Body Mass Index and Angiotensin-Dependent Control of the Renal Circulation in Healthy Humans


Abstract—Obesity is increasingly recognized as a risk factor for renal disease, but the mechanism is unclear. Renal plasma flow response to captopril, as an index of renin-angiotensin system activity, was measured by para-aminohippurate clearance technique in 100 healthy, normotensive subjects in balance on a high-salt diet. Of the 100 subjects, body mass index exceeded 25 in 56 and exceeded 30 in 22. The average vasodilator response to captopril was 27±7 mL/min per 1.73 m² (P<0.0001). After adjustment for other predictors of the renal plasma flow response to captopril using a multivariate linear regression model, there was a highly significant relationship between age- and plasma renin activity–adjusted body mass index and the renal plasma flow response to captopril; however, a quadratic model provided a substantially better fit (r=0.55; P<0.0001; P=0.03 versus linear correlation). The strong association between increasing body mass index and angiotensin-dependent control of the renal circulation suggests that this may be a mechanism by which obesity contributes to renal disease. Weight loss should be considered in the overweight or obese patient for renal protection. (Hypertension. 2005;46:1316-1320.)

Key Words: obesity ■ hemodynamics ■ body mass index ■ renin-angiotensin system ■ angiotensin II ■ kidney

During the past 20 years, there has been a dramatic increase in obesity in the United States.¹ Currently, a third of American adults are obese (body mass index [BMI] ≥30)¹ and each year, an estimated 300 000 US adults die prematurely of obesity-related causes.²

Obesity is an independent risk factor for the development of kidney disease.³–⁶ There is little doubt that excess weight gain is a major cause of hypertension and type 2 diabetes, which, together, account for >70% of end-stage renal disease in the United States.⁷ Moreover, evidence also suggests that even in nondiabetic obese patients, there is some degree of renal dysfunction that can lead to more serious injury to the kidneys because metabolic and hemodynamic disturbances worsen with prolonged obesity.⁶,⁷,⁸

The mechanism by which obesity predisposes to kidney damage is unclear, but animal studies suggest an important role for the renin-angiotensin system (RAS).⁹–¹¹ Because animal studies typically involve rapid weight gain from overfeeding, and obesity in humans represents a much more gradual weight gain over years, it has not been clear to what extent these observations in animal models apply to humans. Two observations from our laboratory brought this potential relationship to our attention. Hopkins et al observed that obesity was associated with a blunted renovascular response to angiotensin II (Ang II) infusion, a finding consistent with increased intrarenal Ang II production.¹² Price et al later reported that BMI accounted for ≈50% of the renal plasma flow (RPF) response to irbesartan in type 2 diabetic subjects.¹³ Because activation of the RAS is associated with progression of kidney disease,¹⁴ these observations raised the question of whether obesity is associated with activation of the intrarenal RAS. We hypothesized that a positive relationship existed between BMI and activation of the intrarenal RAS. We thus examined renal hemodynamic function at baseline and in response to the angiotensin-converting enzyme (ACE) inhibitor captopril in 100 nondiabetic, normotensive subjects.

Methods

Subjects

One hundred healthy, normotensive (defined as baseline blood pressure <140/90 and not on antihypertensive medications) subjects were enrolled in the study. Each subject had a normal blood pressure and fasting blood sugar. Subjects completed an initial medical history and underwent a physical examination, ECG, and laboratory screening. All subjects gave written informed consent. The study protocol was approved by the Brigham and Women’s Hospital institutional review board and conducted in accordance with institutional guidelines.

Protocol

Subjects were instructed to consume >200 mmol sodium per day for 4 days before the study. A 24-hour urine collection was used to measure sodium, creatinine, and protein excretion. Subjects were studied in the supine position after an 8-hour fast. At 7 AM, an intravenous catheter was placed in each arm (1 for infusion and 1 for
blood sampling). Fasting plasma glucose concentration was measured at the start of the study in a random subset of subjects. Blood pressure was recorded every 15 minutes by an automatic recording device (Dinamap; Critikon). Each subject was given a loading dose of 8 mg/kg of para-aminohippurate (PAH), followed by a constant infusion at 12 mg/min for 90 minutes to establish baseline renal hemodynamic measurements, followed by a single oral dose of 25 mg of captopril. PAH clearance and plasma renin activity (PRA) were measured at baseline and up to 240 minutes after ingestion of captopril. A random subset of subjects returned on a separate day for a repeat study, when they received either 150 mg of irbesartan or 16 mg of candesartan instead of captopril. All agents were used at the top of the dose–renal response relationship.20,21

### Analytical Methods

Renal clearance studies were assessed with PAH (Clinalfa) as described previously.17,18 Serum PAH was measured by autoanalyzer. PRA was assayed by radioimmunoassay.18 Urinary albumin concentration was measured by immunonephelometry (Behring).

### Data Analysis

Controversy exists over the ideal method of indexing renal hemodynamics in the obese. Because large people have large kidneys, and small people have small kidneys, it has been conventional that measures of RPF and function be normalized on the basis of body size. Thus, common practice dictates that renal hemodynamic parameters be indexed to body surface area, yet, it has been suggested that normalizing to body surface area may be inappropriate in the obese and that height is a more suitable index.19 However, body surface area and height are correlated to BMI, which would introduce bias into the analysis. Others have only reported the “unadjusted” renal hemodynamics in the obese.20,21 We measured unadjusted RPF and subsequently also indexed these values according to body surface area and height. All analyses were repeated using all 3 methods of reporting renal hemodynamics.

The primary analysis tested associations between BMI and renal hemodynamics. Subject baseline and response to captopril measures were compared by nonparametric tests. A nonparametric test was used to test for trend across ordered groups. χ² tests were used to compare frequencies. Associations were analyzed by univariate regression analysis (Pearson) and Spearman correlation coefficients. In addition, multivariate linear regression analysis was applied to evaluate the relative contributions of covariates to the change in renal hemodynamics in response to captopril. The following variables were included: age, sex, BMI, smoking status, MAP, baseline PRA, fasting glucose, and baseline RPF. A stepwise backward selection was used. A partial F-test was used to compare linear models to quadratic models. Statistical analyses were performed using Stata (version 8.2; Stata Corp), with 2-tailed significance levels of 0.05.

### Results

#### Baseline Characteristics

Subject characteristics are presented in Table 1. All subjects had normal renal function. The obese group was older than the lean 

#### Renal Hemodynamic Responses to Captopril

The average vasodilator response to captopril was $27\pm7$ mL/min per 1.73 m² ($P<0.0001$). On univariate analysis, the relationship between BMI and the RPF response to captopril was modest ($r=0.18$; $P=0.07$); however, multivariate analysis showed BMI, age, and baseline PRA to be significant predictors of the RPF response to captopril. Linear correlation analysis showed a highly significant relationship between BMI and the RPF response to captopril indexed to body surface area after adjustment for age and baseline PRA ($P<0.0001$), but a quadratic equation provided a substantially better fit ($r=0.55$; $P<0.0001$; $P=0.03$ versus linear correlation; Figure 1). Gender, fasting glucose, MAP, baseline RPF, urinary sodium, plasma uric acid and smoking status were also not significant predictors of RPF response to ACE inhibition on multivariate regression analysis.

### Table 1. Population Baseline Characteristics (n=100)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BMI &lt;25 kg/m² (n=44)</th>
<th>BMI 25 to &lt;30 kg/m² (n=34)</th>
<th>BMI ≥30 kg/m² (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>33±2 37±3</td>
<td>37±2 48±3§</td>
<td>33±2 48±3§</td>
</tr>
<tr>
<td>Female (%)</td>
<td>52 77</td>
<td>77</td>
<td>77</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>67±1 76±2‡</td>
<td>94±2‡</td>
<td>94±2‡</td>
</tr>
<tr>
<td>Height (cm)*</td>
<td>172±1 168±2‡</td>
<td>162±4‡</td>
<td>162±4‡</td>
</tr>
<tr>
<td>MAP (mm Hg)†</td>
<td>22±0.3 27±0.3‡</td>
<td>35±0.7‡§</td>
<td>35±0.7‡§</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>2 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)*</td>
<td>93±2 81±3</td>
<td>78±5</td>
<td>78±5</td>
</tr>
<tr>
<td>PRA (ng Ang I/mL/hour)*</td>
<td>0.4±0.1 0.4±0.07</td>
<td>0.4±0.08</td>
<td>0.4±0.08</td>
</tr>
<tr>
<td>Urine Na (mmol/24 hours)*</td>
<td>234±20 272±23</td>
<td>273±20</td>
<td>273±20</td>
</tr>
<tr>
<td>Urine protein (mg/24 hours)*</td>
<td>5±0.8 6±0.4</td>
<td>5±1.5</td>
<td>5±1.5</td>
</tr>
<tr>
<td>Plasma uric acid (mg/dL)*</td>
<td>3.7±0.3 4.9±0.7</td>
<td>4.6±0.9</td>
<td>4.6±0.9</td>
</tr>
<tr>
<td>RPF (mL/min/1.73 m²)† (indexed to body surface area)</td>
<td>597±14 565±14</td>
<td>488±17‡§</td>
<td>488±17‡§</td>
</tr>
<tr>
<td>RPF (mL/min/m²)† (indexed to height)</td>
<td>347±12 349±15</td>
<td>340±13</td>
<td>340±13</td>
</tr>
<tr>
<td>RPF (mL/min)† (nonindexed)</td>
<td>615±16 605±18</td>
<td>557±24‡$</td>
<td>557±24‡$</td>
</tr>
</tbody>
</table>

*Mean±SE; †mean of readings at t=−10 minutes, −5 minutes, and 0; $P=0.05$ vs BMI <25 kg/m²; §$P<0.05$ vs BMI 25–30 kg/m².

Figure 1. Age- and baseline PRA-adjusted RPF response to captopril vs BMI.
TABLE 2. Response to Captopril

<table>
<thead>
<tr>
<th>Measurement</th>
<th>BMI &lt;25 kg/m²</th>
<th>BMI 25 to &lt;30 kg/m²</th>
<th>BMI ≥30 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)†</td>
<td>76±2§</td>
<td>84±3</td>
<td>80±2</td>
</tr>
<tr>
<td>ΔMAP (mm Hg)†</td>
<td>-5±2</td>
<td>-6±3</td>
<td>-2±2</td>
</tr>
<tr>
<td>PRA (ng Ang I/mL/hour)†</td>
<td>1.2±0.5§</td>
<td>2.2±1.1§</td>
<td>1.6±0.7§</td>
</tr>
<tr>
<td>ΔPRA (ng Ang I/mL/hour)†</td>
<td>0.7±0.3</td>
<td>1.8±1.0</td>
<td>1.3±0.6</td>
</tr>
<tr>
<td>RPF (mL/min/1.73 m²)‡</td>
<td>609±18</td>
<td>610±25§</td>
<td>534±25§</td>
</tr>
<tr>
<td>ΔRPF (mL/min/1.73 m²)‡</td>
<td>16±8</td>
<td>37±15</td>
<td>46±12</td>
</tr>
<tr>
<td>RPF (mL/min/m)‡</td>
<td>364±11</td>
<td>388±16§</td>
<td>377±19§</td>
</tr>
<tr>
<td>ΔRPF (mL/min/m)‡</td>
<td>10±5</td>
<td>23±10</td>
<td>33±9</td>
</tr>
<tr>
<td>RPF (mL/min)‡</td>
<td>628±19</td>
<td>650±28§</td>
<td>620±35§</td>
</tr>
<tr>
<td>ΔRPF (mL/min)‡</td>
<td>17±9</td>
<td>40±16</td>
<td>55±15</td>
</tr>
</tbody>
</table>

*Mean±SE; †mean of 2 readings at nadir of response to captopril; ‡mean of 2 readings at peak response to captopril; §P<0.05 vs baseline.

As stated previously, controversy exists over the optimal way of presenting renal hemodynamics in the obese. Accordingly, we presented RPF as indexed to body surface area, indexed to height, and nonindexed (Tables 1 and 2). All analyses of RPF response to captopril were repeated using RPF indexed to height and nonindexed RPF, with similar analyses of RPF response to captopril were repeated using RPF indexed to body surface area, nonindexed RPF, and nonindexed RPF. Thus, the influence of obesity on the renal hemodynamic response to blocking the RAS was evident, whether the data were normalized to body surface area, normalized only to height, or were not normalized.

Baseline PRA predicted 14% of the RPF response to ACE inhibition (r=0.38; P=0.0003). Change in PRA and change in RPF in response to captopril were similarly significantly correlated (r=0.46; P<0.0001). There was no association between the change in PRA in response to captopril and BMI (P=0.5).

Fasting glucose levels were not associated with the change in RPF in response to captopril by either univariate (P=0.9) or multivariate analysis (P=0.9). Fasting glucose levels were not different according to BMI classification (P=0.8).

MAP fell significantly in response to captopril (-5±1.3 mm Hg; P=0.003), but this decrease was not correlated with renal response to captopril (P=0.3) or BMI (P=0.7) by univariate analysis.

Responses to captopril, stratified by BMI class, are shown in Table 2. When analyzed by BMI group, only the lean subjects had a significant drop in MAP in response to ACE inhibition (P=0.01 versus baseline overweight; P=0.07 versus baseline obese; P=0.5 versus baseline). All groups displayed an increase in PRA (lean P=0.0006 versus baseline; overweight P=0.0003 versus baseline; obese P=0.003 versus baseline).

As anticipated, the lean group had a nonsignificant increase in RPF in response to captopril (P=0.09 [indexed to body surface area]; P=0.08 [indexed to height]; P=0.08 [nonindexed]; all versus baseline). Although the overweight group increased RPF in response to ACE inhibition (P=0.01 [indexed to body surface area]; P=0.01 [indexed to height]; P=0.01 [nonindexed]; all versus baseline), the largest increases were seen in the obese group (P=0.001 [indexed to body surface area]; P=0.001 [indexed to height]; P=0.001 [nonindexed]; all versus baseline), with a significant trend toward the obese having the greatest increases (P=0.07 [indexed to body surface area]; P=0.04 [indexed to height]; P=0.04 [nonindexed]).

We compared the RPF response to ACE inhibition with the RPF response to angiotensin receptor blocker (ARB) in a subset of subjects (n=25) and found them to be highly correlated (r=0.73; P<0.0001; Figure 2).

Discussion

Our study examined the state of the RAS at baseline and the renal hemodynamic response to ACE inhibition and Ang II receptor blockade in healthy, normotensive subjects. A significant relationship was observed between BMI and the renovasodilator responsiveness to acute ACE inhibition. Concordance in the response to ACE inhibition and ARBs makes it extremely likely that the RPF response reflects reversal of an increase in Ang II–mediated renal vascular tone.

There are many factors associated with activation of the RAS. As an important relevant example, acute hyperglycemia results in an enhanced renal vasodilator response to interruption of the RAS with either ACE inhibition or Ang II receptor blockade in normal subjects. However, the fasting blood glucose values of the subjects in this study were well within the euglycemic range, and no relationship was observed between glycemic level and RPF response to captopril, even after adjustment for other factors. Black race is associated with a significantly more robust renovasodilatory response to captopril compared with whites, but on subgroup analysis, BMI remained a predictor of RPF response to captopril independent of race. Several experimental models of hypertension support an overactive RAS in the development and maintenance of hypertension, but all of our subjects were normotensive.

PRA showed a statistically significant but weak correlation with BMI, accounting for only 15% of the variation. Thus, it is likely that the quantitatively important changes in renin...
system activity actually occurred in the kidney and not systemically. Multiple lines of evidence in animal models suggest a link between obesity and RAS activation, at least within the kidney. Obese Zucker rats have an increased Ang II type 1 receptor number, increased responsiveness to Ang II in the proximal tubule,26 and have a more marked diuresis and natriuresis after treatment with candesartan or ramipril compared with their lean counterparts.27 Obesity is associated with a tissue-specific increase in ACE activity in the kidney in the mouse model.28 Benazepril and irbesartan in combination reduce renal damage in obese Zucker rats more than either agent alone, suggesting that maximizing RAS suppression affords greater renal protection.29 Dogs fed a high-fat diet exhibited significantly higher PRA values and abnormal structural changes in the kidney compared with controls, suggesting that changes deleterious to renal function occur even in the early stages of obesity.30

In obese human subjects, a blunted renovascular response to infused Ang II has been reported,12 consistent with increased intrarenal Ang II formation. A linear relationship between BMI and RPF response to irbesartan has been described in subjects with type 2 diabetes.13 However, the link between animal and human data must be viewed with caution because the mechanism by which obesity is associated with the RAS in animals may be significantly different from that found in humans, given that laboratory animals gain weight at a rate measured in weeks, whereas humans tend to increase BMI slowly over years.

The mechanism by which obesity is associated with a more activated RAS remains elusive and may be multifactorial. Adipocytes generate angiotensinogen (AGT), and a significantly positive relationship exists between plasma AGT levels and BMI.31 An association also exists between AGT gene polymorphisms and body fat distribution in men.12 The insulin resistance that accompanies obesity may also contribute to RAS activation. Obesity, particularly central obesity, is related to insulin resistance. Hepatic AGT production is influenced by plasma insulin, and spared from insulin resistance.32,33

Obesity is an important risk factor for renal disease.3,4,8,34–36 A significant increase of histologically proven renal disease in obese patients in the absence of diabetes has been demonstrated.4 Severe obesity is associated with an enhanced albumin excretion rate,37–39 although the renal abnormalities associated with severe obesity improve substantially after weight loss.40

Altered renal hemodynamics have been described in the obese40,41–44 and the overweight,45 although the reports are somewhat conflicting. Some of the discrepancies in the aforementioned studies may be attributable to differences in indexing and fat distribution. We have shown a higher renal blood flow in obese, normotensive subjects compared with lean subjects while on a low-sodium diet, but these differences were abolished with liberal sodium consumption; this study was performed with radioxenon transit, a method that provides a measure of blood flow per gram of tissue perfused and requires no further normalization.20

As obesity becomes an increasingly global epidemic, our finding that rising BMI is associated with a steadily increasing level of angiotensin-dependent control of the renal circulation has significant public health considerations. Whether or not the increased level of RAS activity observed in our study persists after weight loss is unclear. In the meantime, given the many health benefits already associated with weight loss, weight reduction should be advised in overweight and obese patients.

Perspectives
In our study, we report a dramatic renovascular vasodilatory response to captopril as BMI increases, particularly in the very obese. The quadratic relationship noted between RPF response to captopril and increasing BMI deserves attention. It is unclear whether this relationship represents a continuous association or, rather, a “threshold effect” in terms of activation of the intrarenal RAS once the BMI reaches 30 kg/m². The curvilinear association suggests that even a slight reduction in BMI may result in a significant decrease in the RAS activity at the level of the kidney. Given the strong association between RAS activation and nephropathy, our study may help explain a mechanism by which obesity predisposes an individual to renal disease.

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References
12. Hopkins PN, Lilton RP, Hollenberg NK, Jeunemaitre X, Hallouin MC, Skuppin J, Williams CS, Dhahy RG, Lalouel JM, Williams RR, Williams...
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Sofia B. Ahmed, Naomi D.L. Fisher, Radomir Stevanovic and Norman K. Hollenberg

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