Athero-protective actions of two oral antidiabetic drugs: Suppression of inflammation and oxidative stress

Diabetes mellitus increases the risk and accelerates the clinical course of atherosclerosis, and is responsible for majority of the deaths and disabilities in type 2 diabetic population.[1] Optimal strategies to prevent the onset or progression of atherosclerosis will improve the clinical outcome of this high-risk population. In the current study, the research team showed that two antidiabetic agents, namely Glimepiride and Repaglinide, prevent the progression of atherosclerosis in high fat diet fed rabbits, by exerting their anti-inflammatory and anti-oxidative effects.

Clue to these new findings came from prior observations about the effects of Glimepiride in atherosclerosis. Sulfonylureas derivatives stimulated insulin secretion o from the beta cells of the pancreas, and have been widely used in the treatment of diabetes. Glimepiride is a third-generation Sulfonylurea agent with less insulin-secreting effects compared with conventional Sulfonylureas agents. *In vitro*, Glimepiride leads to improved lipid metabolism, enhances endothelial function due to the biosynthesis of nitric monoxide, and has displayed anti-oxidative effects.[2,3] *In vivo* in type 2 diabetic patients, Glimepiride demonstrated anti-atherosclerotic abilities.[4] Consistently, in cholesterol-fed rabbits, Glimepiride treatment produced significant reduction in atherosclerosis lesions with no significant changes observed in the levels of plasma lipids.[5] However, the precise mechanisms of the athero-protective actions of Glimepiride remain unknown.

In the current study, the research team assessed the effect of glimepiride on atherosclerosis using rabbits fed with 1% cholesterol enriched diet.[6] Consistent with previous studies, they found that Glimepiride treatment significantly reduced aortic intimal thickness without modulating lipid parameters, compared with the induced untreated group. They demonstrated that in the Glimepiride-treated group there was a decrease in the levels of pro-inflammatory biomarkers and cytokines, including high sensitive C- reactive protein (hsCRP), Interleukin – 6 (IL-6) and Tumor Necrosis Factor alpha (TNF-α). They further showed that Glimepiride treatment resulted in reduced levels of aortic oxidation biomarkers including Malondialdehyde (MDA) and reduced glutathione (GSH).

In addition, the research team also investigated the effects of another insulin secretagoguo, Repaglinide in the development of atherosclerosis. Repaglinide belongs to the Meglitinide class of blood glucose-lowering drugs. Meglitinide derivatives also stimulate the release of insulin from pancreas. They are able to do so by shutting down Adenosine triphosphate (ATP)-dependent potassium channels in the membrane of beta cells. This action depolarizes cells and stimulates calcium influx by opening up calcium channels, resulting in an increase in insulin secretion. In the current study, the research team found that, similar to Glimepiride, Repaglinide decreased the aortic intimal thickness, reduced the levels of pro-inflammatory biomarkers and cytokines, and displayed anti-oxidative activities in cholesterol-fed rabbits. It achieves this without affecting the levels of plasma lipid. The results suggest that Repaglinide has anti-atherosclerotic effects by suppressing inflammation and oxidative stress.

These observations led to a set of intriguing questions. How do Glimepriride and Repaglinide suppress inflammation and oxidative stress without affecting lipid parameters? Glimepriride has been demonstrated to have actions other than stimulating insulin secretion, including phosphorylation of insulin receptor substrate-1, inhibition of cellular cyclooxygenase pathways and up-regulating antioxidant enzyme levels. It remains to be elucidated whether the anti-inflammatory and anti-oxidative properties of Glimepriride can be attributed to some of these activities. Repaglinide is known for its anti-oxidant effects. Whether its anti-oxidant activity accounts for its anti-inflammatory action also remains to be determined. Finally, it is possible that these two oral antidiabetic agents may have activities beyond their anti-inflammatory and anti-oxidant effects that contribute to their athero-protective effects.

In conclusion, the current study provides useful insights

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into the cardiovascular effects of two commonly-used oral antidiabetic drugs. It also identified two potential mechanisms by which these two insulin secretagogue achieve anti-atherosclerotic effects. These significant findings will have important implications for identifying the optimal strategy for treating patients with atherosclerosis and type 2 diabetes.

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REFERENCES

1. St Onge EL, Motycka CA, Miller SA. A review of cardiovascular risks associated with medications used to treat type-2 diabetes mellitus. P T. 2009;34:368-78.
2. Derosa G, Franzetti I, Gadaleta G, Ciccarelli L, Fogari R. Metabolic variations with oral antidiabetic drugs in patients with Type 2 diabetes: Comparison between glimepiride and metformin. Diabetes Nutr Metab 2004;17:143-50.
3. Ueba H, Kuroki M, Hashimoto S, Umemoto T, Yasu T, Ishikawa SE, *et al.* Glimepiride induces nitric oxide production in human coronary artery endothelial cells via a PI3-kinase-Akt dependent pathway. Atherosclerosis 2005;183:35-9.
4. Koshiba K, Nomura M, Nakaya Y, Ito S. Efficacy of glimepiride on insulin resistance, adipocytokines, and atherosclerosis. J Med Invest 2006;53:87-94.
5. Shakuto S, Oshima K, Tsuchiya E. Glimepiride exhibits prophylactic effect on atherosclerosis in cholesterol-fed rabbits. Atherosclerosis 2005;182:209-17.
6. Hadi NR, Al-Amran F, Hussein MAA, Rezeg FA. Evaluation of the effects of glimepiride (Amaryl) and repaglinide (novoNorm) on atherosclerosis progression in high cholesterol-fed male rabbits. J Cardiovasc Dis Res 2012;3:5-11.

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