Obesity hypertension: the rationale for renin-angiotensin system blockade

Introduction

Obesity has become a worldwide epidemic. In Hong Kong, more than a third of the population is overweight. Elevated arterial pressure is a frequent complication of excess body weight, and both obesity and hypertension are components of insulin-resistance syndrome.[1,2] Many obese hypertensive patients will develop type-2 diabetes, which further increases their cardiovascular risk. While lifestyle modification is the key to weight and blood pressure reduction, pharmacological intervention remains essential to lowering blood pressure to target levels in obese patients with hypertension. Antihypertensive drugs such as thiazide diuretics and β-blockers adversely affect glucose metabolism and increase the risk of developing type-2 diabetes. On the other hand, drugs that interfere with the renin-angiotensin system (RAS) improve insulin sensitivity and reduce the incidence of new-onset diabetes. Therefore, the initial selection of antihypertensive therapy for obese patients could have a significant influence on their overall cardiovascular risk.

Old antihypertensive drugs, new diabetes

Thiazide diuretics and β-blockers have been used for decades as first-line antihypertensive therapy. While effective in blood pressure reduction, these drugs frequently cause glucose intolerance.[3] In addition, β-blocker therapy is associated with weight gain,[4] an important determinant of glucose intolerance and diabetes. A systematic analysis of eight large-scale prospective randomised controlled trials lasting over 6 months showed that median body weight was 1.2 kg higher in the β-blocker treatment group than the placebo group.[4] In contrast, blockade of the RAS with either angiotensin-converting enzyme (ACE) inhibitors[5,6] or angiotensin receptor blockers (ARBs)[7-10] improves insulin sensitivity. The Joint National Committee guidelines suggest that multiple drugs are often required to achieve blood pressure goals,[11] and thiazide diuretics and β-blockers might eventually form part of a multiple-drug regimen to reduce blood pressure to target levels. However, the initial choice of antihypertensive therapy remains important given the different potential effects of the various antihypertensive agents on glucose metabolism, and their subsequent effects on overall cardiovascular risk.

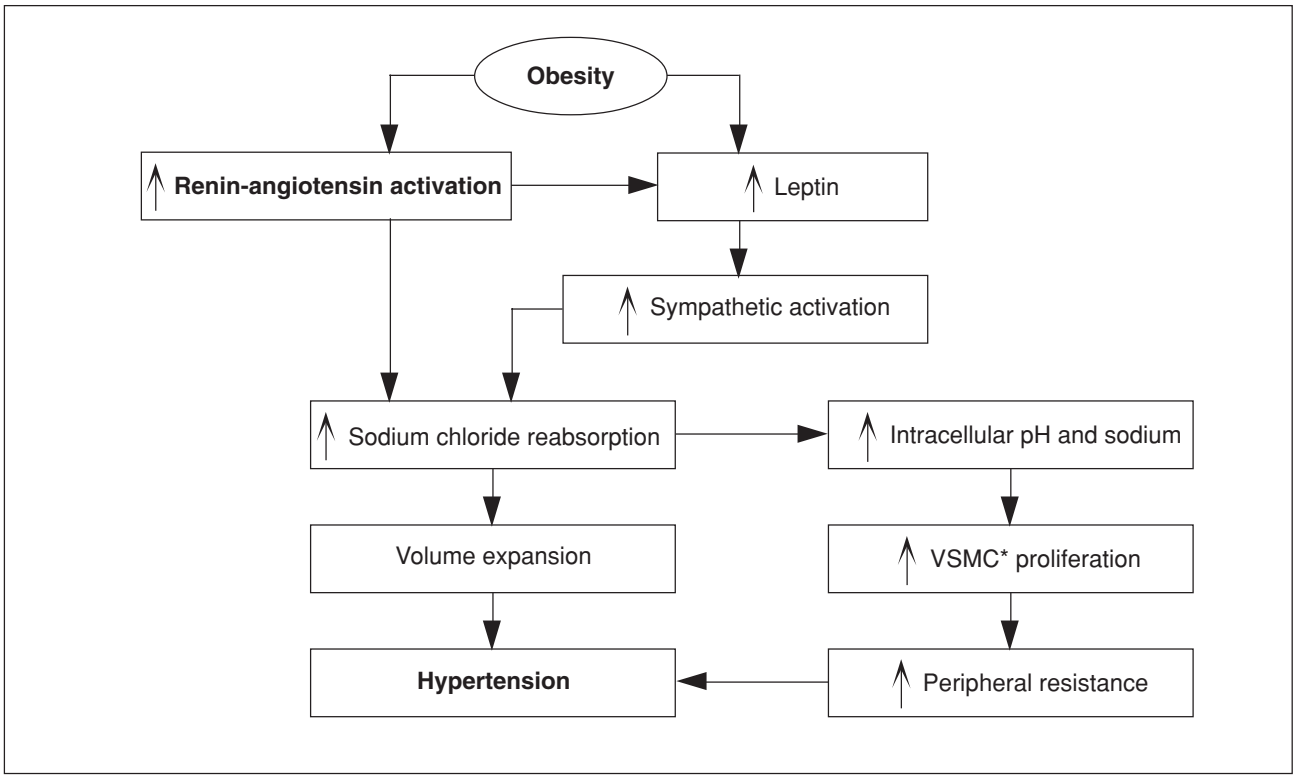
Activation of the renin-angiotensin system: a pivotal pathophysiological link

There is accumulating evidence that the sympathetic nervous system plays a role in the development of obesity-related hypertension. Both animal and human studies have shown that excess weight gain is associated with increased renal sympathetic activity, resulting in sodium retention.[12-14] An activated RAS also contributes to enhanced oxidative stress,[15] vascular remodelling,[16] and pressor response to exercise.[17] The sympathetic nervous system activation associated with obesity is mediated in part by the adipocyte-derived hormone, leptin,[18] which increases in proportion to the degree of adiposity.[19] An increase of leptin in hypertensive individuals is associated with elevated plasma renin activity, aldosterone, and angiotensin concentrations.[20] The Figure illustrates potential mechanisms through which arterial hypertension may be caused by obesity. Weight reduction by as little as 5%, on the other hand, can lead to decreased RAS activation.[14] Given the pivotal role of the RAS in linking obesity with hypertension, do we have clinical evidence to show that blockade of the RAS improves glucose metabolism?

Renin-angiotensin system blockade reduces new-onset diabetes: evidence from clinical trials

The mechanisms whereby blockade of the RAS improves insulin sensitivity are multifactorial. Activation of the bradykinin-nitric oxide system is involved in this process, resulting in an increase in the translocation of glucose transporter 4 (GLUT4),[21] and an increase in plasma adiponectin (an adipocyte-derived cytokine that decreases insulin resistance) as a result of decreased angiotensin II.[22]

In the clinical setting, several large-scale randomised controlled trials have shown that blockade of the RAS with either ACE inhibitors or ARBs significantly reduces the incidence of new-onset diabetes.[5-10] The LIFE (Losartan Intervention For Endpoint reduction in hypertension) and VALUE



* VSMC vascular smooth muscle cell

Fig. Potential mechanisms through which obesity induces arterial hypertension

(Valsartan Antihypertensive Long-term Use Evaluation) studies showed that losartan and valsartan reduce the incidence of new-onset diabetes compared with β-blocker–based and calcium channel blocker–based regimens, respectively.[7,8] In the LIFE study, the incidence of new-onset diabetes was 25% lower in the losartan group than in the atenolol group.[7] Similarly, in the VALUE study, the incidence of new-onset diabetes was significantly lower in valsartan-based regimen (by 23%) compared with an amlodipine-based regimen.[8] Importantly, in the VALUE study, the valsartan group had a greater proportion of patients taking concurrent thiazide diuretics. Despite the negative impact of thiazide diuretics on glucose metabolism, the valsartan group had a lower incidence of new-onset diabetes than the amlodipine group.[8]

In the SCOPE (Study on COgnition and Prognosis in the Elderly) trial, elderly patients (aged 70-89 years) with isolated systolic hypertension who were randomised to a candesartan treatment group were found to have a 28% reduction in the risk of developing new-onset diabetes over 3.6 years compared with those randomised to the placebo group.[9] Similarly, in the recent PEACE (Prevention of Events with Angiotensin Converting Enzyme inhibition) trial, patients with stable coronary artery disease had a significantly lower incidence of new-onset diabetes when randomised to trandolapril than the placebo over a median follow-up period of 4.8 years.[10]

Nevertheless, there is little long-term data as to whether the incidence of new-onset diabetes affects long-term prognoses. The results of a recent long-term cohort study provide some important insight. A total of 795 untreated hypertensive patients were followed up for 1 to 16 years (median, 6.0 years).[23] New-onset diabetes occurred in 5.8% of the subjects who were initially without diabetes. Of the patients who developed diabetes, 53.5% received diuretics as antihypertensive therapy compared with 30.4% of those in whom diabetes did not develop. After adjusting for other confounders, the relative risk of developing a first cardiovascular event was also significantly higher in patients who developed new-onset diabetes.[23]

Improvement of insulin sensitivity beyond renin-angiotensin system blockade

Although it is clear that ARBs improve insulin

sensitivity, the relative effects of different ARBs on insulin resistance is not known. Telmisartan is an ARB which may have a specific antihyperglycaemic effect beyond angiotensin II receptor antagonism. This is due to its partial peroxisome proliferator-activated receptor (PPAR)–gamma action, a biological effect that is not present to the same extent in other ARBs.[24,25] Animal studies have shown that, when compared with other ARBs of similar dosage, telmisartan significantly decreases indices related to insulin resistance (fasting plasma glucose, fasting insulin, and triglycerides), an effect similar to that of thiazolidinediones.[24] In humans with metabolic syndrome, telmisartan was shown in a small-scale (n=40) preliminary study to be superior to losartan in improving glucose metabolism and indices of insulin resistance.[25] Two recent preliminary reports suggest that another ARB, irbesartan, may also possess a partial PPAR-gamma effect that results in glucose lowering.[26,27]

The partial PPAR-gamma effect of telmisartan and irbesartan suggests that these agents may provide greater improvements in insulin sensitivity than other ARBs or ACE inhibitors. In this regard, the results of ongoing trials, such as ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), comparing the effects of dual RAS blockade (telmisartan in combination with ramipril) with monotherapy (telmisartan or ramipril) are highly anticipated.[28]

Conclusions

Obese patients with hypertension are often insulin resistant and have an increased risk of developing type-2 diabetes. This risk is further exacerbated by thiazide diuretics and β-blockers. While low-dose thiazide diuretics pose minimal risk, the use of β-blockers should preferably be reserved for patients with coronary heart disease or thyrotoxicosis, or for cases where blood pressure control is not achieved with initial regimens. In contrast, ARBs and ACE inhibitors have favourable effects on glucose metabolism, as supported by large-scale clinical trials, and should be considered the first-choice antihypertensive therapies for obese patients. The recommendation of antihypertensive agent(s) should carefully consider the risk of new-onset diabetes in addition to blood pressure lowering efficacy.

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