

Obesity, essential hypertension and renin–angiotensin system

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Abstract

Abdominal obesity is a risk factor for cardiovascular disease worldwide, and it is becoming a dramatic issue for national health systems. Overweight and obesity are highly associated with multiple comorbidities, elevated blood pressure values, dyslipidaemia, reduced insulin sensitivity and alterations of large and minor vessels.

Activation of the renin–angiotensin system (RAS) in adipose tissue may represent an important link between obesity and hypertension. Angiotensin II has been shown to play a role in adipocyte growth and differentiation. Adipocytes also secrete adiponectin, enhancing insulin sensitivity and preventing atherosclerosis. Blockade of the RAS with either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker results in a substantial increase in adiponectin levels and improved insulin sensitivity. Obesity-related hypertension needs a comprehensive approach to treatment including both weight loss and pharmacological therapies. Antihypertensive drugs prescription should be based on guidelines recommendations for management of hypertension, taking into account the growing evidences about the relationship between some antihypertensive drugs and the development of new-onset diabetes.

This review discusses the role of RAS in the relationship between obesity, essential hypertension and insulin resistance.

Keywords

Obesity
Essential hypertension
Renin–angiotensin system

Abdominal obesity is characterised by the accumulation of visceral adipose tissue, and it 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 diabetes³. Hypertension in obese individuals is commonly complicated by the concomitant presence of dyslipidaemia, hyperinsulinaemia, impaired glucose tolerance and other components of the metabolic syndrome⁴. 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 (RAS). Recent data show increased expression of angiotensin II-forming enzymes in adipose tissue, and increased activity of the RAS has recently been implicated in the development of insulin resistance and type 2 diabetes⁵. These evidences could explain the relevance of obesity as an important predictor of overall cardiovascular morbidity and mortality^{1,2}.

This review discusses the role of RAS in the relationship between obesity, essential hypertension and insulin resistance.

Renin–angiotensin–aldosterone system and obesity-related hypertension

Although excess weight gain is associated with marked sodium retention and expansion of extracellular fluid volume, obese subjects usually have increases in plasma renin activity, plasma angiotensinogen (AGT), angiotensin-converting enzyme (ACE) activity and plasma angiotensin (Ang) II levels⁶. Figure 1 summarises the mechanisms by which obesity increases renal tubular sodium reabsorption, impairs pressure natriuresis and causes hypertension as well as progressive glomerular injury⁶. A significant role for Ang II in stimulating sodium reabsorption, impairing renal-pressure natriuresis and causing hypertension in obesity is supported by the finding that treatment of obese dogs with an Ang II antagonist or ACE inhibitor blunts sodium retention and volume expansion, as well as elevated arterial pressure^{7,8}. Also, ACE inhibitors are effective in reducing blood pressure in obese humans, particularly in young patients⁹.

Activation of the RAS in adipose tissue may represent an important link between obesity and hypertension¹⁰. Adipose tissue is an important production site of AGT¹¹,

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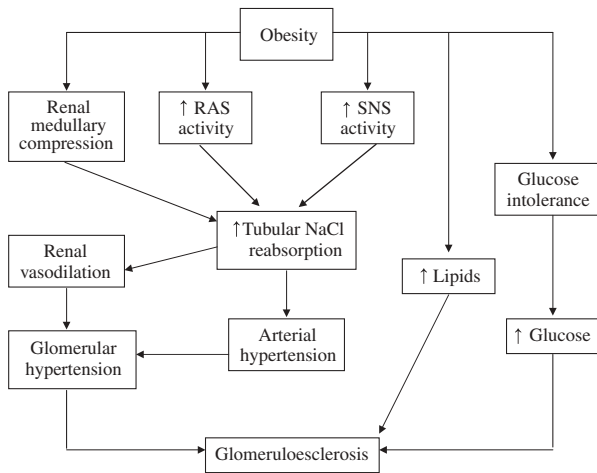


Fig. 1 Mechanisms involved in development of obesity-related hypertension and subsequent renal damage (modified from Hall⁶)

and several studies have reported correlations between plasma AGT concentrations, blood pressure and body mass index^{12,13}. 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, restoration of sodium balance and augmented adipocyte size¹⁴, whereas RAS suppression by either an ACE inhibitor or deletion of the type-2 angiotensin-II receptor leads to a decrease of adipocyte size^{15,16}. Ang II has also been shown to play a role in adipocyte growth and differentiation¹⁷. Furthermore, locally produced Ang II may directly stimulate leptin release from adipocytes, an effect that may be counterbalanced by increased sympathetic activity¹⁸. Adipocytes also secrete adiponectin, a plasma protein that is down-regulated in obese individuals¹⁹. Adiponectin enhances insulin sensitivity and prevents atherosclerosis²⁰. Recently, it has been shown that blockade of the RAS with either an ACE inhibitor or an Ang II receptor blocker results in a substantial increase in adiponectin levels associated with an increase in insulin sensitivity²¹. Further support for the involvement of RAS activation in obesity-associated hypertension came from a dietary intervention study in menopausal women. Engeli *et al.*²² showed that 5% weight loss resulted in a 7 mmHg reduction of ambulatory blood pressure and that the decrease was accompanied by significant declines of serum AGT (27%), renin (43%) and ACE activity (12%) as well as AGT expression in adipose tissue (20%).

Aldosterone has been implicated in the development of hypertension associated with obesity²³. Plasma aldosterone levels are elevated in obese hypertensives, especially in those with visceral obesity²⁴. The mechanisms by which excess fat could increase aldosterone are unknown, but it may relate to the production by adipocytes of potent mineralocorticoid releasing factors²⁵ or to the ability of oxidised derivatives of linoleic acid to

induce aldosterone synthesis²⁶. The involvement of aldosterone in obesity-associated hypertension has been demonstrated by the blockade of mineralocorticoid receptors with the specific antagonist eplerenone in high-fat-fed dogs²⁷.

Insulin resistance and obesity-related hypertension

Resistance to insulin-mediated glucose uptake by the skeletal muscle, which is often linked with abdominal obesity, greatly increases the likelihood of developing abnormalities such as type 2 diabetes, hypertension and dyslipidaemia²⁸. The cluster of these independent cardiovascular risk factors is known as metabolic syndrome, described by the NCEP ATP III²⁹, and it is well-recognised that hypertensive patients presenting metabolic syndrome show an increased cardiac, renal and vascular damage^{30–32}. In the general US population, the age-adjusted prevalence is 24.0% for men and 23.4% for women³³, and it rises continuously in an epidemic progression^{34,35}. Among hypertensive patients attended to in our hospital-based hypertension unit, the overall prevalence of metabolic syndrome rose to 49.4%, with no difference between genders (47.8% in men and 50.5% in women)³⁶. Finally, in a population-based cohort of type 2 diabetes, a prevalence of metabolic syndrome of 75.6% has been recently described³⁷. The International Diabetes Federation has recently described a new definition of metabolic syndrome, with more strict criteria for waist circumference (≥ 94 cm for European men and ≥ 80 cm for European women)³⁸. According to this new definition, the prevalences described above would be increased.

The metabolic syndrome is associated with an increased risk of both diabetes³⁹ and cardiovascular disease^{40,41}. Abdominal obesity is a risk factor for cardiovascular disease worldwide⁴², and it is becoming a dramatic issue for national health systems⁴³. Specifically, overweight and obesity in childhood are highly associated with multiple comorbidities, elevated blood pressure values, dyslipidaemia, reduced insulin sensitivity and alterations of large and minor vessels^{44,45}. Obesity is often associated with insulin resistance and the components of metabolic syndrome. In fact, the degree of insulin resistance impacts the risk for obesity-related metabolic comorbidities, with a greater risk for type 2 diabetes and cardiovascular disease in patients who are severely insulin-resistant⁴⁶.

Recently, we published the first study in Spain to report on the degree of blood pressure control achieved in hospital-based hypertension units across the whole nation in light of recommendations contained in international guidelines⁴⁷. We performed a survey covering 4049 patients, aged 18 years or older, who had a diagnosis of essential hypertension, had been using antihypertensive

therapy at least for 1 year, had been seen at 47 hospital-based hypertension units nationwide and had been regularly followed up by the same medical team in each unit. Baseline data for the 4049 hypertensives studied are shown in Table 1. It should be highlighted the increased mean body mass index $29.5 \pm 5 \text{ kg m}^{-2}$ and the high prevalence of overweight (42.3%) and obesity (41.1%) among hypertensive patients attended in hospital-based hypertension units⁴⁷. The univariate analysis showed that poorer blood pressure control occurred in older patients, females, obese patients, diabetic patients and in those treated with two or more antihypertensive drugs, and all variables, except for gender, remained statistically significant in the multivariate analysis⁴⁷. Table 2 shows the percentages of systolic and diastolic blood pressure control according to body mass index, which is significantly lower among obese hypertensive patients. From the whole group, 63.7% were using two or more antihypertensive drugs. ACE inhibitors, Ang II receptor antagonists and calcium channel blockers were

the drugs most frequently prescribed. These data confirm that hypertensive patients followed up in hospital hypertension clinics exhibit an increased cardiovascular risk linked to a high prevalence of target organ damage, associated clinical conditions, diabetes or other major cardiovascular risk factors, with a great relevance of overweight and obesity.

Clinical management of obesity-related hypertension

Despite the fact that an increasing number of hypertensive patients now present with a body mass index in excess of 30 kg m^{-2} , there are currently no specific recommendations or treatment algorithms for obesity hypertension^{48,49}.

The lack of an established approach to the management of obesity hypertension is perhaps largely caused by the lack of data from prospective intervention studies on obese hypertensives⁵⁰. Despite the fact that many recent intervention trials comparing different antihypertensive drugs have been reported, they have not been designed specifically for obese hypertensive patients. Although some patients participating in these trials may have been obese, general extrapolation of these data may not be justified³. 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 warranted⁵. Antihypertensive drugs prescription should be based on guidelines recommendations for management of hypertension^{48,49}, taking into account the growing evidences about the relationship between some antihypertensive drugs and the development of new-onset diabetes. Compared to diuretics or 'conventional' (diuretic and/or beta blocker) therapy, blockers of the RAS, and to a lesser extent calcium antagonists, reduced the risk of new-onset diabetes substantially⁵¹. Physicians should take notice of the presence of several characteristics related to the development of diabetes (prediabetic state, metabolic syndrome, glucose intolerance, overweight-obesity) when they select long-term medications devoted to cardiovascular protection for hypertensive patients⁵¹.

Combination therapy for multiple cardiovascular risk factors is critical for the successful management of patients presenting obesity-related hypertension. Either ACE inhibitors or Ang II receptor blockers are preferable antihypertensive drugs as initial therapy of these patients,

Table 1 Baseline demographic and clinical characteristics of the sample (from Ref. 47 with permission)

Variable	
Age (years) \pm SD	55.6 \pm 12
<60 years, n (%)	2006 (49.5)
Gender	
Male, n (%)	2001 (49.4)
Female, n (%)	2048 (50.6)
Blood pressure (mmHg) \pm SD	144 \pm 20/85 \pm 10
BMI (kg m^{-2}) \pm SD	29.5 \pm 5
<20 (%)	0.8
20–25 (%)	15.8
25–30(%)	42.3
≥ 30 (%)	41.1
Diabetes* (%)	
Type 1	1.5
Type 2	20.6
Renal failure*	16.5
Proteinuria* (%)	
30–300 mg day^{-1}	29.4
300–1000 mg day^{-1}	8.3
>1000 mg day^{-1}	5.7
Other TOD/clinical CVD* (%)	
Left ventricular hypertrophy	22.4
Angina/previous MI	8.5
Heart failure	2.5
Stroke or transient ischaemic attack	9.2
Retinopathy grades 3 and 4	2.7
Other risk factors* (%)	
Smoking	15.1
Hypercholesterolaemia	35.5

SD – standard deviation; BMI – body mass index; TOD – target organ damage; CVD – cardiovascular disease; MI – myocardial infarction.

For definitions of clinical characteristics see Methods.

* The percentages listed are those for the population with the characteristic divided by the population in whom the condition was determined.

Table 2 Systolic and diastolic blood pressure control according to BMI (from Ref. 47 with permission)

BMI	n	SBP/DBP < 140/90 mmHg (%)	SBP < 140 mmHg (%)	DBP < 90 mmHg (%)
<30 kg m^{-2}	2385	46	50	71
$\geq 30 \text{ kg m}^{-2}$	1664	34	39	63

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure.

unless contraindications or compelling indications for other drugs. Considering that most patients will need more than one antihypertensive drug to achieve the blood pressure goal, a calcium-channel blocker, α -blocker or thiazide diuretic could be considered for combined therapy⁵².

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