

Effects of telmisartan on fat distribution in individuals with the metabolic syndrome

Michio Shimabukuro, Hideaki Tanaka and Takeshi Shimabukuro

Background Visceral fat obesity plays an essential role in the clustering of atherosclerotic multiple risk factors in the metabolic syndrome. Telmisartan, an angiotensin II type 1 receptor blocker, has partial agonistic properties for peroxisome proliferator-activated receptor gamma, which is a key regulator of adipocyte differentiation and function.

Methods This study aimed to clarify the impact of telmisartan on fat distribution and insulin sensitivity in the metabolic syndrome. In this open-label, prospective, randomized study, patients with the metabolic syndrome (waist circumference: men ≥ 85 cm, women ≥ 90 cm) were treated either with amlodipine ($n = 26$) or with telmisartan ($n = 27$) for 24 weeks, and fat distribution and insulin sensitivity were determined.

Results Systolic and diastolic blood pressure were decreased in both groups to a comparable level. However, insulin and glucose levels during an oral 75 g glucose loading were decreased only in the telmisartan group. The visceral fat area, determined by abdominal computed tomography scan, was reduced in the telmisartan group

after 24 weeks' treatment, but the subcutaneous fat area did not change in either group.

Conclusion The results imply that telmisartan could treat both the hemodynamic and metabolic aberrations seen in patients with the metabolic syndrome, improving insulin resistance and glucose intolerance at least partly through visceral fat remodeling. *J Hypertens* 25:841–848 © 2007 Lippincott Williams & Wilkins.

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Keywords: amlodipine, metabolic syndrome, telmisartan

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Introduction

The metabolic syndrome is a cluster of common cardiovascular risk factors including hypertension, glucose intolerance, dyslipidemia and visceral fat obesity [1–3]. The notion has been proposed that visceral fat obesity is the central element in this syndrome and could be causally involved in the clustering of the other components [4,5].

Large clinical trials have shown that angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor blockers (ARB) reduce glucose intolerance in high-risk patients, compared with other classes of antihypertensive agents [6,7]. Although inhibition of the renin–angiotensin system (RAS) may improve metabolic derangement by reducing insulin resistance, actions beyond angiotensin-receptor blockade might be involved [8,9]. Recent in-vitro studies showed that telmisartan, unlike other ARB, activates peroxisome proliferator-activated receptor gamma (PPAR γ) and increases the expression of PPAR γ target genes in preadipocytes [10–12]. If telmisartan could act clinically as a PPAR γ agonist, its metabolic impact [13–15] should be by changing abdominal fat distribution and

insulin sensitivity [16]. However, there is no clinical evidence to show this link.

In this open-label, prospective, randomized study, patients with elevated blood pressure and the metabolic syndrome, who have metabolic derangements possibly caused by visceral fat obesity, were treated either with telmisartan or with amlodipine, a calcium antagonist, for 24 weeks, and fat distribution and insulin sensitivity were determined.

Materials and methods

Participants

Participants visited our hospital by self-referral or by recommendation for further check-up at a local screening centre. The individuals studied included men and women aged between 26 and 67 years, with elevated blood pressure and the metabolic syndrome without a history of cardiovascular complications. All individuals were newly diagnosed to have elevated blood pressure (office systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg). Metabolic syndrome was defined according to the 2005 International Diabetes Federation guideline [2]. In the International Diabetes Federation criteria, to be

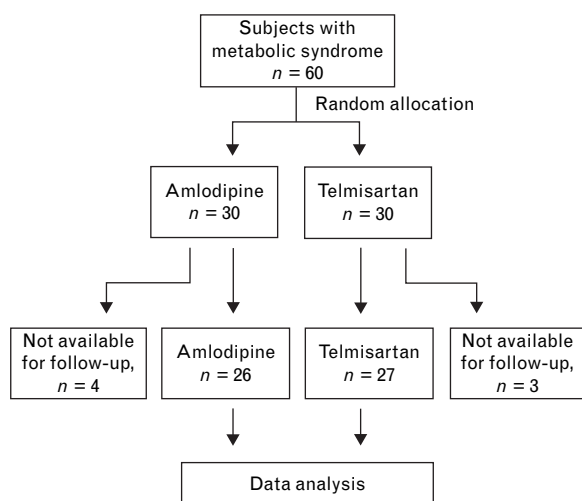
defined with the metabolic syndrome individuals have abdominal obesity (in Japanese defined as a waist circumference ≥ 85 cm in men and ≥ 90 cm in women), plus any two of the following four factors: (i) hypertriglyceridemia (serum triglyceride concentration ≥ 150 mg/dl; 1.69 mmol/l); (ii) low high-density lipoprotein (HDL) cholesterol [serum HDL cholesterol concentration < 40 mg/dl (1.04 mmol/l) in men and < 50 mg/dl (1.29 mmol/l) in women]; (iii) elevated blood pressure: systolic blood pressure of 130 mmHg or greater or diastolic blood pressure of 85 mmHg or greater, or both; (iv) high fasting glucose: serum glucose concentration of 100 mg/dl (5.6 mmol/l) or greater.

Sixty drug-naïve patients were randomly allocated to either the amlodipine ($n=30$) or telmisartan ($n=30$) groups and were treated once a day by amlodipine 2.5–5 mg or telmisartan 20–40 mg for 24 weeks (Fig. 1). Before and 24 weeks after treatment, participants underwent an oral glucose tolerance test with 75 g glucose. Blood samples were taken at 0, 30, 60, and 120 min after the glucose load. Investigators for abdominal fat, pulse wave velocity (PWV), and biochemical parameter measurements were blinded to the group of treatment. All patients were encouraged to continue a standard diet and physical activity during the course of the study. The study protocol was approved by the local ethical committee and carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000, and all participants gave informed consent.

Anthropometry and abdominal fat distribution

After overnight fasting, anthropometric measurements were taken in a standing position. Body mass index was calculated as the ratio of weight (kg) to height² (m²).

Fig. 1



Enrollment flow chart. See details in text.

Waist circumference was measured at the umbilical level in the late exhalation phase [17]. Blood pressure was measured using an automatic blood pressure monitor (BP-203RV2; Colin Corp., Nagoya, Japan) in a sitting position. The subcutaneous fat area (SFA) and intra-abdominal visceral fat area (VFA) were measured at the level of the umbilicus using a standardized method with a computed tomography scan [18].

Pulse wave velocity

After at least 10 min rest in a supine position, the arm–ankle PWV was measured using a volume-plethysmographic apparatus as described (Form/ABI; Colin Corp.) [19]. The cuff, which was placed around the arms and ankles, was connected to a plethysmographic sensor to determine volume pulse form and to an oscillometric sensor to measure blood pressure. The brachial and post-tibial arterial pressure waveforms were stored for 10 s using a 5 Hz pass filter. The arm–ankle PWV was calculated as $(La - Lb)/\Delta T_{ba}$ (cm/s), where La is the path length from the suprasternal notch to the ankle ($0.8129 \times \text{height of the individual (in cm)} + 12.328$); Lb is the path length from the suprasternal notch to the arms ($0.2195 \times \text{height of the individual (in cm)} - 2.0734$); and ΔT_{ba} is the time interval between the wave front of the arm waveform and that of the ankle waveform.

Biochemical measurements

Venous blood was withdrawn after an overnight fast. Plasma concentrations of adiponectin were measured using a sandwich enzyme-linked immunosorbent assay system (adiponectin ELISA kit; Otsuka Pharmaceutical Co., Tokushima, Japan) [20]. Plasma glucose concentrations were determined by the glucose oxidase method. The value of haemoglobin A1c was determined by high-performance liquid chromatography. Serum total cholesterol and triglyceride concentrations were determined by routine enzymatic methods. HDL-cholesterol was also measured by the enzymatic method after heparin and calcium precipitation. The serum concentration of C-reactive protein (CRP) was measured using a highly sensitive CRP assay (Denka Seiken Co. Ltd., Tokyo, Japan).

Statistical analysis

Values are expressed as the mean \pm standard deviation (SD). A two-tailed unpaired Student's *t*-test or one-way factorial analysis of variance (ANOVA), followed by Bonferroni's post-hoc comparison, was used to compare intergroup or intragroup means. A Kruskal–Wallis test (non-parametric ANOVA), Wilcoxon matched-pairs signed-rank test or χ^2 test was used for non-parametric data. Comparisons of time course curves during glucose loading were analysed by two-factor repeated measures ANOVA. Relationships between variables were estimated using the simple regression analysis. A *P* value of less than 0.05 was considered statistically significant.

Analyses were processed using the StatView J-5.0 software package (SAS Institute Inc., Cary, North Carolina, USA) or InStat 3 for Macintosh version 3.0b (GraphPad Software, Inc., San Diego, California, USA).

Results

General characteristics

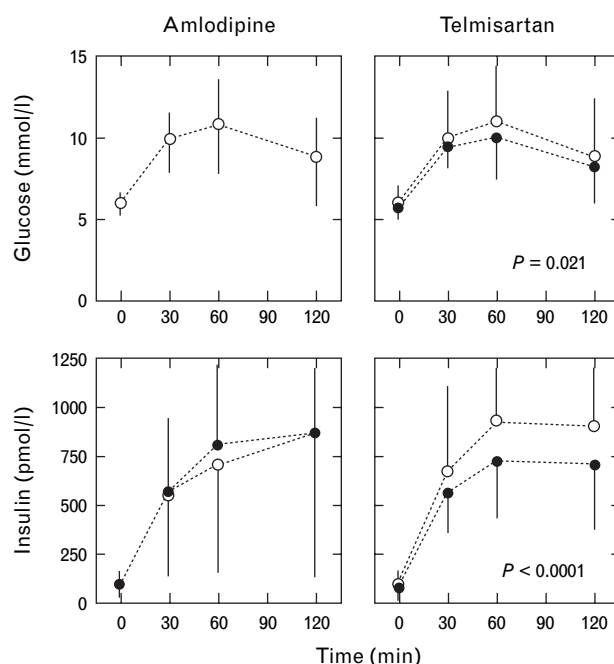
A total of 60 patients were enrolled, with 30 randomly assigned to the amlodipine and 30 to the telmisartan group; 26 of the amlodipine and 27 of the telmisartan groups were available for analysis (Fig. 1). Baseline characteristics did not differ between the two groups: the amlodipine group included 16 men and 10 women with mean age of 52 ± 9 years, and the telmisartan group included 15 men and 12 women with mean age of 49 ± 11 years. All patients ranged from high normal to grade 1–3 hypertension (2003 ESH/ESC guidelines): systolic and diastolic blood pressures ranged from 190 to 127 mmHg and from 110 to 67 mmHg in the amlodipine-treated group, and from 184 to 129 mmHg and from 107 to 44 mmHg in the telmisartan-treated group. The mean doses of amlodipine and telmisartan were 3.3 ± 1.3 mg (range 2.5–5) and 24 ± 8 mg (range 20–40), respectively. Both telmisartan or amlodipine were well tolerated, with no major adverse events reported.

Effects of telmisartan on metabolic parameters

Changes in blood biochemical parameters are shown in Table 1. Baseline levels of plasma glucose, insulin, haemoglobin A_{1c} and lipids were comparable between the amlodipine and telmisartan groups. Plasma glucose and haemoglobin A_{1c} did not change in either group during 24 weeks. However, plasma insulin levels and calculated homeostasis model assessment–insulin resistance (HOMA–IR) were decreased only in the telmisartan group, but not in the amlodipine group.

According to the oral glucose tolerance test, 17 out of 26 patients had glucose intolerance [12 impaired glucose tolerance (IGT) and five diabetes mellitus] in the amlo-

Fig. 2



Glucose and insulin responses during 75 g oral glucose loading before (○) and after 24 weeks (●) of treatment either with amlodipine ($n = 26$) or telmisartan ($n = 27$) in subjects with the metabolic syndrome. Note that glucose curves before and after amlodipine treatment were exactly similar and overlapped. Data represent the mean \pm SD. P values for curve difference by two-factor repeated measures analysis of variance were shown.

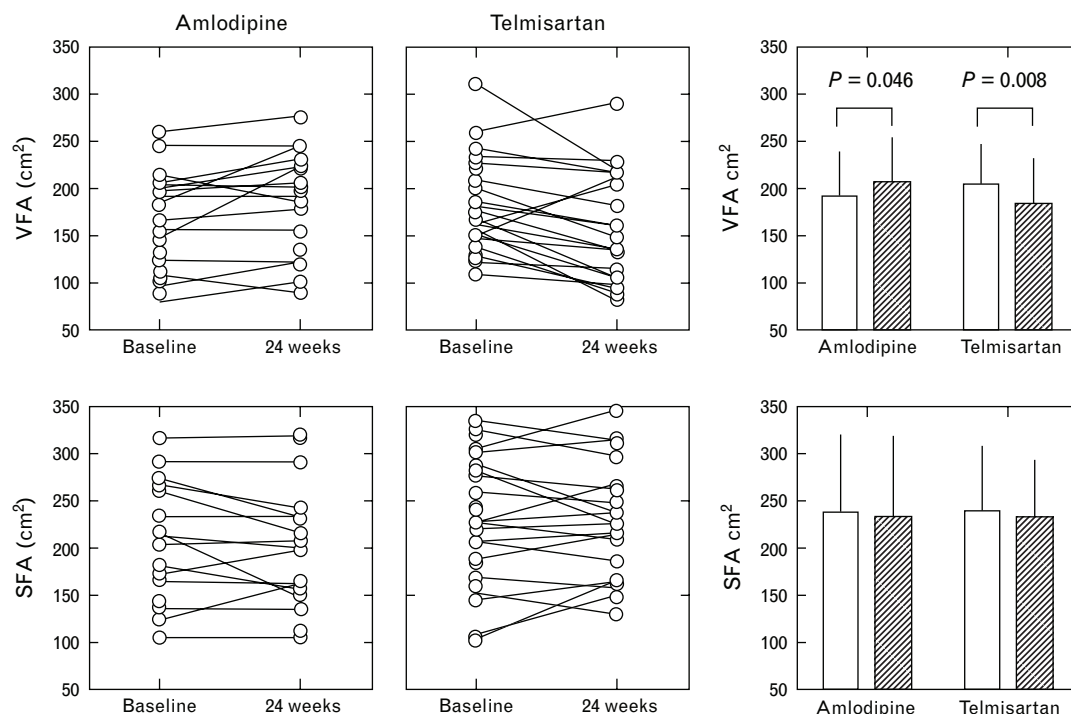
dipine group, and 17 out of 26 patients (12 IGT and five diabetes mellitus) in the telmisartan group. After 24 weeks' treatment, the number with glucose intolerance changed to 17 (12 IGT, five diabetes mellitus, $\chi^2 = 0.500$ versus baseline) in the amlodipine group, and 12 (seven IGT, five diabetes mellitus, $\chi^2 = 0.086$) in the telmisartan group. The glucose increase during oral glucose loading was decreased in the telmisartan group in spite of decreased insulin secretion (Fig. 2). The glucose

Table 1 Changes in blood biochemical parameters

	Amlodipine ($n = 26$)			Telmisartan ($n = 27$)		
	Baseline	12 Weeks	24 Weeks	Baseline	12 Weeks	24 Weeks
Glucose (mmol/l)	5.69 ± 1.34	5.36 ± 1.95	6.00 ± 0.70	5.87 ± 1.02	6.04 ± 1.51	6.00 ± 1.15
Insulin (pmol/l)	109 ± 53	120 ± 60	102 ± 56	111 ± 53	$77 \pm 41^*$	$71 \pm 35^*$
HOMA–IR	4.01 ± 1.91	4.49 ± 2.20	4.09 ± 2.43	4.18 ± 2.08	$3.08 \pm 1.85^*$	$2.74 \pm 1.41^*$
$\Delta AUC_{\text{glucose}}$ (min/mmol per litre)	422 ± 177		418 ± 197	428 ± 283		$374 \pm 152^\dagger$
$\Delta AUC_{\text{insulin}}$ ($\times 10^4$ /min per pmol/l)	6.47 ± 4.87		6.94 ± 4.69	7.83 ± 4.46		$6.27 \pm 2.25^{\dagger\dagger}$
$\Delta AUC_{\text{glucose}}/\Delta AUC_{\text{insulin}}$	0.78 ± 0.45		0.72 ± 0.61	0.67 ± 0.45		0.57 ± 0.19
Haemoglobin A _{1c} (%)	5.06 ± 0.36	5.13 ± 0.43	5.17 ± 0.37	5.25 ± 0.83	5.32 ± 0.55	5.28 ± 0.44
Total cholesterol (mmol/l)	5.60 ± 0.78	5.52 ± 0.77	5.18 ± 1.65	5.37 ± 0.75	5.52 ± 0.73	5.42 ± 0.68
Triglyceride (mmol/l)	2.02 ± 1.48	1.94 ± 1.17	2.07 ± 1.80	1.82 ± 0.89	1.62 ± 0.63	1.63 ± 0.98
HDL-cholesterol (mmol/l)	1.32 ± 0.45	1.43 ± 0.42	1.41 ± 0.44	1.22 ± 0.28	1.25 ± 0.23	1.25 ± 0.24
Highly sensitive CRP (mg/dl)	0.27 ± 0.14	0.25 ± 0.11	0.29 ± 0.19	0.28 ± 0.24	$0.17 \pm 0.15^\dagger$	$0.16 \pm 0.14^\dagger$
Adiponectin ($\mu\text{g/ml}$)	5.02 ± 1.78	5.00 ± 2.44		4.07 ± 1.89	$6.45 \pm 2.99^{\dagger\dagger}$	

ANOVA, Analysis of variance; AUC, area under the curve; CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA–IR, homeostasis model assessment–insulin resistance. Mean \pm SD. * $P < 0.05$ versus baseline by one-way ANOVA. $^\dagger P < 0.05$, $^{\dagger\dagger} P < 0.01$ versus baseline by Kruskal–Wallis test (non-parametric ANOVA) or by Wilcoxon matched-pairs signed-rank test.

Fig. 3



Visceral fat area (VFA) and subcutaneous fat area (SFA), determined by abdominal computed tomography scan, before and after 24 weeks of treatment either with amlodipine ($n = 26$) or telmisartan ($n = 27$). Data in the right panel represent the mean \pm SD. P values by two-tailed paired t -test were shown. \square Baseline; ▨ 24 weeks.

area under the curve (AUC) and insulin AUC were not changed in the amlodipine group, but both were significantly decreased in the telmisartan group (Table 1).

The highly sensitive CRP level did not change in the amlodipine group after 12 and 24 weeks, but was decreased in the telmisartan group (Table 1). The adiponectin level did not change in the amlodipine group after 12 weeks' treatment, but was increased in the telmisartan group (Table 1).

Effects of telmisartan on fat distribution

The VFA, determined by abdominal computed tomography scan, was not decreased in the amlodipine group but was decreased in the telmisartan group after 24 weeks'

treatment compared with baseline values (Fig. 3). SFA did not change in either group after 24 weeks.

Effects of telmisartan on blood pressure and aortic stiffness

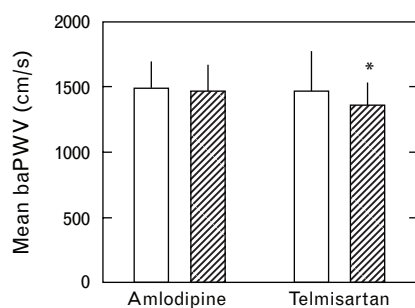
Changes in anthropometry and blood pressure during 24 weeks of treatment are shown in Table 2. Body weight, body mass index and waist circumference did not change during 24 weeks in the amlodipine-treated group, and these values tended to be decreased in the telmisartan-treated group. Systolic and diastolic blood pressures did not change during 12 weeks but decreased at 24 weeks in the amlodipine group. In contrast, systolic and diastolic blood pressures were decreased within 4 weeks

Table 2 Changes in anthropometric parameters and blood pressure

	Amlodipine ($n = 26$)				Telmisartan ($n = 27$)			
	Baseline	4 Weeks	12 Weeks	24 Weeks	Baseline	4 Weeks	12 Weeks	24 Weeks
Body weight (kg)	73 \pm 13	73 \pm 13	74 \pm 14	75 \pm 13	76 \pm 16	73 \pm 12	74 \pm 14	72 \pm 12
Body mass index (kg/m ²)	28.3 \pm 3.4	28.2 \pm 3.5	28.6 \pm 3.7	28.8 \pm 3.6	29.2 \pm 4.0	28.4 \pm 3.5	28.8 \pm 4.0	28.1 \pm 3.8
Waist circumference (cm)	94 \pm 10	95 \pm 11	95 \pm 12	97 \pm 10	98 \pm 11	93 \pm 8	92 \pm 8	93 \pm 9
SBP (mmHg)	146 \pm 15	145 \pm 10	143 \pm 13	134 \pm 23*	146 \pm 14	134 \pm 13*	136 \pm 11*	132 \pm 11*
DBP (mmHg)	91 \pm 12	90 \pm 9	88 \pm 10	86 \pm 8*	86 \pm 12	83 \pm 11*	84 \pm 8*	79 \pm 9*
Heart rate (beats/min)	74 \pm 11	74 \pm 11	73 \pm 13	77 \pm 13	77 \pm 10	76 \pm 9	75 \pm 10	73 \pm 12

DBP, Diastolic blood pressure; SBP, systolic blood pressure. Mean \pm SD. * $P < 0.05$ versus baseline by parametric one-way analysis of variance.

Fig. 4



Pulse wave velocity (PWV) before and after 24 weeks of treatment either with amlodipine ($n=26$) or telmisartan ($n=27$) in subjects with the metabolic syndrome. Data represent the mean \pm SD. * $P=0.007$ versus baseline by two-tailed paired t -test. \square Baseline; ▨ 24 weeks.

and remained decreased up to 24 weeks in the telmisartan group.

At baseline, the mean values of bilateral arm–ankle PWV were comparable between the amlodipine and telmisartan groups (Fig. 4). After 24 weeks' treatment, the mean arm–ankle PWV did not change in the amlodipine group (baseline 1484 ± 203 versus 24 weeks 1454 ± 212 cm/s), but significantly decreased in the telmisartan group (1470 ± 305 versus 1354 ± 179 cm/s, $P=0.007$).

Discussion

The major findings of this study are: first, telmisartan improved indices of glucose intolerance and insulin sensitivity but amlodipine did not; second, telmisartan, but not amlodipine, selectively reduced VFA rather than SFA; third, telmisartan rapidly decreased systolic and diastolic blood pressures and reduced aortic stiffness, determined by the arm–ankle PWV.

Effects of telmisartan on metabolic parameters

The individuals studied, who were recruited for elevated high blood pressure and the metabolic syndrome, had mild fasting hyperglycemia and hyperinsulinemia, without a significant rise in haemoglobin A1c. HOMA–IR, an index of insulin resistance, was significantly higher (4.0 ± 1.9 in the amlodipine group and 4.2 ± 2.1 in the telmisartan group) than the reference value obtained in our community-based study: the mean HOMA–IR was 1.6 for men ($n=3839$) and 1.6 for women ($n=3146$) in participants without the metabolic syndrome [21]. Enhanced and delayed secretion of insulin during glucose loading also indicated the presence of severe insulin resistance in these individuals [22]. Telmisartan decreased fasting plasma insulin and HOMA–IR at 12 and 24 weeks, although plasma glucose and haemoglobin A1c did not change. The glucose level and AUC during oral glucose loading were modestly decreased, but the insulin level and AUC were profoundly decreased in

the telmisartan group (Fig. 2 and Table 1). These observations suggest that telmisartan treatment improved co-existing insulin resistance in individuals with the metabolic syndrome, and then corrected glucose intolerance. After 24 weeks' treatment, the number with glucose intolerance tended to be decreased in the telmisartan group (baseline 63% versus 24 weeks 44%, $\chi^2=0.086$), but not in the amlodipine group (65 versus 65%).

Several earlier studies supported our result that telmisartan had favourable metabolic effects [13–15]. Pershadsingh and Kurtz [13] first reported that telmisartan 80 mg/day, but not valsartan 160 mg/day, had an insulin-sensitizing effect in a hypertensive patient with visceral fat obesity. In a randomized, parallel-group study [15], patients with hypertension and insulin resistance (HOMA–IR > 3.5), impaired glucose tolerance, or type 2 diabetes, telmisartan 80 mg/day, but not losartan 50 mg/day, decreased fasting plasma glucose (by 8%), insulin (by 10%), HOMA–IR (by 26%), and haemoglobin A1c (by 9%). In our study, telmisartan showed favourable metabolic effects compared with a calcium antagonist, amlodipine. The mechanism may include inhibition of the RAS or actions beyond angiotensin receptor blockade, as discussed later.

Effects of telmisartan on fat distribution and adipocytokines

Numerous studies have demonstrated that visceral fat is strongly associated with insulin resistance [4,5]. A class of oral antidiabetic agents, thiazolidinediones, could improve insulin resistance and glycemic control by a shift of fat distribution from visceral to subcutaneous adipose depots [16]. The fat remodeling is generally explained by PPAR γ agonist-induced remodeling of abdominal fat tissue, characterized by the differentiation of preadipocytes into small fat cells in subcutaneous fat depots and apoptosis of differentiated large adipocytes in visceral fat depots [23]. Clinical studies have already demonstrated that telmisartan has beneficial metabolic effects, but the underlying mechanism has not yet been clarified. This was the first clinical trial to ask whether telmisartan could cause abdominal fat remodeling, a possible marker of PPAR γ activation.

The VFA was reduced by 24 weeks' treatment with telmisartan, but SFA was not. In contrast, VFA was not decreased after 24 weeks' treatment with amlodipine. These observations may have clinical relevance to the PPAR γ -modulating actions of telmisartan. Benson and colleagues [10] reported that telmisartan can function as a partial agonist of PPAR γ at concentrations of 5 μ mol/l or less, which is clinically achievable after an oral therapeutic dose.

Telmisartan increased plasma levels of adiponectin and decreased plasma levels of highly sensitive CRP, which is consistent with a previous study [14]. The increase in

adiponectin and the decrease in highly sensitive CRP were associated with the decrease in VFA (data not shown). Such beneficial adipocytokine profiles can be achieved by abdominal fat remodeling typically in pioglitazone-treated patients [16]. A series of PPAR γ agonists increased the expression of adiponectin messenger RNA and adiponectin secretion by activation of the adiponectin promoter [24]. Increased adiponectin effects might be related to abdominal fat remodeling in the telmisartan group. Alternatively, Sugimoto *et al.* [25] reported that telmisartan reduced visceral fat accumulation by increasing caloric energy expenditure in rats fed a high-fat and high carbohydrate diet. The authors also indicated that the telmisartan-induced expression of nuclear and mitochondrial-encoded genes in skeletal muscle could augment energy expenditure. Laplante *et al.* [26] recently indicated that PPAR γ agonism redistributes fat by stimulating the lipid uptake and esterification potential in subcutaneous fat; conversely, energy expenditure is greatly increased in visceral fat with a consequent reduction in fat accumulation. It might be speculated that telmisartan increases energy expenditure in visceral fat preferably to subcutaneous fat with the PPAR γ -modulating activity. Potential mechanisms for abdominal fat remodeling by telmisartan need to be verified in future clinical studies.

As discussed above, beneficial adipocytokine profiles and abdominal fat remodeling can be causally related to insulin sensitivity in the telmisartan group [5,27]. However, it should be taken into account that telmisartan-induced haemodynamic changes may be related to insulin sensitivity. Reportedly, the microvascular recruitment of insulin to enhance skeletal muscle capillary flow correlates closely with normal glucose uptake, and the microvascular recruitment of insulin is impaired in obese insulin-resistant patients [28].

Effects of telmisartan on blood pressure and aortic stiffness

Systolic and diastolic blood pressures did not change during 12 weeks of treatment but decreased at 24 weeks in the amlodipine group. In contrast, systolic and diastolic blood pressures were significantly decreased within 4 weeks in the telmisartan group and remained decreased up to 24 weeks. In a randomized, double-blind, 12-week trial, telmisartan (40, 80, and 120 mg/day) provided a greater decrease in mean hourly systolic and diastolic blood pressures throughout the 24-h dosing interval than amlodipine (5 and 10 mg/day) [29]. The other trials showed that telmisartan 40 or 80 mg was more effective than losartan 50 mg, especially during the last 4–6 h of the dosing interval [15].

A greater reduction in 24-h blood pressure by telmisartan may be partly attributed to its longer duration of action [15,29–31]. In addition, adipocytokine regulation through

PPAR γ activation might be involved. There are experimental and clinical studies to show that the plasma adiponectin level was closely related to obesity-related hypertension [32–34]. Ohashi *et al.* [32] showed that hypoadiponectinemia and high blood pressure seen in obese KKAY mice were decreased by adenovirus-delivered adiponectin replenishment. Reduced mRNA levels of endothelial nitric oxide synthase and prostaglandin I₂ synthase in the aorta and hypertension were seen in adiponectin-knockout mice, and the abnormalities were corrected by adiponectin. Previously, we [33] and others [34] showed that human hypoadiponectinemia is closely linked to endothelial dysfunction and is an independent predictor of hypertension. In patients with visceral fat obesity, hypoadiponectinemia can be causally related to elevated blood pressure, and telmisartan might efficiently lower blood pressure by increasing plasma adiponectin. Endothelium-mediated vasodilatation could be improved by telmisartan [35] or amlodipine [36], and the degree of endothelial function might be correlated with an improvement in insulin sensitivity and blood pressure [37].

The arm–ankle PWV was decreased by 24 weeks' treatment with telmisartan, but not with amlodipine. Munakata *et al.* [38] showed that long-term treatment with valsartan, an ARB, could reduce arterial stiffness better than nifedipine-coat core, a calcium antagonist, in spite of a comparable decrease in systolic and diastolic blood pressures in patients with essential hypertension. Rajzer *et al.* [39] reported that an ACE inhibitor, quinapril 20 mg/day, but not amlodipine 10 mg/day, showed a significant decrease in PWV, aldosterone, and carboxy propeptides (procollagen type I C-terminal propeptide), a marker of arterial fibrosis, in patients with mild-to-moderate essential arterial hypertension. Taken together, the inhibition of RAS, in addition to antihypertensive actions, may be required to prevent the extension of aortic stiffness in hypertensive patients.

Highly sensitive CRP reflects chronic low-grade vascular inflammation and might be a better predictor of aortic stiffness than systolic blood pressure or pulse pressure [40]. In the telmisartan-treated group, there was no significant association between the decrease in PWV ($PWV_{6\text{ month}} - PWV_{0\text{ month}}$) and CRP ($hsCRP_{6\text{ month}} - hsCRP_{0\text{ month}}$) ($r = -0.0186$). Also, PWV was not significantly associated with decreased haemoglobin A1c, adiponectin, or systolic blood pressure, suggesting that aortic stiffness was decreased by unknown factors or multiple mechanisms.

Study limitations

First, we did not use the other ARB as control treatment, and thus we cannot eliminate the possibility of ARB class effects. Large clinical trials had demonstrated that other ARB and ACE inhibitors reduced the incidence of new-onset diabetes. Increased activation of the RAS in

obese individuals might be causally related to glucose intolerance, and inhibitions of the RAS *per se* may prevent the development of glucose intolerance by regulating adipocyte differentiation and adipocytokine production [8]. Second, we did not perform a glucose clamp study to determine insulin sensitivity. HOMA-IR and high insulin response during glucose loading does not necessarily mean insulin intolerance [22]. Third, we did not evaluate endothelium-dependent and independent vasodilatation in the current study. The effects of telmisartan or amlodipine treatment on endothelial function could be related to insulin sensitivity, blood pressure, and aortic stiffness [36]. Fourth, this study only included a limited number of individuals, larger scale studies are thus required.

In conclusion, the results imply that telmisartan could treat both the haemodynamic and metabolic aberrations seen in individuals with the metabolic syndrome, such as insulin resistance and glucose intolerance at least partly through visceral fat remodeling.

References

- 1 Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, *et al.* Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; **112**:2735–2752.
- 2 International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. Available from: http://www.idf.org/webdata/docs/IDF_Metasyndrome_definition.pdf. Accessed: November 2006.
- 3 The Committee for Japanese Definition of Metabolic Syndrome. Definition and criteria of metabolic syndrome. *J Jpn Soc Int Med* 2005; **94**:794–809.
- 4 Kissebah AH, Videlund N, Murray R, Evans DJ, Hartz AJ, Kalkhoff RK, Adams PW. Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab* 1982; **54**:254–260.
- 5 Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S. Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. *Metabolism* 1987; **36**:54–59.
- 6 Abusisa H, Jones PG, Marso SP, O'Keefe JH Jr. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 2005; **46**:821–826.
- 7 Yusuf S. From the HOPE to the ONTARGET and the TRANSCEND studies: challenges in improving prognosis. *Am J Cardiol* 2002; **89**:18A–25A; discussion 25A–26A.
- 8 Sharma AM. The obese patient with diabetes mellitus: from research targets to treatment options. *Am J Med* 2006; **119** (5 Suppl. 1):S17–S23.
- 9 Kurtz TW. New treatment strategies for patients with hypertension and insulin resistance. *Am J Med* 2006; **119** (5 Suppl. 1):S24–S30.
- 10 Benson SC, Pershadsingh HA, Ho CI, Chittiboyina A, Desai P, Pravenec M, *et al.* Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPAR γ -modulating activity. *Hypertension* 2004; **43**:993–1002.
- 11 Schupp M, Janke J, Clasen R, Unger T, Kintscher U. Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor- γ activity. *Circulation* 2004; **109**:2054–2057.
- 12 Schupp M, Clemenz M, Gineste R, Witt H, Janke J, Helleboid S, *et al.* Molecular characterization of new selective peroxisome proliferator-activated receptor γ modulators with angiotensin receptor blocking activity. *Diabetes* 2005; **54**:3442–3452.
- 13 Pershadsingh HA, Kurtz TW. Insulin-sensitizing effects of telmisartan: implications for treating insulin-resistant hypertension and cardiovascular disease. *Diabetes Care* 2004; **27**:1015.
- 14 Miura Y, Yamamoto N, Tsunekawa S, Taguchi S, Eguchi Y, Ozaki N, Oiso Y. Replacement of valsartan and candesartan by telmisartan in hypertensive patients with type 2 diabetes. *Diabetes Care* 2005; **28**:757–758.
- 15 Vitale C, Mercurio G, Castiglioni C, Cornoldi A, Tulli A, Fini M, *et al.* Metabolic effect of telmisartan and losartan in hypertensive patients with metabolic syndrome. *Cardiovasc Diabetol* 2005; **4**:6–13.
- 16 Miyazaki Y, Mahankali A, Matsuda M, Mahankali S, Hardies J, Cusi K, *et al.* Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab* 2002; **87**:2784–2791.
- 17 Tokunaga K, Matsuzawa Y, Ishikawa K, Tarui S. A novel technique for the determination of body fat by computed tomography. *Int J Obes* 1983; **7**:437–445.
- 18 Yoshizumi T, Nakamura T, Yamane M, Islam AH, Menju M, Yamasaki K, *et al.* Abdominal fat: standardized technique for measurement at CT. *Radiology* 1999; **211**:283–286.
- 19 Tomiyama H, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T, *et al.* Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement—a survey of 12517 subjects. *Atherosclerosis* 2003; **166**:303–309.
- 20 Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, *et al.* Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999; **257**:79–83.
- 21 Tanaka H, Shimabukuro T, Shimabukuro M. High prevalence of metabolic syndrome among men in Okinawa. *J Atheroscler Thromb* 2005; **12**:284–288.
- 22 Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 1999; **22**:1462–1470.
- 23 Okuno A, Tamemoto H, Tobe K, Ueki K, Mori Y, Iwamoto K, *et al.* Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. *J Clin Invest* 1998; **101**:1354–1361.
- 24 Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, *et al.* PPAR γ ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 2001; **50**:2094–2099.
- 25 Sugimoto K, Qi NR, Kazdova L, Pravenec M, Ogihara T, Kurtz TW. Telmisartan but not valsartan increases caloric expenditure and protects against weight gain and hepatic steatosis. *Hypertension* 2006; **47**:1003–1009.
- 26 Laplante M, Festuccia WT, Soucy G, Gelin Y, Lalonde J, Berger JP, Deshaies Y. Mechanisms of the depot specificity of peroxisome proliferator-activated receptor γ gamma action on adipose tissue metabolism. *Diabetes* 2006; **55**:2771–2778.
- 27 Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev* 2005; **26**:439–451.
- 28 Clark MG, Rattigan S, Barrett EJ. Nutritive blood flow as an essential element supporting muscle anabolism. *Curr Opin Clin Nutr Metab Care* 2006; **9**:185–189.
- 29 Derosa G, Cicero AF, Bertone G, Piccinini MN, Fogari E, Ciccarelli L, Fogari R. Comparison of the effects of telmisartan and nifedipine gastrointestinal therapeutic system on blood pressure control, glucose metabolism, and the lipid profile in patients with type 2 diabetes mellitus and mild hypertension: a 12-month, randomized, double-blind study. *Clin Ther* 2004; **26**:1228–1236.
- 30 White WB. Comparative effects of telmisartan in the treatment of hypertension. *J Clin Hypertens (Greenwich)* 2002; **4** (4 Suppl. 1):20–25.
- 31 Neutel J, Smith DH. Evaluation of angiotensin II receptor blockers for 24-hour blood pressure control: meta-analysis of a clinical database. *J Clin Hypertens (Greenwich)* 2003; **5**:58–63.
- 32 Ohashi K, Kihara S, Ouchi N, Kumada M, Fujita K, Hiuge A, *et al.* Adiponectin replenishment ameliorates obesity-related hypertension. *Hypertension* 2006; 1 May; E-pub ahead of print.
- 33 Shimabukuro M, Higa N, Asahi T, Oshiro Y, Takasu N, Tagawa T, *et al.* Hypoadiponectinemia is closely linked to endothelial dysfunction in man. *J Clin Endocrinol Metab* 2003; **88**:3236–3240.
- 34 Iwashima Y, Katsuya T, Ishikawa K, Ouchi N, Ohishi M, Sugimoto K, *et al.* Hypoadiponectinemia is an independent risk factor for hypertension. *Hypertension* 2004; **43**:1318–1323.
- 35 Kajihara N, Nishida T, Boku N, Tatewaki H, Eto M, Morita S. Angiotensin II type 1 receptor antagonist protects ventricular and coronary endothelial function after 24-hour heart preservation. *J Heart Lung Transplant* 2005; **24**:2211–2217.
- 36 Hsueh WA, Lyon CJ, Quinones MJ. Insulin resistance and the endothelium. *Am J Med* 2004; **117**:109–117.
- 37 Taubert D, Bartels H, Breitenbach T, Klaus W, Roesen R. Amlodipine increases endothelial nitric oxide by dual mechanisms. *Pharmacology* 2004; **70**:39–45.
- 38 Munakata M, Nagasaki A, Nunokawa T, Sakuma T, Kato H, Yoshinaga K, Toyota T. Effects of valsartan and nifedipine coat-core on systemic arterial stiffness in hypertensive patients. *Am J Hypertens* 2004; **17**:1050–1055.

- 39 Rajzer M, Klocek M, Kawecka-Jaszcz K. Effect of amlodipine, quinapril, and losartan on pulse wave velocity and plasma collagen markers in patients with mild-to-moderate arterial hypertension. *Am J Hypertens* 2003; **16**:439–444.
- 40 Nagano M, Nakamura M, Sato K, Tanaka F, Segawa T, Hiramori K. Association between serum C-reactive protein levels and pulse wave velocity: a population-based cross-sectional study in a general population. *Atherosclerosis* 2005; **180**:189–195.