Relationships of Plasma Renin Levels with Renal Function in Patients with Primary Aldosteronism

Cristiana Catena, GianLuca Colussi, Elisa Nadalini, Alessandra Chiuch, Sara Baroselli, Roberta Lapenna, and Leonardo A. Sechi

Hypertension Unit, Division of Internal Medicine, Department of Experimental and Clinical Pathology and Medicine, University of Udine, Udine, Italy

Background: The renal damage that is present in primary aldosteronism might reflect functional and potentially reversible abnormalities that are initiated by glomerular hyperfiltration. The aim of this study was to investigate the relationships of plasma renin and aldosterone concentrations with renal outcomes after treatment of primary aldosteronism.

Design, setting, participants, and measurements: Fifty-six consecutive patients who had primary aldosteronism and were recruited in a university center were studied. Patients were prospectively followed after either surgical or medical treatment for a mean of 6.2 yr, during which they received antihypertensive drugs to reach a target BP of <140/90 mmHg.

Results: At baseline, patients with primary aldosteronism had higher creatinine clearance and albuminuria than 323 patients with essential hypertension and 113 normotensive individuals. In patients with primary aldosteronism, plasma active renin levels that were higher than the lower limit of detection (2.5 pg/ml) were associated with higher BP, plasma potassium, and albuminuria and lower creatinine clearance. Plasma aldosterone concentrations that were higher than the median value (225 pg/ml) were associated with lower plasma potassium and higher creatinine clearance. Creatinine clearance was correlated directly with plasma aldosterone and inversely with renin. During follow-up, patients with higher baseline plasma renin required use of more antihypertensive drugs to obtain BP control and had a smaller early decline in albuminuria than did patients with suppressed renin.

Conclusions: Escape of renin from suppression by excess aldosterone is associated with evidence of more severe renal damage in patients with primary aldosteronism and predicts less favorable outcomes after treatment.

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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% (1,2), may be the result of a more efficient identification of this endocrine disorder in which excess aldosterone secretion causes hypertension, hypokalemia, and suppression of renin secretion (3). High plasma or urinary aldosterone and low plasma renin concentrations are the typical hormonal findings that lead to a diagnosis of primary aldosteronism, and the aldosterone-to-renin ratio has come to widespread use as a screening diagnostic test (4,5).

Although primary aldosteronism has long been considered a relatively benign form of hypertension (6,7), recent studies suggest that long-term exposure to high aldosterone levels might lead to cardiovascular (8) and renal (9) structural damage that seems to occur independent of the BP level. With respect to the kidney, animal studies support the role of aldosterone in the progression of renal vascular disease (10–13), but the clinical evidence of the contribution of this hormone to renal dysfunction is limited (14–16). In fact, the majority of initial reports indicated that primary aldosteronism is less likely to cause overt renal damage (6,7,17,18), and two recent studies with short-term (19) and long-term (20) follow-up consistently demonstrated that the renal dysfunction of primary aldosteronism is closely related with the hemodynamic adaptation of the kidney to the effect of aldosterone excess.

Because primary aldosteronism is frequently resistant to treatment with common antihypertensive agents, patients could be susceptible of more severe hypertension-related intrarenal vascular injury that might cause glomerular hypoperfusion and subsequent escape of renin from suppression by excess aldosterone. In this study, we evaluated predictors of renal outcomes in patients with primary aldosteronism and tested the hypothesis that lack of complete suppression of plasma renin might be an indicator of more severe renal damage in patients with primary aldosteronism and might predict BP and renal outcomes after treatment.

Materials and Methods

Patients

Fifty-six consecutive patients who received a diagnosis of primary aldosteronism from January 1994 to December 2004 were included in an observational, prospective study. Recruitment of patients, criteria that were used for diagnosis, methods that were used to assess renal

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Address correspondence to: Dr. Leonardo A. Sechi, Clinica Medica, University of Udine, Piazzale S. Maria della Misericordia, 1, 33100 Udine, Italy. Phone: +39-0432-559804; Fax: +39-0432-42097; E-mail: sechi@uniud.it

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function, and follow-up have been described in detail in previous publications (20,21). All patients were referred to the Hypertension Clinic of our university for evaluation of their hypertensive state. BP was measured by a mercury sphygmomanometer after each patient had been supine for at least 15 min. The average of three readings that were obtained in 5 min was recorded. Hypertension was diagnosed according to current guidelines (22). All hypertensive patients who are seen at the clinic are screened with extensive clinical and laboratory testing to determine the cause of hypertension (23). Four (7%) patients with primary aldosteronism were taking no antihypertensive drug, five (9%) patients were on monotherapy, and the remaining 47 (84%) patients had multidrug treatment with a mean of 2.8 antihypertensive agents per patient. Patients who were treated with antihypertensive drugs were withdrawn from treatment a minimum of 2 wk before diagnostic assessment. β blockers, lipophilic calcium antagonists, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were withdrawn for 3 wk (24). No patient was taking mineralocorticoid receptor antagonists before the study.

Patients with primary aldosteronism were screened by the demonstration of an increased plasma aldosterone-to-active renin ratio ($\geq$20 pg/ml) (25) in the presence of a plasma aldosterone concentration of $>$150 pg/ml, and in all patients, the diagnosis was confirmed by the lack of aldosterone suppression after an intravenous saline load (2 L of 0.9% saline infused over 4 h) (26). The suppression test was considered diagnostic when plasma aldosterone concentration was $>$50 pg/ml after saline infusion. This test has been shown to be highly effective in the distinction of both tumoral and idiopathic aldosteronism from low-renin essential hypertension (27). All measurements were performed under a normal sodium diet, and 24-h urinary sodium excretion was assessed in all patients. Renal artery stenosis was excluded in all patients by angiographic computed tomography (CT) scan and, in patients with measurable plasma active renin ($>$2.5 pg/ml), by selective renal angiography (23). Plasma potassium concentration of $\leq$3.5 mmol/L was corrected by oral potassium supplementation before assessment of the plasma aldosterone-to-active renin ratio and saline suppression test (2). Adrenal adenoma was differentiated from idiopathic aldosteronism by high-resolution CT scan, followed by selective adrenal vein sampling with measurements of both aldosterone and cortisol to ensure the adequacy of the cannulation and/or adrenal scintigraphy with iodocholesterol that was performed under dexamethasone suppression. Selective adrenal vein sampling is the gold standard procedure for differentiation between tumoral and idiopathic disease (28) and was performed in 14 of 56 patients. This might have led to underestimation of the relative percentage of adrenal adenoma in our cohort. In all patients who had adrenal adenoma and underwent adrenalectomy, diagnosis was confirmed by histology. Primary aldosteronism was treated by either unilateral adrenalectomy or spironolactone, and treatment was followed by normalization of BP ($<$140/90 mmHg without the aid of antihypertensive agents with the exception of spironolactone) or significant improvement of hypertension (decrease in mean BP by $>$20% and/or fewer antihypertensive agents taken to control BP at follow-up) in all patients.

A total of 323 patients with essential hypertension served as hypertensive control subjects for baseline comparisons. These patients were recruited at our hypertension clinic and selected by frequency matching after specification of inclusion criteria to avoid age, gender, body mass index, and estimated duration of hypertension as potential confounding variables. Among patients with essential hypertension, 12% were taking no antihypertensive drug, 19% were on monotherapy, and 69% had multidrug treatment with a mean of 2.1 antihypertensive agents per patient. In these patients, secondary causes of hypertension were excluded on the basis of exhaustive laboratory testing after appropriate drug washout (24). A total of 113 normotensive individuals served as control subjects. 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 and gender as potential confounding variables. Normotensive control subjects 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 ethics committee of our university.

Renal Function, Treatment, and Follow-Up

Renal function was measured at baseline in patients with primary aldosteronism, patients with essential hypertension, and normotensive individuals and after either surgical or medical treatment in patients with primary aldosteronism. Measurements included assessment of creatinine clearance and albuminuria and were performed as described previously (29). Briefly, duplicate 24-h urine collections were obtained for determination of creatinine clearance and urinary albumin excretion, and the average was considered. Creatinine clearance was normalized for body surface area and expressed in milliliters per minute per 1.73 m^2. Creatinine concentrations in serum and urine were measured by a modification of the Jaffé reaction (30). Urinary albumin excretion was measured by RIA (26). When duplicate measurements of creatinine clearance or albuminuria differed by $>$10%, additional measurements were obtained. Throughout this article, GFR and albuminuria refer, respectively, to the mean of two separate measurements of 24-h creatinine clearance and urinary albumin excretion expressed as the log-transformed urine albumin-to-creatinine ratio. Albuminuria was normalized for urinary creatinine because previous studies consistently demonstrated glomerular hyperfiltration in patients with primary aldosteronism (19,20,31). Plasma active renin and plasma aldosterone concentrations were measured by RIA according to current guidelines (32) in plasma samples that were obtained with patients in the sitting position.

Patients with primary aldosteronism were treated by either adrenalectomy or administration of spironolactone (from 50 to 300 mg/d). Of the 30 patients with adrenal adenoma, 25 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 treatment with periodic visits during which antihypertensive therapy was adjusted according to the physician judgment to reach a target value of $<$140/90 mmHg (20). In addition to lifestyle recommendations, use of all categories of antihypertensive agents was permitted. Creatinine clearance and albuminuria were reassessed at 6 mo and after an average follow-up of 6.2 yr (range 1 to 11 yr). Use of antihypertensive drugs during follow-up was defined as receipt of the specific drug for $>$50% of follow-up visits.

Statistical Analyses

Continuous data are expressed as means $\pm$ SD unless otherwise indicated. Variables with skewed distribution were analyzed after logarithmic transformation. Characteristics of the study participants were compared among groups by analysis of covariance. Baseline P values are reported either for overall comparisons among all groups or for pairwise comparisons, with the Bonferroni correction. Categorical variables were compared with the use of the Pearson χ^2 test. The relationships between variables was examined by linear regression analysis, and the correlation was expressed by the correlation coefficient. Changes from baseline of renal parameters were assessed by two-way ANOVA. Stepwise multivariate analysis was performed to identify variables that were independently associated with changes in renal parameters after treatment and included

all variables that were identified in univariate analysis. All tests for significance and resulting *P* values were two sided, with a level of significance of 0.05. All data analyses were performed with a GBStat 6.5 software (Dynamic Microsystems, Silver Spring, MD).

Results

Adrenal adenoma was demonstrated in 30 of 56 patients with primary aldosteronism, whereas the remaining 26 had idiopathic disease. Baseline clinical and biochemical characteristics of the study participants are summarized in Table 1. Patients with primary aldosteronism and essential hypertension had comparable BP levels and estimated duration of hypertension. Creatinine clearance was significantly higher in patients with primary aldosteronism than in patients with essential hypertensive and normotensive individuals. Urinary albumin excretion was higher in the primary aldosteronism (22 mg/24 h; interquartile range 9 to 38) than in the essential hypertensive (16 mg/24 h; interquartile range 6 to 28; $P < 0.02$) group, but this difference was eliminated when albuminuria was normalized for urinary creatinine concentration, indicating the possibility that increase in absolute values could be due to increased filtration. In patients with primary aldosteronism, no significant differences were observed between those with adrenal adenoma or idiopathic disease.

As shown in Figure 1, despite long-standing hypertension, only four (7%) of the 56 patients with primary aldosteronism had creatinine clearance of <60 ml/min per 1.73 m^2, whereas the prevalence of such patients among those with essential hypertension was 11% ($P = 0.40$). Patients with primary aldosteronism were grouped according to plasma renin, using the lower limit of detection with our method (2.5 pg/ml), and plasma aldosterone concentrations, using the median value for the distribution (225 pg/ml). Frequency of female gender was relatively, although not significantly, higher in patients who had plasma renin >2.5 pg/ml ($P = 0.112$). Patients with primary aldosteronism and plasma renin of >2.5 pg/ml ($n = 16$) had significantly higher BP, plasma potassium, and albuminuria and lower creatinine clearance than patients with suppressed renin levels ($n = 40$; Table 2). Patients who had plasma aldosterone concentrations above the median value had significantly lower plasma potassium (3.1 ± 0.4 mmol/L) and higher creatinine clearance (116 ± 35 ml/min per 1.73 m^2) than patients with aldosterone levels below the median (3.4 ± 0.4 mmol/L [$P < 0.01$] and 96 ± 32

Table 1. Baseline characteristics of the study population[a]

Characteristic	Normotensive Control ($n = 113$)	Essential Hypertension ($n = 323$)	Primary Aldosteronism		
			All Patients ($n = 56$)	Adrenal Adenoma ($n = 30$)	Idiopathic ($n = 26$)
Clinical characteristics					
age (yr)	52 ± 12	52 ± 9	52 ± 11	54 ± 12	52 ± 13
female/male gender (*n* [%])	37/76 (33/67)	103/220 (32/68)	16/40 (29/71)	8/22 (27/73)	8/18 (31/69)
BMI[b]	26.8 ± 3.5	28.1 ± 3.1	28.5 ± 3.6	28.5 ± 3.6	28.4 ± 3.7
SBP (mmHg)[c]	130 ± 12	166 ± 18	167 ± 15	167 ± 14	166 ± 18
DBP (mmHg)[c]	79 ± 8	103 ± 8	103 ± 8	103 ± 8	103 ± 9
estimated duration of hypertension (yr)	—	10 ± 6	10 ± 6	10 ± 6	9 ± 5
Laboratory parameters					
plasma sodium (mmol/L)	139 ± 3	140 ± 3	141 ± 2	141 ± 2	141 ± 3
plasma potassium (mmol/L)	4.4 ± 0.3	4.2 ± 0.4	3.2 ± 0.4[d]	3.2 ± 0.4[d]	3.3 ± 0.5[d]
urinary sodium (mmol/24 h)	118 ± 53	111 ± 46	104 ± 50	101 ± 45	109 ± 57
urinary potassium (mmol/24 h)	46 ± 22	45 ± 18	51 ± 19	52 ± 20	49 ± 17
plasma active renin (pg/ml)[e]	8.9 ± 9.9	9.4 ± 10.9	4.8 ± 6.5	4.6 ± 5.5	5.0 ± 7.6
plasma aldosterone (pg/ml)[f]	129 ± 74	154 ± 99	249 ± 193	264 ± 180	233 ± 207
serum creatinine (μmol/L)	84 ± 22	98 ± 39	90 ± 19	90 ± 19	89 ± 20
creatinine clearance (ml/min per 1.73 m^2)[g]	97 ± 17	89 ± 34	106 ± 31	105 ± 30	108 ± 33
urinary albumin/creatinine ratio (median [IQR])[h]	0.008 (0.002 to 0.019)	0.045 (0.017 to 0.084)	0.046 (0.021 to 0.086)	0.046 (0.020 to 0.086)	0.047 (0.019 to 0.078)

[a]Data are means ± SD unless otherwise indicated. BMI, body mass index; DBP, diastolic BP; IQR, interquartile range; SBP, systolic BP.

[b]BMI is defined as the weight in kilograms divided by the square of the height in meters.

[c]BP was measured after appropriate washout of antihypertensive drugs as referred to in text.

[d]Values are those that were measured before correction with oral supplementation.

[e]Plasma active renin was lower in patients with primary aldosteronism than in patients with essential hypertension ($P = 0.002$).

[f]Plasma aldosterone was higher in patients with primary aldosteronism than in patients with essential hypertension ($P < 0.001$) and normotensive individuals ($P < 0.001$).

[g]Creatinine clearance was higher in patients with primary aldosteronism than in patients with essential hypertension ($P < 0.001$) and normotensive individuals ($P = 0.016$).

[h]Urinary albumin excretion was higher in patients with primary aldosteronism than in patients with essential hypertension ($P = 0.019$).

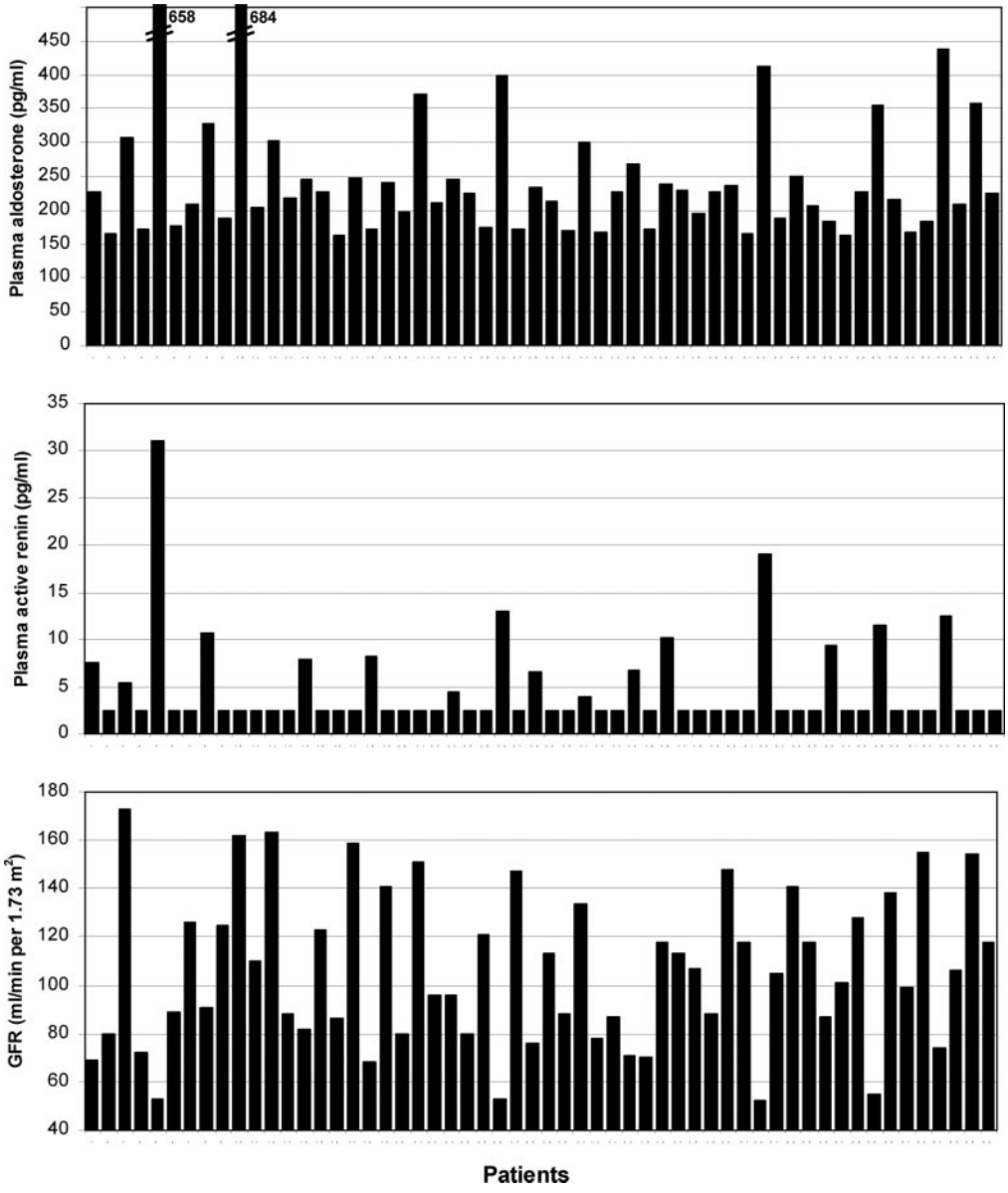

Figure 1. Plasma aldosterone, plasma renin, and GFR values in 56 patients with primary aldosteronism. Four (7%) of the 56 patients with primary aldosteronism had GFR of <60 ml/min per 1.73 m^2. These four patients had plasma active renin in a normal/high-normal range; nonetheless, their aldosterone-to-active renin ratio was elevated and plasma aldosterone levels were not suppressed by the intravenous saline load. Before diagnosis of primary aldosteronism, all four patients had hypertension that was resistant to treatment with four to five antihypertensive drugs, the average estimated duration of their hypertensive disease was 14 yr, and their BP after drug washout was 188/113 mmHg. In these patients, renal arteriography and other tests for secondary hypertensive diseases yielded no pathologic findings. One patient underwent adrenalectomy, and the other three, one with bilateral adenoma, one who refused surgery, and one with idiopathic disease, were treated with spironolactone. In all four patients, hypertension was controlled after treatment with use of only one additional antihypertensive agent. In the patient who underwent adrenalectomy, intraoperative renal biopsy showed arteriolosclerosis of intrarenal vessels with sparse hyalinized glomeruli and mild interstitial fibrosis that were indicative of hypertensive vascular damage.

ml/min per 1.73 m^2 [$P < 0.05$], respectively), whereas there was no difference in albuminuria. Creatinine clearance was correlated inversely with plasma renin ($r = -0.565$, $P < 0.001$) and, after exclusion of patients with levels of <60 ml/min per 1.73 m^2, directly with plasma aldosterone ($r = 0.372$, $P < 0.01$) but not with plasma potassium concentrations.

Follow-Up

Patients with primary aldosteronism were followed up after treatment (25 adrenalectomy; 31 spironolactone) for an average period of 6.2 yr (median 5.9 yr; range 1 to 11 yr). No patient discontinued the study, and compliance at the scheduled visits was superior to 90%. During the first 6 mo, plasma potassium concentrations increased significantly and BP declined with a

Table 2. Characteristics of patients with primary aldosteronism and plasma active renin concentrations that were lower or higher than the limit of detection with our method[a]

Characteristic	Primary Aldosteronism		*P*
	Plasma Active Renin <2.5 pg/ml (*n* = 40)	Plasma Active Renin >2.5 pg/ml (*n* = 16)	
Clinical characteristics			
age (yr)	52 ± 11	54 ± 14	NS
female/male gender (*n* [%])	9/31 (22/78)	7/9 (44/56)	NS
adenoma/idiopathic	21/19	9/7	NS
BMI[b]	28.7 ± 3.7	27.9 ± 4.1	NS
SBP (mmHg)[c]	163 ± 15	175 ± 19	0.015
DBP (mmHg)[c]	101 ± 9	108 ± 9	0.011
estimated duration of hypertension (yr)	9 ± 5	13 ± 6	0.014
Laboratory variables			
plasma sodium (mmol/L)	141 ± 2	140 ± 2	NS
plasma potassium (mmol/L)[d]	3.1 ± 0.4	3.5 ± 0.4	<0.001
urinary sodium (mmol/24 h)	106 ± 39	101 ± 63	NS
urinary potassium (mmol/24 h)	52 ± 16	47 ± 23	NS
serum creatinine (μmol/L)	88 ± 18	94 ± 22	NS
creatinine clearance (ml/min per 1.73 m^2)	112 ± 30	91 ± 33	0.025
urinary albumin/creatinine ratio (median [IQR])	0.042 (0.017 to 0.082)	0.055 (0.031 to 0.122)	0.015
plasma active renin (pg/ml)	<2.5	10.5 ± 6.6	<0.001
plasma aldosterone (pg/ml)	261 ± 149	218 ± 254	NS

[a]Data are means ± SD unless otherwise indicated.
[b]BMI is defined as the weight in kilograms divided by the square of the height in meters.
[c]BP was measured after appropriate washout of antihypertensive drugs as referred in text.
[d]Plasma potassium values are those measured before correction with oral supplementation.

mean value that, during the course of the study, was 136/82 mmHg. After treatment, patients with baseline plasma active renin >2.5 pg/ml reached BP values that were comparable to those of patients with lower active renin (Figure 2), with average values that, during the course of the study, were 138/82 and 135/82 mmHg, respectively. Treatment was followed by normalization of BP in 22 (39%) patients with primary aldosteronism: 19 of these patients had baseline plasma renin <2.5 pg/ml, and three had plasma renin >2.5 pg/ml ($P < 0.05$). Hypertension was significantly improved in the remaining 34 (61%) patients with primary aldosteronism (21 with plasma renin <2.5 pg/ml and 13 with plasma renin >2.5 pg/ml). The average number of antihypertensive agents used during follow-up was significantly greater in patients with higher baseline plasma renin (2.4 ± 0.7) than in those with lower plasma renin (2.0 ± 0.6; $P < 0.05$). Factors that were associated with normalization of BP in a univariate analysis were younger age ($P = 0.021$), shorter duration of hypertension ($P = 0.008$), lower mean BP ($P = 0.012$), higher creatinine clearance ($P = 0.004$), and lower pretreatment renin concentrations ($P = 0.007$). According to a stepwise multivariate logistic analysis, normalization of BP was independently associated with lower pretreatment renin concentrations ($P = 0.011$) and higher creatinine clearance ($P = 0.009$). Neither decrease of BP nor the number of antihypertensive drugs used during follow-up differed between patients with higher and lower pretreatment plasma aldosterone levels.

During the first 6 mo, creatinine clearance decreased in patients with primary aldosteronism, and the decrease was significantly greater ($P = 0.004$) in patients with pretreatment plasma renin <2.5 pg/ml than in patients with plasma renin above this limit (Figure 2). Higher pretreatment plasma aldosterone was also associated with significantly greater decline of creatinine clearance ($P = 0.009$; Figure 2). Subsequent rates of change of creatinine clearance were independent of pretreatment renin or aldosterone levels. Additional variables that were associated with greater decline of creatinine clearance were higher pretreatment creatinine clearance ($P < 0.001$) and lower pretreatment plasma potassium ($P = 0.013$). In the stepwise multivariate analysis, both pretreatment plasma renin ($P = 0.008$) and aldosterone ($P = 0.014$) remained independently associated with the early decline in creatinine clearance. In the initial 6 mo of follow-up, patients with lower pretreatment plasma renin had significantly greater decrease in albuminuria ($P < 0.05$) than patients with higher renin levels, but in the stepwise multivariate analysis, statistical significance was eliminated after inclusion of creatinine clearance. Changes in albuminuria were not significantly different in patients with higher and lower pretreatment plasma aldosterone. Albuminuria did not change significantly during long-term follow-up in all patient subgroups.

Separate analysis of patients who had primary aldosteronism and were treated with adrenalectomy or aldosterone antagonists did not reveal any significant difference between groups

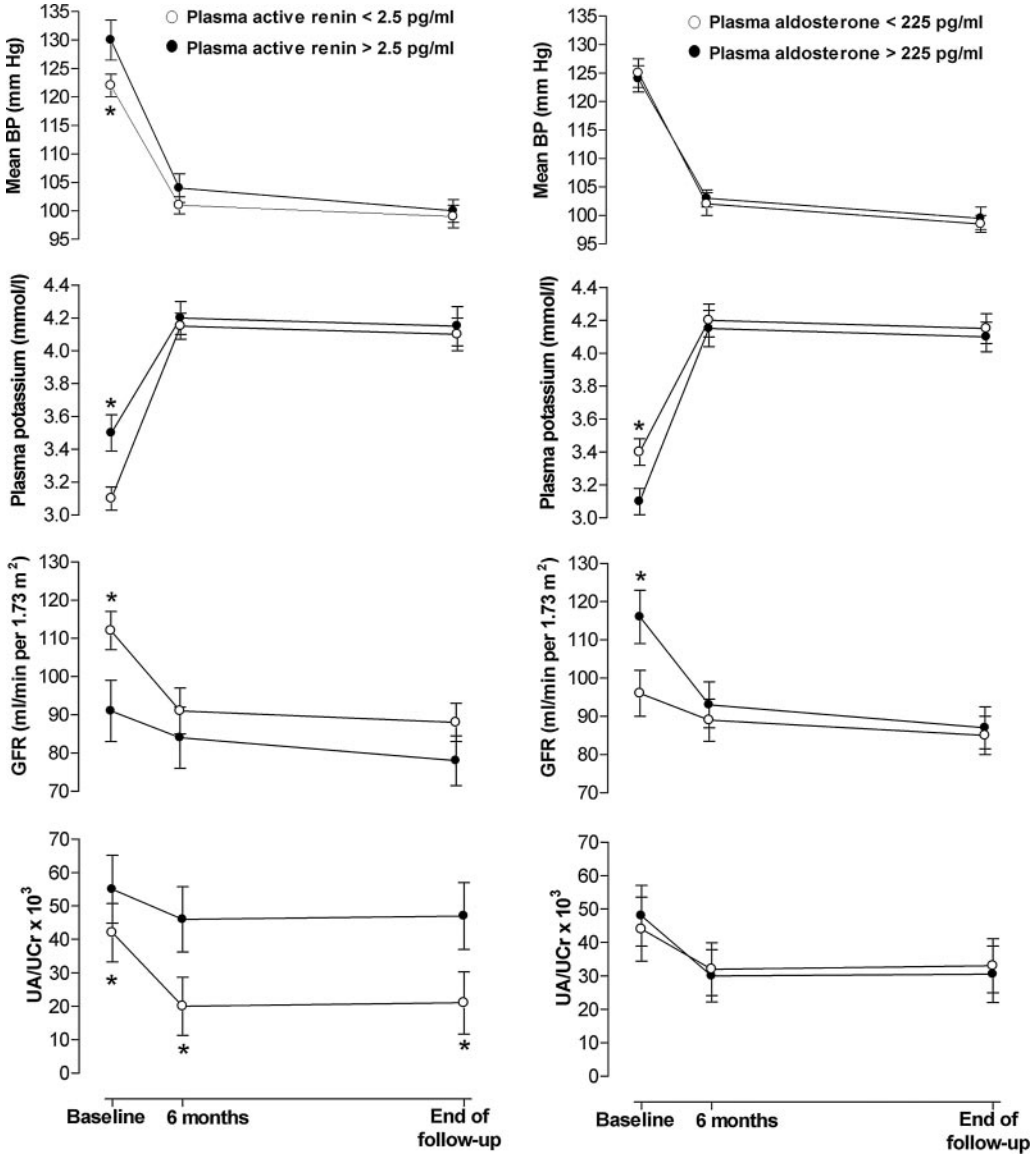

Figure 2. Values (means ± SEM) of mean BP, plasma potassium, GFR, and albuminuria (urine albumin-to-creatinine ratio [UA:UCr]) in 56 patients who had primary aldosteronism and were categorized according to their plasma renin concentrations using the lower limit of detection for plasma active renin with our method (2.5 pg/ml; left) and plasma aldosterone concentrations using the median value of the distribution (225 pg/ml; right). Variables were measured at baseline and after treatment with adrenalectomy ($n = 25$) or mineralocorticoid antagonists ($n = 31$). Short-term and long-term follow-up measurements were done after 6 mo and after an average period of 6.2 yr (range 1 to 11 yr), respectively. *$P < 0.05$ *versus* patients with plasma active renin concentrations <2.5 pg/ml or *versus* patients with plasma aldosterone concentrations <225 pg/ml.

during short-term and long-term follow-up (Figure 3). In the follow-up period, plasma active renin levels increased significantly in all patients (from 4.8 ± 6.5 to 8.7 ± 5.7 pg/ml; $P = 0.014$), whereas plasma aldosterone decreased significantly in adrenalectomized patients (from 259 ± 174 to 188 ± 162 pg/ml; $P = 0.029$) but did not change significantly in patients who were treated with aldosterone antagonists (from 242 ± 211 to 229 ± 187 pg/ml).

Discussion

In a subanalysis of a study that was conducted in a large group of patients with primary aldosteronism, we examined the relationships of plasma renin and aldosterone levels with pre- and posttreatment renal function. Our results demonstrate that suppressed plasma renin and higher plasma aldosterone are associated with higher GFR in these patients and are independent predictors of early decline of glomerular filtration after either surgical or medical treatment. Higher pretreatment plasma renin is associated with less frequent normalization of BP and smaller decline in albuminuria during follow-up, indicating that renin escape from suppression by excess aldosterone might be a marker of more severe hypertension-related renal damage.

This study demonstrates that detection of decreased glomer-

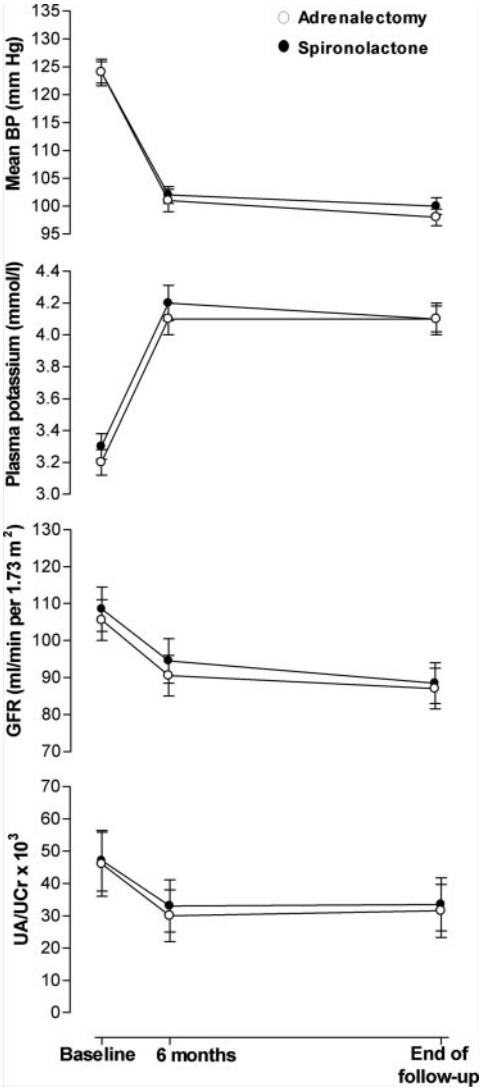

Figure 3. Values (means ± SEM) of mean BP, plasma potassium, GFR, and albuminuria (UA:UCr) in 56 patients who had primary aldosteronism and were treated with adrenalectomy (n = 25) or mineralocorticoid antagonists (n = 31). Thirty patients had adrenal adenoma, and 26 had idiopathic aldosteronism. Of the 30 patients with adrenal adenoma, 25 underwent either surgical or laparoscopic adrenalectomy; among the remaining five patients, two had bilateral adenoma and three refused surgery and were treated with spironolactone. Short-term and long-term follow-up measurements were done after 6 mo and after an average period of 6.2 yr (range 1 to 11 yr), respectively.

ular filtration is not frequent in patients with primary aldosteronism even after many years of disease with BP out of adequate control. GFR of <60 ml/min per 1.73 m^2 was found in only 7% of patients. These patients had more severe hypertension and longer duration of disease than the remaining patients with primary aldosteronism; nonetheless, their BP responded very well to treatment (Figure 2). In these patients, plasma renin activity was in a normal/high-normal range, suggesting underlying intrarenal vascular damage causing glomerular ischemia and renin escape from suppression by aldosterone excess. In one of our patients, secondary hypertensive kidney damage was confirmed by histology. These findings are in agreement with those of Oelkers *et al.* (33), who reported the case histories of three patients who had primary aldosteronism without suppressed plasma renin and in whom severe hypertension was associated with histologic demonstration of arteriolosclerotic renal damage.

Although preclinical studies indicate that aldosterone *per se* might cause important renal damage (9–13), the clinical evidence supporting a direct role of this hormone as a potential contributor to renal dysfunction is limited. In the clinical setting, a simple model to assess possible detrimental effects of aldosterone on the kidney is primary aldosteronism, a condition in which the effects of aldosterone are isolated from those of the renin-angiotensin axis. Past cross-sectional evaluations of renal function in primary aldosteronism showed high variability in the prevalence of clinically relevant renal damage (17,18,34–36). In a 9-yr follow-up study, we showed that primary aldosteronism is characterized by partially reversible renal dysfunction (20), and demonstration that albuminuria is a marker of a hemodynamic rather than a structural renal defect has been reported also by Ribstein *et al.* (19) in a short-term, postadrenalectomy evaluation of patients with adrenal adenoma. In agreement with the findings of studies that were conducted in more experimental settings (37–39), longitudinal studies consistently demonstrate that the hallmark of renal dysfunction in primary aldosteronism is reversible glomerular hyperfiltration that contributes to increase urinary albumin losses.

In our cohort of patients with primary aldosteronism, the percentage of those without suppressed plasma renin was 29%, the same as that found by Blumenfeld *et al.* (34) in their analysis of 82 patients. We observed that these patients have higher BP levels, longer estimated duration of hypertension, lower creatinine clearance, and greater urinary albumin excretion than patients with suppressed plasma renin. These findings suggest the presence of more severe structural, hypertension-related, renal damage in patients with primary aldosteronism and measurable renin, a possibility that is supported also from the follow-up data. In the first 6 mo after treatment, the magnitude of the decline in hyperfiltration and albuminuria was significantly lower in patients with higher pretreatment renin levels, showing that the degree of reversibility of renal damage is significantly smaller when renin is not suppressed.

Hypertension may persist after adequate treatment of aldosteronism, and only approximately one third of such patients normalize BP without the use of additional antihypertensive agents (34,40). In our prospective study, 39% of patients with primary aldosteronism had their BP normalized by treatment, with the remaining 61% requiring persistent use of one or more antihypertensive agents. Retrospective studies identified younger age, shorter duration of disease, and milder antihypertensive therapy as factors that were associated with resolution of hypertension after correction of primary aldosteronism (34,41–44). Our patients with measurable plasma renin had higher baseline BP than patients with suppressed renin and reached comparable BP levels during follow-up but at the

expense of a heavier antihypertensive treatment (2.4 *versus* 2.0 antihypertensive drugs, respectively). Also, normalization of BP after adrenalectomy or treatment with spironolactone was more frequent in patients with suppressed baseline plasma renin. Thus, higher pretreatment plasma renin levels predict lower percentage of cure of aldosteronism and greater need for antihypertensive agents to reach adequate control of BP. Consistent with these findings, lower pretreatment renin levels were reported in patients who had adrenal adenoma and in whom hypertension was cured by adrenalectomy (34).

An elevated plasma aldosterone-to-plasma renin ratio is an indicator of autonomous aldosterone secretion and is widely used as a screening test for primary aldosteronism (2,4,5). Our results indicate that some patients with primary aldosteronism might differ in some respects from the majority of patients with this endocrine disorder, inasmuch as development of intrarenal vascular damage, occurring as a complication of severe hypertension, may lead to a reversal of renin suppression, a condition that may veil the typical hormonal characteristics of this clinical condition. Although, as in our patients, the aldosterone-to-renin ratio can be increased even in the absence of a suppressed plasma renin, this possibility should be kept in mind while performing the diagnostic workup of hypertensive patients, and appropriate use of well-established confirmatory tests, such as the saline infusion or fludrocortisone test, should be considered (45).

Some limitations of this study need to be underlined. First, similar to most studies that included patients with idiopathic aldosteronism (34,36,46), we might have underestimated the number of patients with adrenal adenoma. We performed selective adrenal vein sampling in only 14 of our patients, whereas, in the remaining 42, discrimination from idiopathic disease was based on CT evidence of adrenal masses and adrenal scintigraphy. However, in this respect, it is important to notice that in our study, as in those studies, no significant differences in duration of hypertension, BP levels, and renal function parameters were observed between the two primary aldosteronism subtypes. Also, we found no difference in outcomes between patients who were treated with adrenalectomy or aldosterone antagonists (Figure 3). Second, the use of certain drugs, such as blockers of the renin-angiotensin system, might have influenced renal outcomes, although separate analysis of patients who were and were not taking these types of medications did not show significant differences.

Two different aspects should be taken into account when considering the effects of aldosteronism on the kidney on which we might speculate (Figure 4). On the one hand, there are functional adaptations that are induced by increased renal sodium reabsorption and lead to expansion of extracellular volume, hypertension, increased renal perfusion pressure, and suppression of renin with decreased intrarenal vascular resistance (39). These changes result in glomerular hyperfiltration and increased sodium excretion, with recovery of a steady state. On the other hand, there is structural damage, involving primarily the intrarenal vessels, that might result from chronic hypertensive insult and direct untoward effects of aldosterone (9,10). This might lead to decreased glomerular perfusion and stimulation of renin production that escapes from suppression by excess plasma aldosterone. In this view, lack of complete renin suppression could be a marker of a progressed stadium of the disease, and this would be supported by our observation of more severe hypertension and longer duration of disease in patients with detectable plasma renin. An alternative explanation could be that these patients had less aldosterone excess, which would explain incomplete renin suppression, lesser dependence of high BP from aldosterone-mediated mechanisms,

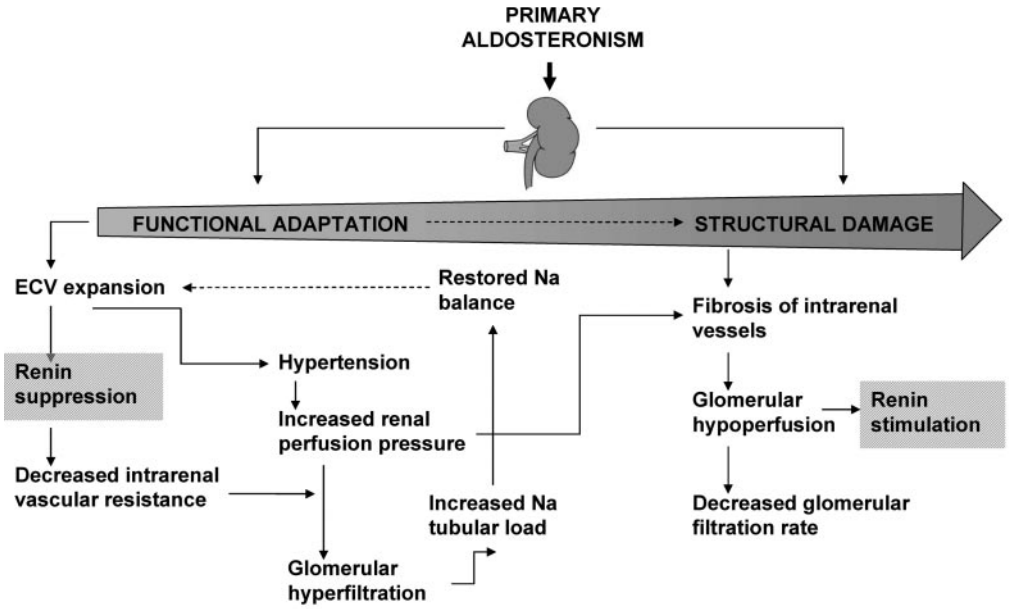

Figure 4. Proposed mechanism for renal functional adaptation and structural damage in primary aldosteronism. ECV, extracellular fluid volume.

and lower reduction of creatinine clearance with treatment. Although presence of a trend to lower plasma aldosterone in these patients could support this possibility, it should be noted that baseline BP was significantly higher and duration of disease was significantly longer than in patients with suppressed renin and that patients with the lowest GFR in our cohort (Figure 1) had plasma aldosterone concentrations at the top of the distribution.

Conclusion

Detection of advanced renal disease is not a frequent event in patients with primary aldosteronism. In these patients, escape of renin from suppression by excess aldosterone might be the marker of structural renal damage that occurs as a consequence of hypertension-mediated intrarenal vascular injury and predicts worse BP and renal outcomes after either surgical or medical treatment. Timely identification of primary aldosteronism is important to maximize the benefits of treatment.

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Disclosures

None.

References

1. Plouin PF, Amar L, Chatellier G; for the COMETE-Conn Study Group: Trends in the prevalence of primary aldosteronism, aldosterone-producing adenomas, and surgically correctable aldosterone-dependent hypertension. *Nephrol Dial Transplant* 19: 774–777, 2004
2. Mulatero P, Stowasser M, Loh KC, Fardella CE, Gordon RD, Mosso L, Gomez-Sanchez CE, Veglio F, Young WF Jr: Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. *J Clin Endocrinol Metab* 89: 1045–1050, 2004
3. Conn JW: Presidential address. Part I: Painting background. Part II: Primary aldosteronism. *J Lab Clin Med* 45: 3, 1955
4. Young WF: Primary aldosteronism-changing concepts in diagnosis and treatment. *Endocrinology* 144: 2208–2213, 2003
5. Gordon RD: The challenge of more robust and reproducible methodology in screening for primary aldosteronism. *J Hypertens* 22: 251–255, 2004
6. Conn JW, Knopf RF, Nesbit RM: Clinical characteristics of primary aldosteronism from an analysis of 145 cases. *Am J Surg* 107: 159–172, 1964
7. Laragh JH: Vasoconstriction: Volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. *Am J Med* 55: 261–274, 1973
8. Rossi GP, Boscaro M, Ronconi V, Funder JW: Aldosterone as a cardiovascular risk factor. *Trends Endocrinol Metab* 16: 104–107, 2005
9. Hollenberg NK: Aldosterone in the development and progression of renal injury. *Kidney Int* 66: 1–9, 2004
10. Rocha R, Stier CT Jr: Pathophysiological effects of aldosterone in cardiovascular tissues. *Trends Endocrinol Metab* 12: 308–314, 2001
11. Ibrahim HN, Hostetter TH: Aldosterone in progressive renal disease. *Semin Nephrol* 21: 573–579, 2001
12. Epstein M: Aldosterone as a mediator of progressive renal disease: Pathogenetic and clinical implications. *Am J Kidney Dis* 37: 677–688, 2001
13. Bianchi S, Bigazzi R, Campese VM: Antagonists of aldosterone and proteinuria in patients with CKD: An uncontrolled pilot study. *Am J Kidney Dis* 46: 45–51, 2005
14. Sato A, Hayashi K, Naruse M, Saruta T: Effectiveness of aldosterone blockade in patients with diabetic nephropathy. *Hypertension* 41: 64–68, 2003
15. Schjoedt KJ, Rossing K, Juhl TR, Boomsma F, Rossing P, Tarnow L, Parving HH: Beneficial impact of spironolactone in diabetic nephropathy. *Kidney Int* 68: 2829–2836, 2005
16. Epstein M: Adding spironolactone to conventional antihypertensives reduces albuminuria in patients with diabetic nephropathy. *Nat Clin Pract Nephrol* 2: 310–311, 2006
17. Beevers DG, Brown JJ, Ferriss JB, Fraser R, Lever AF, Robertson JI, Tree M: Renal abnormalities and vascular complications in primary aldosteronism: Evidence of tertiary hyperaldosteronism. *Q J Med* 45: 401–410, 1976
18. Bravo EL, Fouad-Tarazi FM, Tarazi RC, Pohl M, Gifford RW, Vidt DG: Clinical implications of primary aldosteronism with resistant hypertension. *Hypertension* 11: 207–211, 1988
19. Ribstein J, Du Cailar G, Fesler P, Mimran A: Relative glomerular hyperfiltration in primary aldosteronism. *J Am Soc Nephrol* 16: 1320–1325, 2005
20. Sechi LA, Novello M, Lapenna R, Baroselli S, Nadalini E, Colussi GL, Catena C: Long-term renal outcomes in patients with primary aldosteronism. *JAMA* 295: 2638–2645, 2006
21. Catena C, Lapenna R, Baroselli S, Nadalini E, Colussi GL, Novello M, Favret G, Melis A, Cavarape A, Sechi LA: Insulin sensitivity in patients with primary aldosteronism: A follow-up study. *J Clin Endocrinol Metab* 91: 3457–3463, 2006
22. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med* 153: 154–183, 1993
23. Sechi LA, Kronenberg F, De Carli S, Falleti E, Zingaro L, Catena C, Utermann G, Bartoli E: Association of serum lipoprotein(a) levels and apolipoprotein(a) size polymorphism with target-organ damage in arterial hypertension. *JAMA* 277: 1689–1695, 1997
24. Sechi LA, Zingaro L, Catena C, Casaccio D, De Marchi S: Relationship of fibrinogen levels and hemostatic abnormalities with organ damage in hypertension. *Hypertension* 36: 978–985, 2000
25. Ferrari P, Shaw SG, Nicod J, Saner E, Nussberger J: Active renin versus plasma renin activity to define aldosterone-to-renin ratio for primary aldosteronism. *J Hypertens* 22: 377–381, 2004
26. Kem DC, Weinberger MH, Mayes DM, Nugent CA: Saline suppression of plasma aldosterone in hypertension. *Arch Intern Med* 128: 380–386, 1971
27. Grim CE, Weinberger MH, Higgins JT, Kramer NJ: Diag-

nosis of secondary forms of hypertension. A comprehensive protocol. *JAMA* 237: 1331–1335, 1977
28. Weinberger MH, Grim CE, Hollifield JW, Kem DC, Ganguly A, Kramer NJ, Yune HY, Wellman H, Donohue JP: Primary aldosteronism: Diagnosis, localization, and treatment. *Ann Intern Med* 90: 386–395, 1979
29. Sechi LA, Zingaro L, Catena C, Perin A, De Marchi S, Bartoli E: Lipoprotein(a) and apolipoprotein(a) isoforms and proteinuria in patients with moderate renal failure. *Kidney Int* 56: 1049–1057, 1999
30. Seelig HP: The Jaffe reaction with creatinine: Reaction product and general reaction conditions. *Z Klin Chem Klin Biochem* 7: 581–585, 1969
31. Kimura G, Uzu T, Nakamura S, Inenaga T, Fujii T: High sodium sensitivity and glomerular hypertension/hyperfiltration in primary aldosteronism. *J Hypertens* 14: 1463–1468, 1996
32. Sealey JE, Gordon RD, Mantero F: Plasma renin and aldosterone measurements in low renin hypertensive states. *Trends Endocrinol Metab* 16: 86–91, 2005
33. Oelkers W, Diederich S, Bahr V: Primary hyperaldosteronism without suppressed renin due to secondary hypertensive kidney damage. *J Clin Endocrinol Metab* 85: 3266–3270, 2000
34. Blumenfeld JD, Sealey JE, Schlussel Y, Vaughan D, Sos TA, Atlas SA, Muller FB, Acevedo R, Ulick S, Laragh JH: Diagnosis and treatment of primary aldosteronism. *Ann Intern Med* 121: 877–885, 1994
35. Nishimura M, Uzu T, Fujii T, Kuroda S, Nakamura S, Inenaga T, Kimura G: Cardiovascular complications in patients with primary aldosteronism. *Am J Kidney Dis* 33: 261–266, 1999
36. Rossi GP, Bernini G, Desideri G, Fabris B, Ferri C, Giacchetti G, Letizia C, Maccario M, Mannelli M, Matterello MJ, Montemurro D, Palombo G, Tizzoni D, Rossi E, Pessina AC, Mantero F: Renal damage in primary aldosteronism. Results of the PAPY study. *Hypertension* 48: 232–238, 2006
37. Hall JE, Granger JP, Smith MJ Jr, Premen AJ: Role of hemodynamics and arterial pressure in aldosterone "escape." *Hypertension* 6: I183–I192, 1984
38. Dworkin LD, Hostetter TH, Renne HG, Brenner BM: Hemodynamic basis for glomerular injury in rats with desoxycorticosterone-salt hypertension. *J Clin Invest* 73: 1448–1461, 1984
39. Uhrenholt TR, Schjerning J, Hansen PB, Norregaard R, Jensen BL, Sorensen GL, Skott O: Rapid inhibition of vasoconstriction in renal afferent arterioles by aldosterone. *Circ Res* 93: 1258–1266, 2003
40. Sawka AM, Young WF Jr, Thompson GB, Grant CS, Farley DR, Leibson C, van Herdeen JA: Primary aldosteronism: Factors associated with normalization of blood pressure after surgery. *Ann Intern Med* 135: 258–261, 2001
41. Obara T, Ito Y, Okamoto T, Kanaji Y, Yamashita T, Aiba M, Fujimoto Y: Risk factors associated with postoperative persistent hypertension in patients with primary aldosteronism. *Surgery* 112: 987–993, 1992
42. Celen O, O'Brien MJ, Melby JC, Beazley RM: Factors influencing outcome of surgery for primary aldosteronism. *Arch Surg* 131: 646–650, 1996
43. Lo CY, Tam PC, Kung AW, Lam KS, Wong J: Primary aldosteronism. Results of surgical treatment. *Ann Surg* 224: 125–130, 1996
44. Proye CA, Mulliez EA, Carnaille BM, Lecomte-Houcke M, Decoulx M, Wemeau JL, Lefebvre J, Racadot A, Ernst O, Huglo D, Carre A: Essential hypertension: First reason for persistent hypertension after unilateral adrenalectomy for primary aldosteronism? *Surgery* 124: 1128–1133, 1998
45. Mulatero P, Milan A, Fallo F, Regolisti G, Pizzolo F, Fradella C, Mosso L, Marafetti L, Veglio F, Maccario M: Comparison of confirmatory tests for the diagnosis of primary aldosteronism. *J Clin Endocrinol Metab* 91: 2618–2623, 2006
46. Fallo F, Veglio F, Bertello C, Sonino N, Della Mea P, Ermani M, Rabbia F, Federspil G, Mulatero P: Prevalence and characteristics of the metabolic syndrome in primary aldosteronism. *J Clin Endocrinol Metab* 91: 454–459, 2006