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Effects of valsartan compared with telmisartan in reducing insulin resistance on type 2 diabetes mellitus (T2DM) patients with hypertension

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ABSTRACT

Insulin resistance is a major risk factor for patients with type 2 diabetes mellitus (T2DM). Telmisartan and valsartan are angiotensin II type I receptor blockers (ARBs) that are often used in patients with metabolic syndrome and T2DM. This study aimed to compare the effect of valsartan and telmisartan in reducing insulin resistance on T2DM with hypertension. Patients of T2DM were open-label screened at the Endocrinology Policlinic, Department of Internal Medicine, Dr. Sardjito General Hospital, Yogyakarta, and then randomized into two groups. The first group received valsartan 80 mg per day up to 160 mg per day, the second group received telmisartan 40 mg per day up to 80 mg per day in addition with life-style modifying and diabetes therapy. Homeostasis model assessment of insulin resistance (HOMA-IR), triglyceride and HDL cholesterol levels of patients were measured before and after receiving telmisartan and valsartan for 12 weeks. A total of forty-nine outpatients were involved in this study comprised of 25 female patients (51%) and 24 male patients (49%) with 27 patients (55.1%) received telmisartan and 22 patients (44.9%) received valsartan as the hypertension therapy. No significantl difference were observed between telmisartan group compared with valsartan group in HOMA-IR (14.01 ± 16.39 vs. 5.31 ± 3.51; p=0.053), triglyceride levels (165.71 ± 94.70 vs 144.41 ± 48.33 mg/dL; p=0.620), HDL-C level (48.57 ± 9.78 vs 49.24 vs 49.24 ± 12.56 mg/dL; p=0.999). In conclusion, telmisartan demonstrated no difference compared to valsartan in reducing insulin resistance on T2DM patients with hypertension.

ABSTRAK

Resistensi insulin merupakan masalah utama pada penatalaksanaan pasien diabetes militus tipe 2 (DMT2). Telmisartan dan valsartan merupakan penghambat reseptor angiotensin II tipe I (ARB) yang sering digunakan pada pasien sindrom metabolik dan DMT2. Penelitian ini bertujuan membandingan efek telmisartan dan valsartan dalam menurunkan resistensi insulin pada pasien DMT2 dengan hipertensi. Pasien DMT2 diskrining dengan model terbuka di Poloklinik Endokrinologi, Departemen Ilmu Penyakit Dalam, Rumah Sakit Umum Pusat Dr. Sardjito, Yogyakarta dan kemudian dibagi secara acak menjadi dua kelompok. Kelompok pertama mendapat valsartan 80 mg sampai 160 mg dan kelompok kedua mendapatkan telmisartan 40 mg sampai 80 mg, disamping diet dan terapi diabetes rutin. Nilai HOMA-IR, kadar trigliserid dan HDL kolesterol diperiksa sebelum dan sesudah mendapat telmisartan dan valsartan selama 12 minggu. Total 49 pasien DMT2 dengan hipertensi terlibat dalam penelitian yang terdiri dari 25 pasien wanita (51%) dan 24 pasien laki-laki (49%) dan 27 pasien (55,1%) menerima telmisartan dan 22 pasien (44,9%) menerima valsartan sebagai terapi hipertensinya. Tidak terdapat perbedaan bermakna antara kelompok telmisartan dibandingkan dengan kelompok valsartan untuk nilai HOMA-IR (14,01 ± 16,39 vs. 5,31 ± 3,51; p=0,053), kadar trigliserid (165,71 ± 94,70 vs 144,41 ± 48,33 mg/dL; p=0,620), kadar kolesterol HDL (48,57 ± 9,78 vs 49,24 vs 49,24 ± 12,56 mg/dL; p=0,999). Dapat disimpulkan, tidak terdapat perbedaan efek antara telmisartan dan valsartan dalam menurunkan resistensi insulin pada pasien DMT2 dengan hipertensi.

Keywords:
valsartan;
telmisartan;
insulin resistance;
T2DM;
hypertension;

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INTRODUCTION

Insulin resistance is a major risk factor for type 2 diabetes mellitus (T2DM). Insulin resistance contributes the development of T2DM through the action of attenuating insulin secretion and metabolic action.[1,2] One of the most widely used oral antidiabetic agents aimed to increase insulin sensitivity is thiazolidinedione group. Thiazolidinediones act by activating peroxisome proliferator activated receptor-γ (PPAR-γ).[3]

Several studies concerning angiotensin II type I receptor blocker (ARBs) as hypertension therapy showed significant effect on intracellular insulin signalling pathway repairment and reducing incidence of T2DM. Telmisartan has a unique profile compared to other ARBs by its selective ability to activate PPAR-γ, reducing the risk of oedema and heart failure in patients with hypertension.[4-7] Moreover, telmisartan is more effective to reduce insulin resistance than valsartan in hypertensive patients with metabolic syndrome.[8] This study aimed to evaluate the effect of telmisartan or valsartan in reducing of insulin resistance in T2DM patients with hypertension.

MATERIALS AND METHODS

Subjects

This was open-label, randomization clinical study conducted in the Internal Medicine Clinic, Dr. Sardjito General Hospital, Yogyakarta. Male and female patients aged of 35-60 y.o that fulfilled the ADA 2010 Diabetes Mellitus criteria and JNC VII hypertension criteria, 9 were consented to be included to the research by signing informed consent form. The patients were excluded under certain conditions such as 1) kidney failure; 2) heart failure; 3) lung failure; 4) patients whose blood pressure measurement >160/100 mmHg after being treated with hypertension therapy; 5) pregnant women; 6) smoker; 7) alcohol consumer; and 8) patients who received corticosteroid therapy.

Protocol of study

Subjects who fulfilled the criteria would be measured for waist circumference, body weight and height, and blood pressure, then randomized into 2 groups. The first group was given life-modifying therapy, diabetes therapy, and telmisartan 40 mg per day up to 80 mg per day. The second group was given life-modifying therapy, diabetes therapy, and valsartan 80 mg per day up to 160 mg per day. If the patient's blood pressure failed to achieve 130/80 mmHg, patients were treated with calcium channel blocker (CCB) agents. Insulin as diabetic therapy should not be stopped.

The study was being conducted for 12 weeks. Subject's blood pressure was measured for every 2 weeks. The parameters were collected, including 1) metabolic parameters; (2) waist circumference; 3) body mass index (BMI); 4) homeostasis model assessment insulin resistance (HOMA IR) index determined by fasting insulin level and fasting blood glucose level;[10] 5) triglyceride level; and 6) HDL cholesterol level.

Statistical analysis

Data were presented as mean ± standard deviation (SD). Independent samples t-test analysis was used to compare the difference between means of two independent groups with numerical variables ($p>0.05$) and Mann-Whitney U-test was used if the means of two independent groups were analyzed with non-parametric test ($p<0.05$). Chi square test analysis was used to determine whether there was a significant difference between two groups prescribed with telmisartan and valsartan ($\alpha = 0.05$).

RESULTS

Subjects that enrolled into the study were type 2 DM outpatients with hypertension who attended routine medical care in endocrinology clinic, Dr. Sardjito General Hospital, Yogyakarta. A total of forty-nine outpatients comprised of 25 female patients (51%) and 24 male patients (49%) with 27 patients aged 57.52 ± 5.07 year-old received telmisartan as hypertension therapy (55.1%) and 22 patients aged 56.65 ± 5.07 year-old received valsartan as hypertension therapy (44.9%). HOMA IR profile were not available in all enrolled subjects, therefore only 38 enrolled subjects were analyzed into the study, 21 patients on telmisartan therapy and 17 patients on valsartan therapy. Means of BMI and waist circumference before and after 12 weeks treatment with telmisartan or valsartan is presented in TABLE 1.

TABLE 2 shows the means of homeostasis model assessment insulin resistance (HOMA-IR), triglyceride, and HDL cholesterol level after 12 weeks treatment with telmisartan or valsartan.

TABLE 1. Means values ± SD of BMI and waist circumference before and after 12 weeks treatment with telmisartan or valsartan

Parameters	Before			After		
	Telmisartan (n=21)	Valsartan (n=17)	p	Telmisartan (n=21)	Valsartan (n=17)	p
BMI	28.25 ± 2.96	27.88 ± 3.21	0.690	28.12 ± 3.15	27.11 ± 3.07	0.694
Waist circumference	97.60 ± 6.96	96.47 ± 8.35	0.540	96.10 ± 7.30	97.56 ± 7.17	0.541

TABLE 2. Means values ± SD of homeostasis model assessment insulin resistance (HOMA-IR), triglyceride, and HDL cholesterol level after 12 weeks treatment with telmisartan or valsartan

Parameters	Telmisartan (n=21)	Valsartan (n=17)	p
HOMA-IR	14.01 ± 16.39	5.31 ± 3.51	0.053
Trans HOMA-IR	0.90 ± 0.48	0.64 ± 0.27	
Triglyceride level	165.71 ± 94.702	144.41 ± 48.33	0.620
Trans triglyceride level	2.11 ± 0.21	0.14 ± 0.14	
HDL cholesterol level	48.57 ± 9.78	49.24 ± 12.56	0.999
Trans HDL cholesterol level	1.68 ± 0.08	1.68 ± 0.11	

DISCUSSION

Mean values of BMI and waist circumference evaluation as parameters for obesity did not show different results after patients received insulin and either telmisartan or valsartan at the end of the study. It showed that obesity as causative factor of insulin resistance showed no difference. Obesity is an essential factor for insulin resistance. Adipose tissue, alongside its function as source of energy preservation, is considered an endocrine organ that influences glucose metabolism by releasing adipokines, free fatty acids (FFA), adipokines, leptin, and resistin.[11] Insulin resistance in obesity is associated with impaired inhibition of lipolysis by insulin, resulting in increased release of FFA and glycerol. The release of FFA

solicited insulin resistance in muscle and adipose tissue by impairing GLUT4 receptor translocation and fusion in cell membrane. Visceral adipose tissue is considered more lipolytically active on a per unit weight basis than subcutaneous fat.[12] Abdominal obesity increases the likelihood of FFA circulation as it can directly enter the liver via the portal circulation, which increases lipid synthesis and gluconeogenesis by the increased level of FFA, eventually causing insulin resistance.[13,14]

Lipid profile displayed by patients in this study also did not show any significant difference accordant to the level of insulin resistance between two groups that also did not show significant difference. Dyslipidemia is precipitated by insulin resistance by increasingly active lipolysis mechanisms in adipose tissue. The increased production of FFA resulted in generation of VLDL in liver, a major type of lipoprotein with high degree of lipid density, which initially converted to LDL cholesterol. Subsequently, LDL cholesterol converted to small dense LDL cholesterol (sdLDL), a distinct LDL cholesterol subclass which very dense in triglycerides in smaller particles. HDL cholesterol, which also contains abundant amounts of triglycerides, is transferred to Apo-B and excreted in the renal system, thus HDL cholesterol level in circulation will be lowered.[15]

The results of this study were different from previous meta-analysis study comparing telmisartan with other ARBs agents, which resulted in blood glucose level and insulin sensitivity improvement on subjects who received telmisartan.[7] Another study to compare the effects of telmisartan and valsartan in insulin resistance reduction by evaluation of HOMA-IR demonstrated the improvement of insulin sensitivity within 4 weeks in patients with metabolic syndrome, with means value of subject's age study 65 year-old.[8] This study showed a different outcome compared to the previous studies in which the subjects are T2DM patients treated with insulin with weight gain as the side effect that eventually worsens insulin resistance. Meanwhile, in this study, the patient's mean age was relatively younger, 56 year-old, which may be one of the determinants as to why the studies demonstrated different results. Diet adjustment, physical activities, and patient's compliance also contributed to confounding factors that may influence this study's result, based on the 12 weeks duration of the study.

A study carried out by Derosa *et al.*[16] showed telmisartan prescribed for 12 months also improved insulin resistance with addition of rosiglitazone therapy which amplified the increase in insulin resistance. Compared to this shorter study period of only 12 weeks, the effect of improving insulin sensitivity had not been seen and the experiment did not involve other drugs that can amplify the insulin sensitivity.

This study's result is also similar to other studies investigating the effect of telmisartan on insulin resistance in patients with hypertension and T2DM on improving insulin sensitivity, which is not significant.[17-19] This evidence suggests that telmisartan is not always effective in improving insulin resistance, most likely influenced by unknown factors. Although we failed to obtain data suggesting improvement in insulin resistance by telmisartan, it could be considered a variation in study results that would determine the drug's efficacy in clinical setting.

The main limitations of this study are the open label design, the small number of participants, and the relatively short treatment period. A double blind study with a larger patient population and a longer treatment period is needed to investigated to determine the effect of telmisartan on insulin resistance in patients with hypertension and Ttype 2DM diabetes mellitus with insulin therapy.

CONCLUSION

This study demonstrates no significant difference in insulin resistance reduction in hypertensive T2DM patients with insulin therapy who received telmisartan compared to who received valsartan after 12 weeks treatment.

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