An observational study of the effects of telmisartan on insulin resistance in hypertensive patients with chronic kidney disease undergoing hemodialysis

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Research article

Abstract

Background In the clinical setting, the activity of telmisartan in decreasing insulin resistance has been proven superior to other antihypertensive drugs in hypertensive patients. However, there has been no published study in determining the effect of telmisartan on insulin resistance in hypertensive chronic kidney disease patients undergoing hemodialysis.

Objective To analyze the effect of telmisartan on insulin resistance in hypertensive patients undergoing hemodialysis.

Method It was a prospective observational cohort study in 16 chronic kidney disease patients undergoing regular hemodialysis and using telmisartan who met the inclusion criteria.

Results Sixteen patients received telmisartan, 12 were male patients and four were female. The mean age was 45 ± 8 years and the mean body mass index was 22.85 ± 1.99. Hypertensive chronic kidney disease was the highest etiology (56%) for hemodialysis. Mean percentage of fasting plasma insulin and homeostatic model assessment of insulin resistance concentratons decreased significantly by 22.6% (P<0.05) and 22.9% (P<0.05) respectively after 3-month administration. On the other hand, the mean percentage of fasting plasma glucose concentrations declined by 2.9% (P=0.187, Zcount<1.96) after 3-month of treatment.

Conclusion Administration of telmisartan for three months decreases insulin resistance significantly in hypertensive patients undergoing hemodialysis.

Background

Insulin resistance has been reported in approximately 70% of hemodialysis (HD) patients with comorbid diabetes, while the incidence was found to be far lower (approximately 30%) among similar patients without a diagnosis of diabetes. [1] The development of insulin resistance among patients undergoing HD is thought to be related to a variety of physiological factors including chronic inflammatory changes caused by activation of proinflammatory cytokines, the accumulation of visceral fat, deregulation of adipokine metabolism, intermittent metabolic acidosis, uncontrolled hyperparathyroidism, anemia, and the effects of oxidative stress and uremia. [2] In turn, insulin resistance increases the risk for coronary artery disease (CAD), promoting artherogenesis and advanced plaque progression [3].

In view of the issues outlined above, there is considerable interest in the possibility of using pharmacotherapy in this context, with the aim of improving the extent of insulin sensitivity in hemodialysis patients, but current drug treatment approaches are limited [4]. Recent research has revealed that angiotensin II receptor blocker (ARB) telmisartan may possess significant metabolic modulatory effects, which may in turn underpin unique beneficial properties for people with chronic kidney disease (CKD) [5]. Telmisartan has the greatest affinity for the Angiotensin II receptor type I (ATR–1) relative to other ARBs and is well absorbed due to its lipophilicity [5]. Telmisartan is particularly suited

for use amongst CKD patients because its primary route of elimination is via hepatic metabolism, meaning that there is little of no impact upon the drug's pharmacokinetics mediated through renal impairment or hemodialysis [5].

The activity of telmisartan activity in decreasing insulin resistance has been demonstrated in a previous meta-analysis of 37 randomized clinical trials (RCTs) involving a total of 2,237 hypertensive patients [6]. Telmisartan decreased the concentration of fasting plasma insulin (FPI) and was associated with superior activity in reducing insulin resistance compared to other antihypertensive agents [6]. Furthermore, a systematic review of eight randomised controlled trials involving a total of 763 participants revealed that telmisartan 80 mg had superior effects on improving insulin sensitivity by decreasing fasting plasma glucose (FPG) and increasing adiponectin levels in hypertensive patients with insulin resistance or diabetes, when compared with other ARBs [7]. A further recent meta-analysis of 21 RCTs, which included 1,679 patients, demonstrated that telmisartan was superior in improving homeostatic model assessment for-insulin resistance (HOMA-IR), reducing FPI concentration, and decreasing diastolic blood pressure in patients with obesity, diabetes, impaired glucose tolerance, and metabolic syndrome [8]. As no recent research has addressed the possible effects of telmisartan on insulin resistance in hypertensive CKD patients undergoing HD in daily practice, the present study was conducted analyze the effect of telmisartan upon insulin resistance in hypertensive patients undergoing HD. The research protocol was unconditionally approved by the Hospital Ethics Committee.

Methods

The study was an unblinded prospective observational cohort in patients undergoing regular HD in the H. S. Samsoeri Mertojoso Bhayangkara Hospital, a secondary care hospital in Surabaya, Indonesia. Informed consent was obtained from all individual participants who met inclusion criteria. To be eligible for inclusion, subjects needed to have a diagnosis of CKD and be undergoing regular HD at least twice a week for three months, have pre-dialysis blood pressure higher than 140/90mmHg, to be naïve to telmisartan treatment, and agree to participate in thestudy. The exclusion criteria were as follows: FPG concentration higher than 130 mg/dL, developed side effects, allergies discontinued HD, and withdrawal of consent to participate in the study. All patients underwent regular HD twice a week. Patients were also prescribed other drugs according to their clinical needs, but all were newly-prescribed telmisartan and had no changes in anti-diabetic therapy during the study period. All patients were adjudged by the pharmacists to have had adequate adherence to telmisartan during the study period..

Blood samples were obtained from each patient to assess including FPI, fasting plasma glucose (FPG) and HOMA-IR before the commencement of telmisartan treatment. Telmisartan 80 mg once daily was initiated according to the hospital protocol and pharmacists provided education for patients about antihypertensive therapy. Patients' weight and blood pressure before and after HD were recorded during the standard hemodialysis procedure. Pharmacists assessed adherence using a pill count method. After three months of telmisartan treatment the FPG, FPI, and HOMA-IR were re-assessed. The HOMA-IR was

calculated using a mathematical formula: (FPG (mmol/L) x FPI (mU/L)) / 22.5. Insulin resistance was defined by the HOMA-IR above 1.6 [1].

Changes in FPG, FPI, and HOMA-IR before and after telmisartan were recorded as absolute numbers and also percentage variation. Statistical analysis was performed to test the normality of samples using the Shapiro-Wilk method, followed by paired t-test if data were normally distributed or Wilcoxon if were not normally distributed. A significant change was defined as that associated with $p < 0.05$.

Results

There were 19 patients who met the inclusion criteria, but three patients were excluded from further treatment and analysis because of side effects such as nausea and hypotension: 16 patients received telmisartan, 12 male patients and 4 female. The mean age of the patients was 45± 8 years and the mean Body Mass Index (BMI) was 22.85 ± 1.99. Patients demographic data were presented in Table 1. The most common pathology accounting for the need for HD was hypertensive chronic kidney disease (56%), and six patients had a comorbid of type 2 diabetes mellitus and hypertension.

Statistical testing revealed that the distribution of FPG concentration was non-normal in nature, but there was a normal distribution for FPI and HOMA-IR concentrations. Insulin resistance was assessed by using the HOMA-IR level derived from FPG and FPI before and after three months of treatment with telmisartan (Table 2). In all, a HOMA-IR value greater than 1.6 was observed in 10 patients before the administration of telmisartan, of these 6 patients (60%) had a type 2 diabetes mellitus. The mean FPI and HOMA-IR concentrations decreased significantly after treatment, by 22.6% (from 7.09 ± 4.11 prior to treatment to 5.03 ± 3.15 µU/mL after telmisartan, $p < 0.05$) and from 22.9% (1.69 ± 1.28 to 1.11 ± 0.79, $p < 0.05$) respectively. On the other hand, there was no significant change in the mean percentage of FPG concentration (89.06 ± 20.06 mg/dL to 84.56 ± 10.91 mg/dL, p = 0.187, $Z_{count} < 1.96$).

Discussion

ARB medications, including telmisartan, are widely used for people with CKD undergoing HD, to reduce the impact of cardiovascular complications. It thought that activation of the renin-angiotensin-aldosterone system (RAAS) causes endothelial dysfunction to trigger the development of cardiovascular complications in this context, particularly congestive heart failure (CHF) and left ventricular hypertrophy (LVH). This is indicated by increased levels of angiotensin II and aldosterone as the major mediator of the RAAS. Therefore, ACEI and ARB have become the first line agents to treat hypertension in CKD patients undergoing hemodialysis [9]. Telmisartan also appears to provide other benefits in lowering insulin resistance [10].

In the present study, insulin resistance was observed for more patients with a medical history of diabetes mellitus than non-diabetic patients before the administration of telmisartan, similar to the findings of Takenaka et al. in 2007 [1]. Other research has also revealed an elevated incidence of increased insulin

resistance in CKD patients with hemodialysis, finding a linear correlation between decreased creatinine clearance (CrCl) and significantly increased insulin resistance in patients having CrCl below 60 ml/min. [2].

The results from our study showed that the mean HOMA-IR value declined significantly by (34.32%) from 1.69 to 1.11 after 3 months ($p < 0.05$), suggesting that telmisartan has potential activity in reducing insulin resistance amongst people with dialysis-dependent CKD. The results are consistent with previous findings amongst people with less severe CKD not requiring dialysis [6, 7, 8]. Decreased insulin resistance observed in this study suggests a positive effect of telmisartan in improving insulin sensitivity in CKD-HD patients as showed by decreased plasma insulin, suggesting a lower need of insulin to maintain fasting plasma glucose. This effect of telmisartan may be based on its effect as a partial agonist of peroxisome proliferator-activated receptor ⬜ (PPAR⬜), one of the nuclear hormone receptors that plays a major role as a transcription factor regulating the metabolism of carbohydrates, fats, and inflammation. PPAR ⬜ presents commonly in adipose tissues and small amounts in various cells of vascular smooth muscle, endothelium, and monocytes [10]. This activity may be associated with the chemical structure of telmisartan, which resembles the structure of pioglitazone (a thiazolidinedione compound), and thus telmisartan has been found to have approximately 25−30% of the activity of pioglitazone in activating PPAR⬜ [10]. PPAR⬜ activation can increase the expression of a wide variety of genes and enzymes involved in the metabolism of carbohydrates (adiponectin, glucokinase and glucose transporter−4) and the metabolism of fat (lipoprotein lipase, adipocyte fatty acid transporter protein, fatty-acyl-CoA synthase, and malic enzyme). In addition, activation of PPAR⬜ can also suppress the activity of pro-inflammatory cytokine tumor necrosis factor-α which can suppress the sensitivity of insulin through insulin signal transduction disorder [10].

This study has a range of limitations. The sample size was small, limiting the extent to which it is possible generalize to larger populations. Patient self-report about telmisartan adherence was used and might have overestimated the extent of adherence. Further research is needed with a larger sample size, multicenter setting, and longer duration of follow-up. Future studies could be designed to address specific inclusion criteria to assess specific issues that might cause changes in insulin resistance. In the meantime, this preliminary data suggests that telmisartan appears to be a reasonable choice of antihypertensive agent for dialysis dependent patients.

Conclusion

In this small study, administration of telmisartan for a period of three months appeared to produce a decrease insulin resistance, as reflected by changes in the HOMA-IR parameter measured in hypertensive patients with CKD undergoing HD. This potentially promising approach to treatment in this patient group may provide clinically significant metabolic benefit, and thus probably warrants further attention and research.

Declarations

Ethics approval and consent to participate

The research protocol was approved by the Hospital Ethics Committee of Samsoeri Mertojoso Bhayangkara Hospital.Informed consent was obtained from all individual participants who met inclusion criteria. Consent to participate was given in written format.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

Author Contribution

BS contributed to design and concept the study. MD, WN, ZI, BD searched, acquired and interpreted the data. BS, MD, ZI and WN drafted the manuscript. All authors made important revision and gave final approval of the version to be published.

Consent For Publication

Not Applicable

Abbreviations

Hemodialysis (HD)

Coronary Artery Disease (CAD)

Angiotensin II Receptor Blocker (ARB)

Chronic Kidney Disease (CKD)

Angiotensin II Receptor Type I (ATR–1)

Fasting Plasma Insulin (FPI)

Fasting Plasma Glucose (FPG)

Body Mass Index (BMI)

Renin Angiotensin Aldosterone System (RAAS)

Congestive Heart Failure (CHF) and

Left Ventricular Hypertrophy (LVH)

Creatinine Clearance (CrCl)

Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)

Peroxisome Proliferator Activated Receptor (PPARɣ)

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Tables

Table 1 Demographics of patients[a] (n = 16)

Variable	Category	Number (%)
Age (years)	20 – <40	6 (37.5)
	40 – 60	10 (62.5)
Gender	Female	4 (25)
	Male	12 (75)
BMI	18.5 – <25	13 (81.2)
	25 – 30	3 (18.8)
Etiology of CKD	Hypertensive kidney disease	9 (56.2)
	Daibetic Nephropathy	6 (37.5)
	Kidney infection	1 (6.2)
Comorbid diseases	Type 2 Diabetes Mellitus + Hypertension	6 (37.5)
	Dyslipidemia + Hypertension	3 (18.8)
	Hypertension	7 (43.8)
Duration of	6 – <12	3 (18.8)
hemodialysis	12 – <24	11 (68.8)
(months)	24 – <36	1 (6.2)
	36 – 48	1 (6.2)
Antihypertensive	Amlodipine+Telmisartan	5 (31.2)
Agents	Amlodipine+ISDN+Telmisartan	1 (6.2)
	Amlodipine+Bisoprolol+Telmisartan	3 (18.8)
	Amlodipine+Bisoprolol+Methyldopa+Telmisartan	3 (18.8)
	Amlodipine+Bisoprolol+Methyldopa+Furosemide +Telmisartan	1 (6.2)
	Bisoprolol+Methyldopa+Telmisartan	1 (6.2)
	Bisoprolol+Methyldopa+Nifedipine+Telmisartan	1 (6.2)
	Nifedipine+Telmisartan	1 (6.2)

[a] BMI, body mass index; CKD, chronic kidney disease; ISDN, isosorbid dinitrate.

Table 2 Fasting Plasma Glucose (FPG), Fasting Plasma Insulin(FPI), and Homeostatic Model Assesment-Insulin Resistance(HOMA-IR) concentrations before and 3-months after treatment

Parameters	Mean concentration ± SD				P
	Pre-	Post-	Δ	%	
FPG (mg/dL)	89.06 ± 20.06	84.56 ± 10.91	4.50 ± 12.63	2.9 ± 13.67	0.187
FPI (mU/mL)	7.09 ± 4.11	5.03 ± 3.15	2.06 ± 2.10	22.6 ± 27.9	<0.05
HOMA-IR	1.69 ± 1.28	1.11 ± 0.79	0.59 ± 0.64	22.9 ± 36.05	<0.05