Evidence of Primary Aldosteronism in a Predominantly Female Cohort of Normotensive Individuals: A Very High Odds Ratio for Progression into Arterial Hypertension

Athina Markou, Theodora Pappa, Gregory Kaltsas, Aggeliki Gouli, Kostas Mitsakis, Panayiotis Tsounas, Anastasia Prevoli, Vaios Tsiavos, Labrini Papanastasiou, George Zografos, George P. Chrousos, and George P. Piaditis

Department of Endocrinology and Diabetes Center (A.M., T.P., A.G., K.M., P.T., A.P., V.T., L.P., G.P.P.), Third Department of Surgery (G.Z.), Athens General Hospital, "G. Gennimatas" General Hospital, Department of Pathophysiology (G.K.), Laikon Hospital, National University of Athens, and First Department of Pediatrics (G.P.C.), Children's Hospital Aghia Sophia, School of Medicine, University of Athens, 11527 Athens, Greece

Context: Primary aldosteronism (PA) is an established cause of hypertension, whereas high-normal serum aldosterone levels have been linked to an increased risk for hypertension.

Objective: We aimed to define the post-fludrocortisone-dexamethasone suppression test (FDST) normal cutoff values of aldosterone and the aldosterone to renin ratio and evaluate the presence of PA in normotensive individuals.

Design: This study was designed as a case-control study.

Setting: The study was performed in a tertiary general hospital.

Patients: One hundred normotensive participants (80 females), mean age 53 years, were studied.

Main Outcome Measures: All participants underwent baseline biochemical and hormonal evaluation, FDST, and adrenal computerized tomography. Blood pressure was assessed at baseline and after 5 years.

Results: Sixty-nine participants with normal adrenal computerized tomography who remained normotensive after 5 years were used as a control population to calculate the cutoff values of adequate aldosterone suppression. PA was defined as a combination of post-FDST aldosterone to renin ratio of 0.93 ng/dL · μU/mL or greater (100% sensitivity and 96% specificity) and post-FDST aldosterone of 2.96 ng/dL or greater (100% sensitivity and 61% specificity on receiver-operating characteristic analysis). Thirteen of 100 participants had PA at baseline and 11 (85%) developed hypertension, whereas only 20 of 87 without PA (23%) developed hypertension at 5 years [odds ratio (OR) 18.42, 95% confidence intervals (CI) 3.76–90.10, $P < .0001$]. Logistic regression analysis showed a positive relation of PA [odds ratio (OR) 16.30, confidence interval (CI) 1.78–150.30, $P = .01$] and a negative relation of serum potassium (OR 0.39, CI 0.19–0.79, $P = .01$) with the development of hypertension.

Conclusions: Normotensive PA represents a clinical entity referring to normotensive individuals with PA who are at increased risk for hypertension. **(*J Clin Endocrinol Metab* 98: 1409–1416, 2013)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received September 13, 2012. Accepted February 19, 2013.
First Published Online March 7, 2013

Abbreviations: AH, arterial hypertension; ALD, aldosterone; ARR, aldosterone to renin ratio; BMI, body mass index; BP, blood pressure; CI, confidence interval; CT, computed tomography; CV, coefficient of variation; DBP, diastolic BP; DHEAS, dehydroepiandrosterone sulfate; DM, diabetes mellitus; FDST, fludrocortisone-dexamethasone suppression test; FST, fludrocortisone suppression; HT, hypertension; IGT, impaired glucose tolerance; IRMA, immunoradiometric assay; OR, odds ratio; PA, primary aldosteronism; REN, renin; ROC, receiver-operating characteristic; SBP, systolic BP.

Primary aldosteronism (PA) is a well-established cause of arterial hypertension (AH), which constitutes a major cardiovascular risk factor (1). Aldosterone (ALD) excess causes hypertension through renal retention of water and sodium and is also associated with tissue inflammation that leads to fibrosis and remodeling in the kidney, heart, and vasculature and an increased central sympathetic drive (2–10). Diagnosis of PA is of paramount importance because it can lead to renal impairment, atrial fibrillation, stroke, and myocardial infarction (11). PA is characterized by a consistently elevated serum aldosterone and aldosterone to renin ratio (ARR). The latter is used as a screening test, whereas the diagnosis of PA is documented with further confirmatory tests, such as the saline infusion test, the fludrocortisone suppression (FST) test, and the captopril suppression test (12). However, there is a wide variation of aldosterone cutoff values (ranging from 5.0 to 9.98 ng/dL, 139–277 pmol/L) used to diagnose PA with either of these tests, mainly because of the lack of a well-defined control population (13–15).

We recently introduced a modification of the currently used FST for the diagnosis of PA, the combined fludrocortisone-dexamethasone suppression test (FDST), which involves the coadministration of dexamethasone at midnight of the last day of the FST (16). The addition of dexamethasone is used to eliminate the stimulatory input of ACTH on aldosterone secretion (17–19). In a previous study, we applied the FDST in a normotensive population with normal adrenal morphology on computed tomography (CT), defined as the control group, to establish cutoff values of the post-FDST ALD levels and ARR, indicative of adequate aldosterone suppression (16). Normal adrenal imaging was considered a prerequisite for an individual to qualify as a control because a high prevalence of PA has been described among individuals with adrenal adenomas (20, 21). Using such an approach was considered necessary to identify normotensive individuals with adrenocortical adenomas and PA that could had been otherwise misclassified as normal controls. Furthermore, the elimination of the endogenous ACTH effect has increased substantially the sensitivity and specificity of the FDST and enabled us to detect previously unrecognized cases of PA, thus increasing the overall prevalence of PA in individuals with essential hypertension (16).

It has been reported that baseline serum aldosterone levels, even within the upper normal range, can predict future blood pressure (BP) elevations in normotensive individuals (22, 23). These observations may highlight the presence of a state of relative aldosterone excess, characterized by inappropriately raised aldosterone levels in the presence of a normal BP that could be analogous to that of normocalcemic hyperparathyroidism, a subset of which may evolve to classic hyperparathyroidism (24–26). However, establishing the presence of relative aldosterone excess requires an abnormal response to an aldosterone suppression test. Normotensive individuals with evidence of PA defined by the FDST may actually represent individuals in a prehypertensive stage, and such subjects should probably be excluded from the control population used to calculate normal cutoff levels of aldosterone secretion. Normotensive PA has also been described previously (27, 28), but its clinical relevance remains unknown because affected individuals have not been followed up sufficiently to assess possible development of hypertension.

The aim of the present study was to investigate the secretory pattern of aldosterone using the FDST in a cohort of normotensive individuals, who had their BP reassessed 5 years later, in an attempt to more accurately define the normal cutoff levels of post-FDST ARR and ALD levels and then identify normotensive subjects with PA at an increased risk of developing AH.

Patients and Methods

We evaluated 122 normotensive individuals, aged 31–71 years. These individuals were selected from patients referred to our department for reasons unrelated to hypertension, mainly thyroid goiter or bone mineral density measurements. Normal BP was defined as a systolic BP (SBP) of less than 135 mm Hg and diastolic BP (DBP) less than 85 mm Hg, measured at the outpatient unit for at least 3 consecutive visits (mean of 3 measurements). Exclusion criteria were the presence of hypertension and/or cardiovascular, renal, or hepatic disease; past or present malignancies and rheumatological diseases; and the presence of a known adrenal lesion. All participants were euthyroid at their initial visit, and they remained so during the follow-up period. Postmenopausal women did not receive any hormonal replacement therapy. The reporting of the study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology statement and guidelines. The study protocol was approved by the institution's ethics committee and informed consent was obtained from all study participants.

At baseline, all participants underwent recording of their previous medical history and a routine physical examination, including documentation of anthropometric characteristics [weight (kilograms), height (centimeters), waist circumference (centimeters) and body mass index (BMI) (kilograms per square meter)] by the same physician (A.M.). Blood sampling for routine biochemistry and a full blood count were performed. Participants who had fasting glucose greater than 100 mg/dL underwent an oral glucose tolerance test. All participants underwent a FDST on an outpatient basis as follows: 1) day 1: sampling for serum sodium (Na^+), potassium (K^+), cortisol, ALD, renin (REN), dehydroepiandrosterone sulfate (DHEAS), and plasma ACTH levels; 2) day 2: 24-hour urine collection for Na^+ and K^+ concentration; 3) days 3–6: fludrocortisone acetate (0.1 mg) administered orally every 6 hours and sodium chloride (4 g) administered with meals 3 times daily; 4) day 6: 2 mg of

dexamethasone administered orally at 12:00 AM; 5) day 7: blood sampling for circulating cortisol, ALD, REN, and ACTH levels as well as for the calculation of the ARR. All blood samples were drawn with the participants remaining seated in a nonstressful environment for at least 30 minutes (8:30 AM). Supplementation with potassium gluconate (4.68 g per 8 hours^{-1} per 24 hours^{-1}) was given to all participants during the FDST to maintain serum K^+ levels within the normal range (3.5–5.0 mEq/L). Blood pressure was also monitored every morning in the outpatient unit at the sitting position. An adrenal CT scan with 2-mm sections using the Philips Brilliance 16 Spiral scanner was performed in all participants. Adrenal adenomas were defined as well-circumscribed adrenal lesions greater than 10 mm with a noncontrast CT attenuation coefficient of less than 10 Hounsfield Units. Participants found to have an adrenal adenoma were excluded from further analysis.

Five years after the initial investigation, reassessment of BP, BMI, waist circumference, smoking status, and the presence of diabetes mellitus (DM) or impaired glucose tolerance (IGT) was performed in all participants. Subjects already receiving antihypertensive treatment were considered hypertensive and the date of the diagnosis of hypertension and prescribed medications were recorded. Home BP monitoring was used for assessing the BP status of the rest of the study participants. Participants were asked to record their BP twice daily (morning and evening) for 7 days. For each BP recording, subjects were instructed to take 2 consecutive measurements at least 1 minute apart while they were seated. After discarding the measurements of the first day, we calculated the average value of the remaining measurements to confirm the diagnosis of hypertension (SBP ≥135 and/or DBP ≥85 mm Hg) (26).

Hormone assays

Hormones were measured using the following RIAs: serum insulin was measured by the immunoradiometric assay (IRMA; Biosource Europe S.A., Fleurus, Belgium); sensitivity 1 μIU/mL (7 pmol/L), intra- and interassay coefficients of variation (CVs) of 2.2% and 6.5%, respectively. Serum and urinary cortisol [sensitivity 0.08 μg/dL (2.2 nmol/L) and intra- and interassay CVs of 6.2% and 8.7%, respectively] and serum DHEAS [sensitivity 0.55 μg/dL (0.015 μmol/L) and intra- and interassay CVs of 5.3% and 4.5%, respectively] were measured by RIA (DIAsource ImmunoAssays, Brussels, Belgium). Serum ACTH [sensitivity 2 pg/mL (0.4 pmol/L) and intra- and interassay CVs of 6.1% and 5.3%, respectively] was measured by IRMA (CIS Bio International, Gif-sur-Yvette, France). Plasma renin concentration (renin III generation) was measured by IRMA (CIS Bio International); [sensitivity 2.0 μU/mL (2.0 mU/L) and intra- and interassay CVs of 3.6% and 5%, respectively]. Normal values in the lying position are 1.1–20.2 pg/mL (2.0–36.36 mU/L) and in the upright position, 1.1–59.4 pg/mL (2.0–106.92 mU/L). Serum aldosterone [sensitivity 0.66 ng/dL (30 pmol/L) and intra- and interassay CVs of ≤9.5% and ≤ 9.9%, respectively] was measured by RIA (Immunotech assays, Roissy, France). Normal values in the lying position are 1.08–17.19 ng/dL (30–477 pmol/L) and in the upright position, 2.99–35.50 ng/dL (83–985 pmol/L).

Statistical analyses

Statistical analysis was performed using the SPSS software package (SPSS Inc, version 17.0, Chicago, Illinois). A Student *t* test and the nonparametric Mann-Whitney test were used to compare the continuous variables with and without normal distribution, respectively. The χ^2 test was used to compare the categorical variables. Logistic regression analysis was used to detect the correlation between the development of hypertension and categorical and continuous variables. The mean ± SD was used to express the results, whereas $P < .05$ was considered statistically significant. The 97.5% percentiles were used to define the upper normal cutoffs for aldosterone suppression. Receiver-operating characteristic (ROC) curves have been applied to assess the sensitivity and specificity of the post-FDST ARR and ALD levels and the Youden Index has been calculated.

Results

An adrenal CT scan revealed an adrenal adenoma in 10 of the 122 participants (8%); these individuals were excluded from the study. Twelve of the remaining 112 participants with a normal adrenal CT were lost to follow-up 5 years after the initial investigation and thus were not used in further analyses. Therefore, 22 participants of the initial cohort were excluded from the study analysis. The baseline characteristics of the study population (n = 100) with normal adrenal CT and adequate follow-up data are shown in Table 1. Most the participants were female (80%). All participants demonstrated sufficient suppression of ACTH and cortisol levels after the FDST [6.0

Table 1. Baseline Characteristics of the Cohort of Normotensive Individuals (n = 100)

	Mean (SD)
Male	20
Female	80
Age, y	53 (8)
SBP, mm Hg	118 (11)
DBP, mm Hg	76 (8)
BMI, kg/m^2	27 (5)
Waist circumference, cm	92 (11)
Smoking status	27
DM	3
IGT	9
Fasting glucose, mg/dL	90 (10)
Fasting insulin, μIU/mL	1.25 (0.97)
Na^+, mEq/L	142 (2)
K^+, mEq/L	4.1 (0.3)
Urinary 24-hour Na^+, mEq per 24 hours	149 (62)
Urinary 24-hour K^+, mEq per 24 hours	59 (21)
ACTH baseline, pg/mL	25 (16)
Cortisol baseline, μg/dL	18.0 (7.1)
ALD baseline, ng/dL	9.7 (6.6)
REN baseline, μU/mL	15 (11)
ARR baseline, ng/dL · μU · mL	0.94 (1.01)
DHEAS, ng/mL	367 (252)
ACTH post-FDST, pg/mlL	6 (1)
Cortisol post-FDST, μg/dL	1.0 (0.4)
Post-FDST ALD, ng/dL	2.2 (1.8)
Post-FDST REN, μU/mL	5 (2)
Post-FDST ARR, ng/dL · μU · mL	0.5 (0.4)

pg/mL (1.3 pmol/L) and 1.0 μg/dL (28 nmol/L), respectively]. Sixty-nine participants remained normotensive and 31 developed hypertension at 5 years. Normal cutoff values for ALD levels and the post-FDST ARR, indicative of adequate aldosterone suppression, were defined using the normotensive population at the 5-year follow-up period [5.1 (0.1) years (range 2–7 years)]. Using the 97.5% percentiles, from this population, the basal cutoff level for ARR was 2.43 ng/dL · μU per milliliter (67 pmol/mIU), and the post-FDST cutoff levels for ALD and ARR were defined as 2.96 ng/dL (82 pmol/L) and 0.93 ng/dL · μU per milliliter (26 pmol/mIU), respectively. PA was diagnosed in participants who obtained a post-FDST ARR of 0.93 ng/dL · μU per milliliter or greater (26 pmol/mIU), combined with a post-FDST ALD of 2.96ng/dL or greater (82 pmol/L).

Using these cutoff values, we observed that 11 participants of the group that developed hypertension (HT) (G-1, group of hypertensive subjects with PA) and 2 participants of the normotensive population at the 5-year follow-up (G-2, group of normotensive subjects with PA) had PA. The remaining 20 participants of the hypertensive group (G-3, group of hypertensive subjects without PA) and the 67 participants of the normotensive population (G-4, group of normotensive subjects without PA) showed adequate aldosterone suppression at the 5-year follow-up (Figures 1 and 2).

We evaluated a variety of known risk factors associated with the development of HT such as age, gender, BMI, waist circumference, smoking, and the presence of DM or IGT in patients with PA (n = 13) and in those who obtained adequate aldosterone suppression (n = 87). Smoking was the only risk factor more prevalent in the group with PA (Table 2). The same risk factors were reevaluated at the 5-year follow-up assessment of the participants and there was no significant difference compared with the baseline status.

We also compared the hypertensive patients with PA (G-1, n = 11) with the hypertensive patients without PA (G-3, n = 20). The only differences detected were in the REN levels at baseline and the ALD levels and ARR after FDST. The G-1 cohort had significantly lower REN levels at baseline ($P = .01$) and higher ALD levels and ARR after FDST than the G-3 cohort ($P < .001$ and $P < .001$, respectively) (Table 3). According to our findings, 11 of 13 participants with PA (85%) developed HT, compared with only 20 of the 87 who obtained normal aldosterone suppression to FDST (23%) [odds ratio (OR) 18.42, 95% confidence interval (CI) 3.76–90.10, $P < .0001$]. Logistic regression analysis revealed a significant positive relation of PA [OR 16.3, 95% CI 1.78–150.30, $P = .01$] and a significant negative relation of the serum K^+ level (OR 0.39, 95% CI 0.19–0.79, $P = .01$) with the development of hypertension (Table 4). No such correlation was found when the analysis was performed separately in the group of hypertensive patients without PA.

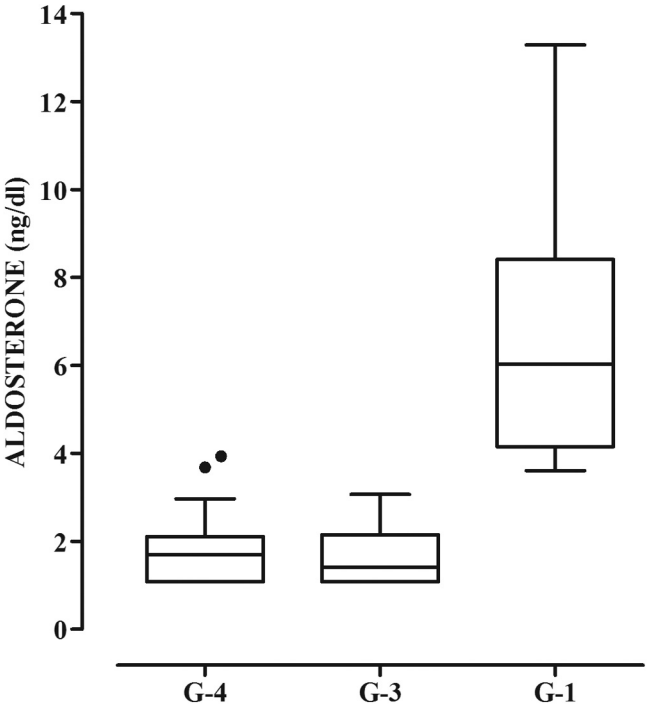

Figure 1. Box and whisker-Tukey plot. Post-FDST aldosterone levels in all subgroups are shown. G-2 is the group of normotensive subjects with PA (n = 2) indicated by the 2 black circles; G-4 is the group of normotensive subjects without PA (n = 67); G-1 is the group of hypertensive subjects with PA (n = 11); G-3 is the group of hypertensive subjects without PA. The horizontal lines represent the mean values, whereas the vertical ones represent the 2.5–97.5% percentiles.

To assess the sensitivity and specificity of the post-FDST ARR and ALD levels in diagnosing PA, we performed ROC analysis. Because in this study the number of participants with PA was rather small, we used a population of 325 individuals with essential hypertension, who also underwent a FDST in our department. Using the previously defined diagnostic criteria, we found that 92 of hypertensive participants (28%) had PA, whereas the remaining 233 (72%) showed adequate aldosterone suppression. The mean age of this group [54 (40–75) years] and gender distribution [245 of 325 (75%) females] did not differ significantly from the controls. ROC analysis showed a sensitivity of 100% with specificity 61% for post-FDST ALD levels and a sensitivity of 100% with a specificity of 96% for the post-FDST ARR. The Youden Index was 0.614 and 0.957, respectively. Furthermore, the sensitivity and specificity for the basal ARR was 35% and 95%, respectively.

Discussion

The main finding of this study is the identification of a cohort of normotensive subjects with elevated post-FDST

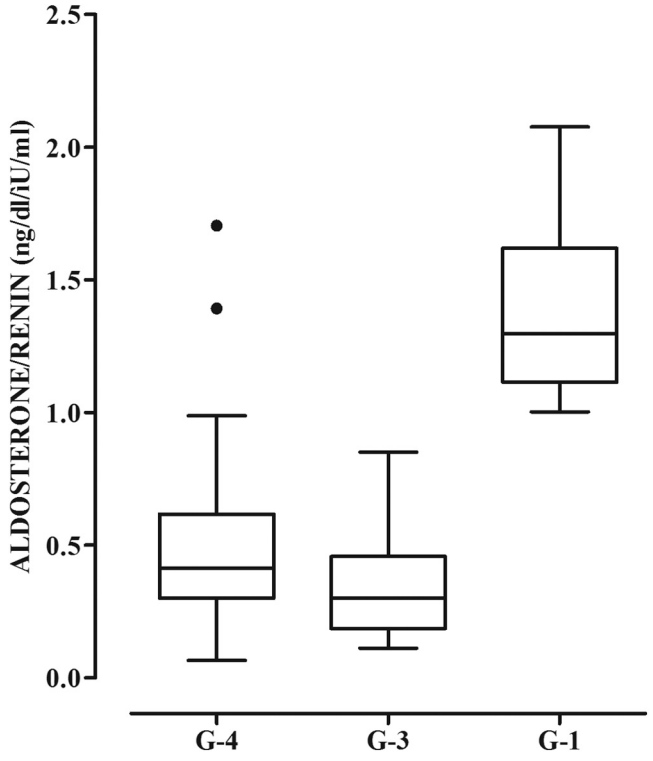

Figure 2. Box and whisker-Tukey plot. Post-FDST ARR in all subgroups is shown. G-2 is the group of normotensive subjects with PA (n = 2) indicated by the 2 black circles; G-4 is the group of normotensive subjects without PA (n = 67); G-1 is the group of hypertensive subjects with PA (n = 11); G-3 is the group of hypertensive subjects without PA. The horizontal lines represent the mean values, whereas the vertical ones represent the 2.5–97.5% percentiles.

serum ALD levels and ARR, being at increased risk for developing hypertension during a 5-year follow-up period. It is therefore possible that this subgroup constitutes a state of aldosterone excess in normotensive subjects that could be termed subclinical hyperaldosteronism or normotensive PA, with potential adverse long-term clinical consequences. An analogous paradigm could be the state of preclinical primary hyperparathyroidism, in which autonomous PTH secretion precedes a period of asymptomatic normocalcemic hyperparathyroidism that may later evolve to clinically evident primary hyperparathyroidism, as recently described (24–26). The findings of the present study are of particular interest because a normotensive population had aldosterone secretory dynamics and BP evaluated at baseline and BP reevaluated after 5 years. Subjects who did not develop hypertension during this period were used to define cutoffs of adequate aldosterone secretion and were thus qualified as a control population.

Table 2. Risk Factors for Hypertension Between Groups With and Without PA

	Group Without PA (n = 87) Mean (SD)	Group With PA (n = 13) Mean (SD)	*P* Value
Male	17	3	
Female	70	10	
Age, y	53 (8)	53 (8)	NS
BMI, kg/m^2	26 (5)	27 (4)	NS
Waist circumference, cm	92 (12)	92 (9)	NS
Smoking status	17	4	.04
Type 2 DM	2	0	NS
IGT	6	0	NS

Abbreviation: NS, not significant.

Using the cutoff values of 2.96 ng/dL (82 pmol/L) and 0.93 ng/dL · μU per milliliter (26 pmol/mIU) for ALD and the ARR, respectively, we subdivided participants into those with PA (n = 13) and those with adequate ALD suppression (n = 87) at baseline. Normotensive subjects with PA at baseline developed hypertension at 5 years at a significantly higher proportion than normotensive subjects with adequate ALD suppression. This is highly relevant because the participants of the 2 subgroups (PA vs non-PA) did not differ in other known risk factors associated with the development of hypertension such as age, BMI, waist circumference, and the presence of DM or IGT except for smoking, which was more prevalent in individuals with PA. However, the difference in smoking habits was marginally statistically significant, and due to the small sample size, it is highly unlikely to be the sole causative factor for hypertension. Furthermore, we reexamined the 2 subgroups for these risk factors at the 5-year follow-up assessment and no significant difference was found.

On the basis of these findings, we hypothesized that the increased risk for developing AH may be due to the presence of PA. In support of this view is the finding that the only differences among hypertensive individuals in the 2 cohorts was the significantly lower basal REN levels and the higher ALD and post-FDST ARR in the group with PA. Logistic regression was in favor of our hypothesis because it showed a positive relation of PA with the development of hypertension.

Our findings are in accordance with those of recent studies reporting an increased risk of developing hypertension in subjects with basal aldosterone levels in the upper normal range (22, 23).

A distinctive feature of our study was the use of an established aldosterone suppression test widely accepted for the diagnosis of PA (12). Specifically we applied a modification of the FST by adding dexamethasone administration to eliminate the effect of ACTH on aldosterone secretion. This test takes into account not only the effect of angiotensin II and potassium but also that of ACTH on aldosterone secretion. Therefore, it lowers the cutoff values used to define aldosterone excess when compared with the widely used fludrocortisone or saline infusion tests

Table 3. Risk Factors for Developing Hypertension and Biochemical and Hormonal Parameters Between the G-3 and the G-1 Cohorts

	G-3 (n = 20) Mean (SD)	G-1 (n = 11) Mean (SD)	*P* Value
Age, y	52 (7)	53 (8)	NS
BMI, kg/m^2	28 (4)	27 (4)	NS
Waist circumference, cm	94 (12)	91 (9)	NS
Fasting glucose, mg/dL	90 (10)	94 (9)	NS
Fasting insulin, μIU/mL	1.25 (0.69)	1.53 (0.97)	NS
Na^+, mEq/L	141 (3)	140 (2)	NS
K^+, mEq/L	4 (0.4)	4 (0.3)	NS
Urinary 24-hour Na^+, mEq per 24 hours	164 (76)	129 (34)	NS
Urinary 24-hour K^+, mEq per 24 hours	56 (21)	48 (15)	NS
ACTH baseline, pg/mL	27 (21)	19 (14)	NS
Cortisol baseline, μg/dL	17.7 (5)	16 (7)	NS
ALD baseline, ng/dL	10.8 (7.1)	11.6 (6.8)	NS
REN baseline, μU/mL	21 (15)	12 (6)	.01
ARR baseline, ng/dL · μU · mlL	1.08 (1.51)	1.23 (0.83)	NS
DHEAS, ng/mL	307 (182)	428 (353)	NS
Post-FDST ACTH, pg/mL	5 (0)	5 (1)	NS
Post-FDST cortisol, μg/dL	1.1 (0.5)	1.1 (0.6)	NS
Post-FDST ALD, ng/dL	1.7 (0.7)	6.9 (3.2)	<.001
Post-FDST REN, μU/mL	5 (2)	5 (2)	NS
Post-FDST ARR, ng/dL · μU · mL	0.3 (0.2)	1.5 (0.6)	<.001

Abbreviation: NS, not significant.

because it enables the detection of milder forms of PA (16). It is noteworthy that 8 of the 13 participants with PA had ARR and ALD levels diagnostic of PA, even when the currently accepted criteria (5.01–9.98 ng/dL, 139–277 pmol/L) for aldosterone were applied. Using the FDST enabled us to detect even milder forms of PA, which otherwise would have been missed.

Furthermore, we used the combination of post-FDST ALD and ARR measures to diagnose PA because if only one of these parameters were used, the percentage of false-positive results would be increased, as in cases of participants with prior low salt intake or poor compliance during the test (16). In such cases, the post-FDST ALD levels could be falsely nonsuppressed, whereas the concomitant posttest ARR facilitates the exclusion of these false-positive results.

Mulatero et al (29) showed that high doses of dexamethasone (2 mg/d for 4 days) led to the suppression of aldosterone in 13% of the hypertensive patients with idiopathic adrenal hyperplasia and 4% of hypertensive patients with an adrenal adenoma, who had the diagnosis of PA and a negative test for the chimeric gene responsible for glucocorticoid-remediable aldosteronism. We believe that such cases are not expected to be missed by using the FDST because the dose of dexamethasone we used is only 2 mg given once (at midnight of the fourth day of the test).

Table 4. Logistic Regression Analysis Shows the OR of 3 Parameters for the Development of Hypertension

				95% CI for Exp(B)	
	B	*P* Value	Exp(B)	Lower	Upper
BMI	0.10	.07	1.10	0.99	1.22
PA	2.79	.01	16.34	1.78	150.30
K^+	−0.94	.01	0.39	0.19	0.79

Abbreviation: Exp(B): odds ratio.

There are several aspects of this study that deserve special consideration. Adrenal imaging revealed that 10 participants harbored an adrenal adenoma, a prevalence of 8% that is in accordance with current literature and signifies the importance of performing a CT scan to exclude such cases when selecting study subjects for a control population (16). Additionally, 2 individuals of the group with PA remained normotensive in the follow-up period. However, one cannot exclude the possibility that these subjects may develop hypertension at a later stage, an issue that remains to be answered with a longer follow-up. The strengths of our study include the use of well-established tests, all performed in standardized conditions. Furthermore, assessing the BP status on follow-up was based on the home BP monitoring, which is a suitable method to confirm the diagnosis of hypertension (30).

There are some limitations that should be noted. Despite the prospective nature of our study, the statistical analysis to define cutoff values for normal aldosterone secretion was performed after taking into consideration the outcome, ie, the development of hypertension at follow-up that might represent a bias in the study methodology. Besides the significantly higher percentage of individuals with PA that developed hypertension and the detection of an association between PA and the development of hypertension, future studies with larger samples of participants are probably necessary to confirm our results.

We should also note that the study protocol is technically demanding, involves recruitment of confirmed healthy normotensive subjects, and a significant attrition may occur during follow-up. In our study attrition was approximately 10%.

Repeating the FDST at the 5-year follow-up provides useful information on the trend of change in aldosterone secretion, even in the absence of hypertension. However, a significant number of participants were reluctant to repeat the FDST, hindering a similar reevaluation of aldosterone secretory dynamics. Another caveat that should be considered involves the presence of other risk factors for the development of hypertension. Yet we should emphasize that risk factors, such as a high BMI, smoking, and the presence of DM, were reexamined at 5 years and there was no significant difference compared with the baseline status of the patients.

Another potentially limiting factor is the increased percentage of female participants (80% of the population studied), which is probably attributed to their increased health awareness leading to outpatient consultation. Although the findings of our study are derived from an outpatient endocrinology clinic, we believe that they reflect mainly the general healthy female population because all study participants were referred for either measurement and assessment of bone mineral density or thyroid goiter and were euthyroid. Clearly a higher percentage of male participants would be of value, even though there are no data to show that there is sexual dimorphism in aldosterone suppression. The overweightness of our study population could represent another bias, although it is of a modest degree and representative of the population referred to an endocrinology outpatient department. Lastly, the recruitment of only Caucasian individuals does not allow extrapolation of our findings to other ethnic groups.

In addition to the classical role of aldosterone in the regulation of sodium and potassium homeostasis, aldosterone exerts multiple adverse actions and predisposes the heart and the kidney to fibrotic changes, increasing cardiovascular risk (31). Defining the level above which aldosterone exerts its unwanted effects and identifying individuals with subclinical hyperaldosteronism may have an important impact in clinical practice. Aldosterone excess has been associated with severe left ventricular hypertrophy and impairment of diastolic cardiac function (3, 4, 32). Theoretically, close monitoring and early intervention in these subjects might help minimize the aldosterone-induced cardiovascular sequelae. The clinical relevance of this novel entity may be of particular significance beyond the increased risk of arterial hypertension documented in the present study. Unveiling the detrimental aldosterone-mediated actions on the cardiovascular system in individuals with subclinical hyperaldosteronism is expected to open a window for future research.

Acknowledgments

Address all correspondence and requests for reprints to: Theodora Pappa, MD, PhD, Department of Endocrinology and Diabetes Center, Athens General Hospital "G. Gennimatas," 154 Mesogion Avenue, 11527 Athens, Greece. E-mail: dorispappas@hotmail.com.

This work was supported by the Union of Friends of the Endocrinology Department of G. Gennimatas Hospital.

Disclosure Summary: The authors have nothing to disclose.

References

1. **Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration.** Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
2. **Briet M, Schiffrin EL.** The role of aldosterone in the metabolic syndrome. *Curr Hypertens Rep*. 2011;13:163–172.
3. **Rossi GP, Sacchetto A, Pavan E, Scognamiglio R, Pietra M, Pessina AC.** Left ventricular systolic function in primary aldosteronism and hypertension. *J Hypertens*. 1998;16:2075–2077.
4. **Rossi GP, Di Bello V, Ganzaroli C, et al.** Excess aldosterone is associated with alterations of myocardial texture in primary aldosteronism. *Hypertension*. 2002;40:23–27.
5. **Rossi GP, Bernini G, Desideri G, et al.** Renal damage in primary aldosteronism: results of the PAPY Study. *Hypertension*. 2006;48:232–238.
6. **Rossi GP, Sechi LA, Giacchetti G, Ronconi V, Strazzullo P, Funder JW.** Primary aldosteronism: cardiovascular, renal and metabolic implications. *Trends Endocrinol Metab*. 2008;19:88–90.
7. **Fritsch Neves M, Schiffrin EL.** Aldosterone: a risk factor for vascular disease. *Curr Hypertens Rep*. 2003;5:59–65.
8. **Gilbert KC, Brown NJ.** Aldosterone and inflammation. *Curr Opin Endocrinol Diabetes Obes*. 2010;17:199–204.
9. **Carey RM.** Aldosterone and cardiovascular disease. *Curr Opin Endocrinol Diabetes Obes*. 2010;17:194–198.
10. **Huang BS, Leenen FH.** Mineralocorticoid actions in the brain and hypertension. *Curr Hypertens Rep*. 2011;13:214–220.
11. **Nishimura M, Uzu T, Fujii T, et al.** Cardiovascular complications in patients with primary aldosteronism. *Am J Kidney Dis*. 1999;33:261–266.
12. **Funder JW, Carey RM, Fardella C, et al.** Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2008;93:3266–3281.
13. **Young WF.** Primary aldosteronism: renaissance of a syndrome. *Clin Endocrinol (Oxf)*. 2007;66:607–618.
14. **Mulatero P, Milan A, Fallo F, et al.** Comparison of confirmatory tests for the diagnosis of primary aldosteronism. *J Clin Endocrinol Metab*. 2006;9:2618–2623.
15. **Stowasser M, Gordon RD, Gunasekera TG, et al.** High rate of detection of primary aldosteronism, including surgically treatable forms, after 'non-selective' screening of hypertensive patients. *J Hypertens*. 2003;21:2149–2157.
16. **Gouli A, Kaltsas G, Tzonou A, et al.** High prevalence of autonomous aldosterone secretion among patients with essential hypertension. *Eur J Clin Invest*. 2011;41:1227–1236.

17. **Crabbe J, Reddy WJ, Ross EJ, Thorn GW.** The stimulation of aldosterone secretion by adrenocorticotropic hormone (ACTH). *J Clin Endocrinol Metab*. 1959;19:1185–1191.
18. **Tucci JR, Espiner EA, Jagger PI, Pauk GL, Lauler DP.** ACTH stimulation of aldosterone secretion in normal subjects and in patients with chronic adrenocortical insufficiency. *J Clin Endocrinol Metab*. 1967;27:568–575.
19. **Hattangady NG, Olala LO, Bollag WB, Rainey WE.** Acute and chronic regulation of aldosterone production. *Mol Cell Endocrinol*. 2012;350:151–162.
20. **Pappa T, Papanastasiou L, Kaltsas G, et al.** Pattern of adrenal hormonal secretion in patients with adrenal adenomas: the relevance of aldosterone in arterial hypertension. *J Clin Endocrinol Metab*. 2012;97:E537–E545.
21. **Piaditis GP, Kaltsas GA, Androulakis II, et al.** High prevalence of autonomous cortisol and aldosterone secretion from adrenal adenomas. *Clin Endocrinol (Oxf)*. 2009;71:772–778.
22. **Vasan RS, Evans JC, Larson MG, et al.** Serum aldosterone and the incidence of hypertension in nonhypertensive persons. *N Engl J Med*. 2004;351:33–41.
23. **Ito Y, Takeda R, Karashima S, Yamamoto Y, Yoneda T, Takeda Y.** Prevalence of primary aldosteronism among prehypertensive and stage 1 hypertensive subjects. *Hypertens Res*. 2011;34:98–102.
24. **Bilezikian JP, Silverberg SJ.** Normocalcemic primary hyperparathyroidism. *Arq Bras Endocrinol Metab*. 2010;54:106–109.
25. **Marques TF, Vasconcelos R, Diniz E, Rego D, Griz L, Bandeira F.** Normocalcemic primary hyperparathyroidism in clinical practice: an indolent condition or a silent threat? *Arq Bras Endocrinol Metab*. 2011;55:314–317.
26. **Carneiro-Pla D, Solorzano C.** A summary of the new phenomenon of normocalcemic hyperparathyroidism and appropriate management. *Curr Opin Oncol*. 2012;24:42–45.
27. **Brooks RV, Felix-Davies D, Lee MR, Robertson PW.** Hyperaldosteronism from adrenal carcinoma. *Br Med J*. 1972;1:220–221.
28. **Medeau V, Moreau F, Trinquart L, et al.** Clinical and biochemical characteristics of normotensive patients with primary aldosteronism: a comparison with hypertensive cases. *Clin Endocrinol (Oxf)*. 2008;69:20–28.
29. **Mulatero P, Veglio F, Pilon C, et al.** Diagnosis of glucocorticoid-remediable aldosteronism in primary aldosteronism: aldosterone response to dexamethasone and long polymerase chain reaction for chimeric gene. *J Clin Endocrinol Metab*. 1998;83:2573–2575.
30. **McManus RJ, Caulfield M, Williams B.** NICE hypertension guideline 2011: evidence based evolution. *BMJ*. 2012;344:e181.
31. **Briet M, Schiffrin EL.** Aldosterone: effects on the kidney and cardiovascular system. *Nat Rev Nephrol*. 2010;6:261–273.
32. **Schlaich MP, Schobel HP, Hilgers K, Schmieder RE.** Impact of aldosterone on left ventricular structure and function in young normotensive and mildly hypertensive subjects. *Am J Cardiol*. 2000;85:1199–1206.