Combination of an ACE Inhibitor and Indapamide Improves Blood Pressure Control, but Attenuates the Beneficial Effects of ACE Inhibition on Plasma Adiponectin in Patients With Essential Hypertension

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Background: Antihypertensive agents differentially influence the plasma adiponectin concentration and the effects of fixed-dose combination regimens remain unclear. The influence of a combination of an angiotensin-converting enzyme inhibitor (ACEI) and a thiazide-type diuretic or an ACEI alone on plasma adiponectin concentrations in patients with essential hypertension was evaluated in the present study.

Methods and Results: After a 2-week placebo run-in phase, 30 patients with essential hypertension were randomized to receive preterax (2 mg perindopril/0.625 mg indapamide) or cilazapril (2.5 mg) once daily for 12 weeks. Plasma adiponectin and insulin concentrations were measured before and after treatment. Insulin resistance was measured by homeostasis assessment index (HOMA-IR). Treatment with preterax (P=0.003) and cilazapril (P=0.031) significantly reduced systolic blood pressure (BP), but only preterax reduced diastolic BP (P=0.024). Cilazapril treatment significantly increased the plasma adiponectin concentration (P=0.025) and reduced plasma triglycerides (P=0.041), whereas preterax treatment increased the plasma insulin concentration (P=0.041) and tended to increase HOMA-IR.

Conclusions: The combination of an ACEI and indapamide improved BP control, but attenuated the beneficial effects of ACE inhibition on plasma adiponectin in patients with essential hypertension. Such a combination may be best reserved for improved BP control rather than for metabolic protection in clinical hypertension. (Circ J 2009; 73: 2282–2287)

Key Words: Adiponectin; Combination therapy; Hypertension; Insulin resistance; Thiazides

It has been recently suggested that adipose tissue as an important endocrine organ secreting many biologically active adipokines, which may contribute to the development of cardiovascular diseases including hypertension. Adiponectin is 1 of the most abundant adipokines secreted by adipocytes and plays a major role in the regulation of lipid and carbohydrate metabolism. It has been also suggested that adiponectin improves insulin sensitivity and prevents atherosclerosis. The circulating levels of adiponectin are reduced in patients with cardiovascular diseases, including hypertension, and with states of insulin resistance such as obesity and type 2 diabetes. Further, adiponectin has been recently related to cardiovascular outcomes in subjects with the metabolic syndrome (MetS). Therapeutic strategies that can increase plasma adiponectin levels, such as weight reduction in obese subjects and thiazolidinediones for insulin sensitization, are suggested as clinical cardiovascular protection. Though the detailed mechanisms remain unclear, blockade of the renin–angiotensin system (RAS) also appears to increase plasma adiponectin concentrations and is suggested for both blood pressure (BP) lowering and cardiovascular protection in subjects with MetS.
Antihypertensive Agents and Plasma Adiponectin

Methods

Study Population
A series of consecutive patients with established hypertension either with or without previous treatment were evaluated in the hypertensive outpatient clinic of a single medical center between October 2005 and January 2007. Only those patients with an office systolic BP (SBP) between 130 and 170 mmHg or a diastolic BP (DBP) between 80 and 110 mmHg or both were initially enrolled. The exclusion criteria were: allergy to perindopril, indapamide or cilazapril; using thiazolidinediones or statins; pregnancy; secondary hypertension; complicated hypertension with target organ damage; history of unstable angina, percutaneous coronary intervention or coronary artery bypass surgery within the last 3 months; deep vein thrombosis or pulmonary embolism within the last 6 months; established diabetes mellitus; serum creatinine >2 mg/dl; electrolyte imbalance (serum sodium <110 or >160 mmol/L or serum potassium <3.5 or >5.5 mmol/L). All patients gave informed consent, and the study was approved by the hospital’s research ethics committee.

Study Design
This was a randomized, double-blind, parallel-control study. All patients commenced a run-in period with 1 capsule of placebo orally per day and were evaluated by standard physical examination, routine clinical laboratory tests, including electrolytes, liver and renal function tests, lipid profiles, fasting glucose, chest roentgenography and baseline electrocardiography. After 2 weeks, they were randomly allocated to 1 of 2 groups: preterax (2 mg perindopril/0.625 mg indapamide once daily) or cilazapril (2.5 mg once daily) for 12 weeks if their office SBP was still >130 mmHg or DBP >85 mmHg or both. Participants were scheduled to visit the outpatient clinic every 4 weeks until the end of the study. Once SBP <105 mmHg or DBP <65 mmHg was noted at any visit, the investigator would consider if withdrawal of the subject from the study was necessary.

BP Measurement
At each visit, office BP was measured by a well-trained nurse or assistant with an electronic BP monitor in the morning after the patient had been seated for 10 min in a quiet room. Three consecutive BP measurements were performed and each measurement was separated by a 30-s pulse measurement. BPs were recorded as the average value of the last 2 recordings.

Laboratory Investigations
Blood samples for estimation of plasma adiponectin, insulin,
fasting glucose, total cholesterol, high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol, triglycerides, sodium, potassium and creatinine concentrations were obtained twice (before and 12 weeks after starting the antihypertensive medication). The plasma adiponectin concentration was measured using an ELISA kit (Linco Research Inc, St Charles, MO, USA); the intra- and interassay variation coefficients were not more than 1.4% and 3.4%, respectively. Plasma insulin concentration was assessed using an ELISA kit (Mercodia AB, Uppsala, Sweden) and the intra- and inter-assay variation coefficients were not more than 4% and 2.6%, respectively. Homeostasis model assessment insulin resistance index (HOMA-IR) was calculated according to the formula: fasting plasma glucose concentration [mmol/L] × fasting plasma insulin concentration [μU/ml]/22.5. Plasma lipid profiles, glucose, sodium, potassium and creatinine concentration were assessed using routine laboratory methods.

Statistical Analysis
Data are expressed as the mean ± SD for numeric variables and as the number (percent) for categorical variables. Comparisons of continuous variables between groups were performed by Mann-Whitney U-test. Subgroup comparisons of categorical variables were assessed by chi-square or Fisher’s exact test. A Wilcoxon signed rank test was used for analysis of dependent variables. Data were analyzed using SPSS software (version 15, SPSS, Chicago, IL, USA). A P-value <0.05 was considered to indicate statistical significance.

Results
Characteristics of the Patients
Of the 37 patients initially enrolled, 30 (19 males, 11 females; mean age 52.80±13.28 years) completed the study; 7 patients were excluded mainly because their office BP was <130/85 mmHg after the 2-week placebo run-in period. Thus, 15 patients were randomly allocated to the cilazapril group and the other 15 to the preterax group. The baseline clinical characteristics of the 2 groups are presented in Table 1. There were no significant differences between the 2 groups in age, gender, body mass index (BMI), SBP and DBP, baseline antihypertensive medicines, plasma concentrations of glucose and insulin, HOMA-IR index, plasma levels of triglycerides, HDL-cholesterol, LDL-cholesterol, sodium, potassium and creatinine. However, patients in the cilazapril group had higher total cholesterol levels at baseline.

Table 3. Change in Metabolic Parameters by Antihypertensive Treatments

<table>
<thead>
<tr>
<th></th>
<th>Preterax (n=15)</th>
<th>P value</th>
<th>Cilazapril (n=15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>99.87±16.57</td>
<td>0.802</td>
<td>105.73±13.03</td>
<td>0.589</td>
</tr>
<tr>
<td>Insulin (μU/L)</td>
<td>8.35±4.21</td>
<td>0.041</td>
<td>8.72±4.00</td>
<td>0.551</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.99±1.09</td>
<td>0.272</td>
<td>2.21±0.93</td>
<td>0.875</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>185.47±21.76</td>
<td>0.495</td>
<td>219.40±27.13</td>
<td>0.460</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>127.40±46.25</td>
<td>0.910</td>
<td>179.67±144.00</td>
<td>0.041</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>38.80±11.09</td>
<td>0.326</td>
<td>41.67±6.23</td>
<td>0.888</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>131.20±52.75</td>
<td>0.712</td>
<td>150.33±32.43</td>
<td>0.176</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>141.40±1.60</td>
<td>0.404</td>
<td>140.87±1.41</td>
<td>0.618</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.18±0.40</td>
<td>0.010</td>
<td>4.27±0.36</td>
<td>0.316</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.91±0.25</td>
<td>0.454</td>
<td>0.99±0.26</td>
<td>0.317</td>
</tr>
<tr>
<td>Adiponectin (mg/L)</td>
<td>11.25±8.38</td>
<td>0.211</td>
<td>14.00±10.75</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Values are mean±SD.
Abbreviations see in Table 1.

Figure 1. Plasma adiponectin concentrations in 30 hypertensive patients before and after 12 weeks of treatment with preterax or cilazapril.
Changes in BP With Different Treatments
As shown in Table 2, the change in SBP in the preterax group ranged from +11 to −37 mmHg (mean, −14.40 mmHg) and from +14 to −36 mmHg (mean, −10.13 mmHg) in the cilazapril group. There were significant reductions in SBP after 12 weeks of antihypertensive treatment in both groups (P=0.003 in the preterax group and P=0.031 in the cilazapril group). However, the change in DBP in the preterax group ranged from +6 to −26 mmHg (mean, −6.20 mmHg) and from +16 to −23 mmHg (mean, −3.27 mmHg) in the cilazapril group. There was a significant reduction in DBP in the preterax group (P=0.024), but not in the cilazapril group (P=0.191).

Changes in Plasma Adiponectin and Glucose Profiles With Different Treatments
None of the patients developed de novo diabetes mellitus. As shown in Table 3 and Figure 1, plasma adiponectin concentrations were significantly increased after treatment in patients taking cilazapril (P=0.025) but not in those patients taking preterax. In contrast, a significant increase in the plasma insulin concentrations was found in the preterax group (P=0.041), but not in the cilazapril group (Table 3, Figure 2). Though statistically insignificantly, the HOMA-IR index also tended to increase in patients treated with preterax (Table 3, Figure 2). On the other hand, the changes in the plasma adiponectin level did not correlate with the change in either SBP or DBP (Table 4).

Changes in Lipid and Biochemistry Profiles With Different Treatments
As shown in Table 3, there were no significant changes in the plasma concentrations of total cholesterol, HDL-cholesterol, LDL-cholesterol, sodium and creatinine in either treatment group, except for a significant decrease in the plasma potassium level after 12 weeks of preterax treatment (P=0.010) and the significant decrease in plasma triglyceride concentrations after 12 weeks of cilazapril treatment (P=0.041). Furthermore, as shown in Figure 2, the percentage change in plasma triglycerides was significantly different between the 2 treatment groups (P=0.042).

Discussion
Our data clearly show that in patients with essential hypertension, a combination of perindopril 2 mg and indapamide 0.625 mg (preterax) resulted in a greater BP reduction than monotherapy with cilazapril. This result is compatible with the current suggestion of low-dose combination therapy for BP control. However, cilazapril monotherapy significantly increased plasma adiponectin concentrations, whereas the combination regimen did not. In addition, although the increase in the HOMA-IR index did not reach statistical significance, plasma insulin concentrations were significantly increased with the combination regimen. These findings suggest that while more profoundly reducing BP, the combination regimen may attenuate the increase in plasma adiponectin concentrations because of ACE inhibition and has a neutral or potentially negative impact on insulin resistance. Accordingly, different from ACEI monotherapy, the combination of a thiazide-like diuretic and an ACEI may best be reserved for improved BP control rather than for metabolic protection in patients with clinical hypertension.

As 1 of the standard combination regimens, the combina-
tion of perindopril, an ACEI, and indapamide, a thiazide-type diuretic, has been demonstrated to reduce recurrent stroke, improve arterial stiffness and attenuate left ventricular hypertrophy in clinical hypertension. However, it is unknown whether these clinical benefits are also related to cardiometabolic protection, in addition to the synergistic effects on BP reduction.

It has been shown that diuretics, particularly thiazides, exert a gradual and stable hypotensive effect, especially in the elderly and in patients with poor renal function. They facilitate the excretion of serum sodium accompanied by a reduction in body fluid volume and BP. As BP goes down, the glomerular capillary pressure drops and glomerular filtration rate decreases, leading to activation of the RAS. Simultaneous administration of ACEIs could then promote the natriuretic and hypotensive effects of the diuretics. Besides, blockade of the RAS with either an ACEI or an angiotensin II receptor blocker may cause a substantial increase in the adiponectin level and improved insulin sensitivity. Their effects on plasma adiponectin levels may parallel their effects on BP and insulin sensitivities, however, thiazides and thiazide-like diuretics are known to enhance insulin resistance and worsen glycemic control. Proposed mechanisms include the effect of hypokalemia on insulin secretion (potassium depletion leads to impaired insulin release and a relative increase in the secretion of proinsulin, which is less biologically active), alterations in hepatic gluconeogenesis, an increase in free fatty acids, an increase in catecholamine release and a direct toxic effect on the pancreas.

In patients with essential hypertension, indapamide alone could also decrease plasma adiponectin and increase plasma insulin concentrations, with a significant increase in the HOMA-IR index. It is then uncertain if the combination of an ACEI and a thiazide-type diuretic such as indapamide, in low doses, may have beneficial effects on the metabolic profile of hypertensive patients.

In the present study, the combination of perindopril and indapamide led to a greater BP reduction, a significant increase in the plasma insulin concentration, a reduction in the plasma potassium concentration, and no change in the adiponectin concentration. Given the lesser BP reduction, the significant increase in the adiponectin level and no change in either the plasma insulin level or potassium concentration in patients on cilazapril monotherapy, it is possible that indapamide, though more profoundly reducing BP, has attenuated the beneficial effect of perindopril on the plasma adiponectin concentration. The additional effect of indapamide on plasma potassium might also contribute to the change in the plasma insulin profile of these patients. Thus, one may speculate that the clinical benefits of the combination of perindopril and indapamide on cardiovascular outcome, as shown in the previous studies, might be a function of BP reduction rather than metabolic protection, although the circulating adiponectin level may only be part of whole-body glucose homeostasis and insulin sensitivity. Further larger and more specific trials are required to elucidate the exact interaction between indapamide and adiponectin production, as well as the overall glucose metabolism in different populations.

It has been shown that plasma adiponectin concentrations correlate negatively with most metabolic risk factors, such as obesity, type 2 diabetes mellitus, and hyperlipidemia. In patients with hypertension, reduced adiponectin levels may be related to either increased BP or accompanying factors such as inflammation, oxidative stress or insulin resistance. In the present study, a significant portion of the study patients had a relatively increased BMI (>25 kg/m²), fasting glucose (>100 mg/dl), total cholesterol (>200 mg/dl) and LDL-cholesterol levels (>130 mg/dl) and reduced HDL-cholesterol levels (<40 mg/dl), which may indicate the presence of MetS. Furthermore, baseline adiponectin levels (12.63±7.83 mg/L) were lower in the study patients than in a cohort of normotensive subjects without MetS (15.92±5.1 mg/L), but were similar to that in a cohort of normotensive subjects with MetS (13.42±7.4 mg/L) (unpublished data). It is suggested that up to 50% of hypertensive patients may have MetS by definition. Because adiponectin is also related to the formation and progression of atherosclerosis, our findings suggest antihypertensive therapeutic strategies that could increase plasma adiponectin in hypertensive patients with increased cardiovascular risk.

Another interesting finding in our study is that treatment with cilazapril resulted in a significant reduction in the plasma triglyceride level. Yamauchi et al suggested that adiponectin in skeletal muscle increased the expression of molecules involved in fatty acid transport, combustion, and energy dissipation, such as CD36, acy-CoA oxidase, and uncoupling protein. In addition, a recently published experimental study showed that adiponectin decreases plasma triglyceride levels by increasing skeletal muscle lipoprotein lipase and VLDL receptor expression and, consequently, VLDL-triglyceride catabolism. Whether the reduction in the plasma triglyceride level by cilazapril is related to an increase in the plasma adiponectin concentration remains unclear and further studies are needed to establish a causal relationship.

One of the limitations of the current study is the small number of subjects enrolled. Thus, the current study should be viewed as a pilot. Future studies with a larger population of subjects who receive various types of RAS blocking agents and thiazide-like diuretics are needed to confirm the current findings. Second, body composition or BMI was not checked after 12 weeks of treatment and it is a known factor influencing plasma adiponectin concentrations. Although we cannot exclude the possibility that a change in body fat content or BMI might be a cause of the non-significant increase in the plasma adiponectin levels in patients taking perindopril, previous studies, however, showed that there was no significant change in either the body weight or body fat content of patients treated with perindopril, indapamide, or cilazapril.

In conclusion, ACE inhibition may increase plasma adiponectin concentrations. However, the combination of an ACEI and a thiazide-like diuretic, even in low doses, could improve BP control but not increase plasma adiponectin and have a neutral impact on the metabolic profile of patients with essential hypertension. This combination may be better reserved for advanced BP control rather than for metabolic protection in clinical hypertension. Given the potential impact of plasma adiponectin on atherogenesis, as well as clinical outcomes, future studies are needed to elucidate whether the different effects of antihypertensive regimens on plasma adiponectin levels and metabolic profiles could account for the diversity of clinical outcomes in hypertensive patients with different treatments.

References

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