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Therapeutic effect of ARBs on insulin resistance and liver injury in patients with NAFLD and chronic hepatitis C: A pilot study

MUNECHIKA ENJOJI[1,2], KAZUHIRO KOTOH[1], MASAKI KATO[1], NOBITO HIGUCHI[1], MOTOYUKI KOHJIMA[1], MANABU NAKASHIMA[2] and MAKOTO NAKAMUTA[3]

[1]Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University; [2]Department of Clinical Pharmacology, Faculty of Pharmaceutical Sciences, Fukuoka University; [3]Department of Gastroenterology, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

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Abstract. Fatty liver is one of the local morphological manifestations of metabolic syndrome and is frequently associated with insulin resistance. Insulin resistance is also common in patients with chronic hepatitis C. Hyperinsulinemia is an independent risk factor for hypertension and cardiovascular mortality. The aim of this study was to evaluate the therapeutic efficacy of angiotensin II receptor blockers (ARBs), telmisartan and olmesartan, for patients with non-alcoholic fatty liver disease (NAFLD) and chronic hepatitis C (CH-C). We analyzed the incidence of obesity, insulin resistance, and other disorders in patients with NAFLD (Group A), CH-C (Group B), or other liver diseases (Group C). We evaluated whether the ARBs, telmisartan and olmesartan, improved insulin resistance and liver injury by measuring the homeostasis model assessment ratio of insulin resistance (HOMA-IR) and serum alanine aminotransferase (ALT). The incidence of obesity (BMI ≥25 kg/m^2) was significantly higher in Group A than in Groups B and C. The incidence of insulin resistance (HOMA-IR ≥2.5) in Groups A and B was significantly higher than in Group C. Regular doses of telmisartan and olmesartan significantly improved HOMA-IR and ALT levels not only in NAFLD patients but also in patients with CH-C. The effects tended to be more notable with telmisartan. In conclusion, telmisartan and olmesartan improved insulin sensitivity and may possibly be used as liver protecting agents in CH-C as well as NAFLD patients.

Correspondence to: Dr Munechika Enjoji, Department of Clinical Pharmacology, Faculty of Pharmaceutical Sciences, Fukuoka University, 8-19-1 Nanakuma, Johnan-ku, Fukuoka 814-0180, Japan
E-mail: enjoji@adm.fukuoka-u.ac.jp

Abbreviations: ARB, angiotensin II receptor blockers; NAFLD, non-alcoholic fatty liver disease; CH-C, chronic hepatitis C; HOMA-IR, homeostasis model assessment ratio of insulin resistance; ALT, alanine aminotransferase; BMI, body mass index; DM, diabetes mellitus; PPAR-γ, peroxisome proliferator-activated receptor-γ; IRS, insulin receptor substrate-1

Key words: insulin resistance, angiotensin II receptor blocker, chronic hepatitis C, non-alcoholic fatty liver disease

Introduction

Metabolic syndrome contributes to patient morbidity. It is a syndrome in which metabolic disorders such as obesity, glucose intolerance, insulin resistance, dyslipidemia, and hypertension are associated with each other. Non-alcoholic fatty liver disease (NAFLD) is now regarded as a manifestation of metabolic syndrome and, in many cases, some of these disorders commonly co-exist (1,2). In our experience, in chronic hepatitis C (CH-C), insulin resistance is frequently observed even in non-obese and non-hypertensive patients. Considering patients' prognosis, insulin resistance should be treated and prevented since in a recent study, hyperinsulinemia was shown to be one of the independent risk factors and precursors for hypertension. Hypertensive adults with hyperinsulinemia had an increased risk of cardiovascular mortality (3-7).

Angiotensin II receptor blockers (ARBs) are a new class of anti-hypertensive drugs that are highly selective for the angiotensin II type 1 receptor and block diverse effects of the agonist angiotensin II. ARBs are also expected to have organ-protective effects independent of their anti-hypertensive action. In addition to their beneficial effects against hypertension, ARBs delay the progression of renal dysfunction, protect against heart failure and reduce the incidence of cardiovascular disease (8-10). ARB-based therapy may be effective for preventing recurrent stroke (11). ARBs also have anti-diabetic and anti-atherosclerotic properties (12,13). In addition to these organ protective activities, metabolic aspects, such as improving insulin sensitivity, are also important (14). Thus, it is expected that ARBs may be effective in preventing cardiovascular events and death, not only by their vascular actions, but also by their metabolic effects in various patient populations. However, since it is apparent that not all types of ARBs have the same effects with respect to receptor selectivity, binding mode, and metabolism, the benefits should be evaluated for each type of ARB.

In this study, we analyzed the incidence of obesity, insulin resistance, and other disorders in patients with NAFLD, CH-C, and other liver diseases. In hypertensive patients with insulin resistance, we evaluated whether olmesartan or telmisartan improved levels of a homeostasis model assessment of insulin resistance (HOMA-IR) and serum alanine aminotransferase (ALT).

Patients and methods

The study population included men and women aged between 19 and 82 years, with liver diseases. Patients were divided into three groups based on their type of liver disease; Group A, NAFLD (n=46); Group B, CH-C (n=68) and Group C, chronic hepatitis B (n=19), primary biliary cirrhosis (n=8), autoimmune hepatitis (n=6), hyperlipidemia without fatty liver (n=8), alcoholic hepatitis (n=9), Wilson disease (n=2), idiopathic portal hypertension (n=1), citrullinemia (n=1) and primary sclerosing cholangitis (n=1). Cirrhotic patients were included in each group, Group A (n=1, Child B); Group B (n=21, Child A/B=14/7) and Group C (n=9, Child A/B=7/2). Incidence of obesity (body mass index: BMI ≥25 kg/m^2), insulin resistance (HOMA-IR ≥2.5), hyperuricemia (≥7.0 mg/dl in males and ≥6.5 mg/dl in females), hypertension, fatty liver (abnormal 'bright' hepatic ultrasonography) and diabetes mellitus (DM) were examined.

In patients with insulin resistance and hypertension (n=24), ARB medication (telmisartan or olmesartan) was started either newly (n=9) or in place of Ca-blockers (n=8), ACE-inhibitors (n=3), or other ARBs (valsartan and candesartan, n=4). The change in HOMA-IR and serum ALT levels was evaluated at intervals of 2 months (Fig. 1A). Then, for 28 patients (NAFLD, 14; CH-C, 14 cases), olmesartan was administered either newly (n=11) or in place of Ca-blockers (n=8), ACE-inhibitors (n=3), or other ARBs (losartan, valsartan and candesartan, n=6). At intervals of 2 months, olmesartan was replaced by telmisartan, and then again by olmesartan. HOMA-IR and serum ALT levels were examined every 2 months (Fig. 1B). The level of high molecular weight adiponectin was determined using an enzyme-linked immunosorbent assay (human high molecular weight adiponectin ELISA kit, Fujirebio Inc., Tokyo, Japan). There were no differences between the groups in terms of age, gender, or BMI.

All patients provided written informed consent before entering the study and starting treatment. Significant differences in HOMA-IR, ALT, and adiponectin levels were statistically evaluated using the Mann-Whitney U-test.

Results

Incidence of insulin resistance in NAFLD and CH-C patients. The incidence of obesity (BMI ≥25.0 kg/m^2), fatty liver, hypertension, DM, hyperuricemia, and insulin resistance was examined in patients with NAFLD (Group A), CH-C (Group B), or other liver diseases (Group C). The results are shown in Table I. The incidence of insulin resistance and DM was significantly higher in Groups A and B than in Group C. A significant difference was shown in the percentage of patients with obesity, fatty liver, and hyperuricemia between Groups A and B. The results support the commonly approved theory that HCV infection induces insulin resistance and oxidative stress in the liver, independent of obesity.

Pilot study of ARB effects on insulin resistance and hepatic injury. We evaluated the therapeutic effect of olmesartan and telmisartan on insulin resistance and hepatic injury in 24 patients (NAFLD, 10; CH-C, 10; CH-B, 1; autoimmune hepatitis, 3 cases) with hypertension and insulin resistance (HOMA-R ≥2.5). The test schedule is shown in Fig. 1A. Patients were randomly assigned to either olmesartan (20 mg/day, n=12) or telmisartan (40 mg/day, n=12), which were administered newly or in place of another anti-hypertensive drug. The characteristics of the patients are shown in Table II. Before, and 2 months after the administration, HOMA-IR and ALT levels were examined. As a result, telmisartan significantly lowered HOMA-IR and ALT levels and olmesartan significantly lowered HOMA-IR (Fig. 2). There were no significant increases in high molecular weight adiponectin in either group (data not shown).

Comparison of the therapeutic effects of olmesartan and telmisartan. Olmesartan and telmisartan were then alternately administered for 6 months to 28 patients (NAFLD, 14; CH-C, 14 cases). The test schedule is shown in Fig. 1B. Characteristics of the patients are shown in Table III. Before and after administration, HOMA-IR and ALT levels were examined every 2 months. In the analysis of NAFLD patients, HOMA-IR decreased significantly with olmesartan and continued to decrease significantly with telmisartan; the reduced level was maintained after the change to olmesartan (Fig. 3A). Serum ALT also significantly decreased with olmesartan and the level tended to decrease in the following telmisartan and olmesartan periods but was not significant (Fig. 3B). In the analysis of CH-C patients, HOMA-IR significantly decreased with olmesartan, and continued to decrease with telmisartan, but the level rose again significantly during the olmesartan period (Fig. 4A). Serum ALT decreased with olmesartan but not significantly; transfering to telmisartan decreased the level significantly (Fig. 4B). After changing to olmesartan, ALT tended to increase, although not significantly (Fig. 4B).

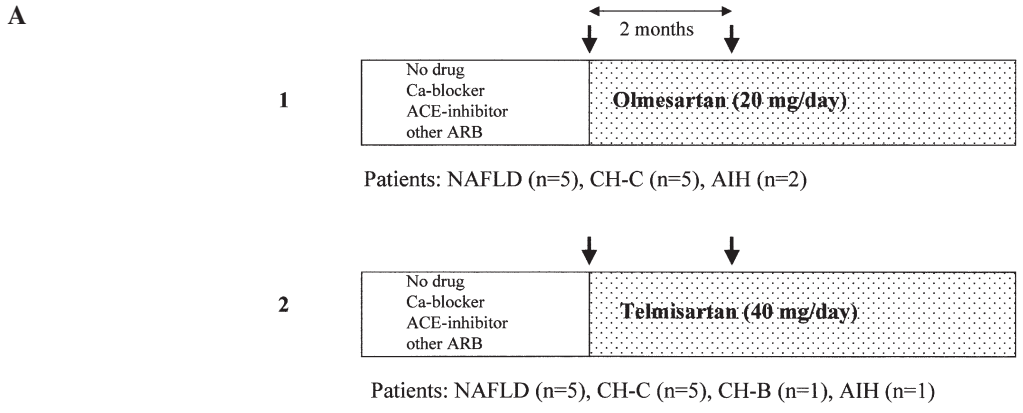
Discussion

ARBs are now widely used for the treatment of hypertension. Recent studies have suggested that the rennin-angiotensin system functions in the regulation of adipogenesis as well as in hepatocellular insulin signaling (15-18). Angiotensin II, acting via the angiotensin type 1 receptor, inhibits the differentiation of preadipocytes into mature adipocytes and this may result in the ectopic storage of fat in skeletal muscle and liver, thereby decreasing insulin sensitivity (17). Various insulin-sensitizing medications such as pioglitazone, a thiazolidinedione derivative, have confirmed the beneficial effects on biochemical and histological data in patients with steatohepatitis (18,19). Evidence is accumulating to show that ARBs can restore impaired intracellular insulin signaling and promote redistribution of excess fat from those ectopic sites to mature adipocytes, resulting in improved insulin sensitivity (20,21). In patients with DM, ARBs, especially olmesartan and telmisartan, have been reported to be notably effective in

ıcidence of metabolic disorders in patients.

	Obesity	Insulin resistance	Hyperuricemia	Fatty liver	Hypertension	DM
Group A	65.2%[a] (30/46)	45.7%[b] (21/46)	32.6%[a] (15/46)	97.8%[a] (45/46)	39.1% (18/46)	23.9%[b] (11/46)
Group B	22.1% (15/68)	36.8%[b] (25/68)	26.5% (18/68)	14.7% (10/68)	33.8% (23/68)	23.5%[b] (16/68)
Group C	21.8% (12/55)	16.4% (9/55)	20.0% (11/55)	10.9% (6/55)	29.1% (16/55)	14.6% (8/55)

[a]Significantly higher than groups B and C. [b]Significantly higher than group C. Obesity, BMI ≥25 kg/m^2. Insulin resistance, HOMA-R ≥2.5. Hyperuricemia: serum uric acid ≥7.0 (male) or ≥6.5 (female) mg/dl. DM, diabetes mellitus.



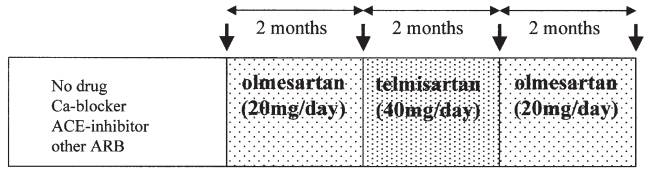


Figure 1. (A) Test schedule 1. Patients with hypertension and HOMA-IR ≥2.5 were randomly assigned to two groups and treated with olmesartan or telmisartan. (B) Test schedule 2. Olmesartan and telmisartan were administered to the patients with hypertension and HOMA-IR ≥2.5 in the following order: olmesartan, telmisartan and olmesartan. HOMA-IR, ALT, and other indices were measured twice at intervals of 2 months (arrows). NAFLD, non-alcoholic fatty liver disease; CH-B, chronic hepatitis B; CH-C, chronic hepatitis C; AIH, autoimmune hepatitis.

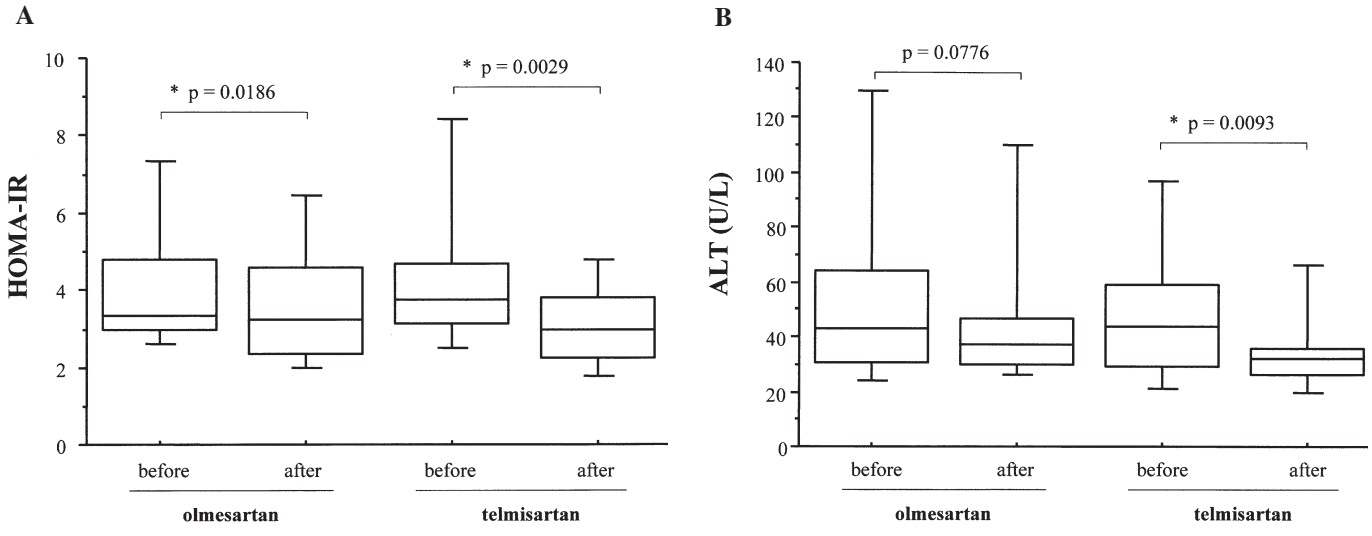


Figure 2. HOMA-IR (A) and serum ALT (B) levels before and after administration of olmesartan or telmisartan. *Significant difference.

Table II. Background of the patients (1).

	Olmesartan group	Telmisartan group	
Number of patients	12	12	
NAFLD	5	5	
CH-C	5	5	
CH-B	0	1	
AIH	2	1	
Age	63.33±12.72	61.33±11.36	NS
Gender (males/females)	5/7	6/6	
BMI	27.44±6.27	26.61±2.56	NS
Fatty liver	7	6	
DM	4	3	

NS, not significant.

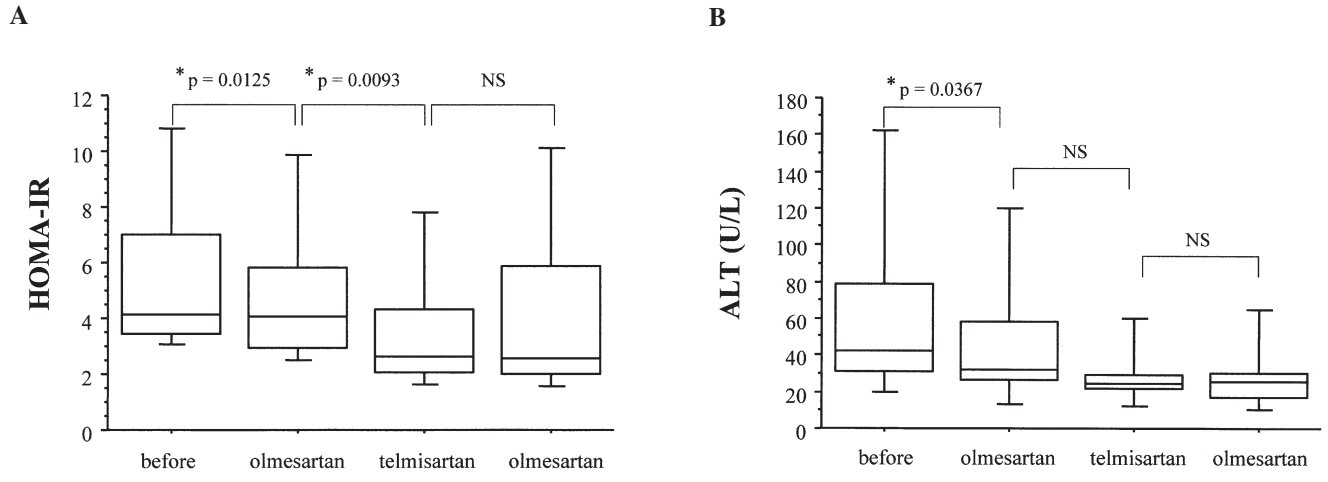


Figure 3. HOMA-IR (A) and serum ALT (B) levels before and after administration of olmesartan or telmisartan in patients with NAFLD. *Significant difference.

improving insulin sensitivity (21-23). Therefore, we tested the therapeutic effect of these two ARBs for the treatment of patients with NAFLD and CH-C.

Insulin resistance is a key pathogenic factor resulting in hepatic fat accumulation and is the common factor that links obesity, diabetes, hypertension, and dyslipidemia, with fatty liver. A recent study has shown that excessive hepatocytic triglyceride accumulation resulting from insulin resistance is the first step in the pathogenesis of NAFLD, and NAFLD exacerbates hepatic insulin resistance even more (24). NAFLD ranges from simple fatty liver to steatohepatitis that may be responsible for the increased oxidative stress within hepatocytes. Oxidative stress, due to the generation of reactive oxygen species resulting from mitochondrial fatty acid oxidation, mitochondrial abnormalities, and the induction of the cytochrome P450 system, is considered to be a potential factor that leads to hepatocyte injury, inflammation, and fibrosis (24,25). In NAFLD, it is now recognized that non-hepatic mechanisms, such as gut-derived lipopolysaccharide, NFκB-dependent inflammatory cytokine expression and adipocytokines, are largely responsible for the development of insulin resistance (24-27). Once developed, oxidative stress and diminished antioxidants within the liver initiate the progression from simple steatosis to steatohepatitis (24-27). In this study, olmesartan and telmisartan significantly improved insulin resistance and attenuated liver injury in NAFLD patients, although the effects tended to be more evident with telmisartan (Figs. 2 and 3). This may be because telmisartan is a partial agonist of peroxisome proliferator-activated receptor-γ (PPAR-γ) but without causing the fluid collection associated with full agonists of PPAR-γ, such as pioglitazone or rosiglitazone (28-31). Therefore, extrahepatic effects may be greater with telmisartan although an ameliorative effect of olmesartan on adipocytokine dysregulation has also been reported (32).

From the metabolic aspect, CH-C resembles certain features of NAFLD, such as the presence of insulin resistance and oxidative stress in the liver (33-36). Consistent with

Background of the patients (2).

	NAFLD	Chronic hepatitis (C)	
Number of patients	14	14	
Age	60.00±13.52	67.07±12.44	NS
Gender (males/females)	7/7	7/7	
BMI	26.54±3.17	25.09±7.66	NS
Fatty liver	13	3	
DM	3	3	

NS, not significant.

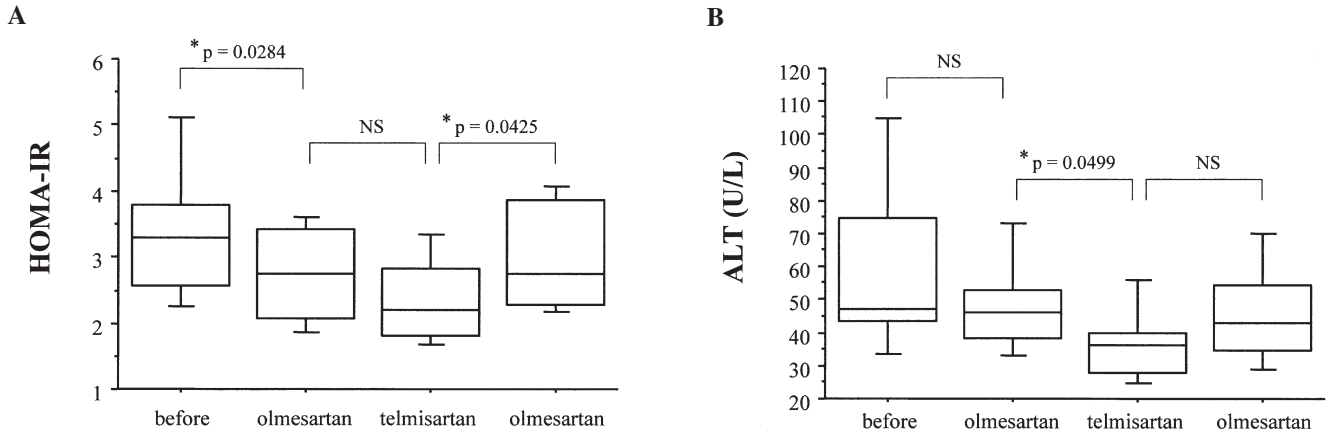


Figure 4. HOMA-IR (A) and serum ALT (B) levels before and after administration of olmesartan or telmisartan in patients with CH-C. *Significant difference.

reports from other studies, many of the CH-C as well as the NAFLD patients, showed insulin resistance; however, the percentage of CH-C patients with fatty liver or obesity was low (Table I). HCV is directly associated with insulin resistance in a dose-dependent manner, independent of the visceral adipose tissue area (37). HCV, by itself, can induce insulin resistance by disturbing the intracellular insulin signaling pathway through the function of the HCV core protein. The insulin receptor substrate-1 (IRS-1) level is known to be reduced by HCV core protein (38). The HCV core protein activates c-Jun N-terminal kinase, mitogen-activated protein kinase and transcription factor activator protein-1, up-regulates serine phosphorylation of the IRS-1, and impairs the downstream Ser/Thr kinase protein kinase B (Akt/Pkb) signaling pathway involved in insulin resistance (39). Therefore, the major component of insulin resistance in CH-C patients may be hepatic rather than extrahepatic. In our study, telmisartan appeared to be more effective than olmesartan for attenuating insulin resistance and liver injury in CH-C patients although olmesartan also elicited significant improvements (Figs. 2 and 4); however, we cannot clearly explain these results. We speculate that it may be because HCV itself suppresses hepatocellular insulin signaling as previously described. The suppressive effect may impair the improvement in insulin signaling that is normally achieved with ARBs. Therefore, telmisartan, which also has a partial PPAR-γ agonist role, may have a more pronounced therapeutic ability than olmesartan. Furusyo *et al* suggested that insulin resistance in patients with CH-C was related to adiponectin secretion (40). However, there are some contrasting data. Cua *et al* reported that insulin resistance and liver injury in hepatitis C was not associated with adipocytokines (41). Also in our study, before and after the treatment of telmisartan or olmesartan, there were no significant differences in adiponectin levels in patients (data not shown). However, a significant change in serum adiponectin levels might occur with a longer duration of telmisartan use. Therefore, we should consider other factors more precisely such as an influence of low-grade inflammation and mitochondrial dysfunction in the skeletal muscle as well as in the liver and adipose tissue (42-48). Hereafter, we intend to collect and analyze more data including other adipokines and cytokines from more patients.

We did not investigate the effect of other ARBs (losartan, valsartan, candesartan), but for all the patients (n=8) whose hypertensive drug was changed from these ARBs to olmesartan or telmisartan, their HOMA-IR and ALT levels were significantly lowered. Therefore, olmesartan and telmisartan

may have stronger therapeutic effects in terms of attenuating insulin resistance and liver injury than the other three ARBs perhaps as a result of more intrahepatic and extrahepatic actions.

In conclusion, olmesartan and telmisartan significantly improved insulin resistance and liver injury. The effect tended to be more distinct with telmisartan. These two ARBs may therefore be used as liver protecting agents in CH-C patients as well as NAFLD patients.

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