International Journal of Advances in Medicine
Jayakrishnan B. Int J Adv Med. 2022 Mar;9(3):356-361
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20220442

Review Article

Utility and benefits of sulfonylureas beyond glycemic control

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Received: 24 January 2022
Accepted: 08 February 2022

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ABSTRACT

Department of medicine, Educare institute of dental science Malappuram, Kerala and SafeCare clinics, Tirur, Kerala sulfonylureas (SUs) are one of the oldest, time tested and most commonly used oral antidiabetic agent in Type 2 diabetes. Modern SUs like glimepiride and gliclazide XR were preferred over conventional SUs due to its better efficacy and minimal side effects. The use of Modern SUs in the treatment armamentarium of T2DM has evolved, over past few decades. Modern SUs possesses beneficial pancreatic glucose lowering effect and more interestingly extra-pancreatic pleiotropic benefits. This review article discusses on the utility and benefits of SUs beyond glycemic control and explaining on their pleiotropic effects.

Keywords: SUs, Pleiotropic, Glimepiride, Gliclazide, Adiponectin

INTRODUCTION

Diabetes mellitus is a major health issue that has reached alarming levels. Today, more than half a billion people are living with diabetes worldwide. The recently published international diabetes federation (IDF) atlas 10th edition confirms that diabetes is one of the fastest growing global health emergencies of the 21st century. In 2021, it is estimated that 537 million people have diabetes, and this number is projected to reach 643 million by 2030, and 783 million by 2045.[1] A wide array of anti-diabetic agents are currently available for the management of type 2 diabetes mellitus (T2DM).[2] The drug class called SUs has been used consistently for the past six decades for T2DM treatment. SUs is a well-established glucose-lowering drugs, with action on pancreatic β-cells. In past two decades modern SUs (Glimepiride and gliclazide XR) was developed, with different affinity to bind with sulfonylurea receptor (SUR) proteins which also provides better efficacy and lesser side effects.[3] Multiple published evidence shows that apart from glucose lowering efficacy, the modern SUs have added pleiotropic benefits. This review article discusses on the utility and benefits of SUs beyond glycemic control.

SULFONYLUREAS IMPROVING INSULIN SENSITIVITY

Inukai et al in 2005 investigated the pleotropic effects of glimepiride in obese Japanese patients with T2DM in whom glycemic control had been inadequate with the use of conventional SUs. A total of 172 patients, who were already maintained on either gliclazide or glibenclamide therapy, were randomly assigned into 2 groups: group A, who were switched from conventional SU to glimepiride (from gliclazide 40 mg to glimepiride 1 mg or glibenclamide 2.5 mg to glimepiride 2 mg); and group B, for whom the treatment was not changed. The duration of treatment was 6 months.

At the end of 6 months, glycemic control (HbA_{1c} and fasting plasma glucose) did not change significantly in either of the groups. This may indicate glimepiride to be therapeutically equivalent to conventional SU treatment with respect to glycemic control. The homeostasis

assessment model of insulin resistance (HOMA-IR) was decreased by more than 10% (p=0.015) in group A, whereas no change was observed in group B. There was a non-significant decrease in the triglyceride level by approximately 10% in group A (p=0.080). There was no change in total cholesterol, HDL-cholesterol, or body weight with glimepiride treatment. HOMA-IR was significantly reduced (from 4.61 to 3.97) in obese subjects (BMI>25) after glimepiride therapy. In the subjects with severe insulin resistance (HOMA-IR=3.0), HOMA-IR was markedly reduced (from 4.98 to 4.15) after administration of glimepiride. HbA_{1c} was remarkable improved in both these subgroups of patients. These results strongly suggest that glimepiride improves glycemic control by reducing insulin resistance. The response to glimepiride was independently influenced by high BMI (OR 1.133 [1.007-1.275, p=0.0388). This study stated that switching conventional SUs to glimepiride reduced insulin resistance without improving glycemic control. A notable finding of this study is that glimepiride was more beneficial in obese than in non-obese Japanese patients with T2DM.[4]

Muller et al in 1995 through their in-vivo and in-vitro studies, suggested that SUs may decrease blood glucose independent of their capacity to stimulate insulin release, the results also demonstrate that SUs with different structures exhibit variable degrees of this extra-pancreatic activity.[5]

Glimepiride improves insulin sensitivity in peripheral tissues. Studies have suggested the insulin-sensitizing effects of glimepiride in cultured skeletal muscle cells.[6] The underlying mechanisms of such insulin-sensitizing effects of glimepiride in fat and muscle cells possibly involve the facilitation of glucose transporter type 4 (GLUT4) transport protein activation and/or translocation to the cell surface, thereby increasing glucose uptake by the cells of peripheral tissues.[7]

SULFONYLUREAS INCREASES ADIPONECTIN LEVELS

Adiponectin is a protein hormone produced by adipocytes that regulates glucose and fatty acid catabolism. Adiponectin plays an important role in the suppression of the metabolic derangements that cause insulin resistance. It has been negatively correlated with obesity-related diseases such as type 2 DM. Low adiponectin levels predict the incidence of T2DM.[8] Adiponectin, which is derived from adipose tissue, has pleiotropic protective effects like reducing metabolic and inflammatory derangements that might lead to T2DM, metabolic syndrome, insulin resistance, and cardiovascular diseases.[9] In cultured human skeletal muscle cells, glimepiride has been reported to increase insulin-stimulated glycogen synthesis. Glimepiride has also been found to increase insulin sensitivity in people with T2DM. It has been suggested that the increase in adiponectinemia might be associated with increased insulin sensitivity. The decrease in insulinemia when treated with glimepiride is thought to be associated with the increase in the concentration of circulating adiponectin.[10] High level of adiponectin is inversely correlated with changes in glycated hemoglobin (HbA1C), thereby lowering insulin requirement and leading to improved glycemic control.[11]

The study conducted by Li et al assessed the relationship between changes in the serum high-molecular-weight (HMW) adiponectin levels and glycemic control during glimepiride treatment. A total of 56 patients with poorly controlled insulin-treated T2DM were randomly assigned to either the glimepiride-added group (group A, n=29) or the insulin-increasing group (group B, n=27) while continuing current insulin-based therapy. Various parameters, such as glycosylated hemoglobin (HbA1c) value, daily insulin dose, serum HMW adiponectin level, body weight, waist circumference, plasma lipid concentration, and the number of hypoglycemic events, were evaluated before and after treatment. After 24 weeks period. The mean HbA1c, fasting blood glucose (FBG), and 2-hour postprandial blood glucose (P2BG) were significantly reduced in the glimepiride-added group compared with the insulin-increasing group (p<0.01). There was no significant change in body weight in the glimepiride-added group, but body weight increased significantly during the course of the study in the insulin-increasing group (p>0.05). Serum HMW adiponectin levels were significantly increased in the glimepiride-added group (from 3.12±1.56 μg/mL to 5.86±1.62 μg/mL) when compared to the insulin-increasing group (from 3.22±1.54 to 3.24±1.53 μg/mL). Notably, the changes in HbA1c were inversely correlated with changes in serum HMW adiponectin in the group A (R=-0.452, p=0.02). This study suggested that the addition of glimepiride to conventional insulin-based therapy results in a better improvement in glycemic control with a significant smaller daily insulin dose. The increase in the serum HMW adiponectin levels may directly contribute to the improvement glycemic control.[12]

Araki et al in 2009 demonstrated the effect of glimepiride on plasma adiponectin levels and assessed the effect of adiponectin on change in high-density lipoprotein cholesterol (HDL-C) levels in patients with T2DM. A total of 40 patients with T2DM were included in the study. All the patients received glimepiride 1 mg/day for a duration of 3 months; and parameters such as plasma adiponectin, fasting plasma glucose, insulin, hemoglobin A_{1c}, and cholesterol were evaluated before and after treatment. At the end of 3 months, FPG and HbA_{1c} significantly decreased; and IRI and HOMA-β significantly increased. Both plasma adiponectin levels (from 7.5±4.5 to 8.3±4.5 μg/mL, p=0.040) and HDL-C levels increased significantly (from 50±11 to 53±10 mg/dL, p=0.041) after glimepiride treatment. The change in plasma adiponectin level was positively correlated with the increase in HDL-C level in all patients (r=0.411, p=0.008) after adjustment for other factors. The change in plasma adiponectin levels was inversely correlated with the decrease in HbA_{1c} levels (r=-0.473, p=0.002). This study stated that glimepiride

improves plasma adiponectin levels, and the effect may directly contribute to improved HDL-C levels.[13]

SULFONYLUREAS REDUCE INSULIN METABOLIC CLEARANCE IN LIVER

The theory that SUs reduce insulin clearance in the liver was proposed in the late 1950s. The mechanism involved is non-competitive inhibition of the insulinase system in the liver. However, the sulfonylurea concentration needed to inhibit insulinase should be much higher than the concentration required to lower blood glucose. Two experimental studies conducted by Brazilai et al in 1995 demonstrated the inhibitory effect of glipizide on the metabolic clearance rate (MCR) of insulin during an euglycemic insulin clamp on 19 healthy participants, under steady-state conditions. The first study included a total of 10 participants who received a 3-h oral glucose load with and without 2 mg of glipizide given 30 min before glucose ingestion. In the second study, a total of 9 participants were subjected to 4-hour insulin euglycemic clamps with and without 5 mg of glipizide given at 120 min after the initiation of glucose ingestion. In the insulin euglycemic clamps performed on 9 subjects, the metabolic clearance rate was similar during the 2nd and 4th hours after oral glucose load without administration of glipizide (594±121 and 581±117 ml/m^2 min, respectively), whereas the metabolic clearance rate decreased significantly ($p<0.005$) from the 2nd to 4th hour after the administration of glipizide (from 621±127 to 503±126 ml/m^2 min). In conclusion, the present study suggested that SUs not only increase peripheral insulin concentrations by stimulating pancreatic insulin release but also act by reducing insulin clearance in the liver.[14]

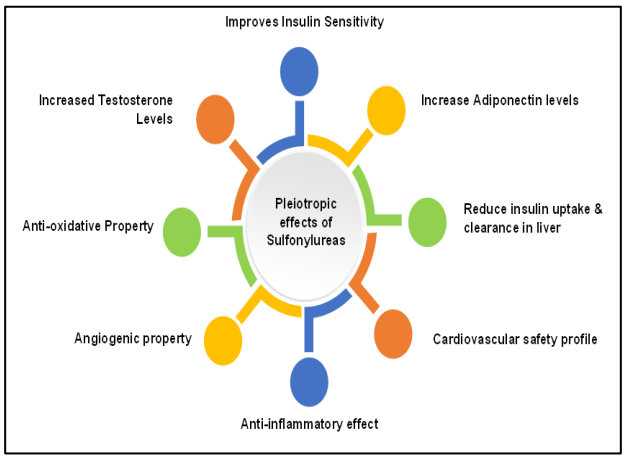

Figure 1: Pleiotropic effects of SUs.

SULFONYLUREAS AND CARDIOVASCULAR SAFETY PROFILE

It has been studied that in comparison to other SUs, modern SUs like glimepiride and gliclazide are cardiovascular neutral. In the case of T2DM patients treated with, the extent of inhibition of K_{ATP} channels is less severe as compared to other SUs. An international expert group has recommended that this modern sulfonylurea can be safely used for the treatment of type 2 diabetes mellitus patients with coronary artery disease. Several recent cardiovascular outcome trials show that glimepiride is safe in major adverse cardiovascular events, heart failure, and hospitalization for heart failure.[15]

Conventional SUs such as glibenclamide are associated with adverse effects on the cardiovascular system. Glibenclamide may lead to the closure of mitochondrial KATP channels, which are essential in ischemic preconditioning (IP) protection.[16] Glimepiride, a Modern SU that reportedly has a minimal effect on KATP channels unlike glibenclamide. It has fewer cardiac actions compared to other SUs, which makes it a preferred therapy for the treatment of type 2 diabetes mellitus patients with concurrent coronary artery disease. A pre-clinical trial conducted by Mocanu et al in 2001 compared the effect of glimepiride vs. glibenclamide on IP protection and the protection afforded by diazoxide, an opener of mitochondrial KATP channels. The study also assessed the effect of glimepiride and glibenclamide directly on sarcolemmal KATP channel currents in isolated ventricular myocytes, besides assessing their effect on membrane potential in isolated cardiac mitochondria. This study concluded that although glimepiride blocks sarcolemmal currents in rat cardiac myocytes, the drug does not block the beneficial effects of mitochondrial KATP channel opening in the isolated rat heart.[16]

Rados et al in 2016 conducted a meta-analysis of 47 randomized controlled trials (RCTs) involving 37,650 T2DM patients of 52-week duration, the association between second- and third-generation Sus and all-cause and cardiovascular mortality (CV) was assessed. The analysis revealed that SUs are not associated with an increased risk of myocardial infarction (MI) (odds ratio [OR] 0.92 [95% confidence interval {CI} 0.76 to 1.12]), all-cause (OR 1.12 [95% CI 0.96 to 1.30]) and cardiovascular mortality (OR 1.12 [95% CI 0.87 to 1.42]).[17]

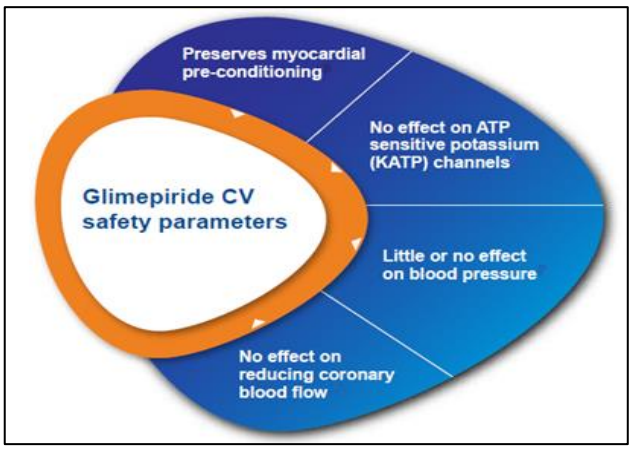

Figure 2: Glimepiride cardiovascular safety parameters.[18]

The thiazolidinediones or SUs cardiovascular accidents intervention trial (TOSCA.IT), a multicenter, randomized trial, long-term cardiovascular effects of pioglitazone vs. SUs, as an add-on therapy to metformin, in patients with T2DM (n=3028) were studied. The primary outcome studied during the study included a composite of first occurrence of all-cause death, nonfatal myocardial infarction, nonfatal stroke, or urgent coronary revascularization. The study reported that the primary outcome occurred in 105 patients treated with pioglitazone and 108 persons on SUs. This study concluded that the incidence of CV events was similar in patients treated with SUs (mostly glimepiride and gliclazide) and those treated with pioglitazone, as an add-on treatment to metformin.[19]

In the cardiovascular outcome study of linagliptin vs. glimepiride in type 2 diabetes (CAROLINA) trial, which included 6042 patients with type 2 diabetes mellitus, effects of the treatment with linagliptin were compared to those of glimepiride on the cardiovascular (CV) safety of patients. The mean duration of follow-up was 6.3 years. The primary outcome assessed during the study was first occurrence of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. The study reported that there was no significant difference in occurrence of 3P-MACE in patients treated with glimepiride as compared to those treated with linagliptin (12.0% vs. 11.8%), with a hazard ratio of 0.98 (95.47% confidence interval [CI] 0.84-1.14, p<0.001 for noninferiority). The trial results put concerns about SUs' cardiovascular safety to rest and reaffirmed clinical recommendations to choose an oral agent after metformin based on proven cardiovascular benefits.[20]

SULFONYLUREAS AND ANTI-INFLAMMATORY EFFECT

Modern SUs like glimepiride possesses anti-inflammatory effects by reducing the levels of interleukin-6, tumor necrosis factor-α, and high sensitivity C-reactive protein, modern SUs, such as glimepiride, exert their anti-inflammatory effects.[21] Koshiba et al in 2006, analyzed the effects of glimepiride on insulin resistance, inflammatory cytokines, and anti-atherosclerotic action in patients with T2DM. A total of 46 patients with T2DM who were already on glibenclamide therapy were included in the study. The patients were randomized to 2 groups: 20 patients, who were switched to glimepiride 1-mg therapy (GP group), and 14 patients, who continued to receive glibenclamide 1.25 mg therapy (GB group). An additional 12 patients, who were receiving insulin therapy, were included as the comparator group (INS group). Parameters including plasma adiponectin levels, high-sensitive C-reactive protein, tumor necrosis factor-α, interleukin-6, homeostasis model assessment for insulin resistance (HOMA-IR), brachial-ankle pulse wave velocity (baPWV), and augmentation index were assessed before and 28 weeks after glimepiride treatment. After 28 weeks: HOMA-IR was significantly decreased in the GP group when compared to the GB group (p<0.05). Plasma adiponectin levels were significantly increased in the GP group alone (p<0.05). High sensitive C-reactive protein, tumor necrosis factor-α, interleukin-6, brachial-ankle pulse wave velocity, and augmentation index (AI) levels were significantly decreased in the GP group, but not in the other 2 groups (p<0.05). This study revealed that glimepiride results in improved insulin resistance; the drug possesses an inhibitory effect on the initiation and development of atherosclerosis.[22]

ANTI-OXIDATIVE AND ANGIOGENIC EFFECT

Glimepiride has been found to exert angiogenic effects by reducing the plasma levels of fibroblast growth factor 2 and vascular endothelial growth factor. The antioxidative effects (by decreasing toxic advanced glycation end-products [AGEs] and receptors of AGEs).[21] Nakumara et al in 2014 investigated the beneficial effects of glimepiride on the levels of biomarkers related to cardiovascular regulation in patients with type 2 diabetes mellitus. A total of 34 patients with type 2 diabetes mellitus (T2DM) were included in the study. All the patients received glimepiride 1 mg for a duration of 24 weeks. At the end of 24 weeks, a significant decrease in the levels of glyceraldehyde-derived advanced glycation end-products, (glycer-AGE: toxic age; p=0.0452), eotaxin (p=0.0347), and fibroblast growth factor (FGF-2; p=0.0429) was observed after the administration of glimepiride. Moreover, a trend toward an increase in the levels of granulocyte-colony stimulating factor (G-CSF; p=0.1725) and granulocyte macrophage-colony stimulating factor (GM-CSF; p=0.0525) and a decrease in the levels of fractalkine (p=0.0542), soluble CD40 ligand (sCD40L; p=0.1923), macrophage inflammatory protein (MIP-β; p=0.1126), vascular endothelial growth factor (VEGF), and soluble receptor for AGE (sRAGE; p=0.1655)-was observed. Glimepiride, thereby, was proved to have potent anti-oxidative, anti-inflammatory, and angiogenic properties; and it may potentially repair tissue damage by decreasing the levels of toxic AGE and increasing colony-stimulating factors.[21]

SULFONYLUREAS AND TESTOSTERONE LEVELS IN MALES

Studies indicate that treatment with glimepiride leads to a significant elevation in the levels of testosterone in male patients with type 2 diabetes mellitus. This leads to improved erectile function and sex drive in such patients.[22] Wong et al in 2015, evaluated the effect of glimepiride on testosterone levels in middle-aged men with T2DM. A total of 15 patients from a phase IV clinical trial of glimepiride with T2DM were included in this study. All the patients were given a dose of oral glimepiride 1 mg/day for a duration of 16 weeks. An additional 5 healthy age and body mass index-matched males were assigned to the control group. The study patients had significantly decreased total testosterone levels and a lower testosterone secretion index when compared to the control group. Blood glucose and lipid profile levels were significantly improved, with no significant differences noted in

bodyweight and waist circumference compared with baseline values. This study suggested that glimepiride may help improve total serum testosterone levels and testosterone secretion index values in middle-aged men with type 2 diabetes mellitus.[23]

CONCLUSION

Even after 6 decades of use, SUs (especially modern SUs) continues to play an important role in the management of T2DM. Modern SUs (glimepiride and gliclazide XR), as monotherapy and combination therapy, offer good glycemic control, with lesser side effects in a cost-effective manner. Their pleiotropic benefits, with good CV safety profile, improving insulin sensitivity, increase adiponectin levels, anti-inflammatory, anti-oxidative, angiogenic properties and role in testosterone levels are a good value-added benefit in treatment of T2DM. SUs are here to stay with their efficacy, safety and because they are the most time-tested of all antidiabetic agent.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Jayakrishnan B. Utility and benefits of sulfonylureas beyond glycemic control. Int J Adv Med 2022;9:356-61.