Primary Aldosteronism in Diabetic Subjects With Resistant Hypertension

GUILLERMO E. UMPIERREZ, MD
PAUL CANTEY, MD, MPH
DAWN SMILEY, MD
ANDRES PALACIO, MD
DIANA TEMPONI, MD
KAREN LUSTER, MD
ARLENE CHAPMAN, MD

OBJECTIVE — Despite the high prevalence of hypertension in patients with type 2 diabetes, the prevalence of primary aldosteronism in this population has not been determined.

RESEARCH DESIGN AND METHODS — One hundred subjects with type 2 diabetes and resistant hypertension, defined as blood pressure >140/90 mmHg despite the use of ≥3 antihypertensive agents, were screened for primary aldosteronism. Screening was performed by measuring the plasma aldosterone (PAC)-to-plasma renin activity (PRA) ratio. Subjects with a PAC-to-PRA ratio >30 ng · ml^{-1} · h^{-1} underwent confirmatory salt load testing. Diagnostic criteria included 24-h urine aldosterone ≥12 μg during the 3rd day of the oral salt load or a PAC ≥5 ng/dl after the 4-h intravenous saline load.

RESULTS — Thirty-four subjects had a PAC-to-PRA ratio >30 ng · ml^{-1} · h^{-1}. Fourteen subjects (14% [95% CI 7.2–20.8]) had a confirmed diagnosis of primary aldosteronism. Ninety-three patients were African Americans. There were no differences in age, glycemic control, and number of antihypertensive drugs between subjects with and without primary aldosteronism. Subjects with primary aldosteronism had lower serum potassium (3.7 ± 0.4 vs. 4.0 ± 0.4 mmol/l, $P = 0.012$), higher PAC (15.6 ± 8 vs. 9.1 ± 6 ng/dl, $P = 0.0016$), and higher PAC-to-PRA ratio (98 ± 74 vs. 21 ± 30 · ml^{-1} · h^{-1}, $P < 0.001$) than patients without primary aldosteronism.

CONCLUSIONS — Primary aldosteronism is common in diabetic patients with resistant hypertension, with a prevalence of 14%. Our results indicate that diabetic subjects with poorly controlled hypertension who are taking ≥3 antihypertensive drugs should be screened for primary aldosteronism.

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Diabetes and hypertension coexist in ~40–60% of patients with type 2 diabetes (1,2). Diabetic subjects have a 1.5–3 times increased prevalence of hypertension compared with nondiabetic subjects (2,3), with 50% of adults with diabetes having hypertension at the time of diagnosis (4). The coexistence of these two conditions is associated with increased risk of retinopathy, nephropathy, and cardiovascular disease (1,5). Randomized prospective clinical trials have shown that rigorous blood pressure control in patients with diabetes reduces the risk of microvascular complications, cardiovascular events, and death (6–8). The risk reduction seen with hypertension control in patients with diabetes is substantially greater than that seen in individuals in the general population who have similar blood pressure levels (9). Epidemiological analyses have shown that in diabetic subjects blood pressure >120/70 mmHg is associated with increased cardiovascular event rates and mortality (3,9). There is no threshold value for blood pressure, and risk continues to decrease well into the normal range. Based on these findings, the Professional Practice Committee of the American Diabetes Association recommended a blood pressure goal of <130/80 mmHg for adult patients with diabetes (2,8). Achieving blood pressure control in subjects with diabetes, however, is difficult and frequently requires the use of ≥3 antihypertensive agents (10,11). Less than 50% of people with diabetes achieve blood pressure goals (5).

Resistant hypertension, defined as a failure of concomitant use of ≥3 different classes of antihypertensive agents to control blood pressure to <140/90 mmHg, is a serious and common problem. It is present in 10–30% of patients with essential hypertension (12,13). Patients with resistant hypertension seem to differ from other hypertensive subjects in three ways: they have more severe hypertension at diagnosis, they develop more end-organ damage, and they are more likely to have secondary hypertension (12,13). Primary aldosteronism is the most common cause of mineralocorticoid hypertension. Primary aldosteronism was previously believed to account for <1% of hypertensive patients; however, recent studies applying the plasma aldosterone (PAC)-to-plasma renin activity (PRA) ratio as a screening test have reported a much higher prevalence of this disease, accounting for 10–32% of the patients with essential hypertension (11,14–16) and 50% of patients with nondiuretic-induced hypokalemia (17). Despite the high prevalence of resistant hypertension among diabetic patients, the prevalence of primary aldosteronism is not known because screening for primary aldosteronism is seldom performed. Accordingly, in this study we aimed to determine the prevalence of primary aldosteronism in diabetic subjects with poorly controlled hypertension despite treatment with multiple antihypertensive agents.

RESEARCH DESIGN AND METHODS

— A total of 100 consecutive adult subjects with type 2 diabetes and resistant hypertension, defined as blood pressure >140/90 mmHg despite the use of ≥3 antihypertensive agents,

From the Department of Medicine, Emory University School of Medicine, Atlanta, Georgia.
Address correspondence and reprint requests to Guillermo E. Umpierrez, MD, Associate Professor of Medicine, Associate Director, General Clinical Research Center, Emory University School of Medicine, Director, Diabetes and Endocrinology Section, Grady Health System, 49 Jesse Hill Jr. Dr., Atlanta, GA 30303. E-mail: geumpie@emory.edu.
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Abbreviations: ARB, angiotensin receptor blocker; PAC, plasma aldosterone; PRA, plasma renin activity.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

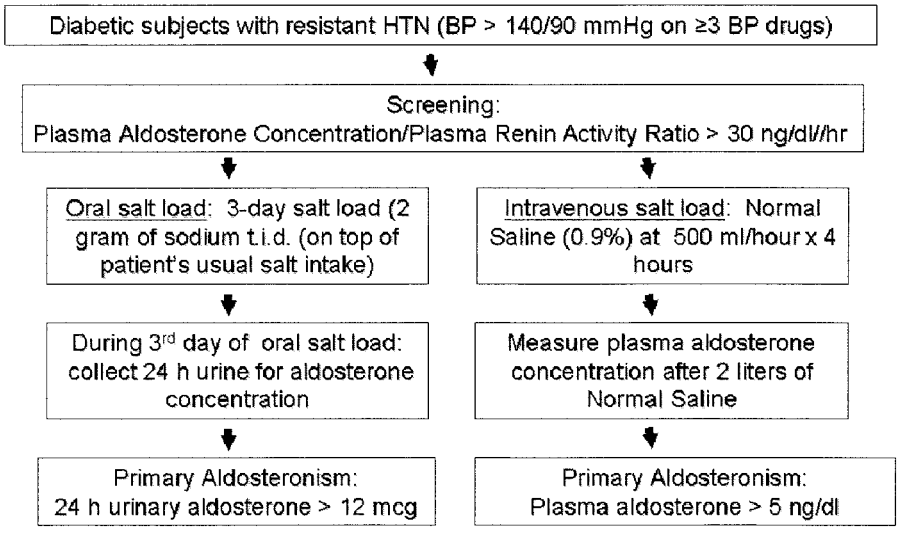

Figure 1—*Proposed diagnostic algorithm for primary aldosteronism. BP, blood pressure; HTN, hypertension.*

were screened for primary aldosteronism. Screening was performed while subjects continued their usual blood pressure medications, as stopping blood pressure medications in this high-risk population was thought to be unethical. Subjects taking aldosterone antagonists were excluded from the study. Three blood pressure measurements were taken 5 min apart, and the average of the last two measurements was used for data analysis. Blood samples were drawn in the morning after the subject had been resting in a sitting position for 30 min. Screening studies included measurement of PAC and PRA and the calculation of the PAC-to-PRA ratio (18–20). Hypertensive subjects with a PAC-to-PRA ratio >30 ng · ml^{-1} · h^{-1} underwent further studies to confirm the diagnosis of primary aldosteronism. Subjects with serum potassium <3.5 mEq/l received KCl (40 mEq/day for 1 week). Once serum potassium was ≥3.5 mEq/l, subjects were rescreened (because hypokalemia suppresses PAC and lowers the PAC-to-PRA ratio). Confirmatory studies included measurement of urinary aldosterone after a 3-day oral salt load or the measurement of PAC after an intravenous saline load (Fig. 1). The first 11 subjects in this study underwent the 3-day oral salt load. Most subjects were instructed to add 2-g NaCl packages to each meal in addition to routine salt use for three consecutive days. During the 3rd day of the oral salt load, a 24-h urine collection was performed, and subjects brought the urine to the laboratory on the following morning before 9:00 A.M. To facilitate the conduct of the study by avoiding the 24-h urine collection, we modified the protocol by substituting the oral salt load with a 4-h intravenous saline suppression test, and this test was used for all remaining subjects. For this test, 2 l of normal saline (0.9% solution) were infused over 4 h at 500 ml/h. The diagnosis of primary aldosteronism was established if the 24-h urinary aldosterone concentration was ≥12 μg (33.3 nmol/day) during the 3rd day of salt load or if PAC was ≥5.0 ng/dl after the 4-h intravenous saline load (21–23). Subjects with a confirmed diagnosis of primary aldosteronism were referred to the endocrine service for adrenal imaging, localization studies, and management. The research protocol was performed in the outpatient Grady Diabetes Clinic Research Laboratory or the Grady Clinical Research Center.

All subjects in this study had a known history of type 2 diabetes for >3 months, were aged between 18 and 75 years, and were treated with ≥3 antihypertensive drugs. Exclusion criteria included treatment with spironolactone or eplerenone, A1C >9.0%, severe uncontrolled hypertension (>180/110 mmHg), a history of heart failure (New York Heart Association class III or IV), angina pectoris, serum creatinine >1.8 mg/dl, pregnancy, breast-feeding, use of oral contraceptives, clinically relevant hepatic disease (alanine aminotransferase 2.5 times the upper limits of normal), drug or alcohol abuse, and known primary aldosteronism or a history of pheochromocytoma, Cushing's syndrome, or hyperthyroidism.

Plasma aldosterone concentration, PRA, and urinary aldosterone were measured by commercial laboratories using standard techniques. PRA and PAC levels were measured by radioimmunoassay. The reference range for PRA is 1.31–3.95 · ml^{-1} · h^{-1}. The reference range for PAC is 4.0–31.0 ng/dl. The reference range for urinary aldosterone is 2–16 g/24 h. Plasma glucose was measured using the glucose oxidase method.

Statistical analysis

All data in the text, table, and figure are expressed as means ± SD unless otherwise noted. Comparisons of continuous variables between groups were carried out using unpaired *t* tests. The Wilcoxon test was used when data were skewed (i.e., PRA). For comparison of categorical variables, χ^2 analyses were performed. A two-tailed $P < 0.05$ was considered significant. All analysis was performed using SAS statistical software (version 9.1; SAS Institute, Cary, NC).

RESULTS — A total of 100 consecutive subjects with diabetes and resistant hypertension underwent screening. The clinical characteristics of study subjects are shown in Table 1. Most subjects in this study were from minority ethnic groups and included 93 blacks, 5 Caucasians, 1 Hispanic, and 1 Native American. Study subjects had a mean ± SD age of 59 ± 9 years (range 32–74 years), a duration of diabetes of 8.9 ± 7 years (range 3 months to 30 years), and a history of hypertension of 16.2 ± 12 years (range 1–8 years). The BMI was 34.4 ± 8 kg/m^2, with three-fourths of subjects having a BMI >30 kg/m^2. Serum electrolyte levels were within normal limits. The serum potassium was 4.0 ± 0.4 mmol/l with only 15 subjects having a serum potassium ≤3.5 mmol/l. Systolic blood pressure was 157 ± 16 mmHg and diastolic blood pressure was 90 ± 9 mmHg. The number of antihypertensive drugs taken was 3.7 ± 0.8; 98% of the subjects were taking an ACE inhibitor or an angiotensin receptor blocker (ARB), 92% were taking a diuretic, 73% were taking a β-blocker, 62% were taking a calcium channel blocker, and 31% were taking an α-blocker or other agent such as clonidine or hydralazine.

There were no statistically significant differences in ethnic distribution, age, years of hypertension, years of diabetes, BMI, blood pressure, A1C, number of antihypertensive agents, or types of antihypertensive agent between subjects with and without primary aldosteronism. The mean systolic and diastolic blood pres-

Table 1—*Clinical characteristics of subjects with resistant hypertension with and without primary aldosteronism*

Variables	All subjects	No primary aldosteronism	Primary aldosteronism
n	100	86	14
Age (years)	59 ± 9	60 ± 9	57 ± 6
Race			
Black (%)	93 (93)	80 (93)	13 (93)
Caucasian/Hispanic/other	5/1/1	4/1/1	1/0/0
BMI (kg/m^2)	34.4 ± 8	34.5 ± 8	34.2 ± 8
Duration of diabetes (years)	8.9 ± 7	8.7 ± 7	9.8 ± 8
Duration of hypertension (years)	16 ± 12	16 ± 12	15 ± 7
Systolic BP (mmHg)	157 ± 16	158 ± 17	157 ± 15
Diastolic BP (mmHg)	90 ± 9	89 ± 8	93 ± 10
Number of BP drugs	3.7 ± 1	3.7 ± 1	3.6 ± 1
Subjects taking a BP agent			
ACE inhibitor or ARB	96 (98)	83 (99)	13 (93)
Diuretic	90 (92)	77 (92)	13 (93)
β-Blocker	72 (74)	61 (73)	11 (79)
Calcium channel blocker	61 (62)	52 (62)	9 (64)
Other	30 (31)	26 (31)	4 (29)
Potassium (mEq/l)	4 ± 0.4	4 ± 0.4*	3.7 ± 0.4*
Creatinine (mg/dl)	1.0 ± 0.2	1.0 ± 0.2*	0.9 ± 0.2*
A1C (%)	7.1 ± 1.4	7.1 ± 1.4	6.9 ± 1.1
PAC (ng/dl)	10 ± 7	9.1 ± 6†	15.6 ± 8†
PRA (ng/ml)	4.8 ± 11	5.5 ± 12	0.2 ± 0.1†
PAC-to-PRA ratio (ng · ml^{-1} · h^{-1})	33 ± 47	21 ± 30†	98 ± 74†

Data are means ± SD or *n* (%). *$P < 0.05$; †$P < 0.001$. BP, blood pressure.

sures were 157 ± 15 and 93 ± 10 mmHg in subjects with primary aldosteronism and 158 ± 17 and 89 ± 8 mmHg in subjects without primary aldosteronism. Similarly, we did not observe differences in the number of antihypertensive agents with 43 and 53% of subjects with and without primary aldosteronism receiving ≥4 drugs.

A total of 34 subjects (34%) had an increased PAC-to-PRA ratio >30 · ml^{-1} · h^{-1}, and 14 subjects (14%) had a confirmed diagnosis of primary aldosteronism. Compared with subjects without primary aldosteronism, subjects with primary aldosteronism had a lower serum potassium (3.7 ± 0.4 vs. 4.0 ± 0.4 mmol/l, $P = 0.012$), a lower serum creatinine (0.9 ± 0.2 vs. 1.0 ± 0.2 mg/dl, $P = 0.018$), a higher PAC (15.6 ± 8 vs. 9.1 ng/dl ± 6, $P = 0.0016$), a lower PRA (0.2 ± 0.1 vs. 5.5 ± 12 ng/ml, $P < 0.001$), and a higher PAC-to-PRA ratio (98 ± 74 vs. 21 ± 30 · ml^{-1} · h^{-1}, $P < 0.0001$).

Of the subjects with resistant hypertension, 55 (55%) had suppressed PRA (<1 ng/dl) or salt-sensitive hypertension. All subjects with primary aldosteronism and 41 subjects without primary aldosteronism had a PRA <1 ng/dl. Twenty-two subjects without primary aldosteronism had a PAC-to-PRA ratio >30 · ml^{-1} · h^{-1}. A PAC ≥15 ng/dl, a commonly used criterion for identifying primary aldosteronism (20,21,23), was observed during the initial screening in 18 subjects. Although the mean PAC level during screening was 15.6 ± 8.3 ng/dl, eight subjects with documented primary aldosteronism had a PAC <15 ng/dl.

CONCLUSIONS — Approximately 20 million people in the U.S. have diabetes (24), and another 50 million have hypertension (25). Between 8 and 12 million diabetic subjects have hypertension (1,2,25). The coexistence of hypertension and diabetes accelerates the course of microvascular and macrovascular disease (1,26,27). Hypertension markedly increases the risk for CVD and mortality in patients with type 2 diabetes. Randomized prospective clinical trials have shown that rigorous blood pressure control in patients with diabetes reduces macrovascular as well as microvascular complications (2,6,28,29). It was estimated that for each 10 mmHg reduction in systolic blood pressure, there is a 13% reduction in microvascular complications, a 12% decreased risk of fatal and nonfatal myocardial infarction, and a 17% decreased risk of death (6,29). In the Hypertension Optimal Treatment (HOT) trial, a 4-point difference in diastolic blood pressure (85 vs. 81 mmHg) resulted in a 51% decrease in risk for cardiovascular events in patients with diabetes (28). Despite this strong evidence on the benefit of blood pressure control, nearly 75% of diabetic patients do not achieve good blood pressure control (25).

Primary aldosteronism is the most common endocrinologic cause of secondary hypertension. In recent years, with increased awareness and screening, the number of patients in whom primary aldosteronism is diagnosed has increased by 5- to-10-fold accounting for 5–32% of the population with resistant hypertension (11,14–16,18,19,30–32). Notably, however, there are few data that specifically examine the prevalence of primary aldosteronism in diabetic patients. Our study indicates that the prevalence of primary aldosteronism in patients with type 2 diabetes is similar to that reported in nondiabetic subjects with resistant hypertension (13,20). Of interest, we observed no differences in age, in glucose control, or in the number or type of antihypertensive drugs between patients with and without primary aldosteronism. Given the importance of blood pressure control and the significant prevalence of primary aldosteronism in subjects with poorly controlled hypertension, all diabetic subjects who have not met their blood pressure goals despite treatment with ≥3 drugs should be screened for primary aldosteronism.

The PAC-to-PRA ratio is considered the screening test of choice for primary aldosteronism (33,34). In the current study, patients were screened while they were taking their prescribed antihypertensive medications. ACE inhibitors, ARBs, and diuretics have been reported to increase PRA, calcium channel blockers to suppress aldosterone release, and β-blockers to suppress PRA, thereby potentially confounding the assessment of the PAC-to-PRA ratio (35–37). Recent studies, however, have demonstrated that measurement of the PAC-to-PRA ratio to screen for primary aldosteronism is not significantly affected by concurrent use of antihypertensive agents (19,20,34,38). In addition, if there is a confounding ef-

fect, it would most likely result in an underestimation of a higher PAC-to-PRA ratio because the most commonly used antihypertensive agents in the current study (ACE inhibitors, ARBs, and diuretics) tended to increase PRA, resulting in an increased number of false-negative results (11,13). In our study population, the possible effects of continuing therapy during screening were unavoidable, as we felt that it would be unethical and unsafe to discontinue prescribed therapies in subjects who already had uncontrolled blood pressure.

The PAC-to-PRA ratio has been criticized by some who claim that the ratio is overly renin dependent and has low specificity (39). The specificity of a high PAC-to-PRA ratio is only modest, whether measured in participants receiving or not receiving antihypertensive drug therapy (74 and 75%, respectively). To improve the specificity of the ratio (decrease the number of false-positive results), some have advocated the addition of a threshold value of aldosterone (>15 ng/dl) as part of the screening criteria (20,31). Although such a strategy increases the specificity of the test, it has been shown to markedly decrease its sensitivity (increases the number of false-negative results). Recently, Schwartz and Turner (19) reported that using a threshold value of PAC >15 ng/dl increased the specificity from 74 to97% but markedly decreased the sensitivity from 73 to 33%. In agreement with this report, all subjects with primary aldosteronism in our study had a high PAC-to-PRA ratio ($>30 \cdot ml^{-1} \cdot h^{-1}$); however, only 43% of the subjects had a PAC >15 ng/dl during the initial screening. Given the importance of blood pressure control in the diabetic population, using screening criteria that would miss a substantial number of patients with an endocrinologic cause of hypertension does not make sense. Although eliminating a PAC threshold will increase false-positive screens, these are easily distinguished from true positive results with salt suppression testing. Thus, based on our findings and previous reports, the use of the PAC-to-PRA ratio may be preferable in screening for primary aldosteronism in patients with resistant hypertension.

We acknowledge several limitations in our study including a relatively small number of subjects, the fact that most subjects (93%) were African American, and the lack of a nondiabetic control group. The small number of subjects limits what can be said about the positive and negative predicative values of the PAC-to-PRA ratio. There are few data specific to African Americans for primary aldosteronism. Several reports have shown that extracellular fluid volume is an important contributor to the pathogenesis of low-renin hypertension and to hypertension in blacks (37–39). Blacks have lower levels of plasma renin activity and more salt-sensitive (salt-dependent) hypertension than Caucasians (40,42). It has been estimated that the prevalence of salt-sensitive hypertension in hypertensive blacks is 50–73 versus 27–56% in hypertensive Caucasians (41,43,44). Salt dependency is associated with a favorable response to diuretics but poorer efficacy of ACE inhibitors or angiotensin receptor antagonists when these drugs are used as monotherapy (40,41). Moreover, salt dependency is not only a determinant of blood pressure response but is now also classified as a risk factor for cardiovascular and renal complications, including left ventricular hypertrophy, microalbuminuria, insulin resistance and metabolic syndrome, and increased systemic and renal vascular resistance (12,38,40–42). Despite the presence of lower renin activity in blacks, Calhoun et al. (11) reported that in subjects with resistant hypertension, blacks have a prevalence of primary aldosteronism similar to that for Caucasians.

The American Diabetes Association advocates that hypertension should be treated aggressively to achieve and maintain a target blood pressure <130/80 mmHg (3). In our study, we limited screening to subjects with blood pressure >140/90 mmHg while taking ≥3 different antihypertensive agents. Thus, the prevalence of primary aldosteronism and the cost-effectiveness of screening diabetic patients with blood pressure >130/80 mmHg needs to be examined in future studies.

In summary, we observed a prevalence of 14% of primary aldosteronism in diabetic subjects with poorly controlled hypertension while taking ≥3 antihypertensive agents. These results are of great clinical importance because patients with primary aldosteronism have a high incidence of renal and cardiovascular complications and increased mortality and because aldosterone blockade can ameliorate renal and cardiovascular complications in patients with hypertension and with primary aldosteronism (34,46–50). Accordingly, diabetic patients with poorly controlled hypertension while taking ≥3 antihypertensive drugs should be screened for primary aldosteronism using the PAC-to-PRA ratio followed by salt suppression testing in those with a positive screening ratio.

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