although genital infections were reported more often in patients taking dapagliflozin regimen.	Poland	[33]
Glimepiride (8 mg/day) + Metformin (2000 mg/day) + Dapagliflozin (10mg/day) Or Glimepiride (8 mg/day) + Metformin (2000 mg/day) + Empagliflozin (25 mg/day).	Clinical study was performed on 350 T2DM patients for 52 weeks.	These triple combinations introduced a great alternative for patients who rejected taking insulin injections after reaching the maximal dose of glimepiride and metformin combination. Both combinations showed a significant control on glycemic parameters with a decrease in blood pressure and weight gain. Empagliflozin triple combination is superior to dapagliflozin due to regulating cardiometabolic parameters.	Korea	[34]
Glimepiride (4 mg/day) + Rosiglitazone (4 or 8 mg /day).	Clinical study was performed on 102 T2DM patients for 16 weeks.	Rosiglitazone and low dose glimepiride combination significantly decreased the negative effect of glimepiride on pancreatic beta cells function, cardiovascular risk markers, and inflammatory markers beside the adequate control of glycemic parameters.	Germany	[35]

Glimepiride (1or 3 mg /day) + Pioglitazone (15 or 30 mg/day).	Clinical study was performed on 70 T2DM Japanese patients for 8 weeks.	Combination regimen significantly decreased glycemic parameters and dyslipidemia. This combination therapy is approved by many countries all over the world.	Japan	[36]
Glimepiride (1-6 mg/day) + Liraglutide (.6 or .9 mg/day).	Clinical study was performed on 264 T2DM Japanese patients for 24 weeks.	This combination showed a significant decrease in glycemic parameters in dose –dependent manner without weight gain or hypoglycemia versus glimepiride monotherapy.	Japan	[37]
Glimepiride (1-6 mg/day) + Dulaglutide (1.5 mg/ once a week).	Clinical study was performed on 300 T2DM patients for 24 weeks.	Glimepiride and dulaglutide combination produced a sufficient decrease in glycemic parameters. This trial suggested that when patient is no longer achieving the required glycemic control by glimepiride monotherapy so the best option is add -on therapy with dulaglutide weekly dose.	USA	[38]

According to the previous studies: add-on therapy of different drug classes to glimepiride may produce hypoglycemic effect but this effect is not highly significant when compared to control drug regimen, every drug class generated a single extra medical effect like antihyperlipidemic effect in case of rosuvastatin and anti-inflammatory effect in case of ketotifen add -on therapy, **table.2**.

Table 2: Add- on therapy to other drug classes:

Combination regimen	Type of study	Results	Country	Ref.
Glimepiride (4 mg/day) + metformin (500 mg/day) + Hydroxychloroquine (200 mg or 300 mg or 400 mg/day)	Clinical study was performed on 304 T2DM patients for 3 months.	This combination significantly improved glycemic parameters and safety profile in dose dependent manner of hydroxychloroquine except for gastrointestinal disturbance which is more frequent with 400 mg.	India	[40]
Glimepiride (2 mg/ twice daily) + L-carnitine (1 gm /twice daily)	Clinical study was performed on 58 T2DM patients for 6 months.	This combination had a better therapeutic strategy for controlling diabetic patients than glimepiride alone introducing a beneficial effect against insulin resistance.	Egypt	[41]

Glimepiride (1 mg/kg/day) + Rosuvastatin (10 mg /kg/day)	Experimental study was performed on alloxan-induced type2 diabetic rats having dyslipidemia for two weeks.	Rosuvastatin add-on therapy did not show a significant change in glycemic parameters when compared to glimepiride monotherapy, although it showed a significant decrease in lipid profile and weight gain.	Banglade sh	[42]
Glimepiride (1 mg/kg/day) + Vitamin D (400 IU/kg/day)	Experimental study was performed on streptozotocin-induced type 2 diabetic rats for three weeks.	This combination regimen had a favorable effect on glycemic parameters, also produce a significant decrease in blood pressure and lipid profile.	India	[43]
Glimepiride (1 mg /once daily) + Metformin(500 mg /twice daily) + Omeprazole (20 mg /twice daily)	Clinical study was performed on 80 T2DM patients for 90 days.	Omeprazole increased the bioavailability of glimepiride and metformin resulting in a significant decrease in glycemic parameters. This conclusion may introduce omeprazole as a favorable combination with other oral antidiabetic drugs.	Pakistan.	[44]
Glimepiride (3 mg/day) + Ketotifen (1 mg/twice daily)	Clinical study was performed on 48 obese patients with T2DM for 12 weeks	This combination produced a significant antiinfalmmatory effect without a significant effect on glycemic parameters.	Egypt	[45]
Glimepiride (1 mg/day) + Metformin (500 mg/day) + Vitamin E (400 mg/day).	Clinical study was performed on 87 T2DM patients for 12 weeks.	This combination was unable to produce a significant decrease in glycemic parameters, however it produced a significant decrease in dyslipidemia.	India	[46]

The previous studies showed the ability of natural products combination with glimepiride to produce a highly significant control over diabetic and lipid parameters. Also, natural products had a marked role in producing anti-inflammatory and antioxidant effects. Antioxidant and anti-inflammatory effects generated by natural products introduce them as the best candidates for glimepiride add-on therapy for management of type 2 diabetes and its complications**,** **table.3**.

Table 3: Add -on therapy to nutraceuticals:

Combination regimen	Type of study	Results	Country	Ref
Glimepiride (1mg/kg/day) + Black rice bran ethanol extract(EEBRB) (50 mg/Kg/day)	Experimental study was performed on Alloxan induced type 2 diabetic rats for 21 days.	This combination produced a significant decrease in glycemic parameters and oxidative stress resulting in a protective effect on pancreatic beta cells and kidneys.	Indonesia	[47]
Glimepiride (1 mg/day) + Aloe. Vera (100, 200, and 400 mg/kg, postoperatively)	Experimental study was performed on streptozotocin-induced type 2 diabetic rats for two weeks	(Aloe. Vera - glimepiride) combination increased the serum insulin levels, also produced a potent decrease on glycemic parameters.	India	[48]
Glimepiride (8mg/kg) once daily + Bitter melon extract (500mg/kg)	Experimental study was performed on Streptozotocin-induced diabetic rats for two weeks.	Bitter melon- glimepiride combination showed promising and synergistic hypoglycemic properties, also maintained normal lipid profiles which may establish a protective mechanism against atherosclerosis. This combination regimen could be a cost-effective, less toxic, and optimistic remedy for the treatment of diabetes and dyslipidemia.	Jordan	[49]
Glimepiride (2 mg/kg/day) + Trigonella foenum-graecum seeds (HEF) (500 mg/kg/day)	Experimental study was performed on alloxan-induced type 2 diabetic rats for one month.	This combination regimen produced a hypoglycemic effect statistically equivalent to glimepiride 4 mg monotherapy, in addition this combination generated antiinflammatory and antioxidant effects resulting in a protective effect on kidneys and pancreas.	India	[50]
Glimepiride (1 mg/kg/day)+ Myristica fragrans Houtt(MFSE) (5 g/kg/day)	Experimental study was performed on alloxan-induced type 2 diabetic Swiss albino mice for 28 days.	This combination showed a significant decrease in glycemic parameters without induction of hypoglycemic effect.	Bangladesh	[51]
Glimepiride (0.5	Experimental study	Rutin –glimepiride combination produced	India	[52]

mg/kg/day) + Rutin (50 mg/kg or 100 mg/kg).	was performed on streptozotocin – induced type 2 diabetic rats for 25 days.	a significant decrease in glycemic parameters, dyslipidemia and inflammatory cytokine resulting in a renoprotective effect.		
Glimepiride (0.1 mg/kg /day) + Naringin (100 mg/kg /day).	Experimental study was performed on streptozotocin – induced type 2 diabetic rats for 28 days.	This combination promoted a significant decrease in glycemic parameters, dyslipidemia and oxidative markers	India	[53]

3. Conclusion:

Type 2 diabetes mellitus is a worldwide major health problem that acts as a burden on health and economic organizations, so finding proper and available medicine with low side effects has become an urgent necessity. Glimepiride has many advantages as an oral hypoglycemic drug ,however we cannot turn a blind eye to its side effect (severe hypoglycemia , weight gain and destruction of pancreatic beta cells at high doses) which act as a great obstacle to many patients for using it as a first-line treatment .There are many trials to improve its efficacy through add-on therapy with other oral antidiabetic drugs, other drug classes, and natural product. Natural products combination with glimepiride showed a hopeful management of type 2 diabetes and its complications through generating an augmented hypoglycemic, lipid lowering, antioxidant and anti-inflammatory effects. However, most of the natural product studies were done on developing countries due to its availability, low cost and ability to deal with its side effects easily. Most of these studies were done on animal scales and provided a great result but clinical studies have not been done up till now due to lack of financial resources.

Conflict of Interest

There is no conflict of interest.

Author contribution

The author was responsible for conception and design of the study, acquisition of data, analysis and interpretation of data, in addition to drafting and revising the manuscript and approving it for submission

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