Review Paper

Progress and Controversies: Treating Obesity and Insulin Resistance in the Context of Hypertension

Janet B. McGill, MD;[1] Steven Haffner, MD;[2] Tomas J. Rees, PhD;[3]
James R. Sowers, MD;[4] Andrew M. Tershakovec, MD, MPH;[5] Michael Weber, MD[6]

Improvements in hypertension treatment and control are challenged by the increasing incidence of metabolic risk factors for hypertension, in particular, obesity and insulin resistance. Such risk factors can increase the severity of hypertension and can interact via a multitude of hormonal and inflammatory pathways. Their presence may affect antihypertensive agent choice with regard to antihypertensive efficacy as well as potential synergistic or antagonistic effects on inflammatory status and progression to diabetes. Furthermore, an increasing number of pharmacologic options are available to promote weight loss and insulin sensitivity that may affect blood pressure directly and indirectly. This review considers the metabolic basis for the complex interactions of hypertension with obesity and insulin resistance, and it assesses the clinical evidence for an impact of weight loss and insulin-sensitizing treatment on blood pressure. Awareness of these pathophysiologic interrelations and their implications for treatment are likely to be of increasing importance for successful blood pressure management.
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From the Washington University School of Medicine, Division of Endocrinology, Metabolism and Lipid Research, St Louis, MO;[1] Division of Clinical Epidemiology, University of Texas Health Science Center, San Antonio, TX;[2] PAREXEL MMS, Worthing, West Sussex, UK;[3] Department of Internal Medicine, Division of Endocrinology, University of Missouri, Columbia School of Medicine, Columbia, MO;[4] Clinical Research, Merck Research Laboratories, Merck & Co., Inc. Boston, MA;[5] and Medical College of the State University of New York, New York, NY[6]
Address for correspondence: Janet B. McGill, 660 South Euclid, Campus Box 8127, St Louis, MO 63110
E-mail: jmcgill@im.wustl.edu
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The management of hypertension, a mainstay of cardiovascular protection, has improved significantly in recent decades as new treatment options have become available and the implementation of evidence-based guidelines has increased. Goal blood pressure levels are being reached in more patients than ever before.[1] However, control rates may be set to decline due to the increasing prevalence of factors that are associated with hypertension, most notably obesity and insulin resistance.[2] This rising prevalence of comorbidities is occurring at a time when there is increasing understanding of the clustering of hypertension with obesity and insulin resistance. However, separating lifestyle from genetic and physiologic components is problematic, given the limited understanding of the causes of these diseases. Thus, the management of hypertension in individuals with metabolic comorbidities, which is complicated due to underlying pathophysiologic and genetic differences, will become an increasingly common part of clinical practice. Meeting this challenge will require the aggressive management of risk factors based on a clear understanding of the pathophysiologic interactions and implications for treatment.

DIAGNOSTIC EVALUATION

One of the objectives of the evaluation of individuals with hypertension is the identification of cardiovascular risk factors that can affect prognosis and may guide treatment. Assessment for obesity and type 2 diabetes is essential. A further poorly recognized but highly important risk factor is albuminuria. Even low levels of albuminuria can reflect significantly increased cardiovascular risk, since it is linked to systemic vascular inflammation and oxidative stress.[3] To aid in the identification of at-risk patients, evaluation should include waist circumference, body mass index, clinical and family history, as well as lifestyle. Laboratory tests in individuals in whom cardiometabolic complications are suspected should include an assessment of glycemic status, primarily fasting glucose but optionally fasting insulin (enabling estimation of insulin resistance via homeostatic model assessment) and glycosylated hemoglobin. Lipid profile and renal function (estimated glomerular filtration rate and albuminuria) should also be assessed. An assessment of fasting high-sensitivity C-reactive protein should also be considered.

PATHOPHYSIOLOGIC CONSIDERATIONS

Hypertension, diabetes, and obesity are not isolated findings but represent a series of interacting physiologic derangements. An understanding of interactions among these pathophysiologic pathways can inform treatment choice and thereby improve the management of total cardiovascular risk.

Hypertension and Obesity

Observational evidence indicates a link between increased blood pressure and obesity. For example, in a multinational study (conducted in Finland, Italy, the Netherlands, the United Kingdom, and the United States), being overweight or obese was estimated to carry a population attributable risk for hypertension of 11% to 17%.[4] There are numerous pathophysiologic pathways that may link obesity to hypertension. Positive correlations have been revealed between leptin and blood pressure[5] and between leptin and insulin resistance,[6] although the mechanistic link is unclear. Another adipokine, adiponectin, is inversely related to leptin and is decreased in both type 2 diabetes and obesity.[7] Leptin is a marker of increased cardiovascular risk and may contribute directly to hypertension as a consequence of its inflammatory effects on the vasculature.

Sympathetic tone, which is increased in obesity for a number of reasons, may further contribute to hypertension. There may be an indirect effect, since hyperinsulinemia activates the sympathetic nervous system. However, this is likely to explain at most only part of the sympathetic activation observed in obese individuals, with leptin likely to play a more significant role. A small study of 30 healthy old and young men found that the relationship between body fat and muscle sympathetic nerve activity could largely be explained by plasma leptin, with a negligible contribution from insulin.[8] The increase in sympathetic activity in the obese state in turn contributes to an increase in sodium reabsorption, both directly and also via activation of the renin-angiotensin system (RAS).[9] Furthermore, adipose tissue contains all components of the RAS, and obesity may contribute to local and systemic increases in RAS activity. RAS activation not only leads to increased blood pressure but also generates a proinflammatory state with negative consequences for the vasculature and, in the long term, heightened cardiovascular risk.[9]

Hypertension and Insulin

The role of insulin in modulating blood pressure is controversial, with evidence for both positive and negative effects dependent on patient age and glycemic status. Insulin modulates sympathetic tone, causing vasodilation in younger patients and vasoconstriction in the elderly.[10] Insulin also has direct and opposing vascular effects. The vasodilator effect is down-regulated in the insulin-resistant condition, while the opposing vasoconstrictor action is unaffected by insulin resistance.[11] Based on these findings, insulin may exert a vasoconstrictor effect in insulin-resistant individuals but have no net effect in insulin-sensitive individuals.

Insulin also induces renal sodium retention, and this likely contributes to volume-dependent, salt-sensitive hypertension.[12] Although the evidence is suggestive, there remains the possibility that causality operates in both directions, with sympathetic activation (frequently present in salt-sensitive hypertension) leading to insulin resistance via vasoconstriction and reduced peripheral blood flow.[12] Thus, multiple mechanisms may account for the link between insulin resistance and hypertension, although much work remains to be done to clarify the clinical relevance of these potential pathways.

Hypertension and Renal Disease

The kidney is a key regulator of blood pressure. Overt kidney disease contributes to secondary hypertension, but even essential hypertension is frequently linked to structural and functional changes in the kidney that likely exacerbate blood pressure

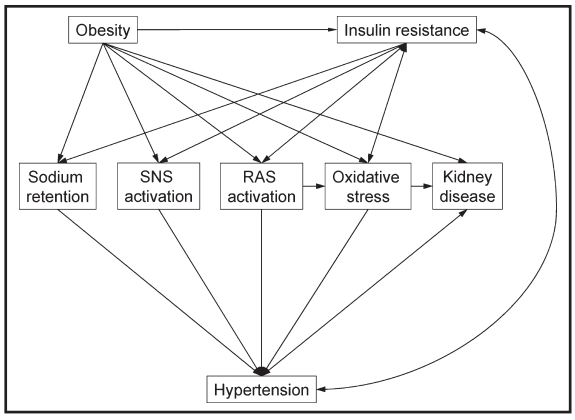

Figure. A simplified depiction of the potential interrelationships among obesity, insulin resistance, and hypertension.

changes. Treatments that reduce the progression of renal damage may help control blood pressure in the long run.

THE VICIOUS CIRCLE OF HYPERTENSION, OBESITY, INSULIN RESISTANCE, AND RENAL DISEASE

The pathophysiologic basis for the epidemiologic association between hypertension and other metabolic factors is still uncertain, but it is clear not only that there is cross talk between the various cellular and physiologic pathways but that the potential for recursive feedback is widespread, leading to the possibility of vicious circles of increasing pathophysiologic derangement (Figure). For example, observational studies suggest not only that insulin resistance increases with increasing adiposity and with hypertension but that obesity and hypertension have additive effects.[13]

The link between obesity and insulin resistance is complex and lies outside the scope of this article, but the causal relationship between hypertension and insulin resistance is of direct relevance to the treatment of hypertension. Of major importance is reduced peripheral blood flow consequent to sympathetic nervous system activation, inflammation-induced endothelial dysfunction, and RAS activation. Multiple pathways connect the RAS to insulin signalling. Insulin up-regulates the local RAS in endothelial and vascular smooth muscle, potentially leading to vascular hypertrophy and impaired endothelial function. The RAS, meanwhile, not only affects insulin resistance by hemodynamic pathways but also has significant nonhemodynamic effects. For example, a local RAS exists in pancreatic acinar and islet cells, which contributes to the regulation of local blood flow and islet β cell (pro)insulin release.[14] Both insulin resistance and increased angiotensin II combine to affect insulin- and insulin-like growth factor-1–mediated nitric oxide production, resulting in vascular inflammation and potentiating atherogenic effects.[15] The RAS also affects glucose transport and insulin-signaling pathways.[16]

The interactions with renal disease are likewise complex. Hypertension contributes to a long-term decline in renal function as a consequence of intimal hyperplasia, hyalinosis, and smooth muscle cell hypertrophy.[17] This leads to a potential for a "vicious circle," whereby treating renal disease may reduce hypertension and thereby reduce disease progression. However, there is some evidence that obesity and insulin resistance play a major role in renal failure conventionally attributed to hypertension.[18] Because of this, effective treatment of insulin resistance and obesity may exert a favorable effect on blood pressure as a consequence of slowing the progression of renal damage. Thus, hypertension management becomes fundamentally related to management of the whole patient.

MANAGING PATIENTS WITH HYPERTENSION AND ADDITIONAL RISK FACTORS

The management of total cardiovascular risk in patients with hypertension, as in those without hypertension, requires aggressive, multifactorial intervention. The American Diabetes Association suggests that aspirin therapy should be considered a primary prevention strategy in all patients with a history of diabetes and hypertension.[19] Similarly, the American College of Physicians recommends statins for all patients with type 2 diabetes and hypertension.

Treating Obesity and Insulin Resistance in the Context of Hypertension

For patients with hypertension and obesity or insulin resistance, special consideration must be given to their treatment, since treatments for each one of these factors may impact the other. Most important, reducing weight or improving insulin sensitivity may reduce blood pressure and thereby lower the requirement for antihypertensives. Further, specific interventions for obesity/insulin resistance may have secondary effects on blood pressure that may make them particularly suitable (or particularly to be avoided) in this patient population.

Obesity/Overweight

There is conclusive evidence showing the benefit on hypertension of lifestyle intervention to reduce

weight in obese patients. A modest weight reduction of 5.8% (as a result of energy intake restriction or increased physical activity or both) is associated with a reduction in systolic blood pressure (SBP)/diastolic blood pressure (DBP) of 4.4/3.6 mm Hg.[20] The effect on blood pressure reduction was greater in persons who lost more than 5 kg of body weight compared with those who lost less.

Pharmacologic intervention to reduce weight has provided mixed results with regard to effects on blood pressure—some weight loss medications increase blood pressure, which offsets the blood pressure reductions associated with weight loss. Orlistat, a gastrointestinal lipase inhibitor that blocks dietary fat absorption, has reduced blood pressure in some studies but not in others.[21,22] Rimonabant, a cannabinoid-1 receptor antagonist, caused significant weight loss accompanied by SBP/DBP reductions of 2.8/2.2 mm Hg (placebo-adjusted) in patients who were hypertensive at baseline.[23] The reductions were greatest in patients with dyslipidemia and type 2 diabetes and were similar to those that might be expected from the observed weight loss. Sibutramine, a monoamine reuptake inhibitor, resulted in a weight loss of around 5 kg in clinical trials but is associated with increases in blood pressure and also in pulse rate.[24] Topiramate, a sulfamate-substituted monosaccharide with antiobesity effects, was found in one trial in obese patients with type 2 diabetes to cause weight loss of 4.5% to 6.5%, and this was accompanied by decreases in SBP/DBP of 2/3 mm Hg.[25]

Weight loss intervention should therefore be considered as a tool to reduce total cardiovascular risk, as well as a blood pressure reduction measure. Within this context, it should be noted that a J-shaped curve relationship between body mass index and mortality (especially death from stroke) was noted in the Systolic Hypertension in the Elderly Program (SHEP), with optimal body mass index falling in the range of 25 to 30 kg/m^2.[26] Furthermore, the effect on cardiovascular outcomes of weight loss therapy has not yet been demonstrated.

Insulin Resistance

The first-line treatment for insulin resistance is lifestyle management—in particular, weight loss and increased physical activity. Intensive lifestyle modification in the Diabetes Prevention Program reduced the incidence of new-onset diabetes by 58% over 2.8 years, mainly as a result of reduced visceral fat.[27] These beneficial changes were associated with a decrease in SBP/DBP of around 3.3/3.8 mm Hg (although there is likely to have been an impact of increased use of hypertensive medication over the course of the trial, from 17% at baseline to 23% by year 3).[28]

Metformin has no intrinsic effects on blood pressure in patients with type 2 diabetes, despite significantly improved glycemic control.[29] There is, however, some evidence for the antihypertensive effects of peroxisome proliferator-activated receptor (PPAR) γ agonists such as the thiazolidinediones. In a randomized double-blind study of nondiabetic patients with hypertension, pioglitazone reduced DBP by around 6 mm Hg compared with placebo (the effect on SBP was similar in magnitude but not statistically significant).[30] In nondiabetic persons with insulin resistance, small but significant reductions in SBP/DBP of 3.1/3.1 mm Hg have been reported with pioglitazone compared with placebo.[31]

The mechanism by which PPARγ agonists exert their antihypertensive effect is unknown. PPARγ is a nuclear receptor predominantly expressed in adipose tissue and promotes adipogenesis and fatty acid storage.[32] PPARγ agonists, in addition to improving insulin resistance, can promote the uptake of free fatty acids and reduce oxidative stress. However, they also promote sodium retention.[33] A clinical trial has found that in patients with type 2 diabetes and microalbuminuria, rosiglitazone reduced blood pressure independent of effects on glycemic control.[34]

Thus, PPARγ agonists might be considered the antidiabetic agent of choice in individuals with insulin resistance and hypertension. However, safety concerns have been expressed, with evidence from a meta-analysis suggesting that rosiglitazone increases the risk of myocardial infarction and cardiovascular death.[35] This meta-analysis has been criticized on methodological grounds,[36] and alternative analyses have found no overall increase in cardiovascular mortality (despite an increased risk of myocardial infarction and heart failure).[37] Pioglitazone does not appear to have the same adverse effects on cardiovascular events, but it shares an increased risk of fluid retention and heart failure.[38] At present, PPARγ agonists should be used with caution.

A recent development in the treatment of type 2 diabetes are drugs that target the incretin pathway by either mimicking or preventing the breakdown of glucagon-like peptide 1 (GLP-1). GLP-1 stimulates insulin and suppresses glucagon secretion, and it reduces appetite and food intake and inhibits gastric emptying.[39] Parenteral GLP-1 agonists (exenatide, liraglutide) are used in patients for whom oral therapy is ineffective. Oral dipeptidyl peptidase-4

inhibitors, which block the breakdown of GLP-1, may potentially be effective as first-line therapy and seem to prevent weight gain (unlike GLP-1 agonists). For this reason, they may be of benefit in the treatment of individuals with type 2 diabetes, obesity, and hypertension, although no data exist so far on their effects on blood pressure.

In addition to considering the blood pressure effects of antidiabetic agents, antihypertensive treatment choice in individuals at high risk for diabetes must be made in cognizance of the evidence for prodiabetogenic and antidiabetogenic effects of different antihypertensive drug classes. Given the close links among obesity, insulinemia, and the RAS, the use of RAS blockade to treat hypertension in such patients is logical. There is substantial evidence that the incidence of new-onset diabetes in patients treated with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is lower than for other antihypertensive classes, particularly β-blockers and diuretics. However, there is as yet no evidence for the superiority of any antihypertensive class in the treatment of hypertension associated with obesity.[40]

CONCLUSIONS

The continuing increase in the prevalence of obesity and insulin resistance is adversely affecting blood pressure control rates. In response to this, physicians must adapt their treatment strategies in order to provide maximal cardiovascular protection to patients. Tackling obesity and insulin resistance with either pharmacologic or nonpharmacologic strategies may reduce blood pressure and will certainly lower the patient's cardiovascular risk. Conversely, careful choice of antihypertensive intervention may have beneficial effects on insulin resistance. Knowledge of the interrelationships between these common pathophysiologic conditions is increasing and will have implications for the future management of these patients.

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