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ORIGINAL ARTICLE

Prevention of metabolic disorders with telmisartan and indapamide in a Chinese population with high-normal blood pressure

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High-normal blood pressure is considered a precursor of stage 1 hypertension that is associated with metabolic disorders. This study aims to investigate whether the pharmacologic treatment of high-normal blood pressure affects metabolism, especially in abdominally obese individuals, and the pharmacoeconomics of two antihypertensive agents, telmisartan and indapamide. Subjects with high-normal blood pressure were randomly assigned to receive telmisartan, indapamide or placebo for 3 years. All the subjects were instructed to modify their lifestyle to reduce blood pressure throughout the study. A total of 221 subjects were randomly assigned to telmisartan, 213 to indapamide and 230 to placebo. After the 3-year intervention, blood pressure was lower in the telmisartan and indapamide groups ($P<0.05$), FPG in the telmisartan group was lower during the first 2 years ($P<0.05$) and no characteristic differences were found in those with abdominal obesity among the three groups ($P>0.05$). The percentage of subjects with metabolic syndrome was significantly decreased in the telmisartan and indapamide groups ($P<0.05$), but was only significantly decreased in the telmisartan group for subjects with abdominal obesity ($P<0.05$). The acquisition cost for telmisartan was ~1.86 times higher than for indapamide for a similar antihypertensive effect. The intervention for high-normal blood pressure with telmisartan and indapamide appeared to be feasible and reduced the risk of metabolic syndrome. Telmisartan was more effective, whereas indapamide had better pharmacoeconomic benefits.
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Keywords: abdominal obesity; high-normal blood pressure; metabolic syndrome; pharmacoeconomics

INTRODUCTION

Epidemiologic studies have demonstrated that[1] cardiovascular disease risk doubles for each 20/10 mm Hg increase above a baseline blood pressure of 115/75 mm Hg. In 2007, the European Society of Hypertension and European Society of Cardiology[2] classified blood pressure levels of 130–139/85–89 mm Hg as high normal. Recent studies have shown that high-normal blood pressure is associated with metabolic disorders, including obesity[3] and abnormal glucose, as well as lipid metabolism,[4,5] that lead to the development of metabolic syndrome (MetS) and other metabolic diseases. Therefore, interventions aimed at the prevention and treatment of high-normal blood pressure are highly needed to reduce the related metabolic disorders.

Currently, the main prevention and treatment of high-normal blood pressure is lifestyle intervention. Previous studies have shown that[6–8] lifestyle modification, such as weight loss, low-salt diets and intensifying physical exercise, can effectively control blood pressure and reduce cardiovascular complications. However, outside of strict experimental conditions, their effectiveness has been inconsistent owing to poor patient compliance. The TROPHY study[9] found that the relative risk of developing hypertension was reduced by 66.3%, and the progression to hypertension was delayed in prehypertensive individuals who were treated with candesartan for 2 years. In the PHARAO study,[10] patients with high-normal blood pressure were treated with ramipril for 3 years, and their risk for hypertension was decreased by 34.4%. Although these studies confirmed the efficacy of pharmacologic treatment to prevent hypertension in individuals with high-normal blood pressure, in all cases, their primary end point was hypertension. Because high-normal blood pressure is often associated with metabolic disorders that lead to MetS, whether drug intervention

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can improve metabolic disorders in individuals with high-normal blood pressure requires extensive study.

Studies have suggested that angiotensin II receptor blockers (ARBs)[11] and diuretics[12] are more effective in lowering blood pressure in hypertensive patients with obesity. However, diuretics have been associated with adverse effects on glucose and lipid metabolism, whereas ARBs have been shown to be beneficial.[13,14] Telmisartan is an orally effective and specific ARB for the treatment of essential hypertension[15] and the prevention of cardiovascular disease.[16,17] It has also been well established that telmisartan acts as a selective partial agonist of the peroxisome proliferator-activated receptor-γ,[18] an intracellular nuclear hormone receptor involved in the regulation of glucose and lipid metabolism.[19,20] Indapamide is a thiazide-like diuretic that lowers blood pressure primarily through its natriuretic diuretic effect. It has little influence on glucose and lipid metabolism compared with other thiazide diuretics.[21] At present, the acquisition cost of indapamide is lower than telmisartan. Until now, no previous study has evaluated the effects on metabolism of these two drugs when used as an intervention for high-normal blood pressure. Determining the nature of the effects in the population, especially in individuals with abdominal obesity, and determining which drug will be maximally beneficial needs to be verified. Additionally, because the subjects in our study had high-normal blood pressure, we used small doses of antihypertensive drugs in this particular group.

Based on the results of the above studies, this study was designed to investigate the following in individuals with high-normal blood pressure: whether intervening with telmisartan and indapamide can strikingly alter the metabolic risk factors; what pharmacodynamic differences exist between them, particularly in individuals with abdominal obesity; and the pharmacoeconomics of these two drugs.

METHODS

Subjects and study design

This study was a randomized double-blind placebo-controlled trial. The primary objective of the study was to determine whether 3 years of treatment with small doses of antihypertensive agents in individuals with high-normal blood pressure reduced the percentage of subjects with MetS. Participants who met the following study criteria were eligible for inclusion: (1) male or female aged 50–79 years; (2) systolic blood pressure (SBP) of 130–139 mm Hg and diastolic blood pressure (DBP) $<$90 mm Hg; DBP of 85–89 mm Hg and SBP $<$140 mm Hg[2]. Exclusion criteria included the presence of diabetes, hypertension, advanced hepatic renal diseases, stroke, myocardial infarction, cancer, intolerance to the study drugs and pregnancy. Participants were recruited from Shandong Province between March 2009 and September 2009. After the screening visit, blood pressure of potentially eligible participant was measured at three different time points within 2 weeks. Then, the eligible participants were randomized uniformly by the research collaboration center. The collaborating units reported a brief introduction regarding the participants to the random office by email, fax or telephone. The random office carried out the randomization by a computer program and allocated the random groups. The collaborating units distributed the corresponding study drugs to participants according to the random groups. Each study drug had a number on its packing box that was recorded on the study form. The study investigators, research coordinators, attending care teams, the participants and their families were all blinded to treatment allocation. The eligible subjects were randomly assigned to three regimens: telmisartan group—telmisartan 40 mg once daily, indapamide group—indapamide 1.5 mg once every other day and the placebo group—one pill once daily. After the first and third month, the therapeutic dosage was adjusted according to the patient's blood pressure and tolerance. The subjects subsequently underwent follow-up evaluations. Blood pressure and tolerability of treatment were evaluated every 3 months. Waist circumference, SBP, DBP, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), serum potassium and uric acid were measured yearly. In addition, all the subjects were instructed to modify their lifestyle to reduce blood pressure. The lifestyle intervention was based on group sessions in the local community hospital once a year, lasting for 2 days. The curriculum included instructions on the epidemiology and complications of hypertension, diabetes, MetS, smoking, exercise, fat and cholesterol, low-salt diet and so on. We also strengthened the guidance and education of the subjects at each follow-up visit. This protocol was approved by the Medical Ethics Committee of Shandong Academy of Medical Sciences. All the participants provided written informed consent.

Measurements

Blood pressure was measured with the use of an automated reading and recording device (HEM-705CP; Omron Healthcare, Kyoto, Japan) while participants were seated after 5 min of rest. The participant's arm was placed at the heart level, and three measurements, 60 s apart, were taken. SBP and DBP were defined as the average of the three readings.

Age, sex, medical history, medication use, personal health habits (physical activity, smoking, alcohol consumption) and other clinical data were assessed by questionnaire.

Waist circumference was measured two times for each subject, and the average of the two readings was used in the analyses. Venous blood samples were obtained from all subjects after fasting for at least 12 h for biochemical determination and were taken at the central laboratory of the city hospital by standard and quality-controlled procedures. Concentrations of total cholesterol, HDL-C, triglycerides, glucose and uric acid were determined enzymatically using an autoanalyzer (Type 7600; Hitachi, Tokyo, Japan); serum potassium was measured by using a fluorescence turbidity method. LDL-C was calculated by the Friedewald equation[22] when the level of triglycerides was $<4.5\ \mathrm{mmol\,l^{-1}}$.

Definition of MetS

The development of MetS was defined according to the harmonized criteria of 2009[23] that were similar to the International Diabetes Foundation criteria.[24] The harmonized definition of MetS required at least three of the following components: (1) *abdominal obesity*: waist circumference $\geqslant$90 cm for Chinese men and $\geqslant$80 cm for Chinese women; (2) *elevated blood pressure*: SBP $\geqslant$130 mm Hg, DBP $\geqslant$85 mm Hg or known treatment for hypertension; (3) *elevated triglycerides*: fasting plasma triglycerides $\geqslant 150\ \mathrm{mg\,dl^{-1}}$ ($1.7\ \mathrm{mmol\,l^{-1}}$), drug treatment for elevated triglycerides was an alternate indicator; (4) *low HDL-C*: fasting HDL-C $<1.0\ \mathrm{mmol\,l^{-1}}$ in men and $<1.3\ \mathrm{mmol\,l^{-1}}$ in women, drug treatment for reduced HDL-C was an alternate indicator; and (5) *hyperglycemia*: fasting glucose level $\geqslant 5.6\ \mathrm{mmol\,l^{-1}}$ ($\geqslant 100\ \mathrm{mg\,dl^{-1}}$) or known treatment for diabetes, drug treatment of elevated glucose was an alternate indicator.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 statistical software (SPSS 17.0 for Windows; SPSS, Chicago, IL, USA). Continuous values are expressed as the mean values with standard deviation. If not normally distributed, the data are expressed as the median with interquartile range (the range between the 25th and 75th percentile). Nonparametric variables are expressed as percentages. Comparisons of the differences in continuous variables were performed using one-way analysis of variance (ANOVA) and repeated-measures ANOVA, whereas the categorical variables were treated with the χ^2 test. When significant differences among groups were observed, within-group comparisons were performed using the Tukey's *post hoc* analysis. The change rate of variables during the follow-up period was calculated as follows: ((value at end follow-up − value at baseline)/value at baseline) × 100%. A two-sided *P*-value <0.05 was considered statistically significant.

RESULTS

Subject characteristics

We screened 2317 candidates, and 903 participants were eligible for enrollment. After excluding those who did not consent, a total of 664 eligible subjects were randomly divided into three groups, 221 were assigned to telmisartan, 213 to indapamide and 230 to placebo. During

the 3-year follow-up period, nine (0.75%) subjects were lost to follow-up: one in the telmisartan group, two in the indapamide group and two in the placebo group. Four subjects died; the causes of death were trauma (one in the telmisartan group and one in the indapamide group), gastric cancer (one in the indapamide group) and lung cancer (one in placebo group). Because the data from the subjects lost to follow-up were incomplete, and the causes of death were unrelated to the drug intervention, data from those nine subjects were not included in the analysis (Figure 1). The baseline characteristics of the study subjects are shown in Table 1. The three groups were comparable in terms of demographic and clinical characteristics at randomization.

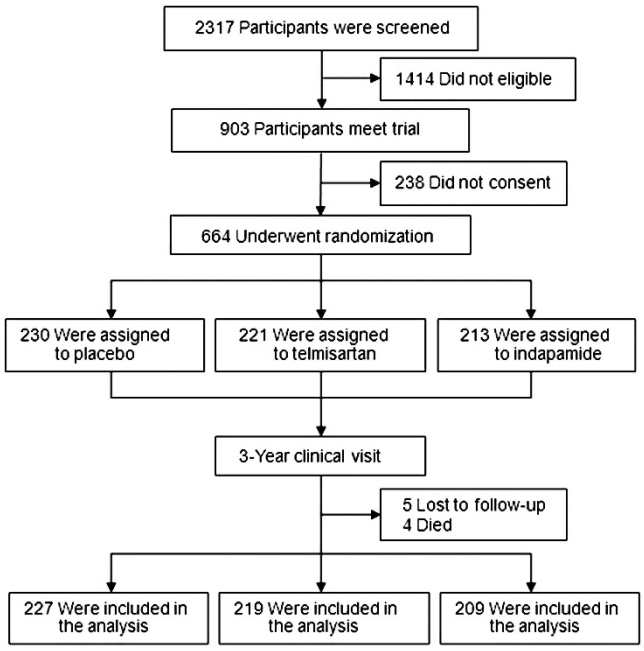

Figure 1 Disposition of subjects.

Drug efficacy comparison

After 3 years of treatment, the percent change from baseline characteristics was lower in WC, SBP, DBP, TG, LDL-C and FPG, but higher in HDL-C (Table 2). Statistically significant differences were found in SBP, DBP and FPG among the three groups ($P<0.05$). Compared with placebo group, the SBP and DBP were significantly lower in the telmisartan group (−11.7 (−14.5, −9.0)/−11.5 (−13.9, −4.8)% change *vs.* −5.0 (−5.0, −1.2)/−5.2 (−5.2, −0.8); $P<0.001$) and indapamide group (−11.4 (−11.4, −8.5)/−10.3 (−10.3, −4.8)% change *vs.* −5.0 (−5.0, −1.2)/−5.2 (−5.2, −0.8); $P<0.001$), but no statistically significant difference was found between the two anti-hypertensive regimens. The differences in SBP and DBP were first noticed by the end of the first year ($P<0.001$). There was a statistically significant difference in FPG ($P=0.022$). The FPG in the telmisartan group was significantly lower than the FPG in the placebo group (−4.8 (−4.8, 0.0) *vs.* −3.5 (−3.5, 0.4); $P=0.015$) and the indapamide group (−4.8 (−4.8, 0.0) *vs.* −3.0 (−3.0, 1.7); $P=0.019$). The differences in FPG were first noticed by the end of the first year ($P=0.014$).

Figure 2 represents the repeated-measures ANOVA comparing the mean values of WC, SBP, DBP, TG, HDL-C, LDL-C and FPG among

Table 1 Baseline characteristics of the study subjects

	Placebo group (n = *227*)	*Telmisartan group* (n = *219*)	*Indapamide group* (n = *209*)	P-*value*
Age (years)	64.9±7.2	65.4±6.9	65.3±7.0	0.800
Male sex, *n* (%)	71 (31.3)	72 (32.9)	65 (31.1)	0.909
WC (cm)	87.2±9.1	87.0±8.5	87.3±8.3	0.935
SBP (mm Hg)	134.5±3.0	134.7±2.6	134.7±2.8	0.613
DBP (mm Hg)	82.0±5.0	82.3±4.8	82.2±4.6	0.859
TG (mmol l^{-1})	1.5±0.4	1.5±0.5	1.5±0.5	0.605
HDL-C (mmol l^{-1})	1.5±0.4	1.5±0.5	1.5±0.4	0.666
LDL-C (mmol l^{-1})	3.1±0.9	3.1±0.9	3.2±0.9	0.620
FPG (mmol l^{-1})	5.3±0.7	5.4±0.7	5.3±0.6	0.902

Abbreviations: DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.

Table 2 Percentage changes from baseline of characteristics after 3-year intervention

	Placebo group (n = *227*)	*Telmisartan group* (n = *219*)	*Indapamide group* (n = *209*)	P-*value*
WC (% change)	−1.1 (−2.6, 0.3)	−1.1 (−2.8, 0.4)	−1.1 (−1.1, 0.0)	0.933
SBP (% change)	−5.0 (−5.0, −1.2)	−11.7 (−14.5, −9.0)[a]	−11.4 (−11.4, −8.5)[a]	0.000
DBP (% change)	−5.2 (−5.2, −0.8)	−11.5 (−13.9, −4.8)[a]	−10.3 (−10.3, −4.8)[a]	0.000
TG (% change)	−0.0 (−14.5, 14.5)	−1.7 (−15.7, 14.3)	−1.6 (−1.6, 11.5)	0.711
HDL-C (% change)	1.8 (−7.5, 16.7)	5.6 (−7.9, 26.8)	3.3 (3.3, 1.6)	0.282
LDL-C (% change)	−8.4 (−2.1, 0.6)	−12.0 (−23.6, 0.8)	−9.1 (−9.1, 1.3)	0.447
FPG (% change)	−3.5 (−3.5, 0.4)	−4.8 (−4.8, 0.0)[a]	−3.0 (−3.0, 1.7)[a,b]	0.022

Abbreviations: DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.
Values are medians (25th, 75th percentiles).
[a]$P<0.05$ *vs.* placebo group.
[b]$P<0.05$ *vs.* telmisartan group.

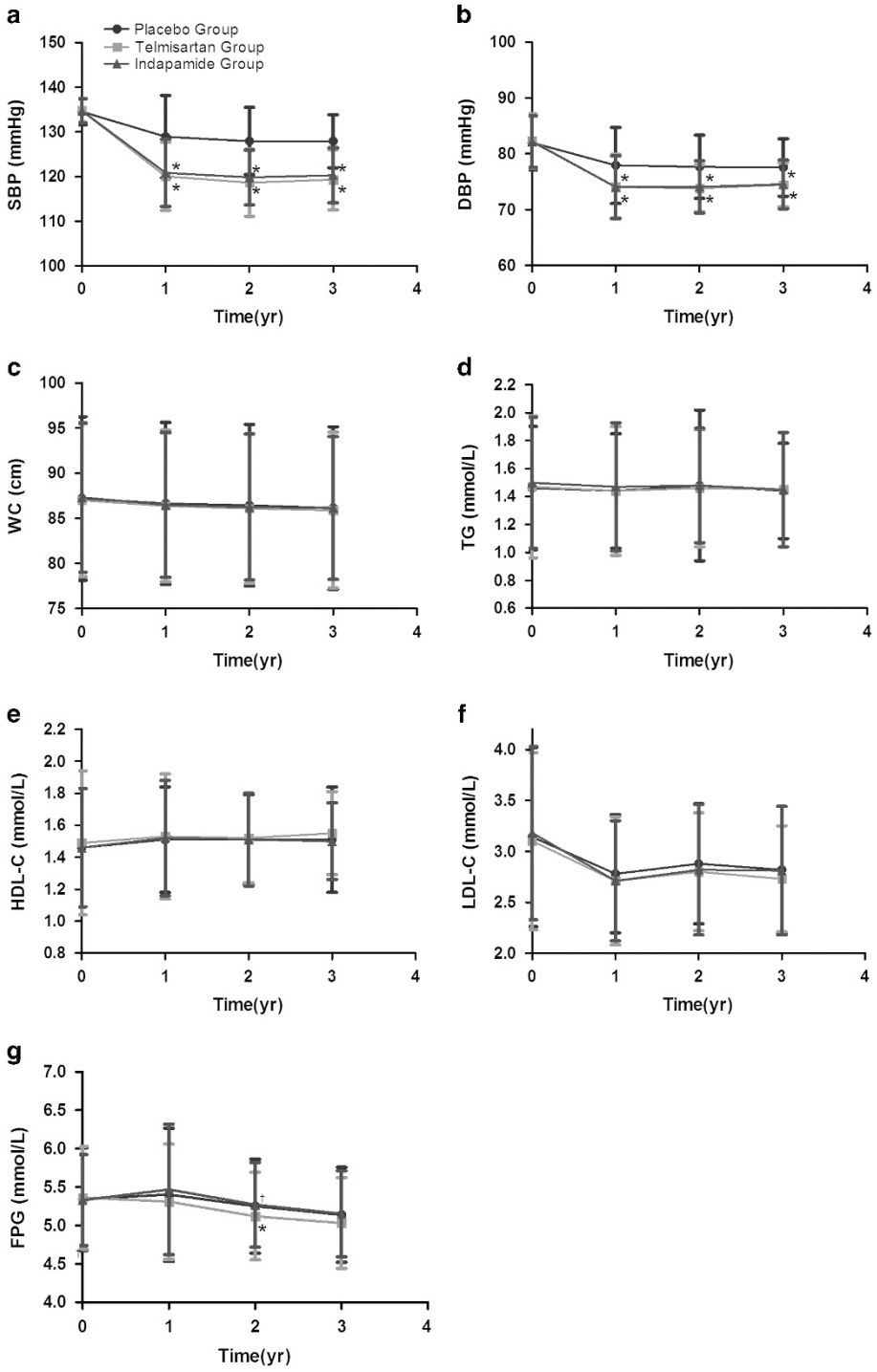

Figure 2 Characteristics of the subjects during the 3-year follow-up period. $^{*}P<0.05$ *vs.* placebo group, $^{\dagger}P<0.05$ *vs.* telmisartan group. This figure represents the repeated-measures analysis of variance (ANOVA) comparing the mean values of systolic blood pressure (SBP) (**a**), diastolic blood pressure (DBP) (**b**), waist circumference (WC) (**c**), triglycerides (TG) (**d**), high-density lipoprotein cholesterol (HDL-C) (**e**), low-density lipoprotein cholesterol (LDL-C) (**f**) and fasting plasma glucose (FPG) (**g**) among the groups, and the within-group comparisons among the three drugs. A full color version of this figure is available at *Hypertension Research Journal* online.

the groups, and the within-group comparisons among the three drugs. Tests of within-subject effects showed that time significantly influenced WC, SBP, DBP, TG, HDL-C, LDL-C and FPG ($P<0.05$); the WC, SBP, DBP, TG, LDL-C and FPG significantly decreased over time, but HDL-C increased. The time and drug effects were associated with a significant decrease in SBP, DBP and FPG ($P<0.05$). Tests of between-subject effects showed that the drug effects were associated with a significant decrease in SBP and DBP ($P<0.05$). In addition, in the first, second and third year, the SBP and DBP in the telmisartan and indapamide groups were significantly lower than the placebo group; in the second year, the FPG in the telmisartan group was significantly lower than the placebo and indapamide groups.

In the first and third year, statistically significant differences were observed in the percentage of individuals with MetS among the three groups ($P=0.001$, Figure 3). In the first year, the percentage of individuals with MetS was significantly decreased in the telmisartan (17.35% *vs.* 30.84%; $P=0.0004$) and indapamide groups (22.00% *vs.* 30.84%; $P=0.0022$) compared with the placebo group. In the third year, these differences still existed ($P=0.016$), but only the percentage of individuals with MetS in the telmisartan group was lower than that in the placebo group (7.76% *vs.* 16.3%; $P=0.006$).

Drug efficacy on abdominal obesity

According to abdominal obesity status, the baseline characteristics of the three groups were still comparable (Table 3). After 3 years of treatment, the percent change from baseline characteristics was lower in WC, SBP, DBP, TG, LDL-C and FPG, but higher in HDL-C (Table 4). Statistically significant differences were found in SBP and DBP among the three groups in those with abdominal obesity ($P<0.001$). Compared with the data in the placebo group, the SBP and DBP were significantly lower in the telmisartan and indapamide groups ($P<0.001$).

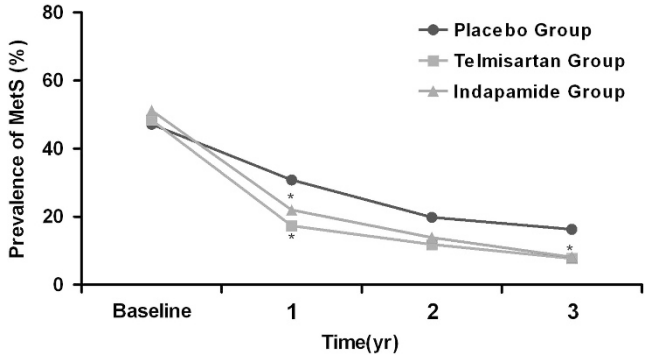

Figure 3 Prevalence of metabolic syndrome (MetS) during the 3-year follow-up period. *$P<0.05$ *vs.* placebo group. A full color version of this figure is available at *Hypertension Research Journal* online.

In individuals with abdominal obesity, the repeated-measures ANOVA comparing the mean values of WC, SBP, DBP, TG, HDL-C, LDL-C and FPG among the groups, and the within-group comparisons among the three drugs are represented in Figure 4. The results of repeated-measures ANOVA were similar to the whole population. In addition, in the first, second and third year, the SBP and DBP in the telmisartan and indapamide groups were still significantly lower than the placebo group; in the first year, the FPG in the indapamide group was significantly higher than the placebo and telmisartan groups; in the second year, the LDL-C in the indapamide group was lower than in the placebo group.

In the first and third year, statistically significant differences were observed in the percentage of individuals with MetS among the three groups in subjects with abdominal obesity ($P<0.001$, Figure 5) and was only significantly decreased in the telmisartan group.

Drug side-effect evaluation

All antihypertensive regimens were generally well tolerated. After 3 years of treatment, one subject (0.44%) experienced hyperkalemia in the placebo group and three subjects (1.44%) experienced hypokalemia in the indapamide group. No significant difference was found among the three groups. A total of 67 subjects experienced

Table 3 Baseline characteristics of the abdominal obesity subjects

	Placebo group (n = *153*)	*Telmisartan group* (n = *149*)	*Indapamide group* (n = *142*)	P-*value*
Age (years)	64.9±7.3	65.1±6.7	65.6±7.1	0.676
Male sex, *n* (%)	31 (20.3)	30 (20.1)	29 (20.4)	0.912
WC (cm)	91.3±7.3	90.8±6.5	91.1±6.1	0.656
SBP (mm Hg)	134.6±3.0	134.7±2.4	134.7±2.7	0.745
DBP (mm Hg)	81.9±5.1	82.2±4.9	82.2±4.6	0.817
TG (mmol l^{-1})	1.6±0.5	1.6±0.9	1.5±0.6	0.698
HDL-C (mmol l^{-1})	1.4±0.4	1.5±0.5	1.5±0.4	0.482
LDL-C (mmol l^{-1})	2.9±0.8	2.9±0.8	3.1±1.0	0.389
FPG (mmol l^{-1})	5.3±0.6	5.4±0.6	5.4±0.6	0.911

Abbreviations: DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.

Table 4 Percentage changes from baseline of characteristics of abdominal obesity subjects after 3-year intervention

	Placebo group (n = *153*)	*Telmisartan group* (n = *149*)	*Indapamide group* (n = *142*)	P-*value*
WC (% change)	−1.1 (−2.4, 0.3)	−1.1 (−2.6, 0.4)	−1.1 (−2.6, 0.0)	0.718
SBP (% change)	−4.7 (−4.7, −1.6)	−11.7 (−14.3, −9.0)[a]	−11.2 (−14.1, −7.8)[a]	0.000
DBP (% change)	−4.3 (−4.3, −0.8)	−10.9 (−13.8, −4.7)[a]	−9.7 (−13.7, −4.7)[a]	0.000
TG (% change)	−0.0 (−12.1, 14.3)	−1.8 (−1.8, −13.4)	−1.3 (−17.6, 10.6)	0.911
HDL-C (% change)	2.7 (−7.0, 22.6)	6.5 (−8.5, 31.7)	2.4 (−9.4, 16.0)	0.217
LDL-C (% change)	−8.5 (−23.9, −1.1)	−12.3 (−24.6, 1.1)	−8.0 (−18.9, −0.1)	0.660
FPG (% change)	−3.3 (−9.3, 0.5)	−4.4 (−10.8, 0.6)	−3.1 (−7.8, 0.5)	0.058

Abbreviations: DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.
Values are medians (25th, 75th percentiles).
[a]$P<0.05$ *vs.* placebo group.

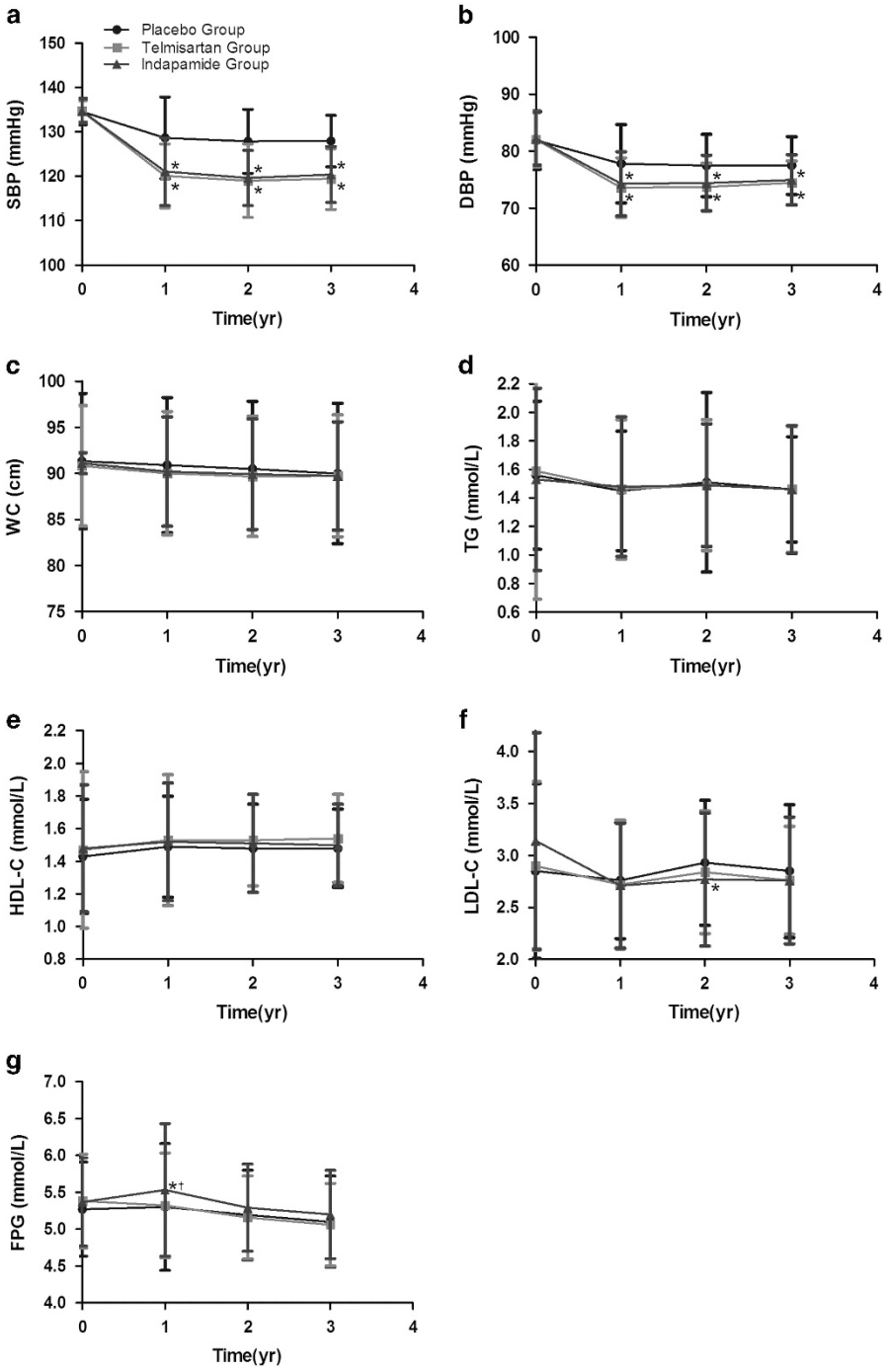

Figure 4 Characteristics of the abdominal obesity subjects during the 3-year follow-up period. *$P<0.05$ *vs.* placebo group, †$P<0.05$ *vs.* telmisartan group. This figure represents the repeated-measures analysis of variance (ANOVA) comparing the mean values of systolic blood pressure (SBP) (**a**), diastolic blood pressure (DBP) (**b**), waist circumference (WC) (**c**), triglycerides (TG) (**d**), high-density lipoprotein cholesterol (HDL-C) (**e**), low-density lipoprotein cholesterol (LDL-C) (**f**) and fasting plasma glucose (FPG) (**g**) among the groups, and the within-group comparisons among the three drugs. A full color version of this figure is available at *Hypertension Research Journal* online.

hyperuricemia (11.45% in placebo group *vs.* 6.39% in the telmisartan group *vs.* 12.92% in the indapamide group; $P=0.063$), which was lower than the baseline (19.38% in placebo group *vs.* 16.44% in the telmisartan group *vs.* 20.10% in the indapamide group; $P=0.584$).

The serum potassium and uric acid level in the three groups are shown in Figure 6. The mean uric acid and potassium level were both within the normal range during follow-up. After 3 years of treatment, a statistically significant difference was detected in serum potassium and uric acid among the three groups ($P<0.05$). The uric acid in the telmisartan group was lower than in the placebo and indapamide groups ($P<0.05$). The potassium in the telmisartan group was higher than in the placebo group ($P<0.05$), and lower in the indapamide group than in the placebo and telmisartan groups ($P<0.05$). The significant changes in uric acid first appeared in the second year,

whereas significant changes in potassium appeared in the first year. In addition, the trends of drug side effect in the subjects with abdominal obesity were similar to the non-obese subjects (Figure 7).

Pharmacoeconomics

The drugs used in this study were all made in China. For the same antihypertensive effect, the 3-year total cost was US$347.62 per patient for telmisartan and US$121.67 per patient for indapamide Thus, the acquisition cost for telmisartan was ~1.86 times higher than indapamide.

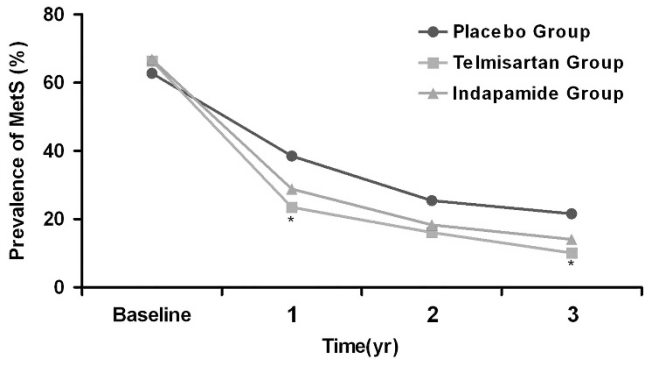

Figure 5 Prevalence of metabolic syndrome (MetS) in subjects with abdominal obesity during the 3-year follow-up period. *$P<0.05$ *vs.* placebo group. A full color version of this figure is available at *Hypertension Research Journal* online.

DISCUSSION

The present study demonstrated that telmisartan and indapamide were equally effective in lowering blood pressure. Telmisartan slightly reduced FPG, whereas indapamide did not have this effect. All of the effects were unrelated to abdominal obesity. Above all, this study indicated that these two drugs reduced the percentage of individuals with MetS, with telmisartan showing greater efficacy in abdominally obese individuals.

In this study, all of the metabolic risk factors evaluated improved with time. Although this improvement may have resulted from effective lifestyle intervention, these benefits were more obvious in the drug-treated groups compared with the placebo group. Telmisartan and indapamide were equally effective in lowering the SBP and DBP to the optimal levels,[2] which suggested the feasibility of using them for blood pressure control in this population. Previous studies have shown that telmisartan improves glucose and lipid metabolism.[25–28] Some studies[29] have also reported that telmisartan does not prevent diabetes or lead to regression of impaired fasting glucose or impaired glucose tolerance in people at high risk for cardiovascular disease but free of diabetes. Our study found that telmisartan only slightly reduced FPG without significantly affecting lipid metabolism, which may be because of the small sample size, the low dose[30] of the drug or the particular characteristics of the subjects.

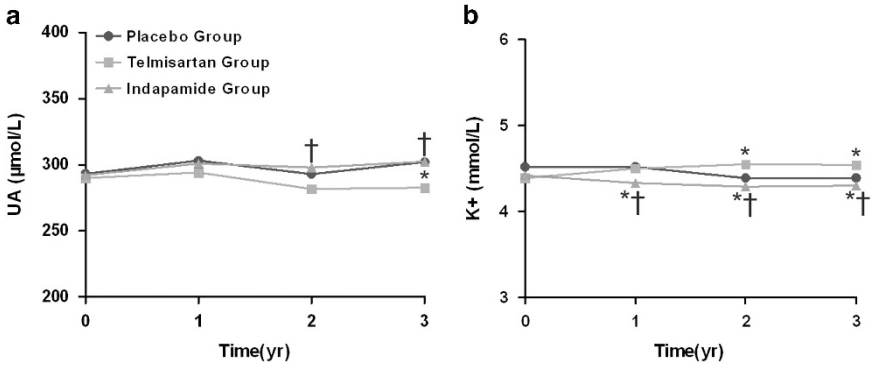

Figure 6 Drug side-effect evaluation. Comparison of the serum uric acid (UA) level (**a**) and the serum K+ level (**b**) of the three groups during the 3-year follow-up period. *$P<0.05$ *vs.* placebo group, †$P<0.05$ *vs.* telmisartan group. A full color version of this figure is available at *Hypertension Research Journal* online.

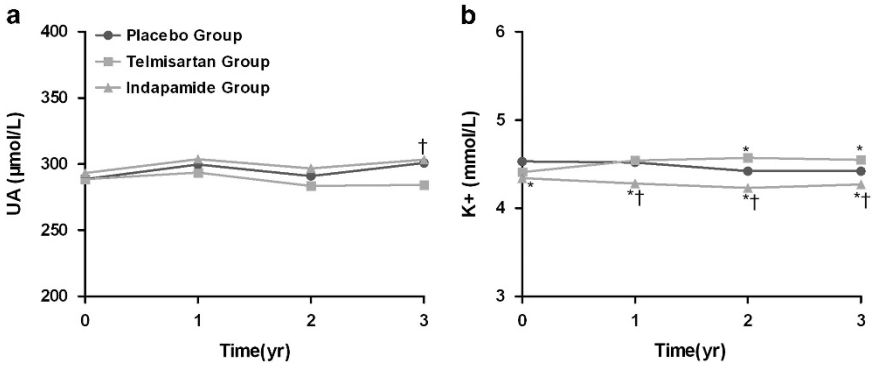

Figure 7 Drug side-effect evaluation. Comparison of the serum uric acid (UA) level (**a**) and the serum K+ level (**b**) in subjects with abdominal obesity in the three groups during the 3-year follow-up period. *$P<0.05$ *vs.* placebo group, †$P<0.05$ *vs.* telmisartan group. A full color version of this figure is available at *Hypertension Research Journal* online.

Consistent with Weidmann's findings,[31] in this study, indapamide did not significantly affect glucose and lipid metabolism. In addition, the two drugs appeared to be effective in reducing the percentage of individuals with MetS, whereas telmisartan was better for long-term use. This effect was mainly due to the lowering of blood pressure because individuals with high-normal blood pressure also carry metabolic risk factors[32,33] that place them at high risk for developing MetS. In addition, telmisartan reduced FPG in our study; Barzilay *et al*.[34] also found that thiazide-related diabetes had less adverse long-term cardiovascular disease impact than diabetes that developed while on other antihypertensive medications, which may explain the metabolic improvement in the subjects.

Previous studies have verified that ARBs and diuretics are effective in lowering blood pressure of obese hypertensive patients.[11,12] However, diuretics have always been associated with side effects that result in abnormal glucose and lipid metabolism, especially in abdominally obese individuals.[35] Our study indicated that in subjects with abdominal obesity, there was no difference among the three groups in the lowering of blood pressure or the regulation of glucose and lipid metabolism. This might be because the drug dosages were lower than what is conventionally used. The blood pressure-independent effects[36] were not obvious. However, telmisartan definitely reduced the percentage of individuals with MetS among individuals with abdominal obesity, suggesting that it is a more suitable drug for that specific population.

ARBs are known to increase potassium levels,[37] whereas diuretics can cause hypokalemia and hyperuricemia.[35,38] Therefore, the present study monitored potassium and uric acid to evaluate the safety of the two drugs. The results showed that although the effects on serum potassium and uric acid levels differed among the three groups, the mean levels were all within the normal range. Therefore, both telmisartan and indapamide appear to be safe. In addition, telmisartan lowered serum uric acid, which might improve metabolism and benefit individuals on MetS.[39] However, because telmisartan and indapamide have the potential to affect potassium, they should be used cautiously in patients at risk of developing hyperkalemia and hypokalemia.

This study also considered the pharmacoeconomics. While there was no difference in the antihypertensive effect, the acquisition cost of telmisartan was ~1.86 times higher than indapamide, although the duration of treatment with indapamide was 2.72 times longer than telmisartan. One advantage of telmisartan, however, was the improvement in metabolic disorders. Therefore, telmisartan could be selected for patients with stable economic means, whereas indapamide could be a good alternative for those with less favorable economic conditions.

This study has several limitations. The sample size was small and the subjects were only from Shandong Province of China. The results may therefore not be broadly applicable across different races and geographic locations. In addition, the analysis of pharmacoeconomics was incomplete because of the limited data. Lastly, while this study demonstrated the effects of drug intervention on metabolism in individuals with high-normal blood pressure, specific mechanisms underlying these effects were not investigated.

In summary, the present study shows that telmisartan and indapamide can effectively lower blood pressure in individuals with high-normal blood pressure and exerts a modest influence on metabolism. Both drugs are associated with a reduced risk of developing MetS. While telmisartan is more effective in individuals with abdominal obesity, indapamide has superior pharmacoeconomic benefits. Additional larger and longer-term studies are needed to confirm these results.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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