*Original Article*

# Losartan Elevates the Serum High-Molecular Weight–Adiponectin Isoform and Concurrently Improves Insulin Sensitivity in Patients with Impaired Glucose Metabolism

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**Adiponectin is an adipocyte hormone that ameliorates insulin resistance and prevents diabetes. Patients with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) are at a high risk of developing diabetes and cardiovascular diseases. Since treatment with angiotensin II receptor blockers retards the development of diabetes, the effects of losartan on serum adiponectin levels were examined with regard to insulin sensitivity in pre-diabetic patients. Sixty-five patients with IFG/IGT (42 males, 23 females, 63±13 years old) were randomized to receive 25–100 mg of losartan ($n$=33) or a calcium channel blocker (CCB, $n$=32) for 3 months. Before and after the treatment, changes in blood pressure, insulin sensitivity (HOMA-R) and serum concentrations of high molecular weight (HMW)-adiponectin and free fatty acid (FFA) were assessed. At baseline, the HMW-adiponectin concentration negatively correlated with the patient's body mass index, HOMA-R and triglyceride levels, and positively correlated with high-density lipoprotein (HDL)-cholesterol levels. However, the HMW-adiponectin concentration showed no correlation with blood pressure. HMW-adiponectin concentrations were similar between the losartan group and the CCB group. Both the losartan and CCB treatments similarly and significantly reduced the mean blood pressure (107±7 mmHg to 95±7 mmHg, $p$<0.0001, and 104±6 mmHg to 93±9 mmHg, $p$<0.0001, respectively). Losartan treatment resulted in a significant increase in HMW-adiponectin concentrations (45.9%) and a significant decrease in HOMA-R (23.9%) and FFA concentrations (26.5%); the percent changes were greater than those induced by CCB treatment ($p$<0.001, $p$<0.05 and $p$<0.01, respectively). We conclude that losartan increases the serum HMW-adiponectin concentration and concurrently improves insulin sensitivity in subjects with IFG/IGT. These results suggest that losartan may prevent diabetes by increasing serum adiponectin levels. (*Hypertens Res* 2008; 31: 1611–1618)**

***Key Words*: adiponectin, insulin resistance, glucose metabolism disorder, renin-angiotensin system**

## Introduction

Diabetes mellitus is a major risk factor for the development of various atherosclerotic, cardiovascular and renal diseases (*1*). The prevalence of type 2 diabetes has been precipitously increasing, rendering diabetes potentially one of the biggest health problems worldwide. Therefore, finding strategies to prevent the onset of new diabetes cases is important. Type 2 diabetes is a multifactorial disease involving genetic predisposition and various environmental factors (*2*). The established risk factors for the development of type 2 diabetes

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include impaired glucose metabolism, obesity, hypertension, low high-density lipoprotein (HDL) cholesterol and a family history of diabetes mellitus (*3*). In particular, impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) are the pre-conditions for type 2 diabetes; thus, patients diagnosed with IFG/IGT are at significant risk of developing diabetes (*4*). Since IFG/IGT are not only associated with progression to type 2 diabetes but are also independent risk factors for cardiovascular diseases (*1*), preventing the development of IFG/IGT into type 2 diabetes is crucial for reducing the morbidity and mortality of atherosclerotic diseases.

Adiponectin is a recently identified and characterized adipocyte-derived specific protein (*5–8*). In contrast to other adipocytokines, the circulating adiponectin concentrations are reduced in patients that are in various states of insulin resistance, such as obesity and type 2 diabetes (*9*). Interestingly, adiponectin has been suggested to enhance insulin sensitivity, and *vice versa* (*10*). In addition, Daimon *et al*. recently reported in the Funagata study that decreased serum adiponectin concentration is an independent risk factor for progression to type 2 diabetes in a Japanese population (*11*). Collectively, these studies suggest that a low concentration of circulating adiponectin is not a result of insulin resistance, but rather a cause of insulin resistance and progression to diabetes. Thus, strategies that explore the anti-diabetic effects of adiponectin may be useful in order to reduce diabetes and atherosclerotic diseases (*12*, *13*).

Angiotensin receptor blockers (ARB) are widely used in hypertension treatment, but also improve insulin sensitivity, inhibit cardiovascular diseases and prevent the development of diabetes by 19% to 25% (*14*, *15*). However, angiotensin II may adversely affect glucose metabolism since it increases reactive oxygen species and induces inflammation, decreases blood flow in many tissue beds and stimulates the sympathetic nervous system. It also inhibits insulin-signaling pathways, pancreatic function (*16*) and adiponectin production during adipocyte differentiation. Recently, Furuhashi *et al*. reported that candesartan, an ARB, increased serum adiponectin concentrations in essential hypertension patients (*17*). Moreover, Watanabe *et al*. showed that losartan, another ARB, significantly increased serum adiponectin concentrations and improved insulin sensitivity when compared with the calcium channel blocker (CCB) amlodipine in patients with essential hypertension (*18*).

Circulating adiponectin predominantly exists in characteristic multimers: a 3× monomer (trimer, low molecular weight form), 3× dimer (hexamer, middle molecular weight form) and 3× tetramer or 3× hexamer (polymers, high molecular weight forms) (*19*). Because only the high molecular weight (HMW)–adiponectin forms are reported to be decreased in the plasma of patients with lifestyle-related diseases (*20*) and are thus considered to be the active isoforms, we measured the concentrations of HMW-adiponectin isoforms in IFG/IGT patients.

In the present randomized clinical study, we compared the effects of losartan and CCB on circulating HMW-adiponectin levels as well as insulin sensitivity in IFG/IGT patients.

## Methods

### Subjects

Among 95 out-patients with hypertension, dyslipidemia, obesity, a family history of diabetes mellitus or suspected glucose metabolism disorder at health checkups, 65 patients with IFG/IGT (42 males, 23 females, mean age 63±13 years old) were enrolled in the present study. Impaired glucose metabolism was diagnosed at our institute based on the WHO 1999 criteria using a 75-g oral glucose tolerance test under fasting conditions. The criteria for IFG were 110 mg/dL≤ a fasting plasma glucose level <126 mg/dL and a 2 h plasma glucose level <140 mg/dL. The criteria for IGT were a fasting plasma glucose level <110 mg/dL and 140 mg/dL≤ a 2 h plasma glucose level <200 mg/dL (*21*).

Subjects included 51 hypertensive patients and 14 normotensive patients. Among the hypertensive patients, 40 patients had been treated with antihypertensive agents other than ARBs or angiotensin-converting enzyme (ACE) inhibitors (CCB: $n=37$, β-blocker: $n=3$), and 11 patients had been untreated. Hypertension was diagnosed according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004) (*22*) by averaging two measurements taken in the sitting position. The blood pressure ranges included in this study were 130 mmHg≤ systolic blood pressure <160 mmHg and/or 80 mmHg≤ diastolic blood pressure <100 mmHg. After a 2 month observation period, all participants were randomized into two groups: the losartan group ($n=33$) that received 25–100 mg of losartan for 3 months, and the CCB group ($n=32$) that received CCB (either amlodipine [$n=21$], azelnidipine [$n=6$], cilnidipine [$n=4$] or benidipine [$n=1$]) for 3 months. Among the subjects who were allocated to the CCB group, those who had already been treated with a CCB received the same CCB and the doses were titrated to achieve the target blood pressure level. Those who had been previously treated with β-blockers or were untreated received amlodipine. Seventeen patients in the CCB group were previously treated with CCB (amlodipine [$n=6$], azelnidipine [$n=6$], cilnidipine [$n=4$] and benidipine [$n=1$]). Twenty patients in the losartan group previously received CCBs (amlodipine [$n=9$], azelnidipine [$n=6$], cilnidipine [$n=3$] and benidipine [$n=2$]). The proportion of patients that had previously received CCBs did not differ significantly between the two groups. The randomization was carried out according to an assignment in a sealed envelope for each subject that indicated their grouping. An investigator (T.S.) who did not treat the study subjects was assigned as the independent monitor and confirmed that the randomization process was valid and that there had been no violation in the patient groupings. No other drugs were added and the dose of the drugs already administered was not changed during the

**Table 1. Baseline Characteristics of the Study Subjects and the Treatment Effects**

| | Losartan | | CCB | |
|---|---|---|---|---|
| Number of subjects (*n*) | 33 | | 32 | |
| Male/female (*n*) | 22/11 | | 19/13 | |
| Age (years old) | 64.2±12.4 | | 61.4±14.6 | |
| IFG/both/IGT (*n*) | 11/13/9 | | 6/19/7 | |
| | Baseline | 3 months | Baseline | 3 months |
| BMI (kg/m$^2$) | 27.3±4.3 | 27.2±4.3 | 25.9±4.0 | 24.9±6.2 |
| Fasting plasma glucose (mg/dL) | 113.5±8.3 | 107.3±10.8†† | 113.9±10.1 | 114.0±14.8 |
| Fasting insulin (μU/mL) | 12.2±8.1 | 8.4±5.8†† | 10.7±6.4 | 10.3±6.2 |
| HOMA-R | 3.4±2.3 | 2.2±1.5†† | 3.0±1.9 | 3.0±2.0 |
| QUICKI | 0.33±0.03 | 0.35±0.03†† | 0.33±0.03 | 0.34±0.03 |
| HMW-adiponectin (μg/mL) | 4.2±2.3 | 5.7±2.9†† | 4.6±2.2 | 4.4±2.2 |
| HDL cholesterol (mg/dL) | 60.7±17.8 | 60.6±19.2 | 57.2±12.9 | 56.9±13.1 |
| LDL cholesterol (mg/dL) | 112.9±24.5 | 115.7±19.8 | 121.0±34.0 | 116.2±25.3 |
| Triglyceride (mg/dL) | 168.4±127.6 | 150.5±80.6 | 161.6±119.3 | 140.3±86.6 |
| FFA (mg/dL) | 0.48±0.26 | 0.29±0.16†† | 0.43±0.29 | 0.43±0.22 |
| Uric acid (mg/dL) | 5.8±1.3 | 5.2±1.2†† | 5.7±1.3 | 5.6±1.4 |
| Systolic blood pressure (mmHg) | 148.8±9.2 | 130.0±8.9†† | 143.8±10.5* | 128.3±9.9†† |
| Diastolic blood pressure (mmHg) | 85.6±8.5 | 76.9±8.2†† | 83.1±6.9 | 73.6±9.2†† |

CCB, calcium channel blocker; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; BMI, body mass index; HOMA-R, homeostasis model assessment insulin resistance; QUICKI, quantitative insulin-sensitivity check index; HMW, high molecular weight; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FFA, free fatty acid. *$p<0.05$ *vs*. losartan, ††$p<0.001$ *vs*. baseline.

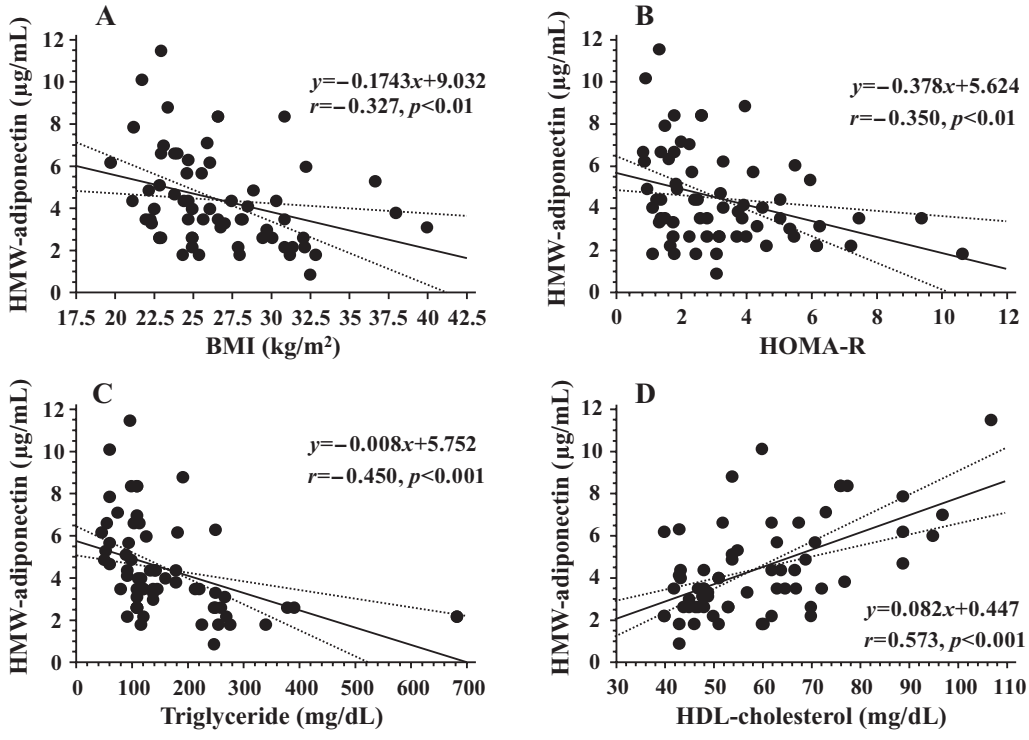


**Fig. 1.** *Relationship between baseline serum high molecular weight (HMW)–adiponectin concentration and A: baseline body mass index (BMI), B: baseline homeostasis model assessment insulin resistance (HOMA-R), C: baseline triglyceride and D: baseline high-density lipoprotein (HDL)-cholesterol.*

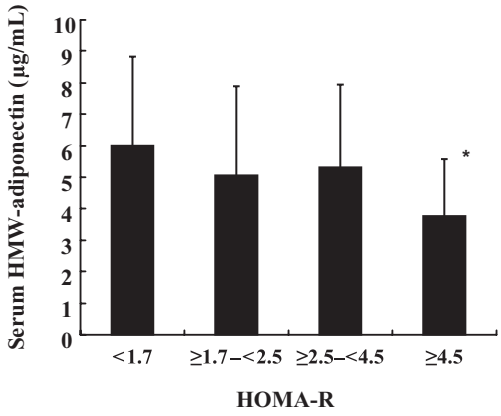


**Fig. 2.** *Mean baseline serum high molecular weight (HMW)–adiponectin concentrations in four groups divided according to HOMA-R index; insulin sensitive groups (I: HOMA-R < 1.7, n = 15; II: 1.7 ≤ HOMA-R < 2.5, n = 14), and insulin resistant groups (III: 2.5 ≤ HOMA-R < 4.5, n = 21, IV: 4.5 ≤ HOMA-R, n = 15). *p < 0.05 vs. HOMA-R < 1.7.*

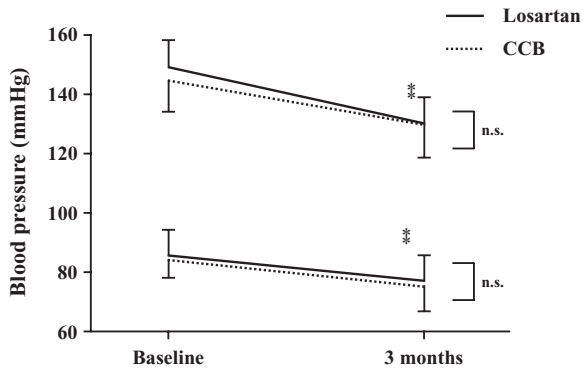


**Fig. 3.** *Blood pressure changes before and 3 months after the treatment with losartan or calcium channel blockers (CCB). *p < 0.001 vs. baseline.*

study period. Exclusion criteria were previous diagnosis with diabetes mellitus, secondary hypertension or severe cardiovascular, hepatic or chronic renal diseases according to the K/DOQI criteria (*23*).

For the hypertensive agents, the dosage was titrated to achieve the target blood pressure 1 month after the initial treatment. The target blood pressure was <130/80 mmHg according to the JSH 2004 criteria (*22*) for patients with impaired glucose metabolism. Before and after treatment, body weight and blood pressure were measured and blood samples were obtained from all subjects. Plasma HMW-adiponectin, fasting plasma glucose, fasting plasma insulin, various lipid parameters and uric acid were then measured. Insulin sensitivity was assessed by homeostasis model assessment insulin resistance (HOMA-R) (*24*) or the quantitative insulin-sensitivity check index (QUICKI) (*25*). We defined a HOMA-R>2.5 as being insulin resistant. The cut-off value 2.5 was adapted from the upper range of the mean HOMA-R (1.6±0.9) in a non-obese and non-diabetic Japanese population (*26*). The study protocol was approved by the Ethics Committee of Tokyo Women's Medical University, and informed consent was obtained from each subject.

## Measurement of HMW-Adiponectin

HMW-adiponectin was measured using a commercially available sandwich enzyme-linked immunosorbent assay kit (Fujirebio Inc., Tokyo, Japan) according to the manufacturer's instructions (*27*). Briefly, each specimen was diluted 1:441 with the supplied dilution buffer, and 100 μL of each diluted sample was then applied to each well along with the supplied standard, incubated at room temperature for 1 h, washed 3 times with the supplied cleaning solution and then incubated with 100 μL of horseradish peroxidase–labeled adiponectin antibody solution at room temperature for another 30 min. After washing 3 times, the samples were reacted with 100 μL of tetramethyl benzidine reagent at room temperature for 30 min, after which the supplied stopping solution was added to each well and the absorbance at 450 nm measured.

## Laboratory Investigations

The level of fasting plasma glucose and fasting plasma insulin were determined by the glucose oxidase method (COBAS INTEGRA 400; Roche, Basel, Switzerland) and the radioimmunoassay method (Insulin RIABEAD II; Dainabot Co., Tokyo, Japan), respectively. Serum lipid profiles, including total cholesterol, HDL cholesterol, triglyceride and free fatty acid (FFA), were estimated by enzymatic methods (Automatic Analyzer 7700 Series; Hitachi, Tokyo, Japan).

## Statistics

Data represent the mean±SD. Group differences were determined using unpaired *t*-tests. Linear regression analysis was used to determine the correlation between two variables. A probability value of <0.05 was considered to be statistically significant.

# Results

At baseline, the participants showed no significant differences in age, gender, body mass index (BMI), HOMA-R, blood pressure level, concentration of serum HMW-adiponectin or lipid profiles in the losartan group *vs*. the CCB group (Table 1). In all subjects, the serum HMW-adiponectin concentration was negatively correlated with BMI ($r=-0.327$, $p<0.01$) (Fig. 1A), HOMA-R ($r=-0.350$, $p<0.01$) (Fig. 1B) and serum triglyceride levels ($r=-0.450$, $p<0.001$) (Fig. 1C). The plasma HMW-adiponectin concen-

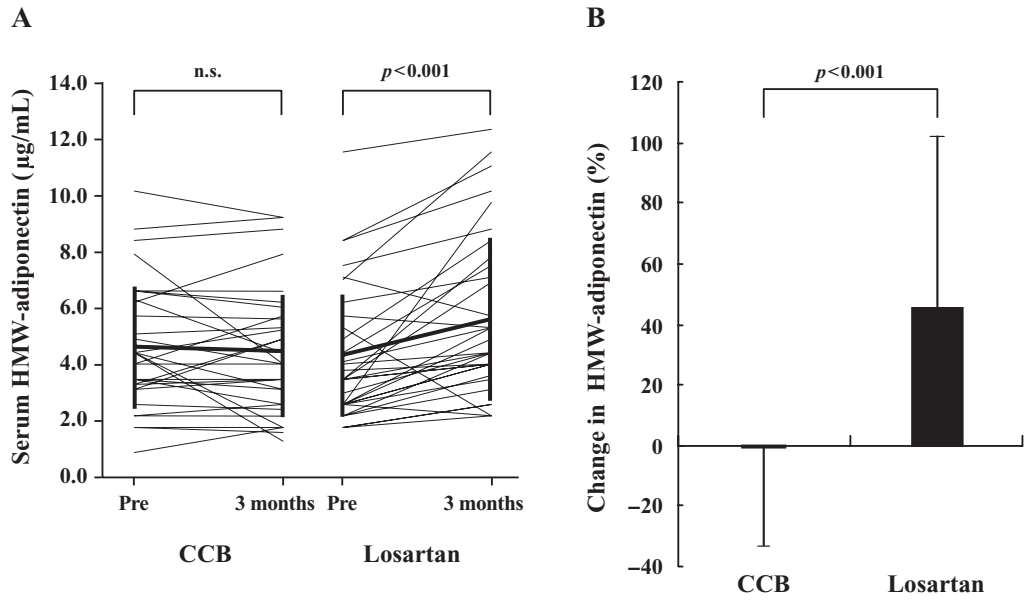


**Fig. 4.** *A: Serum high molecular weight (HMW)–adiponectin concentration before and 3 months after treatment with losartan or CCB and B: the percent changes in serum HMW-adiponectin concentration in the treatment groups.*

tration positively correlated with serum HDL-cholesterol levels ($r=0.573$, $p<0.001$) (Fig. 1D) and the QUICKI ($r=0.380$, $p<0.01$), but was not correlated with blood pressure.

When the subjects were divided into four groups according to the HOMA-R, namely the insulin-sensitive group (I: HOMA-R<1.7, $n=15$; II: 1.7≤HOMA-R<2.5, $n=14$) and the insulin-resistant group (III: 2.5≤HOMA-R<4.5, $n=21$; IV: HOMA-R≥4.5, $n=15$), the insulin resistant-group (IV) had significantly lower serum HMW-adiponectin levels than the insulin sensitive-group (I) (5.99±2.83 *vs*. 3.76±1.83 μg/mL, $p<0.05$) (Fig. 2).

Both losartan and CCB treatment significantly reduced systolic and diastolic blood pressure from baseline after 3 months (losartan group, 149±9 mmHg to 130±9 mmHg and 86±9 mmHg to 77±8 mmHg; CCB group, 144±11 mmHg to 128±10 mmHg and 83±7 mmHg to 74±9 mmHg, both $p<0.001$), but the reductions were not significantly different between the two groups (Fig. 3). Administration of losartan resulted in a remarkable increase in HMW-adiponectin concentration (4.4±2.5 μg/mL to 5.8±3.0 μg/mL, $p<0.001$) (Fig. 4A) and a concurrent decrease in HOMA-R (3.44±2.26 to 2.23±1.52, $p<0.001$). However, CCB treatment had no significant effect on these two parameters (4.5±2.2 μg/mL to 4.3±2.2 μg/mL and 3.05±1.87 to 2.98±1.97, respectively). The CCB group received different drugs, with most of the subjects receiving amlodipine but some receiving other CCBs. Therefore, we re-analyzed the losartan group ($n=33$) and amlodipine group ($n=21$) data and found almost identical results. The HMW-adiponectin concentration increased in 29 of the 33 patients in the losartan group, and in only 14 of the 32 patients in the CCB group. The percent increase in HMW-adiponectin concentration and percent decrease in HOMA-R were significant with losartan treatment compared with CCB treatment (45.9±56.0% *vs*. −0.0±32.8%, $p<0.001$ and −23.9±42.6% *vs*. 7.0±68.1%, $p<0.05$, respectively) (Figs. 4B and 5A).

The FFA levels decreased significantly (26.5%) from baseline with losartan treatment, whereas FFA levels increased by 29.8% in the CCB group (Fig. 5B). The percent changes were significantly different between the two groups ($p<0.01$). Uric acid significantly decreased in the losartan group ($p<0.001$), but not in the CCB group (−9.8±12.9% *vs*. −0.9±13.6%). There were no significant changes in BMI or levels of fasting plasma glucose, total cholesterol, HDL-cholesterol or triglyceride with either treatment.

When the effect of losartan on HMW-adiponectin was compared between the insulin-resistant group and the insulin-sensitive group, the effect was more remarkable in the former group (51.6%, $n=18$ *vs*. 39.1%, $n=15$). However, the percent changes in HMW-adiponectin were not significantly different between the insulin-resistant group and the insulin-sensitive group. With CCB treatment, the HMW-adiponectin concentration did not increase in either group (insulin-sensitive group: −24.7%, $n=14$; insulin-resistant group: −6.3%, $n=18$).

## Discussion

In the present study, we demonstrated that losartan treatment increased the serum HMW-adiponectin concentration and concurrently improved insulin sensitivity in patients with impaired glucose metabolism.

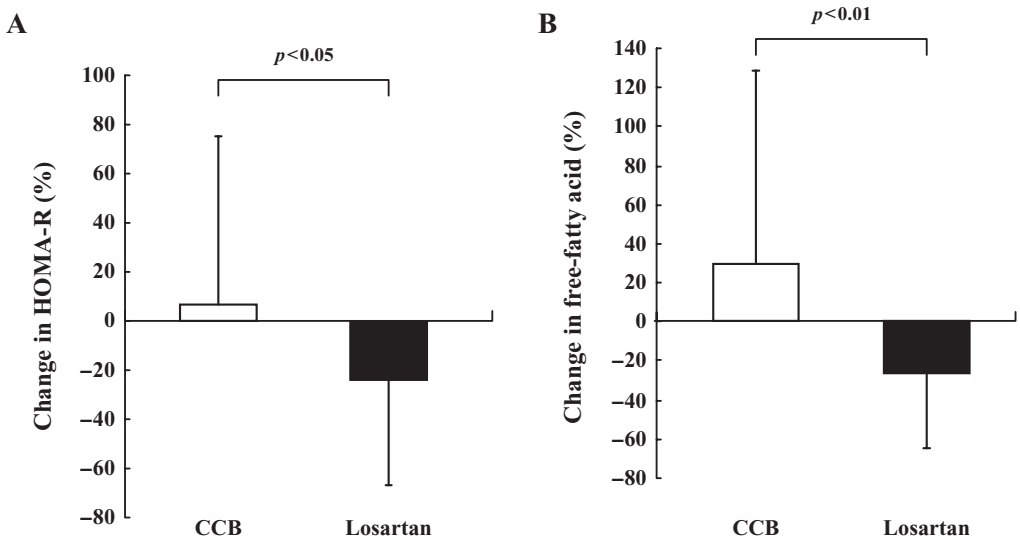


**Fig. 5.** *Percent changes in HOMA-R index and serum free-fatty acid concentration before and 3 months after treatment with losartan or CCB.*

Insulin resistance is well recognized to be associated with an increased risk for the development of type 2 diabetes and cardiovascular diseases. Consequently, timely identification and management of insulin resistance is warranted. It has been established that individuals with IFG/IGT are at high risk for type 2 diabetes, and most may exhibit insulin resistance to some extent. In a recent analysis, the average conversion rate of IFG/IGT to type 2 diabetes was estimated to be as high as 5.8% per year (*4*). In this context, we focused on patients with impaired glucose metabolism (IFG/IGT) and found in the study population that the serum HMW-adiponectin concentration was negatively correlated with BMI, HOMA-R and serum triglyceride levels, positively correlated with serum HDL-cholesterol levels and QUICKI but not correlated with blood pressure, consistent with previous studies on essential hypertension (*18*, *28*). HMW-adiponectin levels were positively correlated with the degree of insulin sensitivity at baseline. Clearly, HOMA-R and QUICKI are independent predictors of adiponectin concentration, and hypoadiponectinemia is associated with insulin-resistance. This finding is in accordance with previous findings that adiponectin levels are reduced in states of insulin resistance, such as obesity and type 2 diabetes (*5*).

Since the HOMA-R and QUICKI indices are based on fasting glucose and insulin values, they primarily reflect hepatic insulin sensitivity. In contrast, the clamp-derived index of insulin sensitivity primarily reflects insulin action in peripheral tissues. Although the euglycemic clamp has been considered the gold standard for measuring insulin resistance, we adopted the HOMA-R and QUICKI indices because both were easier procedures with which to assess insulin resistance in the outpatient environment and because hepatic insulin sensitivity and peripheral insulin sensitivity generally change in parallel with each other (*24*, *25*).

Losartan increased the concentration of serum HMW-adiponectin significantly for 3 months, similar to other studies on essential hypertension patients (*17*, *18*). Our data is more conclusive, possibly because HMW-adiponectin was measured in this study instead of total adiponectin, as other studies have examined (*18*). About half of the studied IFG/IGT individuals showed marked insulin resistance, as defined by HOMA-R>2.5. Although the HMW-adiponectin concentration positively correlated with the degree of insulin sensitivity at baseline, losartan treatment equally increased HMW-adiponectin concentration in both the insulin-resistant group and insulin-sensitive group. In our preliminary study, we could not find any appreciable change in HMW-adiponectin as early as 1 month after treatment, indicating that the effect of losartan on HMW-adiponectin levels requires several months.

In the present study, losartan not only increased serum HMW-adiponectin levels, but also improved insulin sensitivity. HOMA-R and serum FFA levels were significantly lowered by losartan treatment. In previous studies, elevated levels of plasma FFA were responsible for much of the insulin resistance in a concentration-dependent manner and inversely, reducing the levels of plasma FFA improved insulin sensitivity (*29*, *30*). The effect of losartan on insulin sensitization is in agreement with recent clinical studies that have suggested that antihypertensive therapy with ARB provides a risk reduction for the development of type 2 diabetes (*14*, *15*).

One possible mechanism by which losartan improves insulin sensitivity is by blockade of the renin-angiotensin system (RAS). Losartan ameliorates angiotensin II–induced impairment of insulin signaling, leading to increased availability of the glucose transporter GLUT 4 by enhancing the transloca-

tion of GLUT 4 from an intracellular membrane compartment to a plasma membrane fraction (*31*). In addition, losartan increases the blood flow in skeletal muscle by vasodilatation, as reported in a captopril study (*32*). Another proposed mechanism is the improvement of glucose tolerance by improving pancreatic β cell function and protecting progressive cell damage, as seen in an animal model of type 2 diabetes that was reported in a candesartan study (*16*). Furthermore, ARBs inhibit the overproduction and accumulation of triglyceride and FFA in the liver, which is also associated with improved insulin sensitivity (*30*, *33*).

Furuhashi *et al*. suggested that an increase in adiponectin concentration caused by RAS blockade may also be a novel mechanism for RAS blockade–mediated enhancement of whole-body insulin sensitivity (*17*). However, the mechanism by which RAS blockade leads to increased circulating adiponectin levels remains to be clarified. Adipose tissue possesses a local RAS fully capable of producing angiotensin II. Sharma *et al*. (*34*) have hypothesized that locally-produced angiotensin II is involved in regulating adipocyte differentiation and growth. Interruption of this local RAS results in the recruitment and differentiation of preadipocytes. This increased formation of small insulin-sensitive adipocytes counteracts the ectopic deposition of lipids in muscle and liver, thereby improving insulin sensitivity. Adiponectin secretion may be directly affected by adipocyte differentiation. RAS blockade is likely to promote increased adipogenesis that may result in a greater net capacity for adiponectin production. However, these changes have not been clearly demonstrated in human studies.

Recently conducted studies have revealed that some ARBs show partial agonistic activity of peroxisome proliferator activated receptor γ (PPARγ) and improvement in insulin sensitivity both *in vitro* and in an animal model (*35*, *36*). Although losartan, unlike telmisartan, does not act as a partial agonist of PPARγ, its metabolite, EXP3179, has been reported to activate PPARγ. In one study, EXP3179 was partially activated at 51% of the maximum response induced by the full agonist pioglitazone (*37*). Clinically, the main characteristic of PPARγ agonists is their ability to reduce insulin resistance (*38*). The mechanism of this effect is still uncertain, but it appears likely that adipogenesis and remodeling of white adipose tissue are important. The notion that ARBs may increase serum HMW-adiponectin concentrations and improve insulin resistance through activation of PPARγ is intriguing. However, the clinical relevance of this process must be confirmed in a large scale randomized clinical study.

One of the limitations of the present study is that the CCB group received different drugs, with most of the subjects receiving amlodipine but some receiving another CCB. Nevertheless, we re-analyzed the losartan group and amlodipine group data and found almost identical results to those described in this report. In addition, our literature searches have revealed that there are no documented effects of CCB on serum adiponectin levels. Taken together, despite the limitations of the study, it seems plausible that losartan elevates serum HMW-adiponectin levels and concurrently improves insulin sensitivity in patients with impaired glucose metabolism.

In conclusion, our results suggest that hypoadiponectinemia is associated with insulin resistance in patients with impaired glucose metabolism. Furthermore, we show that losartan increases serum HMW-adiponectin concentrations with an improvement in insulin sensitivity. These results provide a sufficient rationale for the use of ARBs for the prevention of diabetes in patients with impaired glucose metabolism.

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