Is There a Rationale for Angiotensin Blockade in the Management of Obesity Hypertension?

Arya M. Sharma

Abstract—Obesity, currently affecting >20% of the adult population in most Western countries, is a major risk factor for the development of hypertension. Hypertension in obese patients is, in the majority of instances, further complicated by the concomitant presence of dyslipidemia and insulin resistance. The latter is reflected by derangement of glucose homeostasis, ranging from hyperinsulinemia to frank type 2 diabetes. Hypertension in obese patients is also associated with an increased risk for left ventricular hypertrophy, endothelial dysfunction, renal hyperfiltration, microalbuminuria, and elevated markers of inflammation. Sodium retention, volume expansion, and increased cardiac output are common findings in obese individuals. These changes are largely attributable to increased activity of the sympathetic nervous system and insufficient suppression of the renin-angiotensin system. Recent data show increased expression of angiotensin II–forming enzymes in adipose tissue, and increased activity of the renin-angiotensin system has recently been implicated in the development of insulin resistance and type 2 diabetes. Accordingly, antihypertensive agents that block the renin-angiotensin system might be a beneficial strategy for treatment of obesity-related hypertension. Both angiotensin-converting enzyme inhibitors and angiotensin type-1 receptor blockers have been associated with favorable metabolic properties and end-organ protection in addition to their antihypertensive effects. Data from ongoing large trials will provide an indication of the protective and preventive effects of these treatment strategies while offering insights into the mechanisms linking obesity, hypertension, and other facets of the metabolic syndrome. (Hypertension. 2004;44:12-19.)

Key Words: obesity ■ hypertension, obesity ■ angiotensin ■ renin-angiotensin system ■ angiotensin-converting enzyme ■ diabetes mellitus

Abdominal obesity, characterized by the accumulation of visceral adipose tissue, is a major risk factor for the development of hypertension.1,2 Abdominal obesity is also the principal risk factor for insulin resistance and the development of type 2 diabetes.3 Hypertension in obese individuals is, therefore, commonly complicated by the concomitant presence of dyslipidemia, hyperinsulinemia, impaired glucose tolerance, and other facets of the metabolic syndrome.4 Furthermore, abdominal obesity is associated with a number of functional and morphological abnormalities including sodium retention, increased cardiac output, renal hyperfiltration, endothelial dysfunction, left ventricular hypertrophy, microalbuminuria and elevated markers of inflammation.5,6 It is, therefore, not surprising that obesity is an important predictor of overall cardiovascular morbidity and mortality.1,2 Sodium retention plays a central role in the development of obesity-related hypertension (Figure). Thus, obese individuals display a lower natriuretic response to a saline load than normal weight individuals.7,8 Although the mechanisms by which obesity alters renal function are not completely understood, results from both animal models and human studies suggest that 3 factors are of particular importance: (1) increased renal sympathetic activity; (2) inadvertent activation of the renin-angiotensin system (RAS); and (3) structural changes in the kidney itself.9 The present review discusses the importance of these factors in the development of hypertension in obesity and explores the rationale for angiotensin blockade in the management of obesity-related hypertension.

Mechanisms Involved in Obesity-Related Hypertension

Activation of the Sympathetic Nervous System

There is now ample evidence for the role of the sympathetic nervous system in the development of obesity-related hypertension.10–12 Both animal and human studies have shown that excess weight gain is associated with increased renal sympathetic activity, resulting in sodium retention.13–15 Conversely, in dogs, renal denervation prevented the sodium retention and increase in blood pressure associated with weight gain.13

Recent evidence suggests that the sympathetic activation associated with obesity is in part mediated by the adipocyte-derived hormone leptin.16,17 Leptin regulates energy balance by decreasing appetite and by stimulating thermogenesis.18,19

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Recent data now also suggest that activation of the RAS in adipose tissue may represent an important link between obesity and hypertension.\(^{35}\) Adipose tissue is an important production site of AGT.\(^ {35} \) Several studies have reported correlations between plasma AGT concentrations, blood pressure, and body mass index (BMI).\(^ {25,34,35} \) Obese Zucker rats have >50% higher levels of AGT mRNA expression in adipose tissue than lean rats.\(^ {36} \) In humans, expression of AGT mRNA was reported to be higher in visceral than in subcutaneous fat.\(^ {37} \)

Overexpression of AGT exclusively in adipose tissue in AGT knockout mice not only resulted in measurable plasma levels of AGT but also resulted in an increase in blood pressure and restoration of sodium balance.\(^ {38} \) Ang II has also been shown to play a role in adipocyte growth and differentiation.\(^ {39,33} \) Furthermore, locally produced Ang II may directly stimulate leptin release from adipocytes, an effect that may be counterbalanced by increased sympathetic activity.\(^ {40} \) In rodents, Ang II has been shown to increase production of prostaglandin E\(_2\) in adipocytes, which in turn stimulates adipogenic differentiation of pre-adipocytes into mature adipocytes.\(^ {42} \) Ang II has also been shown to inhibit adipogenic differentiation of primary cultured preadipocytes in humans.\(^ {43} \) In both murine 3T3 preadipocytes and in human adipocytes, Ang II was shown to elevate triglyceride content as well as increase the activity and transcription rate of glycerol-3-phosphate dehydrogenase and fatty acid synthase, 2 key lipogenic enzymes.\(^ {44,45} \) Furthermore, interstitial Ang II was shown to have tissue-specific effects on lipolysis in human adipose and muscle.\(^ {46} \) These data suggest that Ang II may be involved in the control of adiposity by regulating lipid synthesis and storage in adipocytes.\(^ {57} \) This regulation may be mediated through insulin-response sequences in a glucose-dependent manner.\(^ {48} \) Recent data also suggest that some Ang II type-1 (AT\(_1\)) receptor blockers may specifically affect adipocyte differentiation by direct activation of the peroxisome proliferator-activated receptor-\(\gamma\).\(^ {49} \) The clinical significance of these findings remains to be determined.

Adipocytes also secrete adiponectin, a plasma protein that is downregulated in obese individuals.\(^ {50} \) Adiponectin, which has been shown to adhere to injured vascular endothelium\(^ {51} \) and downregulate the expression of adhesion molecules,\(^ {52} \) has also been shown to enhance insulin sensitivity and to prevent atherosclerosis.\(^ {53,54} \) Several studies have reported a significant inverse relationship between adiposity and plasma adiponectin levels, and reduced levels of adiponectin are associated with increased expression of interleukin-8 and tumor necrosis factor alpha-\(\alpha\) in adipose tissue\(^ {55,56} \) and with elevated levels of C-reactive protein.\(^ {57} \) Recently, it was shown that blockade of the RAS with either an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) resulted in a substantial increase in adiponectin levels associated with an increase in insulin sensitivity.\(^ {58} \)

### Renal Abnormalities in Obesity Hypertension

The renal abnormalities described in obese hypertensive individuals bear a close resemblance to those found in patients with early type 2 diabetes, and the changes in renal structure and function in obesity hypertension result in similar complications as seen in hypertension and diabetes.\(^ {59} \) Thus, obese individuals have been found to have an increased renal plasma flow and increased glomerular filtration rates.\(^ {60} \) At the same time, abdominal obesity has also been associated with a decrease in glomerular filtration rates and an increase in albumin excretion.\(^ {61} \) As in diabetes, these abnormalities in
renal function may be secondary to activation of the intrarenal RAS in obese individuals. In patients with type 2 diabetes, there is evidence for activation of the intrarenal RAS despite the presence of low levels of circulating renin. Intrarenal angiotensin has also been suggested to contribute to nephropathy in several animal models. For example, studies in obese male Zucker rats have shown that these animals develop microalbuminuria, mild hypertension, and mesangial matrix expansion in the kidney, all of which precede the development of spontaneous focal glomerulosclerosis. This is thought to occur as a result of increased local Ang II formation as well as enhanced sensitivity to pressor actions of Ang II. Studies on diet restriction in these animals have shown a significant impact on prevention of renal injury and end-stage renal disease. Obese spontaneously hypertensive rats develop nephropathy with severe proteinuria whereas their lean littermates do not. This could be caused by specific binding sites for angiotensin being reduced in obese rats as a result of changes in the RAS. Similarly, Sprague-Dawley rats fed a high-fat diet developed obesity and hypertension with elevated plasma renin activity, hypertriglyceridemia, mesangial expansion, and focal sclerosis.

Adipose tissue almost completely encapsulates the kidneys. In obese subjects, excess adipose tissue penetrates into the medullary sinuses of the kidneys, causing compression and increased intrarenal pressures. This increased intrarenal pressure may affect pressure natriuresis and contribute to obesity-related hypertension. Obese dogs and rabbits show increased glycosaminoglycan content and hyaluronan, a main component of the renal medullary extracellular matrix. This increased extracellular matrix raises interstitial and solid tissue pressure, possibly further contributing to sodium reabsorption and volume expansion in obesity.

Where Is the Evidence in Guiding Clinical Practice?

Despite the fact that the increasing number of hypertensive patients now present with a BMI in excess of 30 kg/m², there are currently no specific recommendations or treatment algorithms for obesity hypertension. Furthermore, there are currently no specific treatment goals for obese hypertensives, although it may be argued that these goals should be similar to those recommended for other high-risk patients, including patients with diabetes (130/80 mm Hg). Although JNC 7 takes note of obesity as a special situation in hypertension management, these guidelines emphasize weight reduction as the main goal in both obesity and the metabolic syndrome, which unfortunately is rarely achieved in clinical practice. Because obesity hypertension results in significant cardiovascular, neurohormonal, renal, and metabolic changes, a comprehensive approach to treatment including both weight loss and pharmacological approaches would be warranted. As noted previously, the lack of an established approach to the reduction of cardiovascular risk in obesity hypertension is perhaps largely caused by the lack of data from prospective intervention studies on obese hypertensives. This is of concern given the possible exacerbation of metabolic abnormalities by commonly used antihypertensive agents (eg, weight gain with β-blockers), the lack of response to treatment, and the increased need for multiple medications in obese individuals.

Thus, many recent intervention trials have not been designed specifically for obese hypertensive patients. In trials such as Captopril Prevention Project (CAPP), Intervention as a Goal in Hypertension Treatment (INSIGHT), NORdic Diltiazem study (NORDIL), Hypertension Optimal Treatment (HOT), and Heart Outcomes Prevention Evaluation (HOPE) study, the mean BMI of hypertensive patients did not exceed 30 kg/m². Although this would imply that some patients participating in these trials may have been obese, general extrapolation of these data, particularly to patients with a BMI >35 kg/m², may not be justified.

Nevertheless, several lines of evidence suggest that antihypertensive agents that block the RAS may be especially beneficial in treating obese hypertensive patients. Obesity is commonly associated with other elements of the metabolic syndrome, such as dyslipidemia, type 2 diabetes, or microalbuminuria, and studies involving type 2 diabetic patient populations with central obesity and dyslipidemia have shown that RAS inhibitors, such as ACEI and ARBs, can slow the progression of renal disease in these patients. As outlined, Ang II is also implicated in the regulation of lipid synthesis and storage in adipocytes. In addition, the renin, AT₁ receptor, and angiotensin-converting enzyme genes were all found to be significantly upregulated in the adipose tissue of obese hypertensives. Clearly, studies in non-diabetic obese patients would be needed to irrevocably establish the use of RAS inhibitors as a better strategy for preventing renal injury, compared with other classes of antihypertensives.

Clinical Evidence With ACEIs

ACEIs block the conversion of Ang I to Ang II. The efficacy of ACEIs to improve cardiac, renal, and vascular function and their beneficial effects on cardiovascular complications and mortality have been well documented. Blockade of the RAS by ACEIs is known to occur at both systemic and tissue levels and has been shown to restore the ability of the kidney to excrete salt and water, as well as to control glomerular hyperfiltration. However, few studies have specifically addressed the use of these agents in obese patients. One notable exception is the TREATment in Obese Patients with HYpertension (TROPHY) study, which compared the efficacy and safety of the ACEI, lisinopril, and the diuretic hydrochlorothiazide (HCTZ), given at various doses to obese hypertensives, in a 12-week, multicenter, double-blind trial in 232 hypertensive patients with a BMI of 27 to 40 kg/m². The number of blood pressure responders was greater with the ACEI (40% versus 33%, P < 0.05) and, although plasma glucose decreased by −0.21±0.71 mmol/L with lisinopril, there was a small but significant increase of +0.31±0.99 mmol/L with HCTZ treatment.

Trials that have investigated metabolic parameters and diabetes outcome are relevant to the discussion on obesity hypertension, because the presence of type 2 diabetes and/or renal complications can be exacerbated by obesity-related hypertension (Table). Use of the ACEI ramipril in the Heart Outcomes and Prevention Evaluation (HOPE) study was
## Clinical Trials With ACEIs and ARBs in Patients With Renal Complications and/or Type 2 Diabetes

<table>
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<td>ARB Trials</td>
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<td>UAER at 24 wk was reduced by 44% with valsartan and 8% with amloidipine (P&lt;0.001); valsartan significantly reversed MA to normal albuminuria</td>
</tr>
<tr>
<td>RENAA</td>
<td>Type 2 diabetes with nephropathy</td>
<td>Losartan/ placebo</td>
<td>1513</td>
<td>Composite of doubling of BL Cr conc, development of end-stage renal disease or all-cause mortality</td>
<td>Losartan significantly reduced the composite end point by 16% (P&lt;0.02), but not death</td>
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</table>

BL indicates baseline; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; conc, concentration; Cr, serum creatinine; CV, cardiovascular; MA, microalbuminuria; MI, myocardial infarction; N, number of patients enrolled; UAER, urine albumin excretion; wk, weeks; NIDDM, noninsulin-dependent diabetes mellitus; ALLHAT, Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; ABCD, Appropriate Blood pressure Control in Diabetes; FACET, Fosinopril versus Amlodipine Cardiovascular Events randomized Trial; HOPE, Heart Outcomes Prevention Evaluation study; IRMA, Irbesartan in patients with type 2 diabetes with MicroAlbuminuria study; IDNT, Irbesartan Diabetic Nephropathy trial; LIFE, Losartan Intervention For Endpoint reduction in hypertension Study; MARVAL, MicroAlbuminuria Reduction with VAlsratan trial; UKPDS, UK Prospective Diabetes Study; RENAA, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan.

Associated with lower rates of new diagnosis of diabetes in individuals at high risk for cardiovascular events. In this study, 3.6% of the patients in the ramipril group developed diabetes compared with 5.4% in the placebo group (P<0.001). In the Fosinopril versus Amlodipine Cardiovascular Events randomized Trial (FACET) in noninsulin-dependent diabetes mellitus patients with hypertension, both treatments decreased fasting serum glucose, serum insulin, and microalbuminuria by similar magnitudes. Despite slightly greater blood pressure reduction observed with am-
lrodipine, patients randomized to fosinopril had 51% lower incidence of the combination of acute myocardial infarction, hospitalized angina, and stroke (P = 0.03). In the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), ACEI (lisinopril), diuretic (chlorothalidone), and calcium-channel blocker (CCB) (amlodipine) treatments did not result in a difference in all-cause mortality in either diabetic or nondiabetic patients.95 However, the development of diabetes in 11.6% of patients in the diuretic group compared with only 8.1% in the ACEI group and 9.8% in the CCB group has raised concerns about the potential long-term effects of increased incidence of diabetes, particularly in overweight or obese patients already at increased risk for diabetes.90,91

Clinical Evidence for the Benefits of ARBs in Treating Obesity-Related Hypertension

ARBs, in contrast to ACEIs, directly block the binding of Ang II to the AT1 receptor and provide a more specific blockade of Ang II than that seen with ACEIs alone. Importantly, in contrast to ACEIs, direct blockade of the AT1 receptor also blocks the action of Ang II produced via non-ACE–dependent pathways. ARBs further reduce the scope for “ACE escape,” which is the slow return of Ang II to pretreatment levels seen with chronic use of ACEIs.92 Their remarkable tolerability, particularly the virtual absence of cough, makes them a valuable alternative to ACE inhibition.93

To date there is only 1 study on the use of ARBs in obese hypertensive patients. The aim of the Candesartan Role on Obesity and on Sympathetic System (CROSS) study was to determine the antihypertensive, neuroadrenergic, and metabolic effects of an ARB compared with a diuretic in this specific patient group (n = 172). Treatment with candesartan resulted in a significant improvement in insulin sensitivity and muscle sympathetic nerve activity compared with HCTZ, despite similar improvements in blood pressure.94

The Irbesartan Diabetic Nephropathy Trial (IDNT) and the Reduction of Endpoints in Noninsulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan trial (RENAAL) examined the effects of ARBs in reducing end-stage renal disease in hypertensive patients with type 2 diabetes (Table). In both trials, ARBs significantly reduced the composite primary end point of death, worsening of renal function, and development of end-stage renal disease compared with placebo or CCBs.95,96 In a similar setting, the IRbesartan in patients with type 2 diabetes and Microalbuminuria (IRMA-2) and the Microalbuminuria Reduction with VALsartan (MARVAL) trials were conducted in patients with type 2 diabetes and microalbuminuria, a cardiovascular risk factor associated with early-stage diabetic nephropathy.97 In MARVAL, treatment with valsartan reduced urinary albumin excretion rate by 44% compared with 8.5% by the CCB amlodipine (P < 0.001). In addition to the blood-pressure lowering effects of Ang II blockade, specific effects on renal hemodynamics, as well as the blockade of the growth-promoting, profibrotic, nonhemodynamic actions of Ang II may contribute to renoprotection.98 Results from these trials have led to the current recommendation of ARBs as first-line therapy for patients with diabetic nephropathy.99

In the Losartan Intervention For Endpoint reduction of hypertension (LIFE) study, 9193 hypertensive patients with left ventricular hypertrophy were followed-up for 4 years. Patients using losartan showed a significantly lower rate of new-onset diabetes compared with those using atenolol (difference of 25%). Whether this reduction was because of an improvement in insulin resistance with losartan remains to be answered,100 because throughout the study, patients using atenolol showed a consistent decrease in insulin sensitivity, possibly suggesting a negative effect with time of adrenergic β-blockade on insulin and glucose metabolism.101 In the subgroup of hypertensive patients with type 2 diabetes (n = 1195), losartan was associated with a reduction in all-cause mortality and cardiovascular morbidity, showing the potential benefits of ARBs in this patient group.102

At present, there are several large ongoing trials that will provide important information relevant to obese hypertensive patients at high risk for cardiovascular disease. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) is an end point-driven trial with follow-up expected for 4 years.103 This is the largest trial to date evaluating the use of ARBs in hypertension, with >15 000 patients enrolled. The trial will compare valsartan with amlodipine in terms of cardiovascular morbidity and mortality. The trial will also examine the relationship between renal function and cardiovascular outcome in 3 specific patient groups: hypertensive patients, diabetic patients, and those with renal insufficiency. If successful, the trial will determine whether renal protection provides cardiovascular protection and vice versa.104

A second ongoing trial is investigating the effects of cardiovascular protection in patients with impaired glucose tolerance. Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) combines the use of valsartan with nateglinide—an antidiabetic agent that mediates the release of insulin in rapid and short bursts from pancreatic β cells.105 Thus, by lowering postmeal hyperglycemia, nateglinide may delay the onset of diabetes and thereby reduce cardiovascular risks. Valsartan has shown proven benefits in patients with glucose intolerance as a result of its action of RAS blockade. The combined drug regimen should allow for insights into the interaction of hypertension, insulin resistance, and metabolic syndrome.

A third major ongoing trial is the ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study,106 which will assess the effect of telmisartan alone or in combination with ramipril on cardiovascular outcomes in approximately 29 000 patients at high-risk for cardiovascular disease. Although none of these studies is specifically designed to examine the effects of RAS blockade in obese hypertensives, they should provide important insights into the potential benefits of RAS blockade relevant to this population.

Conclusions

The prevalence of obesity is steadily increasing, as is the prevalence of hypertension and cardiovascular disorders. At present, there is no clear recommended treatment for the
References


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