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Effects of Telmisartan and Candesartan on the Metabolism of Lipids and Glucose in Kidney Transplant Patients: A Prospective, Randomized Crossover Study

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Background. The risk of cardiovascular events remains after kidney transplantation (KT). Abnormal glucose metabolism and hyperlipidemia contribute partly to this risk. Among angiotensin II type-1 receptor blockers, telmisartan alone has been shown to ameliorate these effects on glucose and lipid metabolism (GLM). We investigated the effects of telmisartan on GLM in KT patients. **Methods.** This trial had a crossover design. Forty-six KT patients with well-controlled hypertension under angiotensin II type-1 receptor blockers were randomized into telmisartan and candesartan groups. After a 12-week treatment, crossover was initiated, and additional 12-week treatment was administered without a washout period. We examined the laboratory parameters of GLM, blood pressure and graft function before and after each treatment period. **Results.** Forty patients completed the scheduled treatment regimen. Serum levels of triglyceride were significantly lower (114.3 ± 50.8 mg/dL vs 136.5 ± 66.8 mg/dL; $P = 0.019$), and the estimated glomerular filtration rate was significantly higher (50.4 ± 15.1 mL/min per 1.73 m² vs 48.5 ± 12.5 mL/min per 1.73 m²; $P = 0.038$) after telmisartan treatment than after candesartan treatment. There were no significant differences between the 2 treatment groups with regard to the other parameters studied (including serum adiponectin levels and parameters of glucose metabolism). **Conclusions.** These data suggest that telmisartan can improve serum triglyceride levels and graft function for KT patients better than candesartan.

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Kidney transplantation (KT) for end-stage kidney disease has been associated with substantial reductions in the risk of mortality and cardiovascular events, as well as clinically relevant improvements in quality of life.¹ However, post-KT cardiovascular events remain major barriers to long-term survival.^{2,3} In addition to pre-KT kidney failure, the side effects of immunosuppressive agents can cause KT patients to suffer hypertension, hyperlipidemia, and abnormal glucose metabolism,^{4,5} which are risk factors for cardiovascular events after KT.⁶ About 80% of KT patients suffer hypertension.⁷ Risk factors for cardiovascular disease in the general population, such as hypertension and hyperlipidemia, have been found to be predictive factors in KT patients.⁸

Use of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II type-1 receptor blocker (ARB) therapy is associated with longer survival for patients and grafts after KT.⁹ Telmisartan is a unique ARB with selective peroxisome proliferator-activated receptor (PPAR)- γ -mediated properties.¹⁰ Peroxisome proliferator-activated receptors are members of a nuclear receptor superfamily of ligand-activated transcription factors. Among PPARs, PPAR- γ , which is the most abundant isoform in adipose tissue, plays an important part in the regulation of insulin sensitivity and also improves lipid profiles.¹¹ In animal experiments, PPAR- γ agonists have been shown to improve the metabolism of glucose and lipids.^{10,12,13}

A beneficial effect of telmisartan on insulin sensitivity and lipid metabolism compared with non-PPAR- γ -activating ARBs has been reported in several clinical studies.¹⁴⁻¹⁶ However, few studies have focused on the correlation between telmisartan and PPAR- γ -mediated properties in KT patients.

We conducted a prospective randomized crossover study to investigate the effects of telmisartan on the metabolism of glucose and lipids compared with those of a non-PPAR- γ -activating ARB in KT patients. We examined the laboratory parameters of the metabolism of lipids and glucose, blood pressure, and graft function before and after each treatment period.

MATERIALS AND METHODS

Ethical Approval of the Study Protocol

The study protocol was approved by the Ethics Committee of Kyushu University (21048; Fukuoka, Japan). This study has been registered in the University Hospital Medical Information Network Clinical Trials Registry System (UMIN 000003206). Individuals received full verbal and written explanations of the nature and purpose of this study and gave their written informed consent.

Participant Eligibility

Forty-six KT patients with well-controlled hypertension were enrolled between February 2010 and December 2011. Their blood pressure was controlled to less than 130/80 mm Hg¹⁷ with ARBs and more than 3 months had passed since starting administration of ARBs. The renal function of patients was stable without clinical or pathologic findings

of rejection. The immunosuppressive agent was given as a maintenance dose without any need to modify it. The age of the patients was between 20 and 75 years. We excluded patients suffering from diabetes mellitus (DM) to evaluate glucose metabolism for patients undergoing KT.

Patient Grouping

All patients were allocated randomly into 2 groups: telmisartan or candesartan. The ARB taken by each patient was replaced to telmisartan or candesartan based on the group the patient was allocated. After 12 weeks, the allocation was alternated for another 12 weeks.

Exclusion criteria were as follows: (1) patients with active allograft rejection; (2) patients with DM (including new-onset DM after KT); (3) patients taking pioglitazone, ACEIs or fibrates, all of which are agonists of PPAR- α and can act as competitors to telmisartan; (4) patients who had started taking statins in the previous 2 months; (5) serum creatinine (sCr) >3 mg/dL; (6) total bilirubin in serum >2.0 mg/dL; (7) serum glutamic-oxaloacetic transaminase and/or glutamic-pyruvic transaminase >100 IU/L; and (8) serum potassium >5.5 mEq/L. No patients changed their medications or daily dietary habits during the study period.

Study Design

This study had a prospective, randomized crossover design (Figure 1) conducted at the Kyushu University Hospital, Fukuoka, Japan. There were no major changes to the study protocol after initiation of the study. Randomization was undertaken by a third party (Clinical Research Support Center Kyushu, Fukuoka, Japan) using a table of random numbers

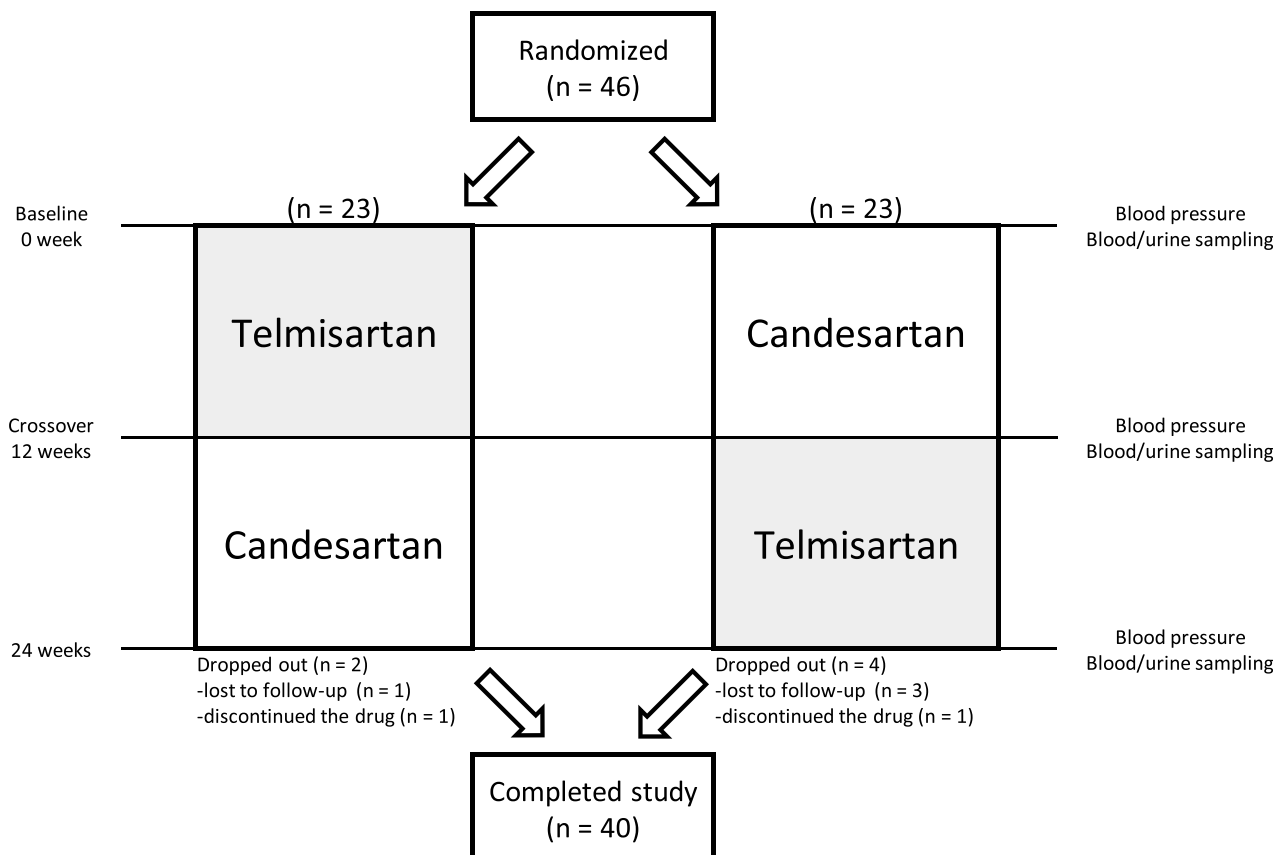


FIGURE 1. Crossover study design. Assessments were made at 0, 12, and 24 weeks after randomization.

TABLE 1.
Dose of each angiotensin II type-1 receptor blocker

Telmisartan, mg	Candesartan, mg	Olmesartan, mg
20	4	10
40	8	20
80	12	40

generated by a block-randomization method with varying block size. After randomization, the starting dose of each agent was decided according to the directions shown in Table 1 and based on the dose and type of ARB the patient was taking. The dose at the time of switching was also decided based on Table 1. ARBs were administered in a crossover manner, each for 12 weeks.

The primary study endpoint of the study was serum levels of triglyceride (TG) and plasma levels of adiponectin upon telmisartan treatment compared with candesartan treatment, which was based on previous studies.¹⁸⁻²⁰ Secondary endpoints were levels of low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), glycated albumin (GA), fasting insulin (FI), and high-sensitivity C-reactive protein (hs-CRP), fasting glucose (FG) glycated hemoglobin (HbA1c), homeostatic model assessment of insulin resistance (HOMA-IR), estimated glomerular filtration rate (eGFR), spot urine protein/creatinine ratio, and blood pressure.

Sampling and Measurements of Blood and Urine

At the beginning of the study and the end of each treatment, a blood sample was taken after 12 hours of fasting. Serum levels of TG, LDL-C, HDL-C, GA, FI, and hs-CRP were measured. Plasma levels of adiponectin, FG, and HbA1c were measured.

Levels of LDL-C, HDL-C TG, GA, sCr, and urinary Cr were measured by an enzymatic method using an automated analyzer (Labospect 008; Hitachi, Tokyo, Japan). The hs-CRP concentrations were measured by a latex immunoturbidimetric method using an automated analyzer (Labospect 008; Hitachi). The FI levels were measured by a chemiluminescence method on an immunoassay analyzer (Architect i2000SR PLUS; Abbott Diagnostics, Abbott Park, IL). Adiponectin concentrations were measured by a latex particle-enhanced immunoassay. Measurement of FG levels was based on the glucose oxidase immobilized electrode method and carried out using an automated glucose analyzer (GA09; A&T, Kanagawa, Japan). The HbA1c concentrations were determined by ion-exchange high-performance liquid chromatography (HLC-723G9; Toso, Tokyo, Japan). Protein levels in urine were measured using the pyrogallol red-molybdate method using an automated analyzer (Labospect 008; Hitachi).

Calculations

The value for HbA1c was estimated using the National Glycohemoglobin Standardization Program. HOMA-IR was calculated according to the formula:

$$\text{HOMA-IR} = \text{FG (mg/dL)} \times \text{FI (\mu U/mL)} / 405$$

According to values for a Japanese population, the eGFR was calculated using a modified 3-variable equation²¹:

$$\text{eGFR (mL/min per 1.73 m}^2\text{)} = 194 \times [\text{sCr (mg/dL)}]^{-1.094} \times \text{age}^{-0.287} (\times 0.739 \text{ if female})$$

A spot urine sample was collected in the morning to measure the levels of protein and creatinine at the beginning and end of each therapy period.

Statistical Analyses

This trial was designed as a crossover test which dealt with intrapersonal differences in the primary endpoint between 2 medicines. According to an observational study,¹⁸ the mean serum level of TG was expected to decrease by 20 mg/dL after switching from candesartan to telmisartan. Another observational study of the intrapersonal variation at Kyushu University Hospital, expressed as a standard deviation, in the serum level of TG was 36.0 mg/dL. Assuming that a 1-sample *t* test is applied to the mean difference in TG with a 2-sided alpha of 0.05, 37 patients would be required to ensure 90% statistical power. The target number of patients was set at 46 in total (23 per group) considering possible dropout of 20% and ineligibility found after registration. Summary statistics are shown as the mean ± SD. Statistical analyses were undertaken using Stata v12 (Stata, College Station, TX). The Student *t* test was used to detect a significant difference in the mean value. Some data were highly skewed to the right, so we reexamined statistical analyses with logarithmically converted values and confirmed the results of statistical tests with raw values. *P* less than 0.05 (2-sided) was considered significant.

RESULTS

Patient Characteristics

All KT were the first KT in a particular patient. Among 6 patients who dropped out, 4 were not followed up due to transfer to another hospital: 3 patients switched from candesartan to telmisartan, and 1 patient switched from telmisartan to candesartan. Another 2 patients discontinued the study drug due to hypotension after switching: 1 switched to telmisartan, and 1 switched to candesartan. Analyses were carried out on the remaining 40 cases. Table 2 shows the baseline characteristics of these 40 patients.

Data for Blood Pressure and Laboratory Indices

Table 3 shows the results of measurements of blood pressure and laboratory indices at baseline and after administration of the 2 agents. New-onset DM after KT did not occur during the study period. No significant differences were observed in systolic or diastolic blood pressure after administration of telmisartan or candesartan. Levels of adiponectin, LDL-C, HDL-C, FG, HbA1c, GA, FI, sCr, hs-CRP, HOMA-IR, or the spot urine protein/creatinine ratio did not show significant differences after administration of each drug. After telmisartan administration, serum levels of TG were significantly lower (*P* = 0.019), and the eGFR was significantly higher (*P* = 0.038) than those after candesartan administration.

DISCUSSION

We conducted a prospective randomized crossover study to investigate the effects of telmisartan on the metabolism of glucose and lipids compared with those of a non-PPAR-γ-activating ARB in KT patients. We showed that telmisartan improved serum levels of TG and the eGFR for KT patients better than candesartan (which is a non-PPAR-γ-activating ARB). However, there were no significant differences between the 2 groups with regard to the other parameters

TABLE 2.**Baseline characteristics of patients**

Characteristics	Telmisartan >candesartan group (n = 21)	Candesartan >telmisartan group (n = 19)	Total (n = 40)
Sex (male/female)	11/10	18/1	29/11
Age, y ^a	45.5 (12.8)	42.1 (12.2)	43.9 (12.5)
Calcineurin inhibitor (tacrolimus/cyclosporin)	20/1	18/1	38/2
No. antihypertensive treatments	1.48 (0.59)	1.57 (0.73)	1.52 (0.66)
ARB before the study (telmisartan/candesartan/olmesartan)	18/1/2	14/5/0	32/6/2
Calcium-blocker (%)	10 (47.6)	10 (52.6)	20 (50.0)
Beta-blocker (%)	1 (4.8)	3 (15.8)	4 (10.0)
Alpha-blocker (%)	0 (0)	0 (0)	0 (0)
Diuretics (%)	0 (0)	2 (10.5)	2 (5.0)
Statin/ezetimibe/fibrate	7/0/0	6/3/0	13/3/0
ABO incompatible	4 (19%)	4 (21%)	8 (20%)
Postoperative period, mo ^a	31.2 (28.1)	20.8 (10.5)	26.2 (22.0)
Primary disease			
Chronic glomerulonephritis/FSGS/alport/others	16/1/1/3	14/1/1/3	30/2/2/6
Deceased/live donor	5/16	5/14	10/30
Donor age, y ^a	59.6 (7.1)	52.1 (10.3)	56.1 (9.4)

^aData are the mean ± SD or numbers.

FSGS, focal segmental glomerulosclerosis.

studied, including serum adiponectin levels or parameters of glucose metabolism.

Several reports have shown that telmisartan can reduce the serum TG level compared with other ARBs.^{18,19} Festuccia and Deshaies²² reported that telmisartan acts on PPAR- γ , the ligand of which markedly increased subcutaneous clearance of a labeled triacylglycerol emulsion, and most of the fatty acids taken up by adipocytes were directed toward triacylglycerol synthesis. The activities of the enzymes in this synthetic pathway (glycerol 3-phosphate acyltransferase, phosphatidic acid phosphatase, and diacylglycerol acyltransferase) were markedly upregulated by the PPAR- γ ligand. They assumed that this phenomenon was part of a mechanism to decrease TG levels.²² Our study also showed that serum levels of TG upon telmisartan administration were significantly lower than those upon candesartan exposure.

Adiponectin is a hormone produced by adipocytes. The association between hypo adiponectinemia and reduced sensitivity to insulin, a less favorable serum lipid profile, and increased risk for cardiovascular diseases are well established.²³ It has been reported that PPAR- γ agonists modulate adiponectin expression, and adiponectin has been postulated to be a biomarker of PPAR- γ activation in vivo.²⁴ Compared with candesartan, telmisartan has been reported to increase adiponectin levels 3 months after administration in patients with type 2 DM.²⁰ In our study, although the difference was not significant, the adiponectin level tended to be higher in patients receiving telmisartan than those given candesartan ($6.14 \pm 3.01 \mu\text{g/mL}$ vs $5.93 \pm 3.13 \mu\text{g/mL}$; $P = 0.44$). Long-term investigation with a larger patient cohort may show the effect of telmisartan on adiponectin levels.

PPAR- γ in muscle tissue aids activation of phosphoinositol-3-kinase after insulin ligates the insulin receptor to help glucose transporter type-4 (a glucose receptor) move to the surface of cell membranes and bring glucose into the cell.²⁵ In subcutaneous fat tissue, glucose transporter type-4 helps bring glucose into the cell and aids subsequent glucose metabolism.²² Based on these effects, thiazolidinediones (glitazones), as full agonists of PPAR- γ , are being used for DM treatment.

Telmisartan is a partial agonist of PPAR- γ and so is expected to improve insulin sensitivity. Hence, telmisartan could be used to prevent the development of new-onset DM after KT. In their meta-analysis, Takagi et al.²⁶ demonstrated a significant

TABLE 3.**Comparison of blood pressure and laboratory data between telmisartan and candesartan groups**

	Baseline	Telmisartan	Candesartan	P ^a
Blood pressure				
SBP, mm Hg	127.2 (12.6)	126.6 (16.5)	123.4 (12.5)	0.19
DBP, mm Hg	75.2 (7.1)	75.9 (10.0)	73.3 (8.0)	0.15
Lipid metabolism				
TG, ^b mg/dL	139.3 (62.3)	114.3 (50.8)	136.5 (66.8)	0.019
LDL-C, ^b mg/dL	105.0 (21.4)	104.5 (31.3)	102.4 (24.5)	0.52
HDL-C, ^b mg/dL	61.0 (17.5)	64.4 (17.5)	62.4 (17.9)	0.19
Adiponectin, ^c $\mu\text{g/mL}$	6.16 (3.24)	6.14 (3.01)	5.93 (3.13)	0.44
Glucose metabolism				
FG, ^c mg/dL	98.1 (10.2)	99.1 (12.8)	98.4 (10.8)	0.76
HbA _{1c} , ^c %	5.33 (0.34)	5.38 (0.34)	5.39 (0.39)	0.7
GA, ^b %	14.4 (1.2)	14.5 (1.3)	14.5 (1.3)	0.53
FI, ^b $\mu\text{U/nL}$	14.1 (17.5)	14.4 (22.0)	14.3 (23.6)	0.95
HOMA-IR	3.46 (4.12)	3.72 (5.47)	3.52 (5.83)	0.98
Graft function				
sCr, mg/mL	1.32 (0.33)	1.29 (0.35)	1.31 (0.30)	0.48
eGFR, mL/min per 1.73 m ²	48.6 (14.5)	50.4 (15.1)	48.5 (12.5)	0.038
UPCR, g/gCr	5.34 (6.22)	4.50 (3.78)	5.37 (5.45)	0.21
Inflammation				
hs-CRP, mg/dL	0.176 (0.653)	0.174 (0.445)	0.221 (0.694)	0.61

Data are the mean ± SD.

^a Telmisartan vs candesartan.

^b Serum.

^c Plasma.

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FG, fasting glucose; FI, fasting insulin; GA, glycated albumin; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; sCr, serum creatinine; TG, triglyceride; UPCR, spot urine protein/creatinine ratio.

reduction in the FI level and improved insulin sensitivity with telmisartan relative to other ARB therapies. In our study, levels of FG, HbA1c, GA, FI, or HOMA-IR showed no significant differences between patients given telmisartan or those administered candesartan. Different from other studies,^{11,12} our study population did not have DM. In our patients, the initial level of these parameters of glucose metabolism was within the normal range upon study initiation. Therefore, there was no difference between these parameters of glucose metabolism before the 2 agents were given.

The effect on the eGFR was significant, but the difference was small, so the effect may not have been clinically useful. We analyzed the association between blood pressure (systolic and diastolic) and eGFR differences. A regression model was adopted and *P* less than 0.05 (2-sided) was considered significant. The blood pressure values and differences in blood pressure were not associated with eGFR differences between the 2 groups. Angiotensin increases the GFR by constricting the efferent arteries of glomeruli. In general, it is thought that ARBs decrease the GFR by blocking this effect.²⁷ Conversely, PPAR- γ has been reported to act as a vasorelaxant, as evidenced by inhibition of insulin-induced expression of endothelin-1 in endothelial cells and enhancement of the release of nitric oxide from these cells.²⁵ It has been hypothesized that the effect of decreasing the GFR could be compensated by increasing blood flow in glomeruli by relaxing the endothelium stimulated by PPAR- γ , and result in an increase in the GFR of a patient taking telmisartan. In addition, different from previous studies,^{20,27} transplanted kidneys are denervated. These phenomena may be why the eGFR in patients taking telmisartan was significantly better than in those taking candesartan. With regard to urinary protein, there were no significant differences between the urine protein/creatinine ratio for patients taking these 2 medications. It has been postulated that the effect on urinary protein is the result of blocking angiotensin, not from activating PPAR- γ . In a study comparing ACEI and ACEI plus a PPAR agonist,²⁸ differences in urinary levels of protein were not observed.

Inflammation decreases insulin sensitivity and can induce hyperglycemia. Chronic inflammation is a cause of cardiovascular disease. PPAR- γ can block the nuclear factor-kappa B pathway (the main pathway that induces the inflammatory response). Therefore, it is expected that telmisartan can reduce inflammation, increase insulin sensitivity and prevent cardiovascular diseases. Miura and colleagues¹⁵ showed a significant effect of telmisartan on adiponectin levels. The hs-CRP levels and glucose metabolism were compared with other ARBs for patients with type 2 DM. Conversely, our study showed no significant differences in these parameters between telmisartan and candesartan groups. One possible explanation is that our cohort comprised non-DM KT patients who had normal levels of inflammation upon study initiation.

Abnormal glucose metabolism and hyperlipidemia contribute to an increased risk of cardiovascular events after KT. Hence, telmisartan, which improves serum TG levels, could be expected to prevent post-KT cardiovascular events and result in better long-term survival of grafts and patients.

The present study had 4 potential limitations. First, the study cohort was small, and this was a randomized crossover study. Although a double-blind randomized controlled study is the "ideal" study design to show differences between groups, it requires a much larger sample size compared with

a crossover trial with regard to statistical power. Considering the expected number of cases to be registered in our institution, we chose a crossover design to reduce the required sample size. Second, patients were under the influence of other ARBs because there was no washout period at study initiation or upon drug switching. The half-life of telmisartan is longer than that of candesartan (approximately 24 hours vs 9 hours). A washout period is commonly set in a crossover trial, but it was not set in the present study because of ethical reasons. The patients recruited in our study were continuing treatment. If the treatment stopped during the washout period, their health would have been affected. Third, we assessed the effects of administration of each drug for 12 weeks. Investigation of the impact of long-term effects, including postprandial parameters and clinical outcomes, would be needed in future studies. Fourth, although TG levels can vary widely with dietary changes, we could not ascertain objective or subjective assessments of patients on an identical diet.

CONCLUSIONS

Our study suggests that telmisartan treatment may have beneficial effects on the level of TG and eGFR compared with candesartan. Prospective investigations with a randomized controlled design and a large population (including patients with DM) and a long period are needed to confirm these findings.

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