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Insulin Sensitivity in Patients with Primary Aldosteronism: A Follow-Up Study

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Context: The relationship between aldosterone and glucose metabolism is poorly understood, and there is substantial disparity among findings of studies that have examined glucose tolerance and insulin sensitivity in patients with primary aldosteronism.

Objective: The objective of the study was to determine the outcome of glucose tolerance and insulin sensitivity in patients with primary aldosteronism after treatment.

Design: This was a prospective study of patients who received a diagnosis of primary aldosteronism and were followed up for an average period of 5.7 yr (range, 3–9 yr).

Setting: The study was conducted at a university referral center.

Patients: A consecutive sample of 47 patients with tumoral or idiopathic aldosteronism was followed up after either surgical or medical treatment. Patients with primary aldosteronism were compared with 247 patients with essential hypertension with the same severity and duration of disease and 102 normotensive subjects.

Main Outcome Measures: Short- and long-term changes in glucose tolerance and insulin sensitivity were measured.

Results: After adjustment for age, gender, and body mass index, patients with primary aldosteronism had greater homeostasis model assessment index ($P < 0.05$) and plasma insulin response to an oral glucose load ($P < 0.05$) and lower quantitative insulin sensitivity check index ($P < 0.01$) than normotensive controls. Changes in insulin sensitivity were significantly greater in essential hypertension than primary aldosteronism, and this difference was confirmed by assessment with the hyperinsulinemic-euglycemic clamp ($P < 0.01$). Treatment of primary aldosteronism decreased blood pressure significantly, and during the initial 6 months of follow-up, parameters of insulin sensitivity were restored to normal. Analysis of subsequent follow-up showed nonsignificant changes in glucose metabolism parameters in both adrenalectomized and spironolactone-treated patients.

Conclusions: Insulin resistance is present in patients with tumoral and idiopathic aldosteronism, but the defect appears less severe than in patients with essential hypertension. Treatment with surgery or aldosterone antagonists restores rapidly and persistently normal sensitivity to insulin. **(*J Clin Endocrinol Metab* 91: 3457–3463, 2006)**

LANDMARK STUDIES THAT were published approximately 20 yr ago demonstrated an association among hyperinsulinemia, insulin resistance, and arterial hypertension (1, 2). This association between elevated blood pressure and decreased sensitivity to insulin was present, even after adjustment for body mass, and was observed in whites but not in blacks or Pima Indians (3). Subsequent population-based studies suggested that hyperinsulinemia and insulin resistance might contribute to progression of cardiovascular disease (4) by multiple mechanisms that include proliferation of the vascular smooth muscle cells in the arterial wall, induction of a more atherogenic plasma lipid pattern, and activation of the sympathetic nervous system.

Recent evidence indicates a greater frequency of primary aldosteronism among hypertensive patients than the previously accepted prevalence of approximately 1%. Such increased frequency, which may exceed 10% (5), may be the result of a more effective identification of this condition due to the widespread use of the aldosterone to renin ratio as a screening test (6). Although primary aldosteronism is considered correctable with either surgical removal of an adrenal adenoma or administration of mineralocorticoid receptor antagonists, in many cases, hypertension may persist after treatment and patients may require chronic use of antihypertensive drugs (7). Past studies examined insulin sensitivity in patients with primary aldosteronism, with substantial disparity in findings that could be ascribed primarily to limited sample sizes (8–14). The present study was designed to evaluate glucose metabolism and sensitivity to insulin in a large group patients with both tumoral and idiopathic primary aldosteronism and to assess the short- and long-term metabolic outcome after either surgical or medical treatment. Furthermore, because the functional link between insulin resistance and high blood pressure remains hypothetical and it could be argued that hypertension *per se* impairs the sensitivity to insulin, we compared patients with primary aldosteronism with patients with essential hypertension and normotensive subjects.

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Abbreviations: ACE, Angiotensin-converting enzyme; AUC, area under the curve; HOMA, homeostasis model assessment; MCR, metabolic clearance rate; QUICKI, quantitative insulin sensitivity check index.

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Patients and Methods

Patients

We conducted an observational, prospective study in 47 consecutive patients who received a diagnosis of primary aldosteronism. All patients were referred to the Hypertension Clinic of our university for evaluation

of their hypertensive state; 32 patients (68%) had persistent hypokalemia, and 23 (49%) had hypertension resistant to a triple-drug regimen. Blood pressure was measured by a mercury sphygmomanometer after each subject had been supine for at least 15 min, and the average of three readings obtained in 5 min was recorded. Hypertension was diagnosed according to established guidelines when blood pressure was 140/90 mm Hg or more at least twice on three different visits. The patients seen at our clinic include individuals with all grades of hypertension living in northeast Italy and are representative of hypertensive patients in this geographic area. All hypertensive patients seen at the clinic are screened with exhaustive clinical and laboratory testing to define the etiology of hypertension (15). Predefined exclusion criteria were as follows: diabetes mellitus; renal insufficiency with 24-h creatinine clearance of less than 30 ml/min per 1.73 m^2 of body surface area; urinary protein excretion of more than 1.0 g/d; and congestive heart failure. Duration of hypertension was estimated by a carefully obtained clinical history and analysis of medical records. Patients treated with antihypertensive drugs were withdrawn from treatment a minimum of 2 wk before diagnostic assessment and measurement of metabolic parameters. β-Blockers, lipophilic calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers were withdrawn for 3 wk (16).

Primary aldosteronism was screened in hypertensive patients by the demonstration of an increased plasma aldosterone to active renin ratio (≥20 pg/ml) in the presence of a plasma aldosterone concentration of more than 150 pg/ml (17), and the diagnosis was confirmed by the lack of aldosterone suppression after an iv saline load (2 liters of 0.9% saline infused over 4 h) (5). The suppression test was considered diagnostic when plasma aldosterone concentration was higher than 50 pg/ml after saline infusion. Plasma potassium concentration of 3.5 mmol/liter or less was corrected by potassium supplementation and maintained for a minimum of 1 wk before diagnostic assessment (5). Differentiation between adrenal adenoma and idiopathic aldosteronism was obtained by high-resolution computerized tomography scan followed by selective adrenal vein sampling with measurements of both aldosterone and cortisol to ensure the adequacy of the cannulation and/or adrenal scintigraphy with iodocholesterol that was performed under dexamethasone suppression. In all patients with adrenal adenoma who underwent adrenalectomy, diagnosis was confirmed by histology. Glucocorticoid-remediable aldosteronism was excluded by performing a dexamethasone trial and a genetic test to detect the chimeric gene in patients with hypertension, hypokalemia, and no evidence of adrenal adenoma who did not respond to treatment. Primary aldosteronism was treated by either unilateral adrenalectomy or spironolactone, and treatment resulted in normalization of blood pressure (<140/90 mm Hg without the aid of antihypertensive agents with the exception of aldosterone antagonists) or significant improvement of hypertension (decrease in mean blood pressure by more than 20% and/or fewer antihypertensive agents taken to control blood pressure) in all patients. The blood pressure decrease used to define significant improvement was defined arbitrarily, as done in previous studies (7).

Patients with primary aldosteronism were compared with 274 patients with essential hypertension who were recruited at our clinic using the same criteria as for patients with primary aldosteronism and were matched for age, gender, body mass index, and estimated duration of hypertension. Patients with essential hypertension were matched for estimated duration of hypertension because this might differ from patients with primary aldosteronism and might affect glucose metabolism. In these patients, secondary causes of hypertension were excluded on the basis of exhaustive laboratory testing after appropriate drug washout (16). One hundred two normotensive healthy subjects served as controls. These subjects were selected from the general population of the same geographic area as the hypertensive patients by frequency matching after specification of inclusion criteria to avoid age, gender, and body mass index as potential confounding variables. Normotensive controls were not taking any regular medications and did not have any concomitant disease. Informed consent was obtained from all patients, and the study protocol was approved by the ethical committee of our university.

Glucose metabolism evaluation

Assessment of glucose metabolism parameters was done at the same time of diagnostic screening after appropriate antihypertensive drug washout. At the time of the study, patients maintained their usual unrestricted diet. A sample of venous blood was obtained after fasting for 12 h and after the patients were in the sitting position for 10 min for analysis of glucose, insulin, and C-peptide. The fasting glucose to insulin ratio (millimoles per picomole), the homeostasis model assessment (HOMA) index, and the quantitative insulin sensitivity check index (QUICKI) were calculated as indexes of sensitivity to insulin (18). The HOMA index was calculated from fasting plasma glucose (millimoles per liter) and insulin (microunits per milliliter) using the formula: [glucose × insulin)/22.5]. Logarithmic values of fasting plasma glucose (milligrams per deciliter) and insulin (microunits per milliliter) concentrations were obtained to calculate the QUICKI using the formula: [1/(log glucose + log insulin]. Glucose tolerance was evaluated with the use of a 180-min oral test as previously described (18). The area under the curve (AUC) for blood glucose and plasma insulin concentration during the test was calculated. Insulin sensitivity was further evaluated in a subgroup of 20 patients with primary aldosteronism and 44 with essential hypertension by a hyperinsulinemic-euglycemic clamp that was performed as described previously (18). Briefly, a priming insulin (Humulin R; Eli Lilly Italia, S.p.A., Sesto Fiorentino, Italy) dose of 100 mU/kg of body weight was administered iv over a period of 10 min, and then a sustained infusion of insulin (dissolved in 0.9% NaCl), at a rate of 2 mU/kg of body weight per minute, was started to maintain serum insulin concentrations at approximately 700 pmol/liter. Concomitantly, an iv infusion of a 20% glucose solution was started to stabilize blood glucose values at 5.0 mmol/liter. For this purpose, plasma glucose was determined every 10 min during the clamp. Sensitivity to insulin was expressed as the glucose metabolic clearance rate (MCR) (milliliters per kilogram of body weight per minute) during 60 min of the clamp.

Plasma glucose, total and high-density lipoprotein cholesterol, and triglycerides were assayed by standard methods, and low-density lipoprotein cholesterol was calculated with the formula of Friedewald. Plasma insulin, C-peptide, active renin, and aldosterone concentrations were measured by RIA (15).

Treatment and follow-up

Patients with primary aldosteronism were treated by either unilateral adrenalectomy or administration of spironolactone (from 50 to 300 mg/d). Of the 25 patients with adrenal adenoma, 20 underwent either surgical or laparoscopic adrenalectomy; among the remaining five patients, two had bilateral adenoma and three refused surgery and were treated with spironolactone. Patients with primary aldosteronism were followed up after baseline evaluations, and clinical assessment and laboratory tests, including serum creatinine and potassium measurements, were performed at 1, 3, and 6 months after enrollment and every 12 months thereafter. At each follow-up visit, three consecutive supine blood pressure readings were obtained after at least 15 min rest and the average of the last two readings was recorded. At each visit, antihypertensive therapy was adjusted according to the physician's judgment to reach a target value of less than 140/90 mm Hg. In all patients, nonpharmacological therapy consisted of recommendations for exercise and weight loss and reductions in intake of dietary sodium and alcohol. For pharmacological treatment, use of all antihypertensive agents was permitted. Parameters of glucose metabolism were reassessed after 6 months and after an average follow-up of 5.7 yr (range 3–9 yr).

Statistical analysis

Continuous variables are expressed as means ± SD unless otherwise indicated. Variables with skewed distribution were analyzed after logarithmic transformation. Characteristics of the study subjects were compared among groups by analysis of covariance after adjustment for age, sex, and body mass index. The Pearson χ^2 test was used to compare categorical variables. Changes from baseline of glucose metabolism parameters were assessed by two-way ANOVA. The relationship between different variables was examined by linear regression analysis. Multiple regression analysis was used to ascertain which variables were independently associated with abnormalities of glucose metabolism. All tests for significance and resulting *P* values were two-sided, with a level of significance of 5%.

Results

Adrenal adenoma was demonstrated in 25 patients (53%) with primary aldosteronism, whereas the remaining 22 (47%) had idiopathic aldosteronism. Baseline clinical and biochemical characteristics of subjects were well balanced among the study groups (Table 1). Patients with primary aldosteronism and essential hypertension had comparable blood pressure levels and estimated duration of hypertension. The plasma lipid profile was comparable in the three groups, with the exception of triglycerides that had a nonsignificant trend to increase in essential hypertension. As expected, patients with primary aldosteronism had higher plasma aldosterone and lower plasma potassium and active renin levels than essential hypertensive and normotensive subjects. Average plasma magnesium concentrations tended to be lower in patients with primary aldosteronism. At baseline, four patients with primary aldosteronism (9%) were taking no antihypertensive drug, three patients (6%) were on monotherapy, and the remaining 40 patients (85%) had multiple-drug treatment (Table 2). Among patients with essential hypertension, 11% were taking no antihypertensive drug, 17% were on monotherapy, and 72% had multiple-drug treatment.

Glucose metabolism parameters are summarized in Table

TABLE 1. Clinical, laboratory, and glucose metabolism parameters of the study population

Characteristic	Normotensive control group (n = 102)	Essential hypertensive group (n = 274)	Primary aldosteronism group		
			All patients (n = 47)	Adrenal adenoma (n = 25)	Idiopathic (n = 22)
Clinical characteristics					
Age (yr)	51 ± 14	53 ± 12	53 ± 12	54 ± 12	52 ± 12
Male sex [n (%)]	71 (70)	192 (70)	34 (72)	19 (76)	15 (68)
Body mass index (kg/m^2)	28.3 ± 3.6	28.4 ± 2.7	28.7 ± 3.8	29.0 ± 3.8	28.3 ± 3.6
Waist circumference (cm)	95.9 ± 8.6	97.3 ± 10.1	98.2 ± 9.8	98.5 ± 9.7	97.8 ± 10.1
Systolic blood pressure (mm Hg)	129 ± 11	167 ± 24	166 ± 17	166 ± 15	166 ± 18
Diastolic blood pressure (mm Hg)	79 ± 7	102 ± 12	103 ± 10	103 ± 8	102 ± 9
Estimated duration of hypertension (yr)		9 ± 6	9 ± 6	9 ± 7	9 ± 6
Alcohol intake (g/d)	34 ± 9	35 ± 7	37 ± 10	39 ± 9	36 ± 10
Laboratory variables					
Total cholesterol (mmol/liter)	5.30 ± 1.04	5.39 ± 1.11	5.13 ± 1.09	5.21 ± 1.06	5.05 ± 1.11
Low-density lipoprotein cholesterol (mmol/liter)	3.31 ± 0.98	3.42 ± 0.98	3.26 ± 0.83	3.40 ± 0.79	3.23 ± 0.85
High-density lipoprotein cholesterol (mmol/liter)	1.43 ± 0.41	1.27 ± 0.36	1.27 ± 0.41	1.31 ± 0.41	1.24 ± 0.40
Triglycerides (mmol/liter)	1.25 ± 0.56	1.48 ± 0.90	1.23 ± 0.70	1.17 ± 0.68	1.29 ± 0.73
Plasma potassium (mmol/liter) [values after oral supplementation]	4.3 ± 0.3	4.2 ± 0.4	3.2 ± 0.4[a] [4.1 ± 0.4]	3.2 ± 0.3 [4.1 ± 0.4]	3.3 ± 0.5 [4.2 ± 0.5]
Plasma magnesium (mmol/liter)	1.0 ± 0.1	1.0 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.1
Serum creatinine (μmol/liter)	84 ± 25	95 ± 28	91 ± 19	92 ± 19	90 ± 20
Plasma active renin (pg/ml)	9.2 ± 10.7	9.6 ± 10.3	4.7 ± 6.4[b]	4.6 ± 5.6	5.1 ± 7.7
Plasma aldosterone (pg/ml)	131 ± 77	161 ± 89	246 ± 196[a]	259 ± 176	232 ± 213
Aldosterone to active renin ratio	14.0 ± 2.1	16.6 ± 1.9	52.3 ± 3.5[a]	56.2 ± 3.8	45.6 ± 3.1
Glucose metabolism parameters					
Plasma glucose (mmol/liter)	4.8 ± 0.9	4.9 ± 1.1	4.9 ± 0.8	4.9 ± 0.8	4.8 ± 0.9
Plasma insulin (pmol/liter)	55.9 ± 21.7	80.7 ± 30.2[c]	67.6 ± 24.6[d]	69.3 ± 24.6	65.1 ± 24.9
Plasma C-peptide (nmol/liter)	0.53 ± 0.20	0.78 ± 0.41[c]	0.66 ± 0.29	0.69 ± 0.29	0.62 ± 0.27
Glucose to insulin ratio × 100	8.59 ± 2.08	6.20 ± 2.73[c]	7.24 ± 2.45[e,f]	7.06 ± 2.39	7.38 ± 2.52
AUC glucose (mmol/liter^{-1}·min)	22.3 ± 5.7	25.4 ± 7.5[c]	24.1 ± 4.3	23.8 ± 4.0	24.4 ± 4.7
AUC insulin (pmol/liter^{-1}·min)	816 ± 398	1116 ± 559[c]	1041 ± 415[g]	1065 ± 429	1015 ± 404
HOMA index	1.65 ± 0.64	2.44 ± 1.09[c]	2.06 ± 0.73[b]	2.11 ± 0.74	2.00 ± 0.70
QUICKI index	0.354 ± 0.013	0.333 ± 0.020[c]	0.343 ± 0.014[a]	0.341 ± 0.015	0.345 ± 0.017
MCR (ml/kg$^-$1·min)		15.1 ± 2.5	18.6 ± 2.7[d]	18.3 ± 2.7	19.0 ± 2.7

Values are means ± SD. Comparisons were done by analysis of covariance. Body mass index is defined as the weight in kilograms divided by the square of the height in meters. The waist circumference was measured at minimal inspiration, midway between the last rib and iliac crest. Blood pressure was measured after appropriate washout of antihypertensive drugs as referred in text. Plasma potassium values are the average of three measurements obtained before correction with potassium supplementation and, in *parentheses*, values measured after supplementation. AUC was for plasma glucose and plasma insulin concentration after oral glucose load (180 min). MCR was assessed by a hyperinsulinemic-euglycemic clamp in a subgroup of 44 patients with essential hypertension and 20 patients with primary aldosteronism. To convert to conventional units, multiply creatinine by 0.0113 (milligrams per deciliter), cholesterol by 38.6 (milligrams per deciliter), triglycerides by 88.5 (milligrams per deciliter), glucose by 0.05551 (milligrams per deciliter), insulin by 0.1394 (milliunits per milliliter), and C-peptide by 3.021 (nanograms per milliliter).

[a] $P < 0.01$ *vs.* essential hypertensive patients and normotensive subjects.
[b] $P < 0.05$ *vs.* essential hypertensive patients and normotensive subjects.
[c] $P < 0.001$ *vs.* normotensive subjects.
[d] $P < 0.01$ *vs.* essential hypertensive patients.
[e] $P < 0.01$ *vs.* normotensive subjects.
[f] $P < 0.05$ *vs.* essential hypertensive subjects.
[g] $P < 0.05$ *vs.* normotensive subjects.

TABLE 2. Antihypertensive medication used before the study and at end of follow-up

Medication	Essential hypertensive group before study (n = 274)	Primary aldosteronism group (n = 47)	
		Before study	End of study
Diuretic	137 (50)	27 (57)	5 (11)
β-Blocker	112 (41)	25 (53)	5 (11)
Calcium channel blocker	118 (43)	26 (55)	13 (28)
ACE inhibitor	101 (37)	19 (40)	9 (19)
Angiotensin receptor blocker	21 (8)	7 (15)	5 (11)
α-Blocker	7 (3)	9 (19)[a]	0
Aldosterone antagonist	0	0	27 (57)
Other antihypertensive agents	0	5 (11)	0
Total	496	118	64

Data represent number (percent). Use at the end of study was defined as receipt of the specific drug for more than 50% of follow-up visits.
[a] $P < 0.01$ *vs.* essential hypertensive patients.

1. Average fasting plasma insulin and C-peptide concentrations and plasma glucose response to the oral glucose load were higher, but not significantly different, in patients with primary aldosteronism than normotensive controls. After adjustment for age, sex, and body mass index, the plasma insulin response to the oral glucose load, fasting glucose to insulin ratio, HOMA index, and QUICKI in patients with primary aldosteronism were significantly different from normotensive controls. Changes of glucose metabolism parameters were greater in essential hypertension than primary aldosteronism, and significant differences between these two groups were observed in fasting insulin concentrations, fasting glucose to insulin ratio, HOMA index, and QUICKI. Presence of a more severe insulin resistance in essential hypertension than primary aldosteronism was confirmed by the observation of a significantly lower glucose MCR during the hyperinsulinemic-euglycemic clamp. Separate analysis of patients with tumoral *vs.* idiopathic forms of primary aldosteronism did not show significant differences in any of the glucose metabolism parameters.

In patients with primary aldosteronism, the body mass index was directly correlated with the fasting plasma insulin ($P < 0.05$) and C-peptide ($P < 0.05$) concentrations, the HOMA index ($P < 0.05$), and plasma insulin response to the oral glucose load ($P < 0.05$), whereas inverse correlations were observed with the fasting glucose to insulin ratio ($P < 0.01$) and the QUICKI ($P < 0.05$). Neither blood pressure nor plasma aldosterone concentrations were significantly correlated with any of the parameters of glucose metabolism considered in the study. The plasma potassium concentrations were directly correlated with fasting plasma insulin ($P < 0.05$) and C-peptide ($P < 0.01$) and inversely correlated with the body mass index ($P < 0.01$) and HOMA index ($P < 0.05$). Stepwise multiple regression analysis in which body mass index was entered at the first step showed that the relationship of plasma potassium concentrations with parameters of glucose metabolism is not independent. In patients with essential hypertension and normotensive controls, the body mass index was correlated with the indices of glucose metabolism and insulin sensitivity as in the patients with primary aldosteronism.

Follow-up

After treatment, parameters of glucose metabolism were reassessed in patients with primary aldosteronism at 6 months and after an average follow-up of 5.7 yr. At the end of follow-up, nine patients with primary aldosteronism (19%) were taking no drugs, 16 patients (34%) were on monotherapy, and the remaining 22 patients (47%) had multiple-drug treatment (Table 2). The trough blood pressure declined significantly in the first 6 months and remained stable thereafter with a mean value during the course of the study of 136/81 mm Hg (Fig. 1). During the study, the percentage of patients with uncontrolled hypertension (blood pressure of more than 140/90 mm Hg while taking antihypertensive medications) decreased from 96 to 17%. In the first 6 months, plasma potassium concentrations increased significantly from baseline levels measured before supplementation (from 3.2 ± 0.4 to 4.1 ± 0.3 mmol/liter, $P < 0.001$) and remained stable thereafter. The plasma magnesium concentrations did not change significantly 6 months after treatment (1.0 ± 0.2 mmol/liter) and during long-term follow-up (1.0 ± 0.1 mmol/liter).

During the initial 6-month period, abnormalities of plasma insulin response to the oral glucose load, fasting glucose to insulin ratio, HOMA index, and QUICKI were restored to normal in primary aldosteronism (Fig. 1). These changes occurred equally in patients with adrenal adenoma who underwent adrenalectomy (n = 20) and patients with adrenal adenoma(s) (n = 5) and idiopathic aldosteronism (n = 22) who were treated with spironolactone. Analysis of the long-term follow-up revealed only nonsignificant changes of glucose metabolism parameters (Fig. 1). Separate analysis of the metabolic outcome in patients with tumoral or idiopathic adrenal disease did not show any significant difference.

Discussion

The results of the present study demonstrate that patients with tumoral and idiopathic aldosteronism are insulin resistant, compared with age-, gender-, and body mass index-matched healthy controls. In these patients, however, the severity of insulin resistance appears less important than in patients with essential hypertension of the same degree and duration. In primary aldosteronism, normal sensitivity to insulin is rapidly restored after treatment with either adrenalectomy or aldosterone antagonists, whereas no further change of glucose metabolism parameters occurs during the long-term follow-up.

A large body of evidence indicates that essential hypertension is associated with insulin resistance and compensa-

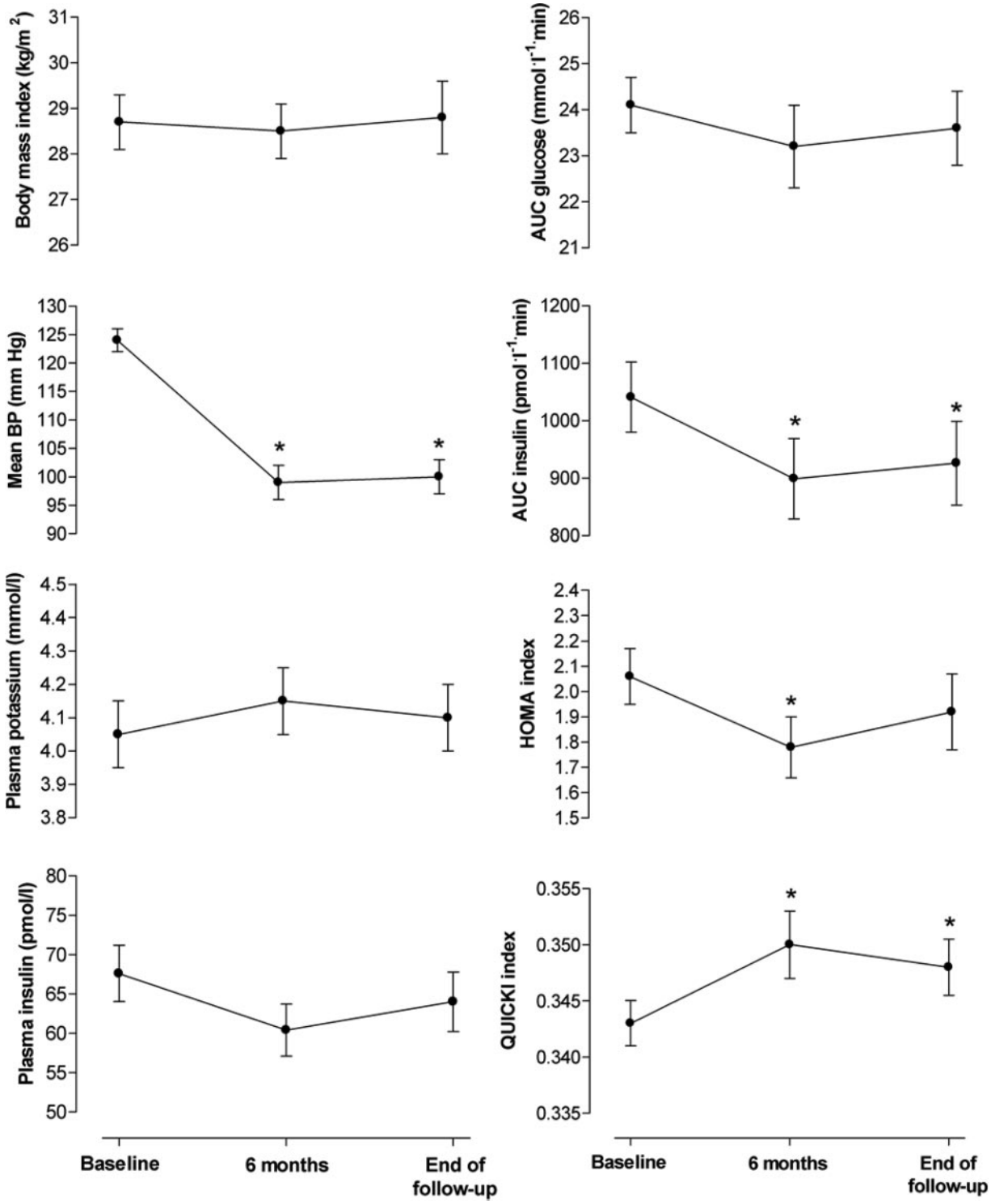

FIG. 1. Mean (SE) of body mass index, mean blood pressure, plasma potassium, plasma insulin, AUC of plasma glucose and plasma insulin after a 75-g oral glucose tolerance test, HOMA index, and QUICKI in 47 patients with primary aldosteronism. Variables were measured at baseline and after treatment with adrenalectomy (n = 20) or aldosterone receptor antagonists (n = 27). Plasma potassium values at baseline are those measured after correction with potassium supplementation. The HOMA index was calculated from fasting plasma glucose (millimoles per liter) and insulin (microunits per milliliter) using the formula: [(glucose × insulin)/22.5] (24). Logarithmic values of fasting plasma glucose (milligrams per deciliter) and insulin (microunits per milliliter) concentrations were obtained to calculate the QUICKI using the formula: [1/(log glucose + log insulin)]. Treatment rapidly (6 months) decreased blood pressure and restored normal sensitivity to insulin. Analysis of subsequent follow-up (mean duration, 5.7 yr; range, 3–9 yr) revealed only nonsignificant changes. *, $P < 0.05$ *vs.* baseline.

tory hyperinsulinemia and that these factors contribute to increased incidence of cardiovascular disease in hypertensive patients (19) as in the general population (4). Although the association between insulin resistance and hypertension does not necessarily indicate a causal relationship, detection of similar abnormalities in normotensive offspring of patients with essential hypertension (20) and results of prospective studies (21) support this possibility. Further indirect evidence of a causal link between insulin resistance and essential hypertension was obtained in studies that demonstrated that patients with secondary hypertensive disease (8–10) are not insulin resistant or hyperinsulinemic. These studies, however, could not reliably distinguish among patients with different causes of secondary hypertension.

Because of its original description, primary aldosteronism has been recognized as one of the possible causes of glucose intolerance (22), and the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus has recently indicated that primary aldosteronism might be *per se* a cause of diabetes (23). However, clinical studies that have assessed insulin sensitivity in patients with primary aldosteronism show substantial inconsistencies. Disparity of findings can be attributed primarily to the small sample size of most of these studies and, to a lesser extent, differences in criteria used for selection of patients and controls and methodology used to evaluate glucose tolerance and insulin sensitivity. Most studies came from the same research group (13, 14, 24–27) and reported that patients with primary aldosteronism are insulin resistant, compared with normotensive healthy controls (14, 24, 26, 27), but do not differ from essential hypertensive patients in terms of plasma glucose and insulin response to an oral glucose load (13, 25). It was reported also that patients with idiopathic aldosteronism are more insulin resistant than patients with tumoral disease (25) and that adrenalectomy, but not treatment with spironolactone, restores normal insulin sensitivity (24), a finding that was not confirmed by the same group in a subsequent study (14). Studies performed by other investigators did not confirm the presence of insulin resistance in patients with primary aldosteronism (11, 12), indicating instead glucose intolerance due to impaired pancreatic release of insulin (11).

In a recent study, Fallo *et al.* (28) reported an increased prevalence of the metabolic syndrome in a very large group of patients with primary aldosteronism who were compared with essential hypertensive controls. This difference was due to higher plasma glucose levels in the former group, which, in turn, could be related to significantly greater prevalence of diabetes mellitus (8.2% in primary aldosteronism *vs.* 3.4% in essential hypertension). Although these findings appear to be in contrast with our present observations, we need to consider that diabetic patients were excluded from our study to maximize the possibility to detect more subtle differences among the groups; that identification of the metabolic syndrome is done using fasting glucose as a categorical variable, whereas we examined a series of continuously distributed parameters; and finally that differences may exist in the population from which the patient samples were selected because the prevalence of diabetes among essential hypertensive patients who are seen at our clinic is significantly higher (approximately 15%) than that reported in that study (18, 29, 30).

In the present study, we examined a substantial patient sample, and although the clamp was performed only in a subset of patients, we included both essential hypertensive patients and normotensive subjects as controls. In primary aldosteronism, we found increased plasma insulin response to an oral glucose load, indicating that insulin secretion from the pancreas is not impaired. Demonstration of elevated HOMA index and decreased QUICKI and glucose MCR during the hyperinsulinemic clamp clearly indicates that patients with primary aldosteronism are insulin resistant, compared with normotensive healthy subjects. Insulin resistance was observed in patients with both tumoral and idiopathic disease, but the magnitude of the defect was smaller than in patients with essential hypertension. We examined also the metabolic outcome of patients with primary aldosteronism after treatment, showing that both adrenalectomy and spironolactone rapidly and significantly improve insulin sensitivity in the short term. In the long term, average variations of glucose metabolism parameters were compatible with increasing age and a trend to increase body mass index. However, no significant changes were observed in both adrenalectomized and spironolactone-treated patients. The latter observation is of relevance because past studies had shown that spironolactone could transiently affect glucose tolerance (31).

Experimental evidence suggests a functional interaction between mineralocorticoid hormones and insulin (32). It was initially thought that the cause leading to glucose intolerance in primary aldosteronism is potassium depletion, which could modulate both insulin secretion and insulin receptor function (11). In fact, experiments conducted on isolated pancreatic islets demonstrated that extracellular potassium stimulates insulin secretion (33), and studies performed in hypertensive patients with thiazide-induced hypokalemia showed decreased peripheral sensitivity to insulin that was not observed when patients were treated with the same diuretics but hypokalemia did not occur (34). On the other hand, aldosterone might exert direct effects on insulin receptor function (35), and recent experiments indicated that aldosterone may decrease insulin sensitivity in human adipocytes (36). Because of possible interference of plasma potassium concentrations with glucose tolerance and insulin sensitivity, appropriate assessment of glucose metabolism in hypokalemic conditions would require prior correction of potassium levels. In our study, we assessed glucose tolerance and insulin sensitivity after correction of hypokalemia with potassium supplementation, showing that primary aldosteronism is an insulin-resistant condition independent of plasma potassium levels.

A limitation of the present study is the fact that the hyperinsulinemic-euglycemic clamp technique, the gold standard for evaluation of insulin sensitivity, was applied only to a subset of patients with primary aldosteronism and essential hypertension. Another limitation was the use of certain types of antihypertensive medications that might have influenced the metabolic outcome during follow-up. For instance, thiazide diuretics and β-blockers have untoward effects on insulin secretion and sensitivity, whereas the use of ACE inhibitors and angiotensin receptor blockers could be beneficial. In this study, slightly different percentages of patients with primary aldosteronism and essential hyper-

tension received these drugs. However, analysis of subgroups based on specific antihypertensive treatments did not show significant differences. Finally, the present data cannot distinguish the mechanisms leading to insulin resistance in patients with primary aldosteronism and essential hypertension. The demonstration of different severity of the defect in the presence of comparable blood pressure levels indicates that insulin resistance is not the result of high blood pressure *per se* and suggests a different pathogenesis for the metabolic abnormality in these clinical conditions. Measurement of adipocytokines known to influence insulin sensitivity in such patients' groups might provide useful information related to these mechanisms.

In conclusion, primary aldosteronism is associated with increased plasma insulin response to an oral glucose load and insulin resistance independent of plasma potassium levels. Impairment of insulin sensitivity in this condition is less important than in essential hypertension and is rapidly and persistently reversed after adrenalectomy or treatment with aldosterone antagonists.

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