Fasting Plasma Glucose and Serum Lipids in Patients With Primary Aldosteronism
A Controlled Cross-Sectional Study

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Abstract—An association between primary aldosteronism and metabolism disorders has been reported. The aim of this retrospective study was to test for this association by comparison between large cohorts of patients with primary aldosteronism and with essential hypertension. We retrieved the records of 460 cases with primary aldosteronism (103 lateralized, 150 not lateralized, and 207 undetermined) and of 1363 controls with essential hypertension individually matched for age and sex. We compared clinical history; blood pressure levels; body mass index; levels of fasting plasma glucose and serum triglycerides; total, high-density lipoprotein, and low-density lipoprotein cholesterol; and the prevalence of diabetes mellitus and impaired fasting glucose among subtypes of primary aldosteronism, as well as between cases with primary aldosteronism and their matched controls. Fasting plasma glucose and serum lipid levels did not differ among the 3 subtypes of primary aldosteronism. The prevalence of impaired fasting glucose was lower in patients with primary aldosteronism than their matched controls, but the prevalence of hyperglycemia (impaired fasting glucose or diabetes mellitus) and blood levels of glucose and lipids did not differ between cases and controls. There was no significant difference between preoperative and postoperative levels of either fasting plasma glucose or serum lipids in patients who underwent adrenalectomy and had follow-up data available. The analysis of this large group of patients with primary aldosteronism and essential hypertension does not confirm a higher prevalence of carbohydrate or lipid metabolism disorders in the former. It is unlikely that the prevalence of metabolic syndrome differs significantly between patients with primary aldosteronism and those with essential hypertension. (Hypertension. 2009;53:00-00.)

Key Words: diabetes mellitus • hyperaldosteronism • primary • hyperlipidemia • hypertension, essential

Primary aldosteronism (PA) is the most frequent form of endocrine hypertension. Patients with PA have a higher prevalence of cardiovascular and renal complications than patients with essential hypertension with similar levels of blood pressure; this suggests that excess aldosterone has harmful nonhemodynamic cardiovascular and renal effects. An association between PA and carbohydrate metabolism disorders was reported by Conn as long ago as 1965, and aldosterone-producing adenoma is mentioned as a possible cause for diabetes mellitus by the American Diabetes Association. A higher prevalence of metabolic abnormalities, like impaired glucose and lipid metabolism or the metabolic syndrome, might contribute to the higher cardiovascular and renal risk in patients with PA than in patients with essential hypertension. Several mechanisms for glucose and lipid metabolism impairments in PA have been discussed, including a diabetogenic effect of hypokalemia and effects of aldosterone on the insulin receptor or on adipose tissue metabolism. However, previous studies of the prevalence of glucose metabolism disorders in PA have reported inconsistent results. The objective of this retrospective cross-sectional study was to compare blood glucose and lipid levels in a large series between cases with PA and controls with essential hypertension and between cases with PA with or without a lateralized aldosterone hypersecretion.

Patients and Methods

Data Retrieval and Patient Selection

Data from all of the patients referred to our hypertension referral center are prospectively entered by physicians into an electronic health record database. Nonpregnant adult patients were considered for inclusion as cases with PA if the item “mineralocorticoid excess” was checked in their electronic record. To ensure retrieval of all of the cases with PA even if the item “mineralocorticoid excess” was not checked in their electronic record, we also screened the laboratory test results database of the biochemistry department, the reports database of the radiology department, the multidisciplinary

Received August 22, 2008; first decision September 12, 2008; revision accepted January 26, 2009.
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Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.108.122002
meetings reports database, and 2 research databases implemented over the same period for patients referred to the same unit, 1 for the genetic study of PA and 1 for the postoperative assessment of lateralized PA. Additional patients were considered for inclusion as cases with PA if they had renin and aldosterone levels compatible with PA, if they had undergone adrenal venous sampling, if a multidisciplinary meeting had concluded that the case presented PA, or if they had given informed consent for the genetic study of PA or had undergone adrenalectomy for PA. The electronic health record database was also searched to identify control subjects with essential hypertension who had been hospitalized in the unit for a diagnostic workup during the same time period.

Cases with PA were included in the final analysis if they fulfilled the diagnostic criteria described below. Nonpregnant adult controls with essential hypertension were included if secondary forms of hypertension were excluded by reviewing records for medical history, physical examination, and appropriate biochemical tests and imaging studies. In particular, only patients who had a normal aldosterone:renin ratio were included as essential hypertensive controls. We analyzed data from cases with PA and controls with essential hypertension who had been referred to our unit between January 1, 2001, and December 31, 2006.

Clinical data were extracted from the electronic health record database and biochemical data from the laboratory test results database of the biochemistry department. Baseline biochemical analyses were performed during the first hospitalization for a diagnostic workup in all of the patients, irrespective of their final diagnosis (PA or essential hypertension).

Biochemical Methods
Hormonal assessment was conducted as reported previously,21,22 Plasma aldosterone concentration was determined by radioimmunoassay. Urinary excretion of aldosterone was measured as the sum of free aldosterone and aldosterone determined by the hydrolysis of aldosterone 18-glucuronide at pH 1.0. Plasma renin was determined by immunoradiometric assay for active renin. For the calculation of the aldosterone:renin ratio, active renin concentrations <5 mU/L (3 ng/L) were set at 5 mU/L to avoid aldosterone:renin ratio overestimation when active renin levels were very low or undetectable. In patients with a family history of hypertension, genetic tests were performed to exclude glucocorticoid-suppressible hyperaldosteronism.23 All of the other biochemical variables were assayed in plasma or serum using standard methods.

Diagnostic Criteria and Patient Classification
Glucose Metabolism Disorders
Diabetes mellitus was defined as a known history of diabetes mellitus, current intake of antidiabetic therapy, and/or 2 documented fasting plasma glucose levels ≥7.0 mmol/L. Impaired fasting glucose was defined as fasting plasma glucose levels ≥5.6 and <7.0 mmol/L in patients without diabetes mellitus.21 Hyperglycemia was defined as diabetes mellitus or impaired fasting glucose.

Glucose challenge tests were not performed in our center. In patients with only a single fasting plasma glucose determination available in their electronic record, we considered diabetes mellitus to be present when fasting plasma glucose was ≥7.0 mmol/L, with hemoglobin A1c >6.5%.23 Patients with a single available plasma glucose determination were classified as having hyperglycemia without further specification if their fasting plasma glucose was ≥5.6 and <7.0 mmol/L or, in the absence of a hemoglobin A1c result, if it was ≥7.0 mmol/L. Diabetes mellitus history extracted from the electronic health record database was systematically cross-checked with fasting blood glucose levels, and inconsistencies were resolved by a trained endocrinologist (L.A.) using additional data (previous fasting blood glucose levels or hemoglobin A1c levels) manually retrieved from electronic and paper records.

Diagnosis of PA and PA Subtypes
Our methods for screening and criteria for diagnosing PA were in accordance with institutional guidelines and have been described recently.20 In brief, after withdrawal of medication influencing the renin-angiotensin system and prescription of potassium supplementation, we considered PA to be present if the aldosterone:renin ratio obtained in standardized conditions was >64 pmol/mU (107 pmol/ng) on 2 occasions and the aldosterone concentration was >500 pmol/L (18 ng/dL) in the supine position or 550 pmol/L (20 ng/dL) in the standing position if urinary aldosterone excretion was >63 nmol/d (23 μg/d). Adrenal venous sampling was offered to patients with PA but without a typical solitary adenoma who had resistant hypertension or were aged ≤55 years and who would consider adrenalectomy if indicated. Catheterism was considered successful if cortisol concentrations were at least twice as high in both adrenal veins as in the inferior vena cava. Aldosterone concentrations were then divided by cortisol concentrations, and aldosterone secretion was considered to be lateralized if the aldosterone:cortisol ratio was ≥5 times higher on the dominant side than on the contralateral side. Patients were classified as having lateralized PA if unilateral overproduction of aldosterone was detected by adrenal venous sampling and/or if they were cured by unilateral adrenalectomy (hormonal cure when postoperative values were available and weaning from all antihypertensive drugs with resolution of hypertension and hypokalemia in other cases). Patients were classified as having nonlateralized PA if they underwent adrenal venous sampling and did not meet the criteria of lateralized hypersecretion. Other PA patients were classified as having PA of undetermined type.

Blood Pressure Measurement
Trained nurses used a validated semiautomatic manometer (Omron 705CP) to determine blood pressure levels. Three measurements of blood pressure were obtained in the sitting position, with a 5-minute rest period between measurements. Office blood pressure was determined by calculating the average blood pressure from the second and third measurements, as described previously.23

Statistical Methods
Before pooling all of the patients with PA, we compared clinical history; body mass index (BMI); blood pressure; fasting plasma glucose; circulating levels of triglycerides, total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol; potassium; plasma renin, and aldosterone among patients with lateralized, nonlateralized, and undetermined forms of PA. In patients with PA or essential hypertension, we performed univariate conditional logistic regression for whom aldosterone measurements in the lying, sitting, and standing positions were available, we observed that lying and sitting values were similar, whereas standing values were consistently approximately twice as high. Therefore, we report aldosterone and renin levels in the lying position when available and in the sitting position otherwise. Differences between the PA subtypes were tested with Kruskal-Wallis and χ² tests (significance threshold: P < 0.05). Multivariable regression was performed to adjust comparisons for age, sex, and BMI, which were potential confounders when comparing the metabolic profile of patients with lateralized, nonlateralized, or undetermined forms of PA (Wald test; significance threshold: P < 0.05).

Up to 3 controls per case, individually matched for age (±1 year) and sex, were then included, and we compared the same clinical and biological variables in patients with PA and their controls with essential hypertension. Univariate conditional logistic regression (Wald test; significance threshold: P < 0.05) was used for matched analyses. Continuous variables were not categorized for regression studies. Conformity to a linear gradient was graphically checked, and polynomial or logarithmic transformations were performed when necessary. Interaction tests were performed to look for heterogeneity in the comparison between patients with PA or essential hypertension in predefined subgroups: men versus women and patients with a BMI <25 kg/m² versus patients with a BMI ≥25 kg/m².

Finally, preoperative and postoperative levels of each fasting plasma glucose and serum lipids were compared in patients with lateralized PA who underwent adrenalectomy and were followed up postoperatively in this hypertension unit. For each variable, the first available postoperative data ≥1 month but before 12 months after surgery was considered. The Wilcoxon rank-sum test was used for
these paired comparisons. All of the statistical analyses were performed with Stata 8.2 (Stata Corp).

Results

Database retrieval yielded 460 cases with PA: 103 lateralized, 150 not lateralized, and 207 undetermined. Among 2308 patients with essential hypertension, 3 matched controls were found for each case with PA, except for 17 cases who had only 2 matched controls; the control group, thus, included 1363 patients.

Comparison of Cases With Different PA Subtypes

We first tested whether the metabolic profile differed between PA subtypes (Table 1). Cases with lateralized PA had a lower BMI than cases with nonlateralized or undetermined PA. However, the between-group difference in BMI was no longer statistically significant after adjusting for age and sex. Cases with lateralized or nonlateralized PA were younger and had a lower prevalence of hyperglycemia than cases with undetermined PA. This age difference reflects the fact that few older patients underwent adrenal venous sampling, because we rarely consider surgery in patients aged ≥56 years. Only a few older patients could, therefore, be classified as lateralized or nonlateralized PA. Between-group differences in the prevalence of hyperglycemia were no longer statistically significant after adjustment for age, sex, and BMI.

Comparison of Cases With PA and Controls With Essential Hypertension

We then compared PA cases and their matched controls with essential hypertension (Table 2). Baseline fasting plasma glucose was missing for 16 patients (0.8%), and both baseline serum triglycerides and total cholesterol levels were missing for 19 patients (0.9%). Fifty patients (2.4%) could not be classified as having or not having hyperglycemia, and among the 835 patients with hyperglycemia, 25 (3.0%) could not be further classified as having impaired fasting glucose or diabetes mellitus.

As expected, cases had lower potassium and renin levels than controls and higher aldosterone:renin ratios and plasma aldosterone levels.
and urinary aldosterone levels. The metabolic profile of patients with PA and essential hypertension differed only as concerned the prevalence of impaired fasting glucose, which was higher in controls with essential hypertension than in cases with PA. However, this difference was compensated by a slightly lower prevalence of diabetes mellitus in patients with essential hypertension, leading to a similar prevalence of hyperglycemia in the 2 groups. No other significant differences in metabolic profile were found between patients with PA or essential hypertension in the population as a whole, and no heterogeneity was found between prespecified subgroups (male or female, BMI over or under 25 kg/m²).

### Effect of Adrenalectomy on Plasma Glucose and Serum Lipids

Sixty-one patients with lateralized PA underwent adrenalectomy and were followed-up in this hypertension unit. The remaining 42 patients with lateralized PA had been referred for adrenal venous sampling in this unit but were subsequently managed by the referring physician. There was no significant difference concerning age, sex, history of diabetes mellitus, BMI, blood pressure levels, and preoperative biochemical data (fasting plasma glucose and serum levels of triglycerides; total, LDL, and HDL cholesterol; potassium; plasma renin; and aldosterone) between patients with or without follow-up in this unit (data not shown). For patients with a follow-up, there was no significant difference between preoperative and postoperative values of fasting plasma glucose or of serum levels of total, LDL, and HDL cholesterol (Table 3). Given the number of comparisons performed in this study, the borderline significantly higher postoperative levels of serum triglycerides should be viewed as a chance finding.

### Discussion

In vitro studies suggest that aldosterone excess may induce defects in insulin secretion, insulin action, or both. Clinical studies of the prevalence of hyperglycemia in patients with PA report conflicting results, however. Some reports found no difference in fasting plasma glucose levels or in the prevalence of diabetes mellitus between cases with PA and controls with essential hypertension, whereas others found a higher prevalence of hyperglycemia or diabetes mellitus in cases with PA than in essential hypertensive controls. These reports were based on the assessment of 14 to 85 patients with PA, generally without discriminating between PA subtypes, and used various definitions of glucose metabolism disorders. In our large, cross-sectional study involving more patients with PA than the total of these previous studies, we found no statistically significant or
clinically relevant differences in metabolic profile between cases with various PA subtypes, between cases with PA and controls with essential hypertension, or between preoperative and postoperative levels in patients who underwent adrenalectomy.

Because waist circumference was not available in our electronic records, we could not document the presence or absence of the metabolic syndrome in our patients. Consequently, we cannot exclude a difference in the prevalence of the metabolic syndrome between hypertensive patients with PA and those with essential hypertension. Any such difference is unlikely, however, because there were no differences in BMI or in all of the other components of the syndrome, namely, blood pressure, fasting plasma glucose, and serum triglyceride and HDL cholesterol levels.

Our study indicates that overweight and glucose and lipid metabolism disorders have a similar prevalence in PA and essential hypertension, and this may well be higher than that in the general population. This hypothesis is in keeping with a recent study that found no difference between patients with PA and normotensive or essential hypertensive patients with respect to fasting glucose and lipid levels but found evidence of greater insulin resistance in patients with PA or essential hypertension than in normotensive subjects.

### Study Limits

Our study is retrospective and cross-sectional. However, it is now the largest controlled study of patients with PA with regard to the analyzed variables, and data were prospectively collected during patient care with few missing values. The presence or absence of hyperglycemia could not be ascertained because of missing data in only 14 patients (3.0%) with PA and 36 patients (2.6%) with essential hypertension. According to the worst-case hypothesis, we should assume that all 14 of the unclassified patients with PA had hyperglycemia and, conversely, that none of the 36 unclassified patients with essential hypertension had hyperglycemia. Even applying these extreme assumptions, the prevalence of hyperglycemia would not differ significantly between the 2 groups: 215 (46.7%) of 460 for the patients with PA and 634 (46.5%) of 1363 for patients with essential hypertension (Wald test P=0.98). Consequently, despite some missing data, we believe that our results are robust. It is nevertheless possible that patients with PA differ from those with essential hypertension with regard to variables that were not available, such as waist circumference, postprandial blood glucose, insulin level, glucose:insulin ratio, or other markers of insulin resistance.

### Perspectives

This study compared 2 groups of hypertensive patients and cannot exclude a difference between patients with PA and normotensive subjects. Future studies of appropriate sample size should further compare patients with PA and normotensive controls to properly assess the metabolic consequences of PA. Moreover, subtle metabolic disorders cannot be excluded and more sensitive markers of carbohydrate metabolism should be used, like the homeostatic model assessment or the quantitative insulin sensitivity check index. If a higher prevalence of insulin resistance was confirmed in patients with PA, the fact that it does not translate into higher fasting glucose should be further investigated, as well as the impact of insulin resistance on cardiovascular and renal morbidity.

### Conclusion

The analysis of this large group of patients with PA does not confirm the hypothesis that high levels of aldosterone and/or low levels of potassium that are associated with PA induce metabolic consequences that are not present in essential hypertension. Although waist circumference measurements were not available, it is unlikely that the prevalence of the metabolic syndrome differs between patients with PA and essential hypertension.

### Sources of Funding

This study was supported by grant AOM 02 068 from the Assistance Publique-Hôpitaux de Paris, Délégation à la Recherche Clinique, for the Cortico et Medullo-surrénale: les Tumeurs Endocrines network.

### Disclosures

None.

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Hypertension. published online February 16, 2009;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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http://hyper.ahajournals.org/content/early/2009/02/16/HYPERTENSIONAHA.108.122002.citation

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