Extrapancreatic Benefits and Pleiotropic Effects of Glimepiride: Value-Added Effects for Therapeutic Preference in Type 2 Diabetes Mellitus

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Abstract

Glimepiride is a third-generation sulfonylurea (SU), which is a potential glucose-lowering agent. It is widely used as monotherapy as well as combination therapy in the treatment of type 2 diabetes mellitus. Because of its safety, higher efficacy and low hypoglycemia potential, glimepiride is a preferred oral antidiabetic drug versus other SUs. Glimepiride has several extrapancreatic and pleiotropic benefits, which include insulin-sensitizing properties and anti-inflammatory, antioxidative and angiogenic effects. Additionally, the cardiovascular-neutral outcome of glimepiride makes it a preferred drug for the treatment of type 2 diabetes mellitus patients with cardiovascular disease or at risk. Here we will discuss various value-added extrapancreatic and pleiotropic benefits of glimepiride.

Introduction

Sulfonylureas (SUs) are glucose-lowering drugs that are known to function by stimulating pancreatic insulin secretion. In this context, the modern SU, glimepiride is unique, as although its glucose-lowering efficacy is similar to conventional SUs, its ability to stimulate insulin secretion is graded with blood glucose level. Evidences clearly demonstrate that glimepiride exerts several extrapancreatic effects, such as improving insulin resistance.[1,2] In addition to the glucose-lowering effect in subjects with diabetes, glimepiride has several extrapancreatic and pleiotropic benefits that are discussed here.

Extrapancreatic Effects of Glimepiride

The relative degree of extrapancreatic activity can be estimated by examining the ratio of mean increase of plasma insulin level as compared to mean decrease in the level of blood glucose. In a study where several SUs were compared, glimepiride was found to have the lowest ratio, thereby, indicating the potential to exert significant extrapancreatic activity.[3] The various extrapancreatic effects of glimepiride are discussed below:

Improves Insulin sensitivity in Peripheral Tissues: Studies have suggested the insulin-sensitizing effects of glimepiride in cultured skeletal muscle cells. 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,[3] thereby, increasing glucose uptake by the cells of peripheral tissues.[4]

Increases the Level of Adiponectin: Adiponectin which is derived from adipose tissue has pleiotropic protective effects like reducing metabolic and inflammatory derangements that might lead to type 2 diabetes mellitus (T2DM), metabolic syndrome, insulin resistance, and cardiovascular diseases.[5] 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.[1] A high level of adiponectin is inversely correlated with changes in Hb_{A1C}, thereby lowering insulin requirement and leading to improved glycemic control.[6]

Promotes Glycogen Synthesis: Glimepiride may increase glycogen synthesis, inhibit gluconeogenesis, and activate lipogenesis.[3]

Reduces Clearance of Insulin in Liver: Glimepiride may also reduce the metabolic clearance rate of insulin in the liver.[6]

Pleiotropic Benefits of Glimepiride

Antioxidative Effects: Modern SUs, including glimepiride, have been found to exert antioxidative effects. This mechanism is mediated through a decrease in toxic advanced glycation end-products and their receptors.[7]

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.[7]

Angiogenic Effects: Glimepiride has been found to exert angiogenic effects by reducing the plasma levels of fibroblast growth factor 2 and vascular endothelial growth factor.[7]

Endocrine Effects: 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.[8]

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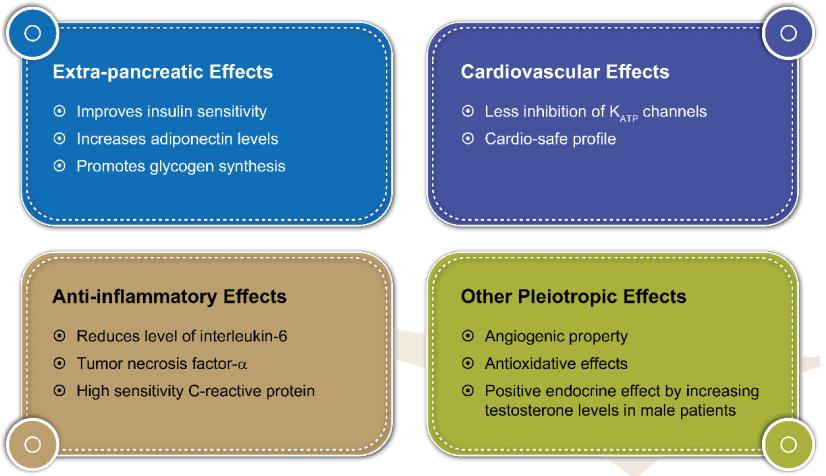

Fig. 1: Extrapancreatic and pleiotropic benefits of glimepiride

Effects on Cardiovascular System: It has been studied that in comparison to other SUs, glimepiride is cardiovascular neutral. In the case of type 2 diabetes mellitus patients treated with glimepiride, 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 SU can be safely used for the treatment of type 2 diabetes mellitus patients with coronary artery disease.[8]

Several recent cardiovascular outcome trials show that Glimepiride is safe in major adverse cardiovascular events, heart failure and hospitalization for heart failure (details are discussed in the other chapters of this supplement).

Renal Benefit: In case of renal failure patients and those patients who are at higher risk of hypoglycemia, modern SUs including glimepiride are preferred over conventional SUs.[8] Since majority of SUs are excreted by the kidney, patients with renal impairment are usually at a greater risk of hypoglycemia. However, in contrast to conventional SUs like glibenclamide and tolbutamide, glimepiride can be used in patients with chronic kidney disease at low dose (1 mg/day).[6]

The extrapancreatic effects and other pleiotropic effects of glimepiride have been shown in Figure 1.

Conclusion

Although several oral antidiabetic medications are available with anti-hyperglycemic effects, the modern SU, glimepiride is a preferred glucose-lowering drug. It is mostly beneficial for patients where first-line therapy and lifestyle changes have not provided satisfactory hypoglycemic effects. Apart from its potential glucose-lowering effects, glimepiride also provides additional benefits owing to its several extrapancreatic and pleiotropic effects. Such effects include increased insulin sensitization in peripheral tissues; increased glycogen synthesis and levels of adiponectin; antioxidative, anti-inflammatory, angiogenic effects; and cardiovascular-safe functions. Among the various additional benefits of glimepiride, its improved insulin sensitization and cardio-safe profiles make glimepiride a preferred choice among SUs for type 2 diabetes mellitus therapy as initiation and add-on therapy.

Conflict of Interest

SRC is an employee of Sanofi India. All other authors report no conflicts of interest.

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