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Effects of Valsartan on Inflammatory and Oxidative Stress Markers in Hypertensive, Hyperglycemic Patients: An Open-Label, Prospective Study

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ABSTRACT

Background: Diabetes mellitus and hypertension are aggravated by activation of the renin–angiotensin system caused by increased oxygen stress and local inflammatory responses. Several studies have suggested that angiotensin II type 1 receptors can reduce inflammatory markers (high-sensitivity C-reactive protein [hs-CRP], interleukin [IL]-6, IL-18, soluble vascular cell adhesion molecule [VCAM]-1, and L-selectin) and oxidative stress markers (urinary 8-hydroxy-7,8-dihydro-2'-deoxyguanosine [8-OHdG] and 8-epi-prostaglandin $F_{2\alpha}$ [8-isoprostane]) in hypertensive patients.

Objective: The aim of this study was to assess the effects of valsartan, an angiotensin II receptor blocker, on inflammatory and oxidative stress markers in hypertensive patients with mild diabetes or impaired glucose tolerance.

Methods: In this open-label, prospective study, hypertensive patients aged >20 years with mild diabetes (requiring treatment by diet alone or an oral hypoglycemic), seen on an outpatient basis at the Division of Diabetes, Metabolism, and Endocrinology, Omori Hospital, Toyko, Japan, who were receiving a therapeutic dietary regimen for ≥1 month in the treatment of diabetes or hypertension, were eligible for enrollment. Blood pressure, inflammatory markers (hs-CRP, IL-6, IL-18, VCAM-1, and L-selectin), and oxidative stress markers (urinary 8-OHdG and 8-isoprostane) were monitored before treatment commencement with valsartan (40–80 mg/d) and after 3 months of treatment.

Results: A total of 26 patients (18 men, 8 women; mean [SD] age, 57.7 [11.3] years; mean [SD] weight, 65.3 [13.1] kg) were enrolled in the study. After 3 months of treatment, patients' mean (SD) blood pressure had significantly decreased from 153.1 (11.2)/88.3 (11.4) to 143.7 (13.7)/85.2 (9.0) mm Hg ($P <$

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0.05). Among the inflammatory and oxidative stress markers, hs-CRP, VCAM-1, and urinary 8-OHdG concentrations decreased significantly from 0.231 (0.199) to 0.134 (0.111) mg/dL ($P = 0.043$), 471.1 (193.9) to 403.2 (135.2) ng/mL ($P = 0.012$), and 12.12 (5.99) to 8.07 (3.36) ng/mg · creatinine ($P = 0.001$), respectively. The reductions in these markers were observed in patients regardless of whether or not their glycosylated hemoglobin (HbA_{1c}) concentration improved (defined as a decrease of ≥1% in HbA_{1c}).

Conclusion: This small, open-label, prospective study found that a 3-month treatment with valsartan was associated with a significant reduction of hs-CRP, VCAM-1, and urinary 8-OHdG concentrations independent of improvement in HbA_{1c} concentration in these hypertensive patients with hyperglycemia. (*Curr Ther Res Clin Exp.* 2007;68:338–348) Copyright © 2007 Excerpta Medica, Inc.

Key words: valsartan, hypertension, diabetes, inflammatory marker, oxidative stress marker.

INTRODUCTION

Hypertension is a risk factor for cardiovascular diseases and frequently develops concurrently with other risk factors, namely, visceral obesity, insulin resistance, glucose intolerance, and abnormal lipid metabolism.[1] Because these disorders are believed to be associated with closely related factors, together they are regarded as metabolic syndrome.[2,3]

Numerous clinical trials[4,5] have found that treatment of hypertension can prevent the onset of cardiovascular diseases. The guidelines from the Japanese Society of Hypertension[6] recommend aggressive antihypertensive treatment. Because etiologic studies[7] of hypertension have demonstrated that activation of the renin–angiotensin (RA) system contributes to the maintenance of high blood pressure or the onset of cardiovascular diseases associated with hypertension, interest in the clinical significance of RA system inhibitors has been increasing. As the relationship between angiotensin II receptors and insulin resistance as well as the roles of genes in glucose metabolism are also becoming more evident,[8,9] there is increasing interest in both the antihypertensive effects of RA system inhibitors and their beneficial effects on carbohydrate metabolism.

Meanwhile, local inflammation has been identified as an etiologic factor for the onset of cardiovascular diseases,[10] and in vitro studies[11] have found that stimulation of angiotensin II receptors accelerates the generation of free radicals and the release of inflammatory cytokines. Thus, hypertension may contribute to increases in the incidence of cardiovascular diseases, not only by imposing a load on the cardiovascular system, but also by promoting cardiovascular inflammation and/or affecting carbohydrate metabolism. Several reports have already found that angiotensin II receptor blockers (ARBs) significantly suppress inflammatory and oxidative stress markers, including high-sensitivity C-reactive protein (hs-CRP), monocyte chemoattractant protein 1, interleukin (IL)-6, and urinary 8-epi-prostaglandin $F_{2\alpha}$ (8-isoprostane).[12–14]

Therefore, we focused on the physiologic activity of angiotensin II and examined the effects of valsartan, an ARB, on inflammatory markers and markers of oxidative stress in hypertension complicated by mild diabetes or impaired glucose tolerance.

PATIENTS AND METHODS

Among hypertensive outpatients at the Division of Diabetes, Metabolism, and Endocrinology, Omori Hospital, Tokyo, Japan, patients aged >20 years who had been receiving dietary treatment for diabetes or hypertension for ≥1 month and had a blood pressure >140/90 mm Hg (mean of 3 measurements at outpatient clinic) were enrolled in this study, regardless of whether they were receiving antihypertensive treatment. Diabetic patients also participated in the study, but only those with mild diabetes (glycosylated hemoglobin [HbA_{1c}] <9.0% and treated by diet alone or an oral hypoglycemic agent) were selected. Patients with a serum creatinine concentration ≥1.5 mg/dL were excluded.

All study protocols and procedures were approved by the Ethics Committee of Toho University Medical Center. The study objectives and intended measures were explained to 27 prospective study patients (individually), and 26 patients completed the study (1 patient discontinued the treatment). Written informed consent was obtained from all patients. Valsartan* was administered at doses of 40 to 80 mg/d. The initial dose of valsartan was 40 mg/d, and the dose was increased to 80 mg/d after 1 month if the systolic and diastolic blood pressures were still >140 and/or 90 mm Hg, respectively. Inflammatory markers (hs-CRP, IL-6, IL-18, soluble vascular cell adhesion molecule [VCAM]-1, and L-selectin) and oxidative stress markers (8-hydroxy-7,8-dihydro-2'-deoxyguanosine [8-OHdG] and 8-isoprostane) were measured before the start of drug administration and also after 3 months of treatment. All hypolipidemic, hypoglycemic, and/or antihypertensive drugs already being administered were continued without any changes in their dosage or mode of administration. Dietary and exercise treatments were also continued, and the patients were advised not to change their current lifestyles.

While in supine position, the patients' height, body weight, and blood pressure (left arm) were measured and recorded at each visit. Blood samples were drawn in the morning after an overnight fast before and after 3 months of valsartan treatment. The blood samples were collected into tubes containing ethylenediaminetetraacetic acid (1.5 g/L) and centrifuged at 1000*g* for 20 minutes at 4°C to obtain plasma. Concentrations of total cholesterol, triglycerides, high-density lipoprotein cholesterol, and serum creatinine were measured using an autoanalyzer. HbA_{1c} was measured using high-pressure liquid chromatography, while hs-CRP was measured by the method of Ledue et al.[15] IL-6 (Quantikine HS human IL-6 kit, R&D Systems Inc., Minneapolis, Minnesota),

*Trademark: Diovan® (Novartis Pharma AG, Basel, Switzerland).

IL-18 (Human IL-18 ELISA kit, MBL Co., Nagoya, Japan), VCAM-1 (Quantikine human sVCAM-1 kit, R&D Systems Inc.), and L-selectin (human sL-Selectin kit, R&D Systems Inc.) were measured by enzyme-linked immunosorbent assays (ELISAs) using the cited kits, while the urinary oxidative stress markers 8-OHdG[16] and 8-isoprostane[17] were measured by ELISA and enzyme immunoassay, respectively. To monitor the adverse effects (AEs) possibly associated with valsartan, clinical symptoms (eg, headache, nausea, stomachache, muscle pain) were assessed by observation at each visit, and routine biochemical analyses (aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, uric acid, creatinine, sodium, potassium, chloride, calcium, phosphorus, and lactate dehydrogenase) were performed simultaneously.

Statistical Analysis

Data are expressed as mean (SD), and the data before and after valsartan administration were compared using a paired *t* test.

RESULTS

Table I illustrates the baseline demographic and clinical characteristics of the 26 patients (18 men, 8 women; mean [SD] age, 57.7 [11.3] years; mean [SD] weight, 65.3 [13.1] kg) enrolled in the study. Type 2 diabetes was detected in 20 (76.9%) patients, hyperlipidemia in 17 (65.4%), glucose intolerance in 6 (23.1%), and hyperuricemia in 2 (7.7%). Nine (34.6%) patients were receiving concomitant treatment with statins. The hypoglycemic drugs used were sulfonylurea compounds in 3 (11.5%) patients and α-glucosidase inhibitors in 2 (7.7%) patients. The antihypertensive drugs used were a calcium channel blocker (CCB) in 4 (15.4%) patients and a β-blocker in 1 (3.8%) patient, who was also treated with a CCB.

In 17 (65.4%) patients, body mass index (BMI) was >25 kg/m^2 before the administration of valsartan. Blood pressure decreased significantly from 153.1 (11.2)/88.3 (11.4) mm Hg at baseline to 143.7 (13.7)/85.2 (9.0) mm Hg ($P < 0.05$) after 3 months of valsartan treatment. However, when the patients were evaluated by CCB use, only systolic blood pressure showed a significant decrease ($P < 0.05$) in non-CCB users (n = 22).

Table II illustrates the changes in indicators of lipid and blood glucose control after 3 months of valsartan treatment. No significant changes were detected in these indicators, with the exception of HbA_{1c} concentration, which decreased from mean (SD) 7.05% (1.47%) to 6.52% (1.04%) ($P = 0.007$). HbA_{1c} improved (defined as a decrease of ≥1%) in 5 (19.2%) patients, while it increased in 8 (30.8%) patients. Serum creatinine concentration increased from 0.77 (0.22) to 0.80 (0.27) mg/dL, but this difference was not significant.

Table III illustrates the changes in inflammatory and oxidative stress markers after valsartan treatment. Among the 7 measured markers, hs-CRP decreased significantly from 0.231 (0.199) to 0.134 (0.111) mg/dL ($P = 0.043$).

Table I. Baseline demographic and clinical characteristics of patients (N = 26) in the open-label, prospective study on the effects of valsartan on inflammatory and oxidative stress markers in hypertensive patients.

Characteristic	Value
Age, mean (SD), y	57.7 (11.3)
Sex, no.	
Male	18
Female	8
Weight, mean (SD), kg	65.3 (13.1)
Concurrent disease, no. (%)	
Type 2 diabetes	20 (76.9)
Hyperlipidemia	17 (65.4)
Impaired glucose tolerance	6 (23.1)
Hyperuricemia	2 (7.7)
Concomitant drugs, no. (%)	
Hypolipidemic	
Statins	9 (34.6)
Hypoglycemic	
Sulfonylurea	3 (11.5)
α-Glucosidase inhibitor	2 (7.7)
Antihypertensive	
Calcium channel blocker	4 (15.4)
β-Blocker	1 (3.8)

Table II. Changes in the states of lipid and blood glucose control in the open-label, prospective study on the effects of valsartan on inflammatory and oxidative stress markers in hypertensive patients. Data are mean (SD).

	Before Valsartan Treatment	After Valsartan Treatment	*P**
Total cholesterol, mg/dL	215.6 (61.2)	207.5 (39.4)	0.351
HDL-cholesterol, mg/dL	52.0 (11.0)	56.3 (20.7)	0.276
Triglycerides, mg/dL	148.4 (83.0)	155.3 (93.8)	0.594
Fasting blood glucose, mg/dL	151.7 (53.2)	140.8 (40.3)	0.234
HbA_{1c}, %	7.05 (1.47)	6.52 (1.04)	0.007

HDL = high-density lipoprotein; HbA_{1c} = glycosylated hemoglobin.
*Determined by paired *t* test.

Table III. Changes in inflammatory and oxidative stress markers in the open-label, prospective study on the effects of valsartan on inflammatory and oxidative stress markers in hypertensive patients. Data are mean (SD).

	Before Valsartan Treatment	After Valsartan Treatment	*P**
hs-CRP, mg/dL	0.231 (0.199)	0.134 (0.111)	0.043
IL-6, pg/mL	7.11 (7.88)	10.36 (16.86)	0.328
IL-18, pg/mL	241.1 (134.3)	236.7 (114.5)	0.769
VCAM-1, ng/mL	471.1 (193.9)	403.2 (135.2)	0.012
L-Selectin, ng/mL	849.8 (198.4)	864.8 (279.7)	0.743
8-Isoprostane, pg/mg · Cr	283.5 (101.5)	302.0 (151.6)	0.559
8-OHdG, ng/mg · Cr	12.12 (5.99)	8.07 (3.36)	0.001

hs-CRP = high-sensitivity C-reactive protein; IL = interleukin; VCAM-1 = vascular cell adhesion molecule; 8-isoprostane = 8-epi-prostaglandin $F_{2\alpha}$; Cr = creatinine; 8-OHdG = 8-hydroxy-7,8-dihydro-2′-deoxyguanosine.
*Determined by paired *t* test.

VCAM-1 and urinary 8-OHdG also decreased significantly from 471.1 (193.9) to 403.2 (135.2) ng/mL (P = 0.012) and from 12.12 (5.99) to 8.07 (3.36) ng/mg · creatinine (Cr) ($P = 0.001$), respectively. The decrease in urinary 8-OHdG concentration remained significant ($P < 0.05$) when the patients were divided into 2 cohorts: CCB users (n = 4) and non-CCB users (n = 22). After grouping the patients according to statin use, the decrease in urinary 8-OHdG concentration remained significant ($P < 0.05$) in both statin users (n = 9) and nonstatin users (n = 17), while hs-CRP concentration did not show a significant change in either group. Concentrations of IL-6, IL-18, L-selectin, and 8-isoprostane did not change significantly after 3 months of treatment.

Analysis of the relationships of markers that exhibited statistically significant changes with HbA_{1c} concentration revealed that hs-CRP, VCAM-1, and urinary 8-OHdG concentrations decreased regardless of whether or not HbA_{1c} showed improvement (**Figure**). In patients who showed no improvement of HbA_{1c} (increase or no change), VCAM-1 and 8-OHdG concentrations decreased significantly from 464.9 (210.3) to 400.5 (131.5) ng/mL ($P < 0.05$) and from 11.53 (5.78) to 7.70 (3.63) ng/mg · Cr ($P < 0.01$), respectively. Furthermore, 8-OHdG concentration decreased significantly from 9.26 (3.93) to 6.56 (2.26) ng/mg · Cr ($P < 0.05$) in patients whose HbA_{1c} improved. In 13 patients with a BMI of ≥25% who were considered to have metabolic syndrome based on the presence of hypertension and diabetes or glucose intolerance, hs-CRP concentration decreased significantly from 0.182 (0.188) to 0.114 (0.118) mg/dL ($P < 0.05$), while VCAM-1 and 8-OHdG concentrations decreased significantly from 506.3 (220.8) to 419.8 (142.5) ng/mL ($P < 0.05$) and from 12.18 (4.95) to 7.71 (2.56) ng/mg · Cr ($P < 0.05$), respectively.

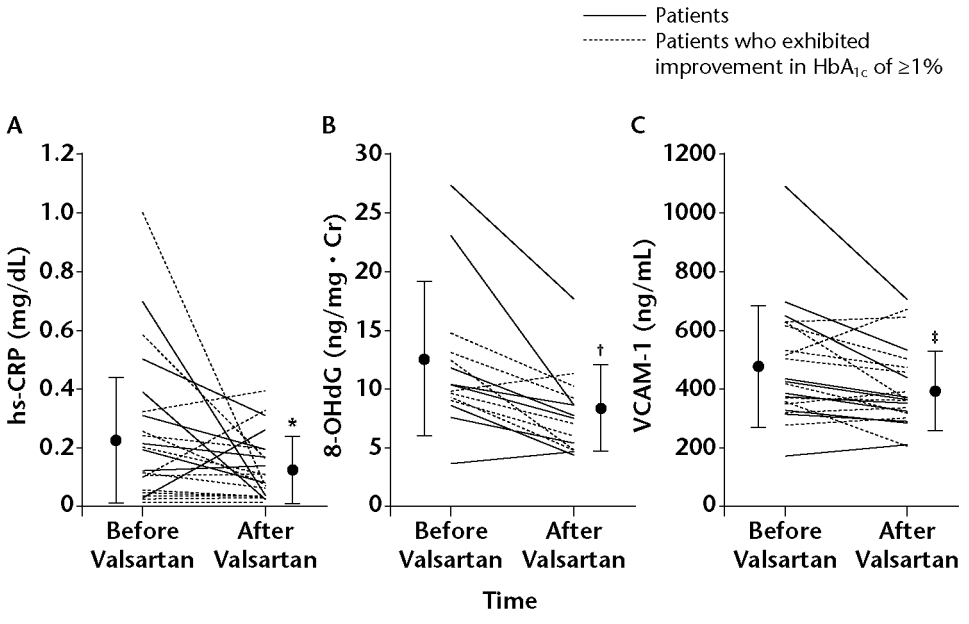

Figure. Changes in high-sensitivity C-reactive protein (hs-CRP), urinary 8-hydroxy-7,8-dihydro-2'-deoxyguanosine (8-OHdG), and soluble vascular cell adhesion molecule (VCAM-1) concentrations after valsartan therapy. Dotted lines represent the data of patients who exhibited improvement in glycosylated hemoglobin (HbA_{1c}) concentration (defined as a decrease of ≥1% in HbA_{1c}). Vertical lines represent the mean (SD). Cr = creatinine. The *P* values in figure are before versus after valsartan treatment. **P* = 0.043; †*P* = 0.001; ‡*P* = 0.012.

During the observation period, no AEs (including the occurrence of the clinical symptoms and changes in the biochemical parameters studied) were detected.

DISCUSSION

In this study, treatment with valsartan for 3 months was associated with significant decreases in 3 (hs-CRP, VCAM-1, and 8-OHdG) of the 7 inflammatory and oxidative stress markers examined in hypertensive patients with mild diabetes or glucose intolerance. Decreases in these markers were detected in obese patients with a BMI ≥25%, which might suggest the clinical utility of valsartan as a therapeutic agent for metabolic syndrome.

It has been scientifically established that increased concentrations of hs-CRP are associated with incident hypertension and cardiovascular events.[18,19] The suppression of hs-CRP by valsartan demonstrated in this study is consis-

tent with previous reports.[20–22] It has been suggested that vascular inflammation regulated in part by the RA system and antagonism of angiotensin II might modulate the atherosclerotic process.[23] Recently, CRP has been found to upregulate angiotensin II receptors.[24] Therefore, it is possible that valsartan blocks angiotensin II receptors, thereby suppressing vascular inflammation.

ILs are inflammatory cytokines secreted by activated monocytes or macrophages. They promote the cell membrane expressions of VCAM-1 and L-selectin, which are molecules in monocyte adhesion to the vascular endothelium.[11] Secretion of these inflammatory cytokines is accelerated by oxidative stress, while angiotensin II increases oxidative stress through the activation and induction of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH).[25] In this study, hs-CRP as well as the adhesion molecule VCAM-1 and urinary 8-OHdG were significantly reduced after valsartan treatment. These findings suggest the possibility that valsartan blocks angiotensin II receptors in vascular tissues, which may suppress both inflammatory and oxidative stress markers. Because CRP is not only an inflammatory marker but also exacerbates inflammation and induces vascular endothelial adhesion factor expression,[26] it seems reasonable that serum VCAM-1 concentration should have decreased after valsartan treatment.

Of the 2 oxidative stress markers measured in this study, urinary 8-isoprostane concentration showed no significant change, whereas urinary 8-OHdG concentration was significantly reduced in the cohort that received valsartan treatment. The former is a metabolite of arachidonic acid, which is cleaved from the phospholipid moiety by phospholipase A_2, and seems to be generated by the direct action of active oxygen on the phospholipid moiety, unlike other prostaglandins formed through the ordinary pathway mediated by a synthetic enzyme (cyclooxygenase).[16] The latter is an oxide of the 8th position of the guanine molecule that constitutes DNA and is a subject of ongoing studies, both as an oxidative stress marker and as a substance that induces DNA mutations.[17] Since NADPH activated or promoted by angiotensin II is present on the cell membrane, it was expected that valsartan would act more readily on 8-isoprostane production. However, in this study, 8-OHdG was more strongly affected by valsartan than 8-isoprostane, which may be attributed to differences in the effects of valsartan that depend on the type of active oxygen or whether the active oxygen was close to the cell membrane or around the nucleus. However, no studies have yet focused on the differences in the oxidative processes between the 2 markers, and it is difficult to clarify differences in the mechanisms of oxidation in clinical settings (as with this current study). Nevertheless, the present findings are interesting from the viewpoint of studies on the mechanisms of action of oxidative stress. Whatever the mechanism, valsartan treatment produced a decrease in urinary 8-OHdG concentration in patients who did not show a decrease in HbA_{1c} concentration, suggesting the possibility that valsartan might suppress not only inflammation but also oxidative stress independently of glucose metabolism.

Metabolic syndrome is defined as the concurrent presence of visceral obesity, glucose intolerance, abnormal lipid metabolism, and hypertension. The incidence rate of cardiovascular disorders is known to be high in such patients.[2,3] However, since metabolic syndrome is a concept that includes the prodromal state of a definitive disease, its treatment is controversial. An aspect that is commonly accepted as a pathophysiologic process is the release of inflammatory cytokines or angiotensinogen from adipocytes, and the insulin resistance mediated by such molecules may be a stimulatory factor for the development of cardiovascular diseases, including hypertension. Since this suggests that the secretion of inflammatory cytokines induced by oxidative stress is the mechanism by which such a pathologic process develops, it would be desirable to aggressively use RA inhibitory drugs if a patient has abnormal glucose metabolism, abnormal lipid metabolism, needs therapy for hypertension, and is considered to have metabolic syndrome. In this study, valsartan produced significant decreases in oxidative stress markers and adhesion factors in patients considered to have metabolic syndrome, suggesting the clinical usefulness of valsartan.

Because we did not have a control group of patients treated with an antihypertensive agent that does not affect the RA system, it is possible that the reduction in blood pressure alone may have resulted in the decreases in oxidative stress and inflammatory markers. However, a previous study[13] reported a blood pressure-independent effect of valsartan on an oxidative stress marker in patients with type 2 diabetes, as evaluated by measuring plasma thiobarbituric acid-reactive substances. Therefore, the reduction in oxidative stress observed in this study could possibly be explained by valsartan. In the Valsartan Antihypertensive Long-term Use Evaluation trial[27] involving high-risk hypertensive patients, valsartan reduced the incidence of diabetes by 23% compared with the reference drug amlodipine, suggesting the clinical significance of RA system inhibitors. Among the 26 patients enrolled in this study, HbA_{1c} improved in 6 patients. Valsartan has been reported to improve insulin resistance in experimental models,[8] but this has not yet been confirmed clinically. Although it remains unclear whether the present results were produced by the aforesaid mechanism of action of valsartan, our findings warrant further clinical investigation.

Limitations

This was a small, open-label, prospective study, and some of the enrolled patients were already receiving statins and/or other hypotensive drugs other than valsartan. Additionally, the observation period was only 3 months, and long-term prognosis remains unclear. The results of ongoing clinical studies[28,29] in Japan are awaiting.

CONCLUSION

Valsartan use for 3 months was associated with a significant reduction of hs-CRP, VCAM-1, and urinary 8-OHdG concentrations independent of improvement

in HbA_{1c} concentration in these hypertensive patients with hyperglycemia included in this small, open-label, prospective study.

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