Body Mass Index Predicts Plasma Aldosterone Concentrations in Overweight-Obese Primary Hypertensive Patients

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Context: Body mass index (BMI) shows a direct correlation with plasma aldosterone concentration (PAC) and urinary aldosterone excretion in normotensive individuals; whether the same applies to hypertensive patients is unknown.

Objective: Our objective was to determine if BMI predicts PAC and the PAC/plasma renin activity ratio [aldosterone renin ratio (ARR)] in hypertensive patients, and if this affects the identification of primary aldosteronism (PA).

Design: This was a prospective evaluation of consecutive hypertensive patients referred nationwide to specialized hypertension centers.

Main Outcome Measures: Sitting PAC, plasma renin activity, and the ARR, baseline and after 50 mg captopril orally with concomitant assessment of parameters, including BMI and daily sodium intake, were calculated.

Results: Complete biochemical data and a definite diagnosis were obtained in 1125 consecutive patients. Of them 999 had primary (essential) hypertension (PH) and 126 (11.2%) PA caused by an aldosterone-producing adenoma in 54 (4.8%). BMI independently predicted PAC ($\beta = 0.153$; $P < 0.0001$) in PH, particularly in the overweight-obese, but not in the PA group. Covariance analysis and formal comparison of the raw, and the BMI-, sex-, and sodium intake-adjusted ARR with receiver operator characteristic curves, showed no significant improvement for the discrimination of aldosterone-producing adenoma from PH patients with covariate-adjusted ARR.

Conclusions: BMI correlated with PAC independent of age, sex, and sodium intake in PH, but not in PA patients. This association of BMI is particularly evident in overweight-obese PH patients, and suggests a pathophysiological link between visceral adiposity and aldosterone secretion. However, it does not impact on the diagnostic accuracy of the ARR for discriminating PA from PH patients. **(*J Clin Endocrinol Metab* 93: 2566–2571, 2008)**

The body mass index (BMI) is reported to be directly related to both plasma aldosterone concentration (PAC) and urinary aldosterone excretion in normotensive women and in healthy normotensive subjects on a high-sodium intake (1, 2). This finding suggests that adipose tissue may be involved in the regulation of aldosterone secretion and/or that aldosterone can

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Abbreviations: APA, Aldosterone-producing adenoma; ARR, aldosterone renin ratio; AUC, area under the curve; BMI, body mass index; BP, blood pressure; CAPT, captopril; CCB, calcium channel blocker; CI, confidence interval; HT, hypertension; IHA, idiopathic hyperaldosteronism; Ln PRA, natural logarithm of plasma renin activity; Na^+_UV, sodium urinary excretion; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PAPY, *Pri*mary *A*ldosteronism *P*revalence in h*Y*pertension; PH, primary hypertension; PRA, plasma renin activity; ROC, receiver operator characteristic.

affect adipogenesis. However, whether this correlation exists in hypertensive patients remains unknown.

Primary aldosteronism (PA) is the most common cause of secondary arterial hypertension (HT) (3). Screening for this curable and often masked form of HT is based on the ratio of PAC to the plasma renin activity (PRA) or active renin (ARR) (4–6). Increased ARR has been previously described in obese hypertensive women (7); if BMI affects PAC, then this may be relevant for interpretation of the ARR in clinical practice. Refinement of the methodology screening for PA is important for early recognition of this condition characterized by a higher prevalence of cardiovascular complications and events than age-, sex-, and BP-matched primary (essential) hypertension (PH) patients (8–10).

In the *P*rimary *A*ldosteronism *P*revalence in h*Y*pertension (PAPY) Study (3), a large multicenter prospective study of newly diagnosed hypertensive patients referred to specialized HT centers, the PAC, PRA, and ARR were measured under different conditions, along with daily Na^+ intake, in the context of a comprehensive collection of anthropometric data. This provided a clear distinction between PA and PH, thus giving the opportunity to investigate whether BMI is correlated with PAC, PRA, and/or the ARR in hypertensive patients, and whether this might affect discrimination between PA and PH patients. This study reports on our findings to these questions.

Subjects and Methods

The PAPY Study protocol followed both the Statement for reporting Studies of Diagnostic Accuracy recommendations (11) and the requirements of the Declaration of Helsinki, as previously detailed (3). Study design and the primary results have been described elsewhere (3, 12, 13). Briefly, consecutive newly diagnosed hypertensive patients referred to specialized HT centers nationwide were enrolled after informed consent was obtained (3). The patient's refusal to participate in the study or a prior diagnosis of any form of secondary HT was the criterion for exclusion.

In all patients, 24-h urinary Na^+ excretion, PAC, and PRA were determined at baseline and after 50 mg oral captopril (CAPT), with patients kept in the sitting position (3). Patients were carefully prepared from the pharmacological standpoint: only treatment with a long-acting calcium channel blocker (CCB) and/or doxazosin was allowed if necessary to minimize the risks of uncontrolled HT.

Methods for the measurement of the biochemical variables and glomerular filtration rate, normal ranges, and intraassay and interassay coefficients of variation have been previously reported (3).

Diagnostic criteria

In PA an unambiguous diagnosis is feasible only for aldosterone-producing adenoma (APA) (14) using tight diagnostic criteria. The latter comprise: 1) biochemical evidence of PA as defined (3); 2) lateralization of aldosterone secretion by adrenal vein sampling; 3) evidence of adenoma at pathology; and 4) demonstration of normokalemia and cure, or improvement, of arterial HT at follow-up after adrenalectomy (3). PA patients without conclusive evidence for a lateralized aldosterone excess were not adrenalectomized and therefore were presumed to have idiopathic hyperaldosteronism (IHA).

Given these considerations our analysis of the potential effect of BMI on the diagnostic accuracy of the ARR was focused on using the diagnosis of APA as the gold standard, with data on IHA reported for completeness with the caveat that this is a less clear-cut diagnosis and that a minority of undiagnosed APA patients might have been included in this group.

For subgroup analysis, patients were defined as lean and overweight-obese by a cutoff for BMI of 25 kg/m^2. However, recognizing that some patients with a BMI exceeding this value might have increased muscle rather than visceral fat mass, an analysis by quartile of BMI was also performed.

Statistical analysis

Log transformation of skewed quantitative variables (PRA, PAC, and plasma cortisol concentration) was performed to achieve a normal distribution. One-way ANOVA followed by Bonferroni's *post hoc* test were used to compare quantitative variables between groups. The distribution of categorical variables was investigated by χ^2 analysis; correlation was assessed by Pearson's coefficient or nonparametric Spearman test.

A regression analysis (backward, Wald) was used to identify variables independently associated with PAC or the ARR, with an inclusion and exclusion level for individual variables of 0.05 and 0.10, respectively. Colinearity testing was used to avoid including interdependent variables in the model.

Analysis of covariance was used to investigate the effect of BMI and other significant covariates on PAC and the ARR in the different diagnosis groups, and to calculate covariate-adjusted ARR values (15). To evaluate the accuracy of raw and covariate-adjusted ARRs, we compared the receiver operator characteristic (ROC) curves with MedCalc (MedCalc version 9.4.2.0; MedCalc Software, Mariakerke, Belgium); SPSS 15.0 for Windows (SPSS Italy Inc., Bologna, Italy) was used for all other analyses. Statistical significance was defined as $P < 0.05$.

Results

Baseline characteristics

The baseline features of the patients divided by diagnosis are shown in Table 1. Briefly, there were no differences in sex across groups. The APA patients were older, had higher systolic blood pressure (BP), PAC, and ARR, and lower PRA and serum potassium levels than the PH patients. The patients with presumed IHA did not differ from the APA patients for PAC, PRA, ARR, and plasma cortisol levels, though their serum potassium level was higher than in APA patients (3). At the screening, 41% of the patients were untreated, 35% were on a CCB or doxazosin, and 24% on both agents. A combination of CCB and doxazosin was required more often (42%) in the APA patients than in the other groups to achieve BP control.

Association of BMI with PAC, PRA, and ARR in HT

Correlation analysis of the whole cohort showed that PAC was positively correlated with BMI, mean BP, and the ARR, and inversely related to sodium intake assessed by 24-h sodium urinary excretion ($Na^+{}_uV$) (Table 2).

Regression analysis of BMI, age, sex, natural logarithm of plasma renin activity (Ln PRA), mean BP, and $Na^+{}_uV$ showed that BMI was correlated with PAC, along with mean BP and $Na^+{}_uV$, whereas the remaining variables did not; a model with BMI, mean BP, and $Na^+{}_uV$ explained 9.6% of PAC variance (adjusted $R^2 = 0.096$; $F = 25.23$; $P < 0.001$). In contrast, BMI showed no significant correlation with PRA or ARR. The latter was directly related with age ($r = 0.162$; $P < 0.0001$) and mean

TABLE 1. Baseline anthropometric and biochemical characteristics of patients with PH, APA, and IHA

Variable	Group					
	PH	PH *vs.* APA (*P* value)	APA	APA *vs.* IHA (*P* value)	IHA	IHA *vs.* PH (*P* value)
Age (yr)	50.5 ± 3.4	NS	55.4 ± 2.4	NS	54.0 ± 5.3	NS
% Men/women	56/44	NS	56/44	NS	62/38	NS
BMI (kg × m^{-2})	27.4 ± 4.7	NS	27.4 ± 4.1	NS	26.9 ± 4.1	NS
Systolic BP (mm Hg)	147 ± 18	0.002	158 ± 23	NS	153 ± 16	0.066
Diastolic BP (mm Hg)	97 ± 11	NS	97 ± 10	NS	100 ± 10	0.035
Serum K^+ (mEq × $liter^{-1}$)	4.1 ± 0.4	<0.0001	3.4 ± 0.5	<0.0001	3.9 ± 0.4	0.028
$Na^+{}_uV$ (mEq × d^{-1})	145 (135–155)	NS	131(110–153)	NS	136(122–151)	NS
GFR (ml × min^{-1})	90 ± 20	NS	84 ± 16	NS	90 ± 20	NS
PRA (ng × ml^{-1} × h^{-1})	1.31 (1.00–1.63)	0.002	0.64 (0.31–0.98)	NS	0.52(0.37–0.68)	<0.001
Plasma aldosterone (ng × dl^{-1})	17.9 (16.3–19.6)	<0.0001	32.1 (26.0–38.2)	NS	25.6 (22.4–28.8)	<0.0001
ARR (ng × dl^{-1})/(ng × ml^{-1} × h^{-1})$^{-1}$	13.7 (12.2–16.3)	<0.0001	50.2 (26.5–123.2)	NS	49.2 (32.9–77.8)	<0.0001
Plasma cortisol (nmol × $liter^{-1}$)	146 (137–154)	NS	131 (120–143)	NS	143 (130–156)	NS
Tumor size (mm)		NS	16 ± 1	NS		NS

Data are mean ± SEM, except for variables not normally distributed for which the median and 95% CI are shown. ARR, Plasma aldosterone (ng × dl^{-1})/PRA (ng × ml^{-1} × h^{-1}) ratio; GFR, glomerular filtration rate; NS, nonsignificant; serum K^+, potassium level.

BP (r = 0.189; $P < 0.001$), and inversely related with $Na^+{}_uV$ (r = −0.091; $P = 0.003$). Practically identical findings were obtained when the post-CAPT PAC data were examined.

When the cohort was split by BMI values into lean (n = 404) and overweight-obese (n = 721), the direct association of BMI with PAC remained significant only in the latter (r = 0.100; $P = 0.004$). Moreover, when the 999 PH patients were similarly examined, the direct association of BMI with PAC was not seen in the lean (n = 363) but became highly significant in the overweight-obese (n = 636; r = 0.182; $P < 0.0001$) patients (Table 3). Moreover, because some patients with a BMI slightly higher than 25 might have increased muscle mass, rather than visceral adiposity, we analyzed PAC by quartiles of BMI. This analysis showed that patients in the highest BMI quartile had significantly higher aldosterone than patients in the lowest quartile (Fig. 1).

We could find no effect of BMI on PAC, PRA, or ARR in the whole group of PA patients (n = 126), or in the APA (n = 54) or IHA (n = 72) group, either baseline or after CAPT. Hence, the direct correlation of PAC with BMI found in the whole cohort largely reflected the PH patients (Table 4).

Of interest, in PH patients a direct correlation existed also between PAC and mean BP (Table 4), suggesting that aldosterone plays a role in increasing or maintaining high BP in the overweight-obese PH patients.

BMI and discrimination of APA from PH

To investigate if BMI had any impact on the discrimination of PA from PH, we used analysis of covariance, (15) entering in the model PAC, age, sex, $Na^+{}_uV$, mean BP, and the diagnosis of APA or PH. We also compared the ROC curve of unadjusted and covariate-adjusted ARR using the diagnosis of APA and PH as category status. Both analyses showed no effect of BMI on either the ARR or its accuracy for distinguishing APA from PH. Formal comparison of the ARR accuracy, estimated by the area under the ROC curve (AUC), showed that the BMI-, mean BP, and $Na^+{}_uV$-adjusted ARR [AUC = 0.886, 95% confidence interval (CI) 0.863–0.906] was slightly better than the raw ARR (AUC = 0.869, 95% CI 0.845–0.891). However, the difference between curves of AUC (0.168 ± 0.027) was not significant ($P = 0.529$) (Fig. 2).

This analysis consistently showed no significant improvement in the accuracy of the ARR for the diagnosis of APA by adjusting the ARR value for its predictors, including BMI. Essentially identical conclusions were reached when all the PA patients (including IHA) were considered, when the post-CAPT ARR was examined, and when the ARR was compared after splitting our patients into lean and overweight-obese, or divided by sex.

TABLE 2. Pearson correlation coefficient between PAC, the ARR, and other variables in the all group

	PAC	ARR	Ln PRA	Age	BMI	$Na^+{}_uV$	Mean BP
PAC	1	0.676[a]	−0.033	0.048	0.087[a]	−0.184[a]	0.224[a]
ARR		1	−0.492[a]	0.174[a]	0.030	−0.092[a]	0.158[a]
Ln PRA			1	−0.215[a]	0.013	0.000	−0.053
Age				1	0.147[a]	−0.040	0.063[b]
BMI					1	0.140[a]	0.074[b]
$Na^+{}_uV$						1	−0.028
Mean BP							1

[a] $P < 0.01$, two-tail.

[b] $P < 0.05$, two-tail.

Discussion

Its large size, the comprehensive collection of anthropometric and hormonal data at enrollment, and the availability of a definitive diagnosis concerning the presence of an APA made the PAPY Study powered to

TABLE 3. Correlation of PAC with BMI in the patients divided according to etiology of arterial HT and into normal weight and overweight-obese

	Pearson's correlation coefficient	Significance
Lean hypertensive patients		
PH (n = 363)	−0.064	NS
APA (n = 17)	−0.117	NS
IHA (n = 14)	−0.270	NS
Overweight-obese hypertensive patients		
PH (n = 636)	0.182	$P < 0.0001$[a]
APA (n = 37)	−0.179	NS
IHA (n = 58)	−0.083	NS

NS, Not significant.

[a] Two-tail.

provide new insight into the determinants of PAC. These insights may be of interest from both the pathophysiological and clinical standpoint. We have thus examined the relationship between BMI and PAC, PRA, and the ARR in hypertensives with PH and with APA.

Relationship between BMI, PAC, and ARR in PH

The first novel finding of this study was that BMI is positively related with PAC, independent of age, BP, gender, and sodium intake, which have a well-established impact on the renin-angiotensin-aldosterone system. These results extend findings in normotensive individuals on a high-sodium intake (1, 2) to the hypertensives. The direct association of BMI with PAC in the overweight-obese subgroup (Table 3) strongly suggests a pathophysiological link between fat deposition and the synthesis and aldosterone secretion. This suggestion is supported also by several lines of evidence (1, 16–18).

The direct association between BMI and PAC in normotensive subjects (2) and in primary hypertensive patients, particularly in those who are overweight-obese (Fig. 1), suggests a role for adipose tissue in regulating aldosterone secretion (19), and/or an effect of aldosterone to increase BMI. Adipogenic factors that stimulate aldosterone secretion *in vitro* have been described in humans (18–20). The novel adipokine complement-C1q TNF-related protein 1 (CTRP1) potently stimulates aldosterone production and mediates, at least in part, the secretagogue effect of angiotensin II on aldosterone in studies on a human adrenocortical carcinoma cell line (H295R) (21). Moreover, complement-C1q TNF-related protein 1 is elevated in hypertensive patients; albeit only lean hypertensives have been studied to date. This protein shares homology with the C1q globular domain of adiponectin, another adipocyte-derived cytokine that acts as an insulin sensitizer. Our finding of type 1 and 2 adiponectin receptor subtypes in the normal human adrenocortical zona glomerulosa and in APA tissue (22) raises the possibility that adipocyte-derived proteins play an important modulatory role in the regulation of aldosterone secretion.

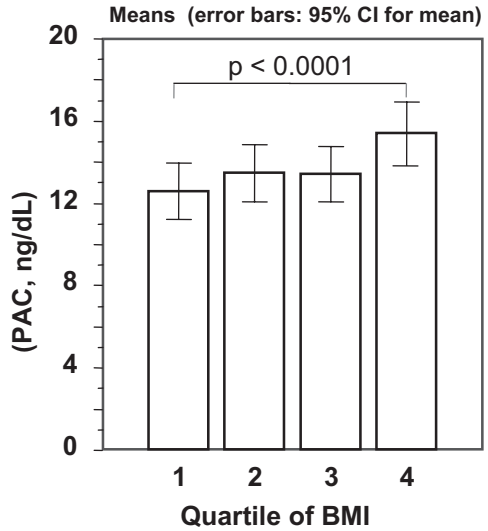

FIG. 1. The *bar graph* shows a stepwise increase of PAC with increasing quartiles of BMI. The *P* value indicates that the difference of PAC between the lowest and the highest quartile was highly significant.

The alternative hypothesis that aldosterone plays a role in determining fat deposition, and therefore BMI, cannot be dismissed in that it was recently shown that aldosterone acts on the mineralocorticoid receptor to induce peroxisome proliferator activated receptor γ mRNA expression, thus promoting white adipose cell differentiation (23). This would support a pathophysiological role of the hormone in adipogenesis, and thereby in the development of the metabolic syndrome and obesity. Of note, PA has been associated with an increased prevalence of the metabolic syndrome, which includes abdominal adiposity (24, 25). In contrast, our two large groups of patients with PA due to APA or IHA showed no higher BMI than PH patients (Table 1).

Whatever the mechanisms, in PH patients the finding of a positive correlation between BMI and PAC, and also between the latter and mean BP (Table 4) suggests that blockade of the mineralocorticoid receptor should be a rational option for the increasing number of PH patients who are overweight-obese.

Effect of BMI on PAC and the ARR in PA patients

From the practical standpoint, the association of BMI with PAC in hypertensive patients could have implications for the discrimination of PA from PH patients. We found neither a significant impact of BMI on the ARR in PH patients nor any effect of BMI on PAC or ARR in PA patients. The latter was not unexpected because in PA the excess aldosterone secretion is held to be largely autonomous. By analysis of covariance and by comparing the accuracy of raw, and BMI-, mean BP-, and $Na^+{}_uV$-adjusted ARR, we found no improvement of the ARR performance for distinguishing PA from PH patients. Thus, adjustment of the ARR for its significant predictors does not translate into a more accurate identification of PA patients (Fig. 2).

Limitations of the study

The number of patients with APA and IHA was much smaller than that with PH; therefore, we cannot totally exclude the possibility that the lack of a significant association of BMI with PAC

TABLE 4. Pearson correlation coefficient in the different HT subgroups (n = 1125)

	PAC	ARR	Ln PRA	Age	BMI	Na^+_uV	Mean BP
Primary HT (n = 999)							
PAC	1	0.370[a]	0.156[a]	−0.066[b]	0.134[a]	−0.182[a]	0.214[a]
ARR		1	−0.639[a]	0.160[a]	0.024	−0.065	0.117[a]
Ln PRA			1	−0.207[a]	0.046	−0.023	0.004
Age				1	0.149[a]	−0.043	0.078[b]
BMI					1	0.144[a]	0.087[a]
Na^+_uV						1	−0.033
Mean BP							1
PA due to an APA (n = 54)							
PAC	1	0.857[a]	0.022	0.350[b]	−0.033	−0.077	0.053
ARR		1	−0.341[b]	0.320[b]	−0.030	−0.182	0.043
Ln PRA			1	−0.165	−0.033	0.143	0.122
Age				1	0.260	0.016	−0.221
BMI					1	0.148	−0.103
Na^+_uV						1	0.026
Mean BP							1
PA due to IHA (n = 72)							
PAC	1	0.506[a]	0.226[b]	0.046	−0.078	−0.132	0.287[a]
ARR		1	−0.459[a]	0.114	0.096	0.078	0.351[a]
Ln PRA			1	−0.094	−0.130	−0.243[b]	−0.164
Age				1	0.016	0.098	−0.093
BMI					1	0.141	−0.001
Na^+_uV						1	0.190
Mean BP							1

[a] $P < 0.01$, two-tail.

[b] $P < 0.05$, two-tail.

in these patients could be due to an insufficient statistical power. Moreover, there are limitations of a prespecified ARR of 40 for screening of PA, of the unavailability of adrenal vein sampling, and of the use of NP59 scintigraphy, which is an outdated method of showing lateralization, at some centers of the PAPY Study as already discussed (3, 13). Moreover, we could not determine if BMI and PAC were associated with insulin resistance because no measurement of the latter was available in the PAPY Study.

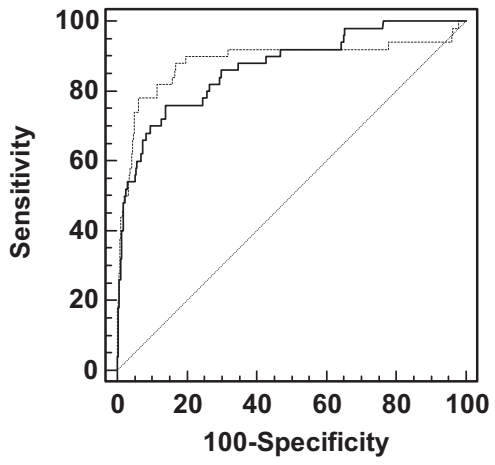

FIG. 2. The *graph* shows the ROC curves of raw (*dashed line*) and covariate-adjusted (*solid line*) ARR for the discrimination of patients with an APA from primary hypertensive patients. The AUC, which estimates the accuracy, of each test, was significantly ($P < 0.001$) higher than the AUC under the identity line (0.500) for both curves (for the BMI-, mean BP, and Na^+_uV-adjusted ARR = 0.886, 95% CI 0.863–0.906; for the raw ARR = 0.869, 95% CI 0.845–0.891). However, the difference between curves of AUC (0.168 ± 0.027) was not significant ($P = 0.529$).

Conclusions

This study allows the following three conclusions. First, in overweight-obese primary hypertensive patients, there is a significant independent positive correlation between BMI and PAC, supporting the hypothesis of a pathophysiological link between adipose tissue and the adrenal zona glomerulosa. Second, this correlation was not detectable in patients with arterial HT caused by PA, due to APA or IHA, and was not seen for ARR. Finally, adjustment for BMI does not improve the accuracy of the ARR for discrimination of PA from primary (essential) hypertensive patients.

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