Effects of telmisartan on hypertensive patients with dyslipidemia and insulin resistance

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The benefits of angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) beyond blood pressure reduction have been proven through many large studies (HOPE, LIFE) in high risk CVD patients; post hoc studies have shown reductions in new onset type 2 diabetes mellitus (DM). However, there are no studies which revealed a strong correlation between impaired fasting glucose (IFG) and cardiovascular disease (CVD); instead, there were correlations with post challenge glucose and post challenge insulin levels. Insulin resistance (IR) is fundamental to high risk CVD situations and high fasting and post challenge insulin levels are surrogate markers for IR, albeit inconsistently. A logical approach to the prevention of type 2 DM and CVD must be therapeutic insulin reduction. Type 2 DM clearly influences the incidence of poor outcomes in CVD patients, and for any level of risk factors analyzed, a mechanism or mechanisms unique to or heavily represented by type 2 DM/impaired glucose tolerance (IGT)/IFG/metabolic syndrome (MetS) makes subjects more prone to CVD. Hyperglycemia is the most prevalent feature in DM, hence it is reasonable to assume that it is an independent risk factor for CVD which could be controlled by euglycemia.

In the UK Prospective Diabetes Study, the results showed a decrease of only 16% in macrovascular complications due to tight glucose control, and without statistical significance. The same study revealed a significant improvement in macrovascular complications among obese patients treated with metformin. So there has to be something beyond euglycemia. In other words, metformin induced the improvement in insulin sensitivity with a concomitant decline in insulin levels, and was a more potent factor in reducing adverse CVD outcomes than an equally significant reduction in glucose levels without a reduction in insulin levels.

Hyperglycemia is a physiological state of reduced biological action of insulin, and hyperinsulinemia is largely a compensatory mechanism to overcome the reduced insulin sensitivity. Glucose homeostasis can be achieved by pharmacological measures, but does not seem to translate into significant CVD event risk reduction unless associated by a significant reduction in serum insulin levels to overcome IR. Hyperinsulinemia is the key feature of MetS/IR, and is a harbinger for accelerated atherosclerosis.

In this September issue of the Journal of Geriatric Cardiology, Xu et al. set out to precisely prove the importance of hyperinsulinemia in CVD risks and to paraphrase the notion that “all ARBs are not created equal”. There is enough evidence that in IR, the defect appears to lie in the insulin signal cascade or signal transduction facilitated by angiotensin (AT) receptors. Both AT receptors and insulin mediate protein tyrosine phosphorylation and dephosphorylation which are two apparently paradoxical events effected by insulin and AT receptors. Both convergent and divergent intracellular signaling cascades are stimulated downstream of their respective receptors, producing diverse cellular responses. Protein tyrosine phosphatase (PTPase), PTP-1B, plays a central role in AT induced insulin resistance by way of inhibition of the insulin receptor, leading to the maladaptive responses observed in diabetic vascular and renal tissue in type 2 DM.

Both ACE inhibitors and ARBs are first line therapies in treatment of hypertensive patients with cardiometabolic syndrome and diabetes. They reduce microvascular and macrovascular complications and appear to improve insulin sensitivity and glucose metabolism. The two classes have been shown to reduce development of type 2 DM in persons with hypertension (HT), a population with high prevalence of IR. ACE inhibition and ARBs have been shown to improve potential surrogate of chronic CV diseases (vascular compliance, endothelium derived nitric oxide production, vascular relaxation and plasma markers of inflammation, oxidative stress and thrombosis), reduce CV and renal diseases, and reduce incidence of strokes by interfering with insulin signaling through P13K and downstream Akt signaling pathways via generation of reactive oxygen species (ROS).

AT signaling, via AT receptors, induces the activation of the vascular NADPH oxidase, leading to increased generation of ROS. ROS are important intracellular second messengers that activate many downstream signaling molecules, such as PTPases and protein tyrosine kinases.
Activation of this signaling cascade leads to endothelial hyperplasia/proliferation, migration modulation of endothelial function, expression of pro-inflammatory mediators, and modification of extracellular matrix. AT₁ receptor infusion has been demonstrated in studies to induce IR, while ACE inhibitors and ARBs enhance IS. Over activity of RAS as observed in CV diseases is likely to impair insulin signaling and enhance IR. AT₂ through AT₂ receptors, inhibits the action of increased insulin action associated with hyperinsulinemia, contributes to atherogenesis via smooth muscle cell hypertrophy and hyperplasia, and increases synthesis of extracellular matrix protein. However, insulin is a weak agonist for these effects and supraphysiologic concentrations were needed in studies to prove this point. In contrast, the vasodilatory actions of insulin are well recognized, and there is evidence that this effect may be in part mediated by nitric oxide (NO). NO has antiatherogenic properties including diminished expression of cell adhesion molecules and inhibition of smooth muscle cell migration and growth.

The gold standard for assessing IR is by hyperinsulinemic-euglycemic clamp study, and the whole body insulin disposal rate is called the ‘M’ value. Homeostatic model assessment of insulin resistance (HOMA-IR) and homeostatic model assessment of insulin sensitivity (HOMA-IS) are mathematical models that calculate IR and IS from a measurement of fasting plasma values and insulin levels. These assays are not standardized and are fraught with much variability, but nevertheless, are a very practical way to assess IR. ⁵

Conclusion:

Hyperinsulinemia is contributory to the excess CVD risk in IR. A paradigm shift targeting insulin reduction to the levels seen in the non diabetic and non-CVD risk population in the community is vital to counter the epidemic of type 2 DM and CVD. It is time to look beyond lifestyle changes, control of glucose, lipids, and BP for CVD risk reduction. Hyperinsulinemia is largely an attempt to overcome the state of reduced insulin sensitivity in a milieu of glucose homeostasis which we all agree may be achieved by pharmacological means, but does not seem to translate into significant CVD event reduction unless there is significant and concomitant reduction in insulin levels due to IR. There are no studies yet which demonstrate the benefits for hard CVD end points with specific use of insulin sensitizers; albeit newer drugs including ARB, cannabinoid receptor blockers, and dual action PPAR alpha/gamma agonists are emerging for their multiple anti-atherosclerotic effects as demonstrated in this study, backed with very relevant hypotheses and research. There are no studies at this time that demonstrate benefits for hard cardiovascular end points by the specific use of insulin sensitizers. ⁴

References