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TELMISARTAN AND INSULIN RESISTANCE

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INTRODUCTION

Coronary heart disease is complicated with diabetes mellitus along with declined insulin sensitivity or insulin resistance, weakened blood pressure regulating ability, damage to vascular endothelial cells, dysfunction of the fibrinolytic system and increased sterile inflammatory responses, all of which are indicators of disease progression and poor prognosis[1]. Insulin resistance is frequently present in obesity, hypertension, coronary artery disease, dyslipidemias, and metabolic syndrome. Insulin, the main anabolic hormone of the body, regulates glucose homeostasis by promoting glucose disposal in skeletal muscle and adipose tissue. In addition to its direct actions on the skeletal muscle, insulin regulates nutrient delivery to target tissues by actions on microvasculature[2]. Insulin resistance is a state of decreased sensitivity in its target organs including the liver, skeletal muscle, and adipose tissue[3]. It is well documented that the association of insulin resistance and hypertension increases the risk of cardiovascular morbidity and mortality[2]. Obesity is strongly associated with insulin resistance along with other factors like aging, sedentary lifestyle, as well as genetic predisposition. Insulin resistance often seems to precede the development of type-2 diabetes and is a marker of the eventual event of type-2 diabetes[4]. Insulin resistance can progress to type-2 diabetes, which is characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production.

Obesity and insulin resistance are the major culprits leading to metabolic syndrome[3]. Metabolic syndrome (MS) is characterized by a low-grade chronic inflammatory state which promotes the development of insulin resistance eventually leading to type 2 diabetes mellitus (T2DM), and cardiovascular diseases. Essentially, the subclinical inflammatory state peculiar of the MS modulates the atherosclerotic process at different stages, resulting in endothelial dysfunction and increased expression of endothelial adhesion

molecules and in enhanced recruitment of monocytes within the arterial wall, in the early stages of the atherosclerotic process[5]. Mechanistically, adiponectin is one of the adipocyte-derived hormones that have anti-inflammatory and anti-atherogenic properties. However, circulating concentrations of adiponectin are decreased in type-2 diabetes mellitus, obesity, and coronary heart disease[6]. Adiponectin has also been postulated to play an important part in the modulation of the metabolism of glucose and lipids insulin-sensitive tissues. Tumor necrosis factor α (TNFα) is the most common proinflammatory factor secreted from adipose tissue that suppresses insulin action on peripheral tissues. While, adiponectin, in contrast to TNFα, is an adipokine that exhibits insulin-sensitizing and anti-inflammatory properties[3].

Peroxisome proliferator-activated receptor γ (PPAR γ) is a member of the nuclear receptor superfamily and is most highly expressed in adipose tissue. PPARγ is considered the "master" regulator of adipocyte differentiation, glucose homeostasis, and lipid metabolism. In addition, activation of PPARγ can improve insulin sensitivity, reduce the level of circulating inflammatory factors, and increase the secretion of adiponectin. Unfortunately, full agonists of PPARγ such as thiazolidinedione drugs (TZDs) results in long term adverse effects including weight gain, osteoporosis, fluid retention and increased risk of heart failure[3]. Also, crosstalk between angiotensin II (AT-II) and insulin intracellular signaling pathways in the peripheral tissues has been reported to interfere with insulin actions. AT-II receptor blockers (ARB) compete with this action of AT-II through AT-II type 1receptors (AT1 receptor) and are thought to improve insulin resistance[7]. Telmisartan is an ARB and a partial agonist of PPARγ. Evidently, in an adipose tissue-specific PPARγ knockout mouse model, the ability of telmisartan to increase insulin-stimulated glucose utilization in adipose tissue and adiponectin level in serum was found to be most impaired, indicating that at least several metabolic actions of telmisartan depend on PPARγ expression in adipose tissue[8]. Telmisartan has emerged as a potential ARB that is effective in increasing insulin sensitivity, especially in hypertensive patients.

To establish the effects of telmisartan on insulin resistance under the usual antihypertensive dosage of telmisartan treatment, Shinohara et al carried out a trial in hypertensive patients [6]. The study was based on the hypothesis that telmisartan increases the serum level of adiponectin in hypertensive patients with insulin resistance, resulting in the improvement of insulin resistance[6]. Insulin resistance was defined as a patient showing ≥2.5 in the homeostasis model assessment (HOMA) index. Subjects were divided into non-insulin resistance (n = 10) and insulin resistance groups (n = 15) based on the HOMA index. Telmisartan was administered (40 mg/day) was administered for 24 weeks. It was found that in the insulin resistance group, telmisartan treatment resulted in a significant decrease in the HOMA index and serum level of C-reactive protein, and it increased the serum level of adiponectin ($P < 0.05$, respectively). Such improvements were not observed in the non-insulin resistance group. This suggests that telmisartan improves insulin resistance that parallels an increase in the serum level of adiponectin in hypertensive patients with insulin resistance.

It is well established that MS is a disease with an inflammatory component. Telmisartan is known to improve insulin resistance in MS, however, its relationship with the inflammatory state is not well established. Mun˜oz-Torrero et al. studied the effect of 3-month telmisartan therapy on homeostatic model assessment-insulin resistance (HOMA-IR) in hypertensive subjects with MS with regard to the levels of circulating plasma cytokines in 42 patients[9]. Cytokines and metabolic parameters were analyzed before and after treatment with telmisartan. Twenty-eight patients showed low

plasma levels of cytokines (group 1) similar to control subjects, and 14 showed high levels (group 2). Treatment with telmisartan diminished by 35% HOMA-IR in group 1 (4.5 ± 3.1 vs 2.9 ± 2.1), without improvement in group 2. The multivariate analysis showed that the predictors of improvement of HOMA-IR in response to telmisartan treatment were low levels of cytokines, whereas systolic and diastolic blood pressure and the elevation of high-sensitivity C-reactive protein had a negative effect. Thus, providing further evidence of a more favorable effect of telmisartan on glucose homeostasis in patients with MS and low levels of serum cytokines[9].

Wang et al. carried out a meta-analysis of a total of 21 randomized clinical trials that were performed on 1679 patients to study the effectiveness of telmisartan in insulin resistance[10]. Meta-analysis confirmed that telmisartan was superior in improving homeostasis model assessment of insulin resistance (mean difference=(-)0.23, 95% confidence interval [CI], -0.40 to -0.06), reducing fasting blood glucose level (mean difference= (-)0.32, 95% CI, -0.57 to -0.07), reducing fasting insulin level (mean difference= (-)1.01, 95% CI, -1.63 to -0.39), and decreasing diastolic blood pressure (mean difference= (-)1.46, 95% CI, -2.10 to -0.82) compared with other ARBs. However, for the decrease in systolic pressure, the difference was not statistically significant (mean difference = (-) 0.73, 95% CI, -1.53 to 0.07). The results of this meta-analysis revealed that telmisartan can significantly reduce fasting blood glucose levels, fasting insulin level, and the HOMA-IR index in hypertensive patients with IR-related diseases compared with other ARBs; and all differences were statistically significant. Among these ARBs, telmisartan is a unique AT1 receptor antagonist that can activate PPARs [10].

Vitale et al. compared the effectiveness of telmisartan and losartan in patients with MS for insulin sensitivity[11]. The study was a double-blind, parallel-group, randomized study in 40 patients with World Health Organization criteria for metabolic syndrome. Patients were given once-daily doses of telmisartan (80 mg, n = 20) or losartan (50 mg, n = 20) for 3 months. At baseline and end of treatment, fasting and postprandial plasma glucose, insulin sensitivity, glycosylated hemoglobin (HBA1c) and 24-hour mean systolic and diastolic blood pressures were determined. It was found that telmisartan, but not losartan, significantly ($p < 0.05$) reduced free plasma glucose, free plasma insulin, homeostasis model assessment of insulin resistance and HbAic. Following treatment, plasma glucose and insulin were reduced during the oral glucose tolerance test by telmisartan, but not by losartan. Telmisartan also significantly reduced 24-hour mean systolic blood pressure ($p <0.05$) and diastolic blood pressure ($p < 0.05$) compared with losartan. Thus, providing superior 24-hour blood pressure control by telmisartan, unlike losartan, along with insulin-sensitizing activity, telmisartan has been proven to be effective in improving insulin sensitivity in patients with MS[11]. Similar findings were reported in another study wherein telmisartan was found to be more beneficial than olmesartan for controlling blood pressure in the early morning, as well as for improving glucose and lipid profiles in patients with hypertension, chronic heart failure, and metabolic syndrome[12]. This unique property of telmisartan amongst other ARBs has been attributed to the agonist activity of telmisartan for PPARγ.

However, the role of telmisartan in obese patients for increasing insulin sensitivity remains inconclusive. Hsueh et al. evaluated the effect of telmisartan in obese patients[13]. For the study, overweight ⁄ obese persons with body mass index≥ 28 kg ⁄m2, waist circumference≥ 35 inches, and components of the metabolic syndrome without hypertension or diabetes that were not preselected for insulin resistance were enrolled. Patients were randomized to telmisartan or matching placebo for 16 weeks. A total of 138 patients were

randomized and given ≥1 dose of study medication; 128 completed the study. At the endpoint of the study, no significant difference was found between telmisartan and placebo groups regarding the change from baseline in insulin sensitivity index or glucose area under the curve. No significant between-group differences were found regarding glucose metabolism or lipoprotein levels. In the population with abdominal obesity and components of the metabolic syndrome, telmisartan did not increase insulin sensitivity. Thus, the role of telmisartan in improving insulin sensitivity remains questionable and calls for detailed and larger clinical trials.

CONCLUSION

Telmisartan has proven to improve insulin resistance that parallels an increase in the serum level of adiponectin in hypertensive patients with insulin resistance. It may, therefore, have advantages in treating such populations. Hypertension and diabetes are often co-existing morbidities. Telmisartan has also been found to have a favorable effect on glucose homeostasis in patients with MS and low levels of serum cytokines. However, the role of telmisartan in obese patients still needs to be further studied. Further studies are also needed to establish the extent of involvement of PPARγ phosphorylation in adipocytes by telmisartan that results in improving insulin resistance.

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