

Insulin Resistance and Hyperinsulinemia are Related to Plasma Aldosterone Levels in Hypertensive Patients

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Running title: aldosterone and insulin resistance

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## **Abstract**

**Objective.** Association between aldosterone and insulin resistance has been demonstrated in obesity, primary aldosteronism, and in blacks with the metabolic syndrome. The aim of this study was to evaluate the relationship of plasma aldosterone with insulin sensitivity in white subjects.

**Research Design and Methods.** In 356 patients with essential hypertension and 102 normotensive controls of comparable age and BMI, we measured, after discontinuation of treatment, plasma active renin, aldosterone, cortisol, glucose, insulin, and C-peptide levels, and calculated markers of insulin sensitivity. Direct assessment of insulin sensitivity was obtained in a subset of 64 hypertensive patients by a hyperinsulinemic clamp.

**Results.** Hypertensive patients had significantly greater fasting plasma insulin and C-peptide concentrations, and HOMA index than normotensive controls. Positive association with increasing plasma aldosterone concentrations was demonstrated for plasma glucose, insulin, C-peptide, and HOMA. Assessment of insulin sensitivity by the clamp showed significant decrease of the metabolic clearance rate (MCR) of glucose with increasing aldosterone levels. Significant correlations were found between plasma aldosterone and plasma insulin, and C-peptide levels, HOMA, and glucose MCR. Blood pressure and plasma potassium, plasma cortisol, and renin levels, but not BMI, were also directly correlated with plasma aldosterone. Multiple regression analysis showed that HOMA, together with plasma potassium, cortisol, and renin levels, was independently correlated with plasma aldosterone.

**Conclusions.** This study demonstrates a direct relationship between aldosterone, insulin resistance, and hyperinsulinemia in white subjects. In patients with hypertension this relationship might contribute to maintenance of high blood pressure and increase cardiovascular risk.

Seminal studies that were published more than twenty years ago demonstrated an association between hyperinsulinemia, insulin resistance, and arterial hypertension (1,2). This association was confirmed even after adjustment for body weight and was present in whites, but not in blacks (3). Population-based studies have subsequently suggested that insulin resistance and hyperinsulinemia might contribute to progression of cardiovascular disease (4).

Elevated plasma aldosterone levels have been implicated in the development and maintenance of high blood pressure in different ethnic groups (5), with a relationship that is stronger in blacks (5) and in obese subjects (6). In the Framingham Offspring Study, normotensive subjects with elevated plasma aldosterone levels, albeit within the normal range, were at high risk of blood pressure elevation and subsequent development of hypertension (7). Moreover, recent evidence indicates that chronic exposure to elevated aldosterone levels might result in substantial damage of the heart and blood vessels. This damage appears to be independent of the blood pressure level and might contribute to an increased risk of cardiovascular events (8).

A relationship between aldosterone and insulin resistance has been consistently demonstrated in obesity (9) and primary aldosteronism (10). Two recent studies that have been conducted in families of African descent in the Seychelles (11) and in African Americans (12) have demonstrated that plasma aldosterone, but not plasma renin, is associated with the metabolic syndrome and with markers of insulin resistance. The present study has evaluated the relationship of plasma aldosterone with glucose metabolism and insulin sensitivity in white patients the majority of whom had essential hypertension.

## **Research Design and Methods**

### **Patients**

A total of 356 patients with mild to moderate essential hypertension who were referred to the Hypertension clinic of our department, were included in a cross-sectional study. High blood pressure (systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg) was measured at least twice on two different occasions and

subsequently confirmed on at least two more visits during the next 4 weeks. Blood pressure was measured by a mercury sphygmomanometer after each subject had been supine for 15 min. The average of three readings obtained in 5 min was recorded. The patients seen at our clinic are white, include individuals with all grades of hypertension living in northeast Italy, and are representative of hypertensive patients in this geographic area. Patients with secondary hypertension, severe hypertension (as defined by diastolic blood pressure  $\geq 120$  mmHg), renal failure with creatinine clearance of less than 30 ml/min per 1.73 m<sup>2</sup> of body surface area, urinary protein excretion of more than  $\geq 1.0$  g/day, pregnancy, chronic debilitating illness, and recent (within 6 months) myocardial infarction, unstable angina, or stroke were excluded. Secondary causes of hypertension were identified on the basis of extensive laboratory testing (13). Primary aldosteronism was screened by the demonstration of an increased plasma aldosterone-to-renin ratio in the presence of a plasma aldosterone concentration of more than 150 pg/ml, and confirmed by the lack of aldosterone suppression following an intravenous saline load (10,14). All measurements were performed under a normal sodium diet, and 24-hour urinary sodium excretion was assessed in all patients. Patients treated with antihypertensive drugs were withdrawn from treatment a minimum of 2 weeks before diagnostic assessment. No patient was taking aldosterone antagonists.

Patients with essential hypertension were compared with 102 normotensive subjects that were selected from the general population of the same geographic area as the hypertensive patients, after specification of inclusion criteria to avoid age and body mass index (BMI) as potential confounding variables. Normotensive controls were not taking any regular medications and did not have any concomitant disease. Informed consent was obtained from the study participants and the study protocol received approval by the local review committee.

## Glucose Metabolism Evaluation and Laboratory Measurements

Assessment of glucose metabolism parameters and insulin sensitivity was done at the same time of diagnostic screening after appropriate antihypertensive drugs wash-out, as described previously (15). At the time of the study, patients maintained their usual unrestricted diet. A sample of venous blood was obtained after fasting for 12-14 hours and after the patients were in the sitting position for 10 min for analysis of glucose, insulin, and C-peptide. The homeostasis model assessment (HOMA) index, and the quantitative insulin sensitivity check index (QUICKI) were calculated as markers of sensitivity to insulin (15). The HOMA index was calculated from fasting plasma glucose (mmol/l) and insulin ( $\mu$ U/ml) using the formula:  $[(\text{glucose} \times \text{insulin})/22.5]$ . Logarithmic values of fasting plasma glucose (mg/dl) and insulin ( $\mu$ U/ml) concentrations were obtained to calculate the QUICKI using the formula:  $[1/(\log \text{glucose} + \log \text{insulin})]$ .

Insulin sensitivity was further and directly assessed in a subgroup of 64 patients with hypertension by a hyperinsulinemic-euglycemic clamp that was performed as described previously (15). Briefly, a priming dose of 100 mU/kg of body weight of rapidly acting insulin was administered intravenously over a period of 10 minutes, and then a sustained infusion of insulin, at a rate of 2 mU per kg of body weight per minute, was started to maintain serum insulin concentrations at approximately 700 pmol/liter. Concomitantly, an intravenous 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 minutes during the clamp. Sensitivity to insulin was expressed as the glucose metabolic clearance rate (milliliters per kg of body weight per minute) during 60 minutes of the clamp.

Sodium, potassium, and creatinine were measured in plasma obtained after fasting for 12-14 hours by automated analyzers. Plasma glucose was assayed using the glucose oxidase method. Plasma insulin and C-peptide were measured by radioimmunoassay (16). Plasma active renin and aldosterone concentrations were measured by radioimmunoassay in plasma samples that were obtained with

patients in the sitting position. Both renin and aldosterone values were referred to the urinary sodium excretion of a 24-hour collection completed on the day of sampling (17).

## Statistical analysis

All values are expressed as mean  $\pm$  standard deviation. Variables with skewed distribution were analyzed after logarithmic transformation. The Student's *t* test was used for comparisons between normotensive and hypertensive subjects. One-way ANOVA was used for comparisons of values when the patients were subdivided in aldosterone tertiles. The Pearson's chi square test was used to compare frequency distributions. The relationship between continuously distributed variables was examined by linear regression analysis, and the correlation was expressed by the Pearson's correlation coefficient. Stepwise multiple regression analysis was used to ascertain which variables were independently associated. Two-tailed probability values  $<0.05$  were considered to indicate statistical significance.

## Results

The clinical, laboratory, and metabolic measurements of the study subjects are shown in Table 1. Plasma aldosterone levels and urinary potassium excretion were greater and plasma potassium was lower in the hypertensive patients than normotensive controls, with no difference in plasma active renin and cortisol levels. In the hypertensive patients, fasting plasma glucose, insulin, and C-peptide concentrations, and HOMA index were significantly different from normotensive controls, indicating the presence of insulin resistance. The percentage of hypertensive patients with plasma aldosterone above the normal range was 14.6% and the percentage of patients with suppressed plasma renin ( $< 2.5$  ng/ml) was 19.1%. Table 2 summarizes the intragroup comparison of patients with hypertension and demonstrates that increasing plasma aldosterone levels were associated with higher diastolic blood pressure and higher potassium, creatinine, and cortisol levels. Significant association with increasing plasma aldosterone was demonstrated for fasting plasma glucose, insulin, and C-peptide levels, HOMA index, and QUICKI.

In patients with hypertension, univariate analysis showed that plasma aldosterone concentrations were directly correlated with fasting plasma insulin ( $r=0.214$ ;  $P<0.001$ ), C-peptide ( $r=0.138$ ;  $P=0.009$ ), and HOMA ( $r=0.228$ ;  $P<0.001$ ), and inversely with QUICKI ( $r=-0.223$ ;  $P<0.001$ ) (Figure appendix). Plasma aldosterone was also positively correlated with systolic ( $r=0.108$ ;  $P=0.041$ ) and diastolic ( $r=0.152$ ;  $P=0.004$ ) blood pressure, and plasma potassium ( $r=0.279$ ;  $P<0.001$ ), cortisol ( $r=0.255$ ;  $P<0.001$ ), and active renin ( $r=0.138$ ;  $P=0.023$ ) levels. No correlations were observed among plasma renin, blood pressure, and parameters of glucose metabolism when compared with each other. BMI was significantly and directly correlated with systolic ( $r=0.110$ ;  $P=0.038$ ) and diastolic blood pressure ( $r=0.152$ ;  $P=0.024$ ), and with HOMA ( $r=0.334$ ;  $P<0.001$ ), but not with aldosterone and renin levels. Additional correlations were found between plasma potassium and HOMA ( $r=0.285$ ;  $P<0.001$ ) and QUICKI ( $r=-0.239$ ;  $P<0.001$ ). Multiple regression analysis was performed with a forward stepwise approach in which variables that were significantly related to aldosterone in univariate analysis were included following the strength of the relationship. Analysis showed that plasma potassium ( $P<0.001$ ), plasma cortisol ( $P<0.001$ ), HOMA ( $P=0.009$ ), and plasma active renin ( $P=0.013$ ) were independently correlated with plasma aldosterone levels (Table 3). The relationship of aldosterone with insulin and HOMA was independent ( $P<0.001$ ) of blood pressure levels and the relationship between aldosterone and blood pressure was independent ( $P=0.013$ ) of cortisol levels.

To further explore the relationship between plasma aldosterone and sensitivity to insulin, we measured the metabolic clearance rate of glucose in a subgroup of 64 patients with hypertension who underwent a hyperinsulinemic-euglycemic clamp. In these patients, we observed a significant decrease of glucose metabolic clearance rate with increasing aldosterone levels (Figure 1), with a highly significant inverse correlation between the rate of glucose disposal and plasma aldosterone ( $r=-0.586$ ;  $P<0.001$ ).

Analysis of correlations that included both healthy controls and hypertensive patients

demonstrated a positive and highly significant relationship between plasma aldosterone and fasting plasma insulin ( $r=0.208$ ;  $P<0.001$ ), fasting plasma C-peptide ( $r=0.161$ ;  $P<0.001$ ), and HOMA ( $r=0.243$ ;  $P<0.001$ ). Multivariate analysis showed that the relationship of plasma aldosterone with HOMA ( $P=0.008$ ) was independent of blood pressure, active renin, and cortisol.

## Discussion

The results of the present study demonstrate that plasma aldosterone levels are associated with plasma markers of insulin resistance and hyperinsulinemia in a white population of patients the majority of whom had high blood pressure. Multivariate analysis demonstrates that this association is independent of plasma potassium and cortisol levels. In patients with hypertension, the relationship between aldosterone and decreased sensitivity to insulin was confirmed by direct assessment of insulin-mediated glucose disposal rate under a hyperinsulinemic-euglycemic clamp.

The issue of a possible relationship between plasma aldosterone and insulin resistance is important because aldosterone has been shown to contribute, independent of blood pressure, to the development of cardiovascular damage (8), and insulin resistance and hyperinsulinemia are predictors of cardiovascular events in hypertensive patients (18) as in the general population (4). Initial demonstrations of an association between plasma aldosterone levels and insulin resistance were obtained in obese subjects (9) and patients with primary aldosteronism (10). In these patients, weight loss (9) and removal of the effects of excess aldosterone with either adrenalectomy or treatment with aldosterone antagonists (10) restored normal sensitivity to insulin. More recently, two large studies have reported that plasma aldosterone, but not plasma renin levels, are associated with the metabolic syndrome (11,12) and markers of insulin resistance (12) in normotensive and hypertensive blacks. At difference, in a subanalysis of the TROPHY study (19), no evidence for elevated aldosterone was found in individuals with high-normal blood pressure and the metabolic syndrome, when compared to controls without the syndrome. In that study, however, 82% of patients were white, raising

the issue of a race-specific effect. Our findings extend the evidence of a significant association between aldosterone, hyperinsulinemia, and insulin resistance to white subjects. Because the majority of the individuals included in our study had hypertension, it could be speculated that aldosterone and insulin resistance might contribute together to blood pressure raise and, eventually, increased cardiovascular risk.

The methodology required to measure insulin sensitivity is complex and this makes the translation of research findings on insulin resistance into clinical practice rather difficult. Previous studies (11,12,19) have defined insulin resistance by use of fasting plasma glucose and insulin values, rather than the gold standard euglycemic-hyperinsulinemic clamp. Our study is the first to provide direct assessment of insulin-mediated glucose disposal rate and to demonstrate, with this technique, a strong association between elevated plasma aldosterone and decreased sensitivity to insulin. Although an association does not necessarily imply causality, the strength of the inverse relationship between aldosterone and the metabolic clearance rate of glucose clearly suggests the possibility that elevated aldosterone might cause or, alternatively, be the result of insulin resistance.

The interaction between mineralocorticoid hormones and insulin that is suggested by the present findings, is supported by substantial experimental evidence (reviewed in 20 and 21). It was initially sought that the cause leading to glucose intolerance in conditions characterized by increased plasma aldosterone, such as primary aldosteronism, is potassium depletion, which could modulate both pancreatic insulin secretion and insulin receptor function (22,23). In this study, plasma aldosterone was correlated with hyperinsulinemia and markers of insulin resistance independent of plasma potassium, ruling out a possible role for this electrolyte in mediating the relationship. On the other hand, aldosterone might exert direct effects on insulin receptors (22), and recent experiments indicate that aldosterone might decrease insulin sensitivity in human adipocytes (24). Finally, it is possible that greater aldosterone levels might result from hyperinsulinemia (25,26) or might be related to the association between insulin resistance and body fat content. Fatty acids and

adipokines that are released from adipose tissue play a key role in the development of insulin resistance (27) and have been shown to stimulate aldosterone production (9,28). Moreover, experimental observations indicate that fat cells can directly stimulate aldosterone secretion by adrenal glands in vitro (29).

Plasma aldosterone (5-7), hyperinsulinemia, and insulin resistance (1-3) can contribute to maintenance of increased blood pressure in the hypertensive population through several mechanism. In this study, we have observed significant reciprocal and independent correlations between aldosterone, insulin, and blood pressure, suggesting the possibility that interactions between these hormones might affect regulation of blood pressure. For instance, insulin has been shown to modulate the blood pressure response to aldosterone (30) and decrease in plasma aldosterone could contribute to the change of blood pressure with weight loss and resulting plasma insulin reduction (31). Also, in studies conducted in hyperinsulinemic rodents, a lack of aldosterone suppression by salt has been demonstrated (32). Relevant to this issue, it should be noticed that, in our study, systolic blood pressure had a weaker relationship with plasma aldosterone than diastolic blood pressure, as a likely result of its greater intrinsic variability. Plasma aldosterone was also positively correlated with plasma cortisol, but this relationship did not appear to be relevant for either blood pressure or insulin sensitivity.

Some limitations of this study need to be highlighted. First, the cross-sectional design does not permit to establish clear evidence of a causal relationship between aldosterone and insulin resistance, nor to establish which of the two is the causative factor. Second, although this study was designed to have high statistical power, some additional associations, such as those between aldosterone and BMI, that have been reported in previous studies (12,33,34) might have been missed because the average BMI of our hypertensive patients was relatively low, as compared to that of hypertensive patients included in those studies. In this context, measurement of waist circumference, as a more specific indicator of visceral adipose tissue, would have been useful.

This study demonstrates a significant relationship between aldosterone and insulin resistance with use of the clamp and extends to white individuals previous demonstrations of such relationship that had been obtained in studies performed in blacks. The interaction between increased aldosterone and insulin resistance could contribute to maintenance of hypertension and increase the risk of cardiovascular events in these subjects. Further studies will be necessary to establish whether increased aldosterone decreases peripheral sensitivity to insulin or, alternatively, insulin resistance with ensuing hyperinsulinemia stimulate aldosterone production. It would be also worth testing the possibility that

pharmacological interventions with aldosterone antagonists would be particularly beneficial on the clinical outcome of patients with insulin resistance, and that insulin sensitizers would affect favorably the course of clinical conditions characterized by high circulating levels of aldosterone.

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**TABLE 1. Clinical Characteristics, Laboratory Variables, and Glucose Metabolism Parameters of the Study Subjects**

	<b>Normotensive group (n = 102)</b>	<b>Hypertensive group (n = 356)</b>	<b>P value</b>
<i>Clinical characteristics</i>			
Age, years	51±14	49±12	0.154
Male sex [n (%)]	71(70)	195(55)	0.028
SBP, mmHg	129±11	160±19	<0.001
DBP, mmHg	79±7	100±11	<0.001
BMI, Kg/m <sup>2</sup>	28.3±3.6	27.9±4.8	0.435
<i>Laboratory variables</i>			
Plasma sodium, mmol/L	141±2	141±3	1.000
Plasma potassium, mmol/L	4.3±0.3	4.0±0.4	<0.001
Plasma creatinine, µmol/L	84±25	88±17	0.062
Urinary sodium, mmol/24h	120±52	132±67	0.098
Urinary potassium, mmol/24h	46±23	56±23	<0.001
Plasma active renin, pg/mL	9.2±10.7	10.8±17.0	0.575
Plasma aldosterone, pg/mL	131±77	167±123	0.005
Plasma cortisol, nmol/L	429±107	420±236	0.709
Triglycerides, mmol/L	1.25±0.56	1.40±0.92	0.118
Total cholesterol, mmol/L	5.30±1.04	5.58±1.13	0.025
HDL cholesterol, mmol/L	1.43±0.41	1.42±0.42	0.831
LDL cholesterol, mol/L	3.31±0.98	3.55±1.05	0.039
<i>Glucose metabolism parameters</i>			
Plasma glucose, mmol/L	4.8±0.9	5.1±1.2	0.020
Plasma insulin, pmol/L	55.9±21.7	70.0±35.1	<0.001
Plasma C-peptide, nmol/L	0.53±0.20	0.69±0.30	<0.001
HOMA index	1.65±0.64	2.29±1.55	<0.001
QUICKI	0.354±0.013	0.348±0.030	0.050

Data are means (SD) unless otherwise specified. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index as defined by the weight in kilograms divided by the square of the height in meters; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index. Comparisons were done by the Student's t test for unpaired data.

**TABLE 2. Clinical Characteristics, Laboratory Variables, and Glucose Metabolism Parameters of Hypertensive Patients According to Plasma Aldosterone Tertiles**

	Aldosterone tertile			P value
	I (n = 119)	II (n = 118)	III (n = 119)	
<i>Clinical characteristics</i>				
Age, years	50±12	49±12	49±11	0.655
Male sex, [n (%)]	62 (52)	73 (62)	60 (50)	0.161
SBP, mmHg	157±18	160±18	162±20	0.088
DBP, mmHg	98±10	100±10	101±11	0.026
BMI, Kg/m <sup>2</sup>	27.3±4.6	28.2±4.7	28.3±5.0	0.193
<i>Laboratory variables</i>				
Plasma potassium, mmol/L	3.8±0.4	4.0±0.4	4.1±0.4	<0.001
Urinary sodium, mmol/24h	133±70	131±68	132±64	0.963
Urinary potassium, mmol/24h	52±23	59±27	58±23	0.113
Plasma creatinine, µmol/L	86±15	91±19	89±17	0.048
Creatinine clearance, mL/min/1.73 m <sup>2</sup>	94±27	90±24	91±22	0.503
Plasma active renin, pg/mL	9.7±17.0	11.7±18.9	11.1±15.1	0.721
Plasma aldosterone, pg/mL	68±22	139±24	293±132	<0.001
Plasma cortisol, nmol/L	356±264	408±213	494±209	<0.001
<i>Glucose metabolism parameters</i>				
Plasma glucose, mmol/L	4.8±0.9	5.2±1.2	5.3±1.3	0.002
Plasma insulin, pmol/L	60.3±31.2	73.1±35.6	76.8±36.1	0.001
Plasma C-peptide, nmol/L	0.66±0.29	0.67±0.32	0.75±0.28	0.043
HOMA index	1.84±1.28	2.40±1.45	2.63±1.77	<0.001
QUICKI	0.359±0.029	0.345±0.030	0.341±0.030	<0.001

Data are means (SD) unless otherwise specified. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index as defined by the weight in kilograms divided by the square of the height in meters; HOMA, homeostatic model assessment; QUICKI, quantitative insulin sensitivity check index. Comparisons were done by one-way ANOVA.

**TABLE 3. Stepwise Linear Regression Analysis of Variables Associated with Plasma Aldosterone Levels in Hypertensive Patients (n = 356)**

Plasma potassium		Plasma cortisol		HOMA index		Plasma active renin	
SC	P value	SC	P value	SC	P value	SC	P value
0.331	<0.001	-	-	-	-	-	-
0.287	<0.001	0.222	<0.001	-	-	-	-
0.257	<0.001	0.211	<0.001	0.153	0.010	-	-
0.259	<0.001	0.200	<0.001	0.155	0.009	0.144	0.013

HOMA, homeostatic model assessment; SC, standard coefficient. Calculations were done with log transformed values.

## Figure Legends

### Figure 1.

Bar graph showing the glucose metabolic clearance rate, as assessed during a euglycemic-hyperinsulinemic clamp, across plasma aldosterone tertiles in patients with essential hypertension (n = 356). Comparisons were done by one-way ANOVA ( $P < 0.001$ ) followed by group-to-group comparisons.

