

Metabolic effect of combined telmisartan and nifedipine CR therapy in patients with essential hypertension

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Background: In addition to exerting a blood pressure (BP)-lowering effect, telmisartan produces favorable metabolic effects via peroxisome proliferator-activated receptor γ activation. While a combination of telmisartan and a calcium channel blocker is often used to achieve a target BP level, the metabolic effects of this drug combination remain unclear. Therefore, this study evaluated the metabolic effects of telmisartan plus nifedipine controlled release (CR) therapy, in hypertensive patients without metabolic disease.

Methods: Sixteen patients with essential hypertension, who had not undergone antihypertensive therapy in the previous 6 months, were studied. Patients were initiated on telmisartan (40 mg/day). If their office BP was not reduced to 140/90 mmHg after 6 weeks, nifedipine CR (20–40 mg per day) was added for 18 weeks. The other patients whose BP had achieved the target of 140/90 mmHg, continued only telmisartan.

Results: Telmisartan reduced BP ($174 \pm 13/92 \pm 10$ to $143 \pm 22/78 \pm 11$ mmHg; $P < 0.01$) at 6 weeks in 16 patients, but eight patients did not achieve target BP levels and required addition of nifedipine. Telmisartan also resulted in a reduction in the homeostatic model assessment of insulin resistance (HOMA-IR) (1.30 ± 0.65 to 1.10 ± 0.42 ; $P < 0.05$) at 6 weeks, but did not affect adiponectin or leptin levels. Addition of nifedipine ($n = 8$) resulted in a reduction in BP ($158 \pm 18/80 \pm 13$ to $131 \pm 8/73 \pm 13$ mmHg; $P < 0.01$) at 18 weeks, but did not affect the HOMA-IR (1.10 ± 0.40 to 1.02 ± 0.56 ; ns). In patients who did not require addition of nifedipine ($n = 8$), BP levels remained nearly identical at 18 weeks ($127 \pm 13/73 \pm 9$ to $128 \pm 13/68 \pm 8$ mmHg; ns), and HOMA-IR also remained nearly identical.

Conclusions: Telmisartan produced a favorable metabolic effect in hypertensive patients without preexisting metabolic disorders. Addition of nifedipine CR produced further BP-lowering effects, and resulted in maintenance of metabolic indices.

Keywords: metabolic effect, essential hypertension, combination therapy, telmisartan, nifedipine CR

Introduction

While the angiotensin receptor blocker (ARB) telmisartan is widely used for its antihypertensive properties,^{1–4} it may also exert favorable metabolic effects through peroxisome proliferator-activated receptor (PPAR) γ activation.^{5,6} In fact, PPAR γ activation is higher with telmisartan than with other ARBs,⁷ and telmisartan has been shown to produce favorable metabolic effects in patients with hypercholesterolemia,^{8–10} diabetes mellitus,^{11,12} and metabolic syndrome.^{13–16} However, the metabolic effects of telmisartan have not been evaluated in hypertensive patients without these metabolic disorders.

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Long-acting calcium channel blockers (CCBs) are also widely used as antihypertensive therapy, and have the advantage of having few contraindications to their use.^{1,2,17,18} Combination of multidrug regimens has been reported to increase the efficiency of blood pressure reduction and to reduce adverse effects for patients who fail to respond to single-drug therapy.^{1,2,17,18} In these patients, a combination of ARB and CCB is a popular option. While several studies^{19,20} have described the effects of CCB on PPAR γ activation, the combined effects of CCB and ARB in the clinical setting have not been investigated. Therefore, the goal of the present study was to evaluate the metabolic effects of a combination of telmisartan and a long-acting CCB, nifedipine (nifedipine controlled release [nifedipine CR]), in patients with essential hypertension.

Methods

Patients and protocol

We enrolled 16 outpatients with essential hypertension (66 ± 9 years old, six males) whose office systolic blood pressure (SBP) was greater than 140 mmHg or whose diastolic blood pressure (DBP) was greater than 90 mmHg on more than two different occasions. Patients did not have diabetes mellitus, hypercholesterolemia, metabolic syndrome or cardiovascular disease, and were not taking any antihypertensive medicines for at least 6 months. Patients were initiated on telmisartan (40 mg per day), and if their office BP was not reduced to 140/90 mmHg after 6 weeks, then nifedipine CR (20–40 mg per day) was added for 18 weeks. Subsequent evaluations included their office BP, heart rate, body weight, blood chemistry analysis, homeostatic model assessment of insulin resistance (HOMA-IR; calculated as fasting blood glucose (mg/dL) \times fasting insulin (μ U/mL)/405), and adiponectin and leptin levels at baseline and with medical therapy. Each patient provided written informed consent to participate in this study, and all protocols were approved by the Ethics Committee of Inoue Hospital. This study complies with the Declaration of Helsinki.

BP and hematological/biochemical analysis

Blood pressure (BP) and heart rate were measured by a nurse, at the brachial artery and in the sitting position, according to the Korotkoff method. Blood samples were taken with the patient in the supine rest position, at 8:00–9:00 am before breakfast and repeated after a 20-minute period. Hematological parameters, including hemoglobin, white blood cell count and platelet count; and biochemical parameters, including

total protein, total bilirubin, aspartate aminotransferase, alanine aminotransferase, creatine kinase, uric acid, blood urea nitrogen, creatinine, sodium (Na) level, and potassium (K) levels, were measured at baseline, at 6 weeks, and at 24 weeks. Other measured parameters included low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides, and glycated hemoglobin (HbA_{1c}), as metabolic parameters; C-reactive protein (CRP) as an inflammatory parameter; serum noradrenaline, renin activity, and aldosterone, as neurohormonal parameters; and leptin, adiponectin, and HOMA-IR, as PPAR γ activation parameters.

Statistical analysis

Results are expressed as mean \pm standard deviation. Statistical significance of mean values was estimated using a paired *t* test and repeated measures analysis of variance (ANOVA), and post hoc comparison was performed using Scheffe's test. A *P* value < 0.05 was considered statistically significant.

Results

Changes in BP and heart rate

Telmisartan reduced BP at 6 weeks ($174 \pm 13/92 \pm 10$ to $143 \pm 22/78 \pm 11$ mmHg; $P < 0.01$) but had no significant effect on heart rate (Figure 1). Eight patients did not achieve the target BP of 140/90 mmHg in response to telmisartan, and required addition of nifedipine. Overall SBP in patients with additional nifedipine was higher than that without nifedipine during the following period (group difference of SBP; $P < 0.01$) (Figure 2). DBP in patients with additional nifedipine tended to be higher, but this was not statistically significant. In patients requiring addition of nifedipine, SBP decreased significantly after taking telmisartan (183 ± 10 to 158 ± 18 mmHg; $P < 0.01$), and decreased further after

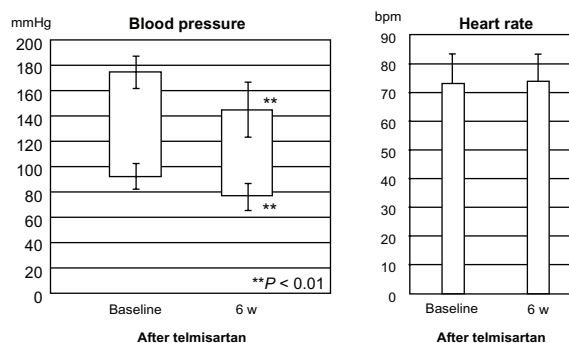


Figure 1 Blood pressure and heart rate in all patients ($n = 16$) at baseline and after taking telmisartan for 6 weeks.

Notes: In the left panel, the upper side of the rectangle shows the mean value of systolic blood pressures, and the lower side shows that of diastolic pressures. Values are mean \pm standard deviation; $**P < 0.01$.

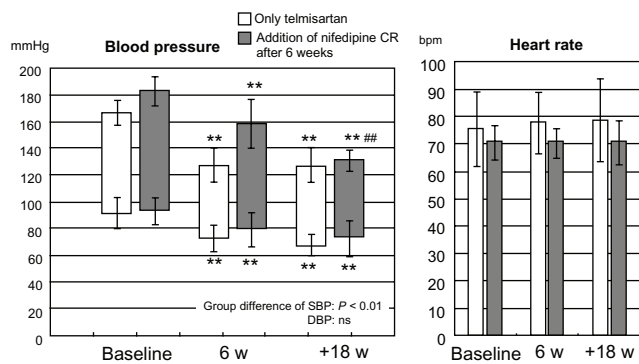


Figure 2 Blood pressure and heart rate at baseline and after taking telmisartan and nifedipine CR.

Notes: White bars represent the group that received only telmisartan ($n = 8$) and grey bars represent the group that received combined treatment of telmisartan + nifedipine CR ($n = 8$). Values are mean \pm SD; ** $P < 0.01$, compared with baseline; *** $P < 0.01$, compared with 6 weeks.

Abbreviation: CR, controlled release.

adding nifedipine (158 ± 18 to 131 ± 8 mmHg; $P < 0.01$). DBP decreased after taking telmisartan (93 ± 10 to 80 ± 13 mmHg; $P < 0.01$), but it did not decrease significantly after adding nifedipine (80 ± 13 to 73 ± 13 mmHg; ns) in these patients. In patients who did not require addition of nifedipine, SBP and DBP decreased after taking 6 weeks of telmisartan ($166 \pm 10/92 \pm 11$ to $127 \pm 13/73 \pm 9$ mmHg; $P < 0.01$), and BP levels remained nearly identical at 18 weeks ($127 \pm 13/73 \pm 9$ to $128 \pm 13/68 \pm 8$ mmHg; ns). Heart rate did not change during the study period regardless of drug regimen (Figure 2). Two patients who required addition of nifedipine CR still did not achieve target BP levels by the end of the study.

Changes in metabolic and neurohormonal parameters

Hematological and biochemical parameters did not change significantly before and after 6 weeks of telmisartan, with the exception of serum creatinine (0.75 ± 0.23 to 0.71 ± 0.21 mg/dL; $P < 0.05$). None of these parameters changed over the study period, regardless of drug regimen (data not shown).

Body weight, serum lipids, HbA_{1c}, CRP, noradrenaline and aldosterone did not change significantly after 6 weeks of telmisartan, whereas plasma renin activity increased (0.8 ± 0.7 to 1.8 ± 1.6 ng/mL/hour; $P < 0.01$) (Table 1). None of these parameters changed over the remainder of the study period, regardless of drug regimen (Tables 1 and 2). Among the PPAR γ activation parameters, however, a 6-week course of telmisartan resulted in reduction of HOMA-IR (1.30 ± 0.65 to 1.10 ± 0.42 ; $P < 0.05$), but no change in adiponectin or leptin levels (Figure 3). Over the remainder of the study,

Table 1 Metabolic and neurohormonal parameters at baseline and after taking telmisartan for 6 weeks

	Baseline	After telmisartan
BW (kg)	55.5 \pm 10.4	55.5 \pm 10.1
LDL (mg/dL)	113 \pm 27	116 \pm 31
HDL (mg/dL)	59 \pm 10	57 \pm 10
T-C (mg/dL)	198 \pm 33	192 \pm 30
TG (mg/dL)	106 \pm 42	98 \pm 34
FBG (mg/dL)	100 \pm 10	97 \pm 8
Insulin (μ U/mL)	5.3 \pm 2.4	4.6 \pm 1.7
HbA _{1c} (%)	5.2 \pm 0.2	5.3 \pm 0.2
Na (mEq/L)	141 \pm 2	142 \pm 2
K (mEq/L)	4.2 \pm 0.6	4.3 \pm 0.2
CRP (mg/dL)	0.09 \pm 0.06	0.16 \pm 0.25
NA (pg/mL)	618 \pm 274	564 \pm 267
PRA (ng/mL/hr)	0.8 \pm 0.7	1.8 \pm 1.6**
ALD (pg/mL)	70.2 \pm 29.3	59.1 \pm 24.6

Notes: Values are mean \pm SD; ** $P < 0.01$.

Abbreviations: BW, body weight; LDL, low-density lipoprotein; HDL, high-density lipoprotein; T-C, total cholesterol; TG, triglyceride; FBG, fasting blood glucose; CRP, C-reactive protein; NA, noradrenaline; PRA, plasma renin activity; ALD, aldosterone; HbA_{1c}, glycated hemoglobin.

HOMA-IR tended to decrease in both groups of patients taking telmisartan for 6 weeks, and decreased significantly after taking telmisartan for 24 weeks from baseline in patients taking telmisartan without additional nifedipine (1.33 ± 0.73 to 1.02 ± 0.44 ; $P < 0.05$). HOMA-IR tended to decrease in patients with additional nifedipine, but these differences did not reach the level of statistical significance. Therefore, addition of nifedipine did not affect the HOMA-IR (1.10 ± 0.40 to 1.02 ± 0.56 ; ns) (Figure 4).

Discussion

In this study, telmisartan exerted a favorable metabolic effect in patients with essential hypertension without metabolic disorders. Moreover, addition of nifedipine CR resulted in further BP-lowering effects and maintenance of metabolic indices.

BP lowering

Although ARBs are recommended as one of the first-line therapies within several recent guidelines for the diagnosis and management of hypertension,¹⁻⁴ target BPs are achieved in only 39%–73% of patients.²¹ Therefore, additional antihypertensive are usually needed. In the present study, 50% of patients did not achieve the target BP of 140/90 mmHg in response to 40 mg of telmisartan per day; these patients were given nifedipine CR as additional therapy. The use of these drugs in combination resulted in achievement of target BP levels in 87% of patients. The BP before medication in the

Table 2 Changes in metabolic and neurohormonal indices after taking telmisartan and nifedipine CR

	Baseline		6 weeks		+18 weeks	
	T	T + N	T	T + N	T	T + N
BW (kg)	56.5 ± 8.5	54.5 ± 12.6	56.1 ± 8.8	55.0 ± 11.9	54.8 ± 8.7	54.2 ± 12.3
LDL (mg/dL)	117 ± 25	109 ± 30	114 ± 28	117 ± 36	102 ± 39	114 ± 32
HDL (mg/dL)	62 ± 14	55 ± 5	57 ± 12	57 ± 7	56 ± 9	57 ± 13
T-C (mg/dL)	196 ± 27	199 ± 40	190 ± 30	194 ± 32	183 ± 34	191 ± 30
TG (mg/dL)	88 ± 41	124 ± 38	97 ± 31	99 ± 39	125 ± 91	104 ± 50
FBG (mg/dL)	100 ± 11	99 ± 9	96 ± 7	98 ± 10	96 ± 10	96 ± 14
Insulin (μU/mL)	5.3 ± 2.3	5.3 ± 2.5	4.5 ± 1.7	4.6 ± 1.8	4.3 ± 0.9	4.4 ± 2.4
HbA _{1c} (%)	5.3 ± 0.1	5.2 ± 0.3	5.3 ± 0.1	5.2 ± 0.3	5.2 ± 0.2	5.3 ± 0.4
CRP (mg/dL)	0.08 ± 0.04	0.10 ± 0.08	0.14 ± 0.15	0.19 ± 0.33	0.09 ± 0.05	0.15 ± 0.16
Na (mEq/L)	142 ± 2	141 ± 2	141 ± 1	142 ± 2	142 ± 2	141 ± 2
K (mEq/L)	4.1 ± 0.2	4.3 ± 0.4	4.2 ± 0.2	4.3 ± 0.2	4.3 ± 0.5	4.3 ± 0.4
NA (pg/mL)	726 ± 297	510 ± 215	593 ± 265	536 ± 285	561 ± 220	523 ± 120
PRA (ng/mL/hr)	0.8 ± 0.8	0.8 ± 0.7	1.7 ± 0.9*	1.9 ± 2.1*	1.5 ± 0.7*	1.4 ± 1.2*
ALD (pg/mL)	59.1 ± 24.0	81.2 ± 31.3	50.1 ± 16.9	68.0 ± 28.7	56.1 ± 15.0	76.4 ± 50.9

Notes: Values are mean ± SD; **P* < 0.05, compared with baseline.

Abbreviations: T, telmisartan; T + N, telmisartan + nifedipine; CR, controlled release; BW, body weight; LDL, low-density lipoprotein; HDL, high-density lipoprotein; T-C, total cholesterol; TG, triglyceride; FBG, fasting blood glucose; CRP, C-reactive protein; NA, noradrenaline; PRA, plasma renin activity; ALD, aldosterone; HbA_{1c}, glycated hemoglobin.

patients with additional nifedipine was higher than those without. Although there has not been previous reports of an effect on BP with the combination of telmisartan and nifedipine CR, Hasebe et al²² reported that a combination of nifedipine CR and candesartan resulted in achievement of target SBP in 28.5% patients, and achievement of target DBP in 40.8% of patients, after 12 weeks of therapy. The overall achievement rate of target BP was higher in our study than in the study by Hasebe and Kikuchi. This may be due to the differences in various factors, including duration of the treatment period and differences in patient backgrounds.

Glucose and lipid metabolism

Among ARBs, only telmisartan is a partial agonist of PPAR γ , which is the likely mechanism by which it favorably regulates lipid and glucose metabolism.^{23,24} In clinical studies,^{8–12,14,15}

telmisartan was reported to improve insulin sensitivity and lipid profile, but the effects were not strong, nor universal. In studies by Derosa et al,^{8,9} telmisartan administration resulted in improvements in the abnormal lipid profile but did not affect glucose abnormalities. By contrast, other studies^{10–12} demonstrated that telmisartan did result in an improvement in glucose metabolic abnormalities. These differences may be due to the dose of telmisartan used, or due to differences in patient backgrounds among the various studies. Patients in most previous studies had metabolic disorders, including diabetes mellitus, hypercholesterolemia, or metabolic syndrome.^{8–12,14,15} Moreover, patients in some of these studies had already taken other antihypertensive medicines when they participated in the protocol. Although activation of

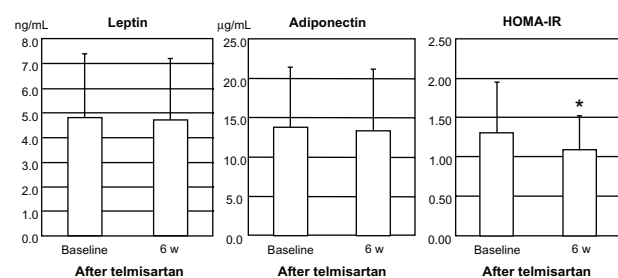


Figure 3 Metabolic parameters in all patients (*n* = 16) at baseline and after taking telmisartan for 6 weeks.

Notes: Values are mean ± SD; **P* < 0.05.

Abbreviation: HOMA-IR, homeostatic model assessment of insulin resistance, SD, standard deviation.

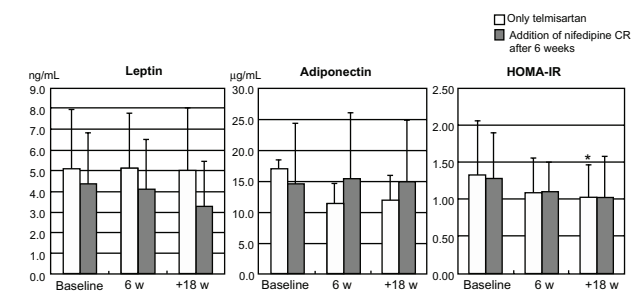


Figure 4 Metabolic parameters at baseline and after taking telmisartan and nifedipine CR.

Notes: White bars represent the group that received only telmisartan (*n* = 8) and grey bars represent the group that received combined treatment of telmisartan + nifedipine CR (*n* = 8). Values are mean ± SD; **P* < 0.05, compared with baseline.

Abbreviations: CR, controlled release; HOMA-IR, homeostatic model assessment of insulin resistance.

PPAR γ is stronger in response to telmisartan when compared with other ARBs, a cell-based transient transfection assay showed that the activation of the receptor in response to telmisartan was 25%–30% of the maximum level achieved by conventional full agonists, such as pioglitazone and rosiglitazone.⁷ Therefore, to evaluate the effects of telmisartan on metabolic profile in a clinical setting, patients must be free of diabetes mellitus and/or lipid disorders, and should not be taking other medications. Indeed, patients in our study had not taken any other antihypertensive medicine over the preceding 6 months. Therefore, the effects of telmisartan on glucose and lipid profile were more purely evaluated in this study. A 6-week course of telmisartan resulted in a significant reduction in HOMA-IR (1.30 ± 0.65 to 1.10 ± 0.42 ; $P < 0.05$) but this decrement was still smaller than that seen in previous studies of telmisartan. Regardless, this is the first report to demonstrate the effects of telmisartan on hypertensive patients without diabetes mellitus or dyslipidemia.

Although the insulin resistance index, HOMA-IR, was reduced in the response to telmisartan, there were no significant changes in leptin or adiponectin levels. Moreover, the lipid profile of patients did not change following a 24-week period of telmisartan administration. Leptin and adiponectin are associated with body weight and are influenced by food intake. Patients in most previous studies had diabetes mellitus, dyslipidemia, or metabolic syndrome.^{10–12,15} Therefore, most of the patients in those studies were initiated on caloric intake control programs and on exercise programs. By contrast, patients in our study were only supervised for salt intake. Differences in results between this study and prior studies may also be related to the dose of telmisartan utilized, or to differences in patient backgrounds.

Nifedipine CR and metabolic effect

CCBs are an antihypertensive and myocardial anti-ischemic agents that do not influence metabolism of glucose, lipid, or electrolytes.^{1,2,17,18} However, nifedipine CR has been reported to be associated with improved insulin sensitivity in patients with essential hypertension.^{19,20} This may be mediated via PPAR γ activation, as Ishii et al²⁵ showed that nifedipine activated PPAR γ by decreasing phosphorylation of PPAR γ , thereby suppressing monocyte chemoattractant protein-1 expression, and inducing adenosine triphosphate-binding cassette transporter A1 expression in macrophages. Hashimoto et al²⁶ also demonstrated that nifedipine significantly inhibited intramyocardial arterial remodeling and perivascular fibrosis, and reduced oxidative stress in stroke-prone, spontaneously hypertensive rat hearts. Nifedipine also restored adiponectin and the

smooth muscle cell phenotype in stroke-prone, spontaneously hypertensive rats, and selectively restored PPAR γ and Cu/Zn superoxide dismutase expression activities to the levels in a normal rat heart.²⁶ Furthermore, nifedipine induced a dose-dependent increase in PPAR γ expression in cultured vascular smooth muscle cells.²⁶ In our study, nifedipine CR maintained improved insulin sensitivity that was induced by telmisartan, but did not have a further favorable effect on the metabolic indices. Hinoi et al²⁷ reported that telmisartan improved coronary flow velocity reserve and HOMA-IR among essential hypertensive patients, but nifedipine did not change them. Thus, it is unclear whether nifedipine had any effect on insulin sensitivity beyond that of telmisartan in the clinical setting.

Study limitations

Although nifedipine CR maintained the favorable metabolic effect induced by telmisartan for 18 weeks, the sample size in the present study was small, and the patients were free of metabolic disorders. Moreover, the doses of telmisartan and nifedipine CR were rather low. Patients with atherosclerotic disease or metabolic disorders need high doses of telmisartan and nifedipine CR, which may have different effects on metabolic parameters. Further studies are needed with a larger number of normal individuals, and with a cohort of hypertensive patients with metabolic disorders.

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Disclosure

The authors report no conflicts of interest in this work.

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