

# Adiponectin and Insulin Sensitivity in Primary Aldosteronism

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**Background:** A high prevalence of metabolic syndrome has been reported in primary aldosteronism. Low levels of adiponectin, an adipokine with insulin-sensitizing properties, are considered a hallmark of the metabolic syndrome. We evaluated the relationship between adiponectin and insulin sensitivity in primary aldosteronism, with and without metabolic syndrome, compared with essential hypertension.

**Methods:** Forty patients with primary aldosteronism and 40 matched patients with low-renin essential hypertension (LREH) were studied. Patients with type 2 diabetes were excluded. Each group was divided into two subsets: one including patients with metabolic syndrome and one including patients without metabolic syndrome (ie, hypertension alone or associated with another component of the syndrome).

**Results:** Insulin resistance, defined by increased homeostasis model assessment (HOMA index), was higher in patients with primary aldosteronism than in those with LREH only in the absence of metabolic syndrome ( $P < .01$ ), whereas in the subsets bearing the syndrome it was

similar. Adiponectin levels were lower in primary aldosteronism than in patients with LREH ( $P < .01$ ). Like HOMA index, the difference was maintained ( $P < .01$ ) only in the subsets without metabolic syndrome. Adiponectin levels were inversely correlated with HOMA index and positively correlated with potassium levels both in primary aldosteronism ( $P < .001$ ) or in LREH ( $P < .05$ ) groups.

**Conclusions:** Lower adiponectin as well as lower insulin sensitivity in primary aldosteronism compared with LREH seem to result from both direct (aldosterone excess) and indirect (hypokalemia) mechanisms. Therapeutic interventions aimed at correcting both potassium and adiponectin levels by specific antihypertensive agents might improve insulin sensitivity, providing better cardiovascular protection in primary aldosteronism. Am J Hypertens 2007;20:855–861 © 2007 American Journal of Hypertension, Ltd.

**Key Words:** Adiponectin, insulin resistance, primary aldosteronism.

**A**lthough there is substantial evidence that patients with essential hypertension are insulin resistant/hyperinsulinemic compared with normotensive subjects, the relationship between insulin resistance, hyperinsulinemia, and blood pressure (BP) is still debated, and the causal nature of this link is unclear.<sup>1</sup> In fact hypertension per se could lead to insulin resistance/hyperinsulinemia, rather than vice versa. The prevalence of insulin resistance and its role in the development of cardiovascular risk has not been sufficiently explored in secondary forms of hypertension. Several clinical studies have shown a state of glucose intolerance and insulin resistance in primary aldosteronism,<sup>2–6</sup> compared with normotensive healthy controls. At variance, using the hy-

perinsulinemic-euglycemic clamp technique, Shamiss et al<sup>2</sup> and more recently Catena et al<sup>5</sup> found that insulin sensitivity was higher in primary aldosteronism than in essential hypertension.

We recently demonstrated, in a large prospective study, a higher prevalence of metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III (ATP III) definition<sup>7</sup> in primary aldosteronism than in essential hypertension.<sup>8</sup> In particular, of the individual components of metabolic syndrome other than hypertension only hyperglycemia was more prevalent in primary aldosteronism than in essential hypertension. The impairment of glucose metabolism linked to insulin resistance, considered the major contributor to the development

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of metabolic syndrome,<sup>9</sup> could have a predominant role in increased rates of cardiovascular events in primary aldosteronism compared with essential hypertension, as recently reported.<sup>10</sup>

Several experimental observations support the possibility that aldosterone directly affects insulin sensitivity acting on insulin receptor function,<sup>3,11</sup> but other mechanisms could be involved. Adiponectin is an adipose-tissue derived protein with positive effects on insulin sensitivity, atherosclerosis, and inflammation.<sup>12</sup> In human cross-sectional studies, plasma adiponectin levels are negatively correlated with obesity and insulin resistance, diabetic dyslipidemia, and BP.<sup>12,13</sup> Because low adiponectin concentrations correlate with the metabolic syndrome components,<sup>14</sup> this adipokine could be seen as a potential link between metabolic syndrome and its cardiovascular consequences. Adiponectin has been found to be low in essential hypertension,<sup>15,16</sup> whereas no data are available on adiponectin in primary aldosteronism.

The purpose of our study was to evaluate the relationship between adiponectin and insulin sensitivity in primary aldosteronism, with and without metabolic syndrome, compared with low-renin essential hypertension patients.

## Methods

### Patients

A group of 40 patients with primary aldosteronism and a group of 40 patients with essential hypertension were prospectively studied. All patients were referred to our two hospital-based specialized hypertension outpatient clinics during the past 2 years. The reasons for patient referral were:<sup>8,17</sup> onset of hypertension at young age, hypertension resistant to conventional antihypertensive therapy, hypertension with unexplained spontaneous or diuretic-induced hypokalemia, high plasma aldosterone, low plasma renin activity (PRA), and an incidentally found adrenal mass. Patients with clinical or laboratory evidence of associated clinical conditions, such as cerebrovascular, coronary, or peripheral artery disease; cardiac insufficiency; renal or hepatic disease; and patients with history of cardiovascular and cerebrovascular events were excluded. Renal disease was defined as the presence of serum creatinine more than 133  $\mu\text{mol/L}$  in men and more than 120  $\mu\text{mol/L}$  in women or albuminuria more than 300 mg/d. Patients with type 2 diabetes (ie, those with fasting glucose levels  $>7.0$  mmol/L on two separate occasions)<sup>18</sup> were also excluded. All BP measurements were performed according to the World Health Organization–International Society of Hypertension.<sup>15</sup> Most patients were receiving antihypertensive treatment at presentation. For those taking medications, any agent was withdrawn at least 3 weeks (up to 2 months for spironolactone) before hemodynamic, biochemical, and hormonal evaluation. In patients in whom treatment could not be withdrawn for ethical reasons, a calcium-channel blocker or an  $\alpha$ -receptor blocker were allowed at the

minimal doses required to achieve BP control. These agents are known to have a neutral effect on renin and aldosterone levels<sup>19</sup> and not to impair glucose and lipid parameters.<sup>20</sup> In patients taking lipid-lowering drugs, treatment was withdrawn at least 3 weeks before biochemical evaluation. Patients smoking at least one cigarette daily for 1 year in the past year were considered current smokers. Alcohol intake was assessed by multiplying the mean daily consumption for each beverage by ethanol content to give grams of alcohol per day. Patients consuming alcohol more than 40 g/d for men and more than 20 g/d for women in the past year were considered current drinkers. The duration of hypertension was obtained by careful investigation of the patient's history and from family practitioner records.

After the first visit at our clinics, all subjects underwent diagnostic procedures as outpatients. During evaluation, they consumed a normal sodium and potassium diet (ie, 100 to 200 mmol/d sodium and 50 to 70 mmol/d potassium). All individuals followed the diet under hospital staff control. After at least a 7-day diet, three 24-h urine specimens were randomly collected from patients to check correspondence of sodium and potassium intake with sodium and potassium urinary excretion. Differential diagnosis criteria for the different forms of primary aldosteronism and for essential hypertension were previously described.<sup>17</sup> Briefly, a cutoff upright plasma aldosterone (in nanograms per deciliter)/PRA (in nanograms per milliliter per hour) ratio more than 40, in the presence of aldosterone more than 15 ng/dL and suppressed PRA, was used as screening test for primary aldosteronism. In the case of an aldosterone/PRA ratio greater than 40, patients underwent a saline infusion (0.9% NaCl 500 mL/h for 4 h) as a confirmatory test,<sup>21</sup> and only those with plasma aldosterone levels that failed to decrease to less than 5 ng/dL after the saline infusion were diagnosed as having primary aldosteronism. In these patients, a computed tomography scan with fine cuts (2.5 to 3 mm) of the adrenal or an adrenal venous sampling were performed to differentiate between aldosterone-producing adenoma (APA) and bilateral hyperplasia (ie, idiopathic hyperaldosteronism [IHA]), resulting in 15 patients with APA and 25 patients with IHA. Sampling was considered successful if the adrenal vein/inferior vena cava cortisol gradient was at least 2; lateralization was considered when the aldosterone/cortisol ratio from one adrenal was at least 4 times the ratio from the contralateral gland. Because only 24 of 40 patients underwent adrenal venous sampling, the proportion of the two groups of patients could be different, owing to underestimation of aldosterone-producing adenoma by the computed tomography scan. In all patients who underwent unilateral adrenalectomy, an adrenal adenoma was confirmed at surgery and histologic examination. The presence of the inherited syndrome of glucocorticoid-remediable hyperaldosteronism was excluded by a long polymerase chain reaction (PCR) test, as previously reported.<sup>8</sup>

Taking into account the role of renin angiotensin in altering insulin sensitivity,<sup>11,22</sup> to minimize the imbalance of renin angiotensin activity between primary aldosteronism and essential hypertension, we compared patients with primary aldosteronism with 40 low renin-type essential hypertension patients. Low-renin essential hypertension (LREH) was identified by an upright PRA less than 1.0 ng/mL/h. The two groups of patients were matched for sex, age, body mass index, BP levels, and duration of hypertension. Patients with LREH were selected from a larger essential hypertensive population (more than 400 patients) seen at our clinics in the same time period. Forty normotensive nondiabetic subjects served as controls for metabolic variables. These subjects were recruited from the general population of the same geographic area and were matched with hypertensive patients for age, sex, body mass index, as well as for lipid and glucose levels. Blood samples for the study were obtained on the last day of a 7-day normal sodium and potassium intake. Each subject provided informed consent for the study, which was approved by an institutional Ethics Committee.

Each group of hypertensive patients was divided into two subsets: one including patients with metabolic syndrome ( $n = 18$  in primary aldosteronism,  $n = 11$  in LREH) and one including patients without metabolic syndrome ( $n = 22$  in primary aldosteronism,  $n = 29$  in LREH), that is, hypertension alone or associated with another component of the syndrome (Table 1).

### Definition of Metabolic Syndrome

The ATP III clinical definition of metabolic syndrome<sup>7</sup> requires three or more of the following findings: (1) abdominal obesity (waist circumference >102 cm in men and >88 cm in women); (2) triglycerides 1.69 mmol/L or greater; (3) HDL cholesterol less than 1.03 mmol/L for men and less than 1.29 mmol/L for women; (4) fasting glucose 6.1 mmol/L or greater; and (5) systolic BP 130 mm Hg or more and diastolic BP 85 mm Hg or more. The waist circumference measurement, taken as reference measure of abdominal obesity, was made at minimal inspiration to the nearest 0.1 cm, midway between the last rib and the iliac crest.

### Definition of Insulin Sensitivity

Insulin sensitivity was calculated according to the formula of the homeostasis model assessment (HOMA index) method: Insulin resistance = Fasting plasma insulin ( $\mu\text{UI/mL}$ )  $\times$  Fasting plasma glucose (mmol/L) / 22.5.<sup>23</sup> The index is highly correlated with the insulin resistance index assessed by the euglycemic–hyperinsulinemic clamp, which is the gold standard of insulin resistance measurement, and is widely adopted in clinical studies for subjects with various degree of insulin sensitivity, including hypertensive subjects.<sup>24</sup>

### Laboratory Methods

In all subjects, blood samples for biochemical and endocrine/metabolic profile were obtained after overnight fasting at 8:00 AM.

Plasma insulin concentration was measured by a chemiluminescence immunoassay using a commercially available kit (Immulite 1 analyzer; DPC, Los Angeles, CA): normal range, 6 to 24  $\mu\text{UI/mL}$ . Plasma adiponectin was measured by specific radioimmunoassay (RIA) obtained from Linco Research, Inc. (St. Charles, MO), with minor modifications, as previously described.<sup>15</sup> Adiponectin standards were prepared using recombinant human adiponectin with a sensitivity of 1 ng/mL. The assay buffer contained 10.0 mmol phosphate buffer, pH 7.6, sodium azide (0.09%), and bovine serum albumin (BSA; 0.15%); normal values,  $29.2 \pm 6.4 \mu\text{g/mL}$ .

The PRA and aldosterone were measured as previously described.<sup>8</sup> Briefly, PRA and aldosterone were determined by radioimmunoassay with kits purchased from Sorin Biomedical Diagnostics, Saluggia, Italy. Normal range for PRA was 0.4 to 3.0 ng/mL/h supine and 1.5 to 5.2 ng/mL/h upright. The lower limit of detection for the PRA assay was 0.1 ng/mL/h. Normal range for plasma aldosterone was 2 to 12 ng/dL supine and 5 to 35 ng/dL upright.

For all hormone measurements, intra-assay and inter-assay coefficients of variation were less than 10%. All other biochemical variables were assayed in plasma or serum using standard methods.

### Statistical Analysis

All results are expressed as mean  $\pm$  SD for continuous variables and as proportion for categorical variables. Continuous data were subjected to the Kolmogorov–Smirnov test to determine their distribution. Statistical significance between groups was assessed in normally distributed data by Student's *t*-test for independent samples and in non-normally distributed data by Mann-Whitney *U* test. Bonferroni adjustment was applied to multiple comparison tests of continuous data.

Categorical variables were analyzed by  $\chi^2$  analysis or Fisher's exact test when appropriate. Pearson's correlation coefficient was calculated to test for a linear correlation between continuous variables. Difference between coefficients of correlation was calculated as reported by Block.<sup>25</sup> A stepwise multiple linear regression analysis was performed in each group (ie, primary aldosteronism and LREH patients) to identify the determinants of plasma adiponectin levels. For this purpose, the relationship between adiponectin (as dependent variable) and the variables shown to be significantly different between the two groups (ie, HOMA index, aldosterone, PRA, and potassium) (as independent variables) was assessed. A *P* value less than .05 was considered statistically significant. Statistical analyses were performed using STATISTICA 6.0 (StatSoft, Tulsa, OK) for Windows.

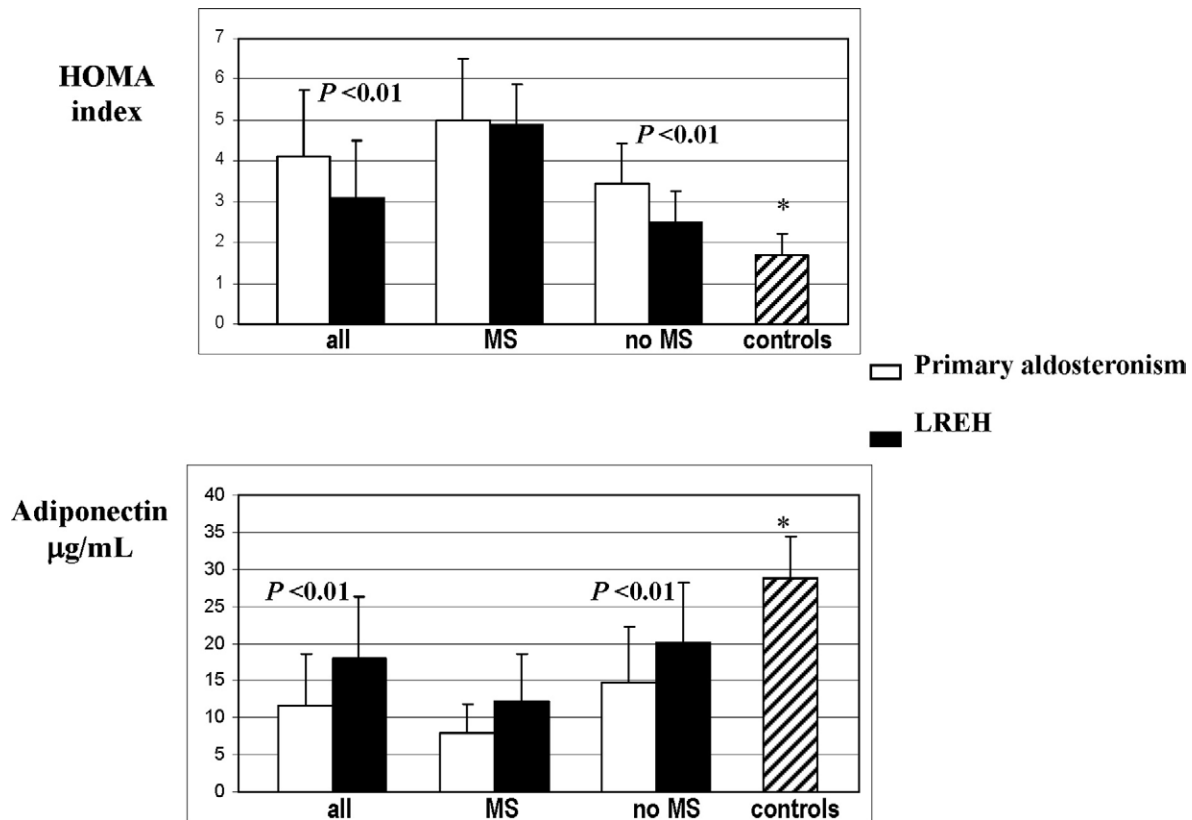
**Table 1.** Baseline characteristics of primary aldosteronism and low-renin essential hypertension patients, with and without the metabolic syndrome (MS)

	Primary aldosteronism			Low-renin essential hypertension			P
	Total (n = 40)	MS (n = 18)	No MS (n = 22)	Total (n = 40)	MS (n = 11)	No MS (n = 29)	
Age (y)	53 ± 10	56 ± 6	50 ± 12	51 ± 11	54 ± 9	50 ± 12	NS
Sex (M/F)	24/16	12/6	12/10	24/16	7/4	16/13	NS
BMI (kg/m <sup>2</sup> )	27.5 ± 3.9	29.7 ± 4.1	25.7 ± 3	26.7 ± 3.9	29.4 ± 2.9	25.7 ± 3.8	NS
Wc (cm)	96.2 ± 10.9	100.8 ± 8.5	92.4 ± 11	93.1 ± 10	101.6 ± 7.0	89.9 ± 8.8	NS
Systolic BP (mm Hg)	162 ± 22	168 ± 22	157 ± 23	161 ± 18	161 ± 20	161 ± 17	NS
Diastolic BP (mm Hg)	101 ± 10	102 ± 10	100 ± 11	100 ± 8	98 ± 7	100 ± 8	NS
Duration of hypertension (mo)	137 ± 111	140 ± 92	136 ± 123	135 ± 100	138 ± 114	133 ± 94	NS
Smokers (%)	13	14	12	17	17	18	NS
Alcohol drinkers (%)	15	16	18	20	22	17	NS
Aldosterone (ng/dL)	39.7 ± 14.2	43.9 ± 14.8	36.2 ± 10.7	24.1 ± 10.6	27.6 ± 10.4	22.7 ± 10.7	*,†,‡
PRA (ng/mL/h)	0.2 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	0.6 ± 0.3	0.6 ± 0.2	0.5 ± 0.3	*,†,‡
Aldosterone/PRA ratio	254 ± 149	299 ± 126	218 ± 159	48 ± 34	40 ± 20	51 ± 38	*,†,‡
Potassium (mmol/L)	3.3 ± 0.6	3.2 ± 0.6	3.4 ± 0.5	4.3 ± 0.4	4.2 ± 0.4	4.3 ± 0.5	*,†,‡
Creatinine (μmol/L)	81 ± 24	81 ± 31	81 ± 18	75 ± 16	82 ± 23	72 ± 12	NS
Triglycerides (mmol/L)	1.1 ± 0.7	1.8 ± 0.9	1.0 ± 0.5	1.3 ± 0.8	2.0 ± 1.3	1.0 ± 0.4	NS
HDL C (mmol/L)	1.3 ± 0.5	1.0 ± 0.5	1.5 ± 0.3	1.4 ± 0.4	0.9 ± 0.4	1.6 ± 0.3	NS
Glucose (mmol/L)	5.2 ± 0.7	5.5 ± 0.8	5.0 ± 0.6	5.2 ± 0.5	5.3 ± 0.5	5.1 ± 0.6	NS
Insulin (μUI/mL)	17.2 ± 5.9	19.3 ± 5.4	15.4 ± 5.8	13.3 ± 6.1	20.1 ± 4.6	10.8 ± 4.5	*,‡

BMI = body mass index; BP = blood pressure; HDL C = HDL cholesterol; NS = not significant; PRA = plasma renin activity; Wc = waist circumference.

To convert values for plasma aldosterone to nanomoles per liter, multiply by 0.0277; to convert values for PRA to nanograms per liter per second, multiply by 0.2778; to convert values for plasma insulin to picomoles per liter, multiply by 6.0.

\*  $P < .01$  primary aldosteronism v low-renin essential hypertension; †  $P < .01$  primary aldosteronism v low-renin essential hypertension with MS; ‡  $P < .01$  primary aldosteronism v low-renin essential hypertension without MS.



**FIG. 1.** The HOMA index and plasma adiponectin levels in primary aldosteronism and in patients with low-renin essential hypertension (LREH) (all), and in the subsets with (MS) and without (no MS) metabolic syndrome, and in normotensive subjects (controls). HOMA index = homeostasis model assessment index. \*Controls v primary aldosteronism ( $P < .001$ ) and v LREH ( $P < .001$ ) patients.

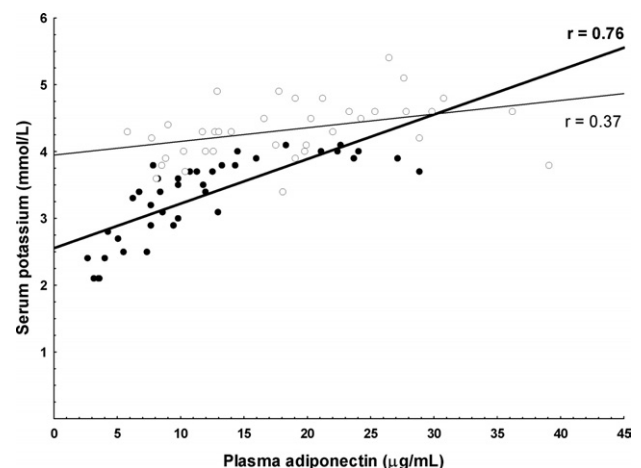
## Results

Details of the two populations are reported in Table 1. Plasma aldosterone, PRA, aldosterone/PRA ratio, and serum potassium were significantly different between the primary aldosteronism and the LREH group, including their subsets ( $P < .01$ ). Waist circumference, smoking habit, alcohol intake, serum creatinine, triglycerides, HDL cholesterol, and fasting glucose were not significantly different between the two groups.

Data on HOMA index and adiponectin are depicted in Fig. 1. The HOMA index was significantly higher in primary aldosteronism than in LREH, and this was confirmed in the subset of patients without the metabolic syndrome. There were no differences in HOMA index between subsets bearing the metabolic syndrome. Adiponectin levels were significantly lower in primary aldosteronism than in LREH groups. As with the HOMA index, the significant difference was maintained only between the subsets without metabolic syndrome. Normotensive subjects had significantly lower HOMA index and higher adiponectin than primary aldosteronism and LREH patients.

Univariate correlation analysis showed that adiponectin was inversely correlated with HOMA index either in primary aldosteronism ( $r = -0.69$ ,  $P < .001$ ) or in LREH ( $r = -0.37$ ,  $P < .05$ ). A direct correlation between

adiponectin and potassium levels was found in both groups (Fig. 2). The correlation coefficient was significantly higher in primary aldosteronism than in LREH ( $r = 0.76$  v  $r = 0.37$ ,  $P < .01$ ). No other correlations among variables, including that between PRA or aldosterone lev-



**FIG. 2.** Relationship between serum potassium and plasma adiponectin in the group of patients with primary aldosteronism (closed circles;  $r = 0.76$ ,  $P < .001$ ) and in the group of patients with low-renin essential hypertension (open circles;  $r = 0.37$ ,  $P < .05$ ).

els and HOMA index, as well as that between PRA or aldosterone and adiponectin, were found to be significant.

When the correlation of adiponectin with the independent variables was analyzed by multiple linear regression, adiponectin levels were inversely correlated with HOMA index ( $r = -0.43$ ,  $P < .01$ ) and positively correlated with potassium levels ( $r = 0.57$ ,  $P < .001$ ) either in primary aldosteronism or in LREH ( $r = -0.35$  and  $r = 0.34$ ,  $P < .05$ , respectively) group. No correlation between adiponectin and either aldosterone or PRA was found in each of the two groups.

Based on our diagnostic assessment, patients with APA were similar to patients with IHA for all variables, except the aldosterone/PRA ratio ( $336 \pm 92$  v  $213 \pm 149$ ,  $P < .01$ ). Therefore, they were not analyzed separately, considering also the relatively small size of the samples.

## Discussion

Our study shows that insulin resistance, as indicated by an increased HOMA index, is greater in patients with primary aldosteronism than in patients with LREH matched for age, sex, body mass index, BP levels, and duration of hypertension. Because our patients with essential hypertension were similar to those with primary aldosteronism for waist circumference, lipid levels, smoking habit, and alcohol intake, we can infer that these factors had no influence on the differences in insulin sensitivity. Furthermore, our patients with LREH still had PRA levels higher than those of patients with primary aldosteronism, indicating that a direct role of renin angiotensin activity in the lower insulin sensitivity of primary aldosteronism is unlikely.

Adiponectin displays a variety of functions, including insulin-sensitizing properties. In our study, adiponectin and HOMA index were inversely correlated both in primary aldosteronism and in LREH. The HOMA index was higher and adiponectin was lower in the group of patients with primary aldosteronism than in the group with LREH, and in their subsets without metabolic syndrome (Table 1, Fig. 1). This supports the concept of a direct negative influence of aldosterone overproduction on glucose metabolism.<sup>3,11</sup> Similar levels of both HOMA index and adiponectin in the subsets with metabolic syndrome might be due to the presence of multiple components of the syndrome masking the effect of aldosterone itself on insulin sensitivity. In addition, the small size of these groups of patients could have introduced a type 2 error, preventing the chance to detect a statistical significance in the difference between variables.

Unlike that of cortisol,<sup>26</sup> the effect of aldosterone on adiponectin production is still unknown. Decreased insulin sensitivity in primary aldosteronism could be linked to decreased adiponectin levels as a result of either direct (aldosterone excess) or indirect (hypokalemia) mechanisms. There is experimental evidence that potassium is involved in the regulation of insulin receptor function as well as of

insulin secretion by pancreatic  $\beta$  cells.<sup>27</sup> In this regard, multiple linear regression analysis showed that adiponectin was correlated with serum potassium in each group of patients, much more markedly in primary aldosteronism than in LREH. Only one study examined a possible association between adiponectin and potassium in humans: in epicardial adipose tissue of patients with cardiovascular disease undergoing an acute potassium or placebo intravenous infusion, there were no differences in adiponectin mRNA expression.<sup>28</sup> On the basis of our data, it cannot be excluded that chronic hypokalemia contributed to reduced plasma adiponectin levels and therefore insulin sensitivity at a greater extent in primary aldosteronism than in LREH. The difference between our findings and those of Catena et al,<sup>5</sup> who showed a lower degree of insulin resistance in primary aldosteronism than in LREH, could be only apparent. Their patients with primary aldosteronism had plasma potassium normalized by oral potassium supplements at the time of metabolic testing. Differences in selection criteria and study conditions might also explain the disparity of our results with those reported by other investigators.<sup>2</sup>

In conclusion, a contribution of low adiponectin to the high cardiovascular risk induced by aldosterone excess<sup>29</sup> can be hypothesized. Adiponectin has been proposed by recent animal studies as a potentially useful treatment for hypertension as well as for insulin resistance in the context of metabolic syndrome.<sup>30</sup> Accordingly, therapeutic interventions aimed at correcting both potassium and adiponectin levels by specific antihypertensive agents<sup>31</sup> might improve insulin sensitivity, providing better cardiovascular protection in primary aldosteronism.

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