There has been an increase in the prevalence of diabetes mellitus over the past 40 years, both in the US and worldwide. The worldwide prevalence of diabetes in 2000 was approximately 2.8% and is estimated to grow to 4.4% by 2030. This translates to a projected rise of diabetes from 171 million in 2000 to well over 350 million in 2030.1 The epidemic of diabetes will continue to rise as there is growing prevalence of obesity in children, which predisposes to diabetes.2 There is considerable evidence for an increased prevalence of hypertension in diabetic persons.3 In a large prospective cohort study that included 12,550 adults, the development of type 2 diabetes was almost 2.5 times as likely in persons with hypertension than in their normotensive counterparts.3,4 Similarly, evidence points to increased prevalence of hypertension in diabetic persons.5,6 Moreover, each pathophysiological disease entity serves to exacerbate the other.5,6 Both hypertension and diabetes predisposes to the development of cardiovascular disease (CVD) and renal disease.7,8 Subjects with diabetes are at about 60% increased risk of early mortality.8,9 The age-adjusted relative risk of death due to cardiovascular events in persons with type 2 diabetes is three-fold higher than in the general population. The presence of hypertension in diabetic patients substantially increases the risks of coronary heart disease, stroke, nephropathy and retinopathy.5,10,11 Indeed, when hypertension coexists with diabetes, the risk of CVD is increased by 75%, which further contributes to the overall morbidity and mortality of an already high-risk population.5,12 Generally, hypertension in type 2 diabetic persons clusters with other CVD risk factors such as microalbuminuria, central obesity, insulin resistance, dyslipidaemia, hypercoagulation, increased inflammation and left ventricular hypertrophy.5 This clustering risk factor in diabetic patients ultimately results in the development of CVD, which is the major cause of premature mortality in patients with type 2 diabetes.

**Pathophysiology of Hypertension in the Diabetic Patient**

Epidemiologic studies provide evidence for co-existence of hypertension and diabetes and possibly point towards a common genetic and environmental factor promoting both diabetes and hypertension. Similarly, clustering of hypertension, insulin resistance or frank type 2 diabetes, hyperlipidaemia and central obesity have been documented in several populations.13 Insulin resistance, increased tissue inflammation and reactive oxygen species (ROS) production resulting in endothelial dysfunction, increased tissue renin—angiotensin—aldosterone system (RAAS) and increased sympathetic nervous system (SNS) activity have all been implicated in this complex pathophysiology of diabetes and hypertension.

### Diabetes, Insulin Resistance and Hypertension – A Complex Interrelated Process and the Crucial Role of RAAS

It is estimated that about 25–47% of persons with hypertension have insulin resistance or impaired glucose tolerance.14 With insulin resistance there are impaired biological and physiological tissue responses to insulin. The relationship of insulin resistance, diabetes and hypertension is complex and interrelated. Untreated patients with essential hypertension have higher fasting and postprandial insulin levels than age- and sex-matched normotensive persons, regardless of body mass; a direct correlation between plasma insulin levels and blood pressure (BP) exists.5,15 Interestingly, the relationship between hyperinsulinaemia and hypertension is not seen in secondary hypertension.15 This indicates that insulin resistance and hyperinsulinaemia are not consequences of hypertension, but rather a genetic predisposition that acts as a fertile soil for both diseases. This notion is supported by the observation that there is abnormal glucose metabolism in the offspring of hypertensive parents.15,16 Thus, there is a strong association between hypertension, diabetes and insulin resistance. There is also a strong association between upregulation of RAAS, hypertension and diabetes.17-19 This upregulation of RAAS results in enhanced generation of ROS and may explain...
impaired glucose utilisation as well as hypertension associated with insulin resistance and type 2 diabetes. It has been proposed that increased autocrine/paracrine activity of angiotensin II (ANG II) results in diminished action of insulin and insulin growth factor-1 (IGF-1) signalling through the PI3K/Akt pathway, resulting in inhibition of mechanisms involved in the vasodilator and glucose transport properties of insulin and IGF-1.20,21 (see Figure 1 and 2). Insulin activates the PI3K/Akt system in skeletal muscle, adipose, and myocardial tissues and initiates translocation of the GLUT4 glucose receptor to the cell membrane. The unregulated ANG II acts through its receptor (AT1R) and results in formation of ROS and the activation of low-molecular-weight G proteins such as RhoA.20 Activation of these small G proteins and consequent enhancement of the generation of ROS inhibits insulin/IGF-1 actions mediated through PI3K/Akt signalling including activation of endothelial nitric oxide (NO) synthase (eNOS) activity, Na+ pump activation, and Ca2+-myosin light chain (MLC) desensitisation.20

Similar RAAS-mediated increases in oxidative stress are likely contribute to insulin resistance in skeletal muscles. This is supported by findings that ROS are increased in skeletal muscle from Ren-2 rats that over-express tissue ANG II, and that this effect is abolished when the animals are treated with an AT1R blocker.22 This and numerous other studies have shown that therapy with angiotensin-converting enzyme inhibitors (ACE-I) decreases the progression to type 2 diabetes in high-risk patients.5,23–25 These and other studies imply the critical role played by RAAS and usefulness of ACE-I in the treatment of diabetes and hypertension.26

Activation of the RAAS also results in increased aldosterone secretion from the adrenal gland and resultant salt retention and volume expansion and consequent hypertension. Further, aldosterone also contributes to hypertension by enhancing SNS activity, decreasing parasympathetic activity, and reducing baroreceptor sensitivity.27 Other effects of aldosterone in kidney, besides the salt retention, include increased extracellular matrix deposition by glomerular cells, leading to glomerulosclerosis and hypertension.27

Blockade of the aldosterone receptor in the Randomized Aldactone Evaluation Study (RALES) using spironolactone in patients with chronic moderate to severe heart failure, corresponding to New York Heart Association (NYHA) class 3 and 4, reduced mortality by 30%.28 More recently, the selective aldosterone receptor antagonist eplerenone in heart failure patients showed a similar decrease in mortality with fewer side effects.29

Other possible causes of hypertension with diabetes and insulin resistance/hyperinsulinaemia include activation of the sympathetic nervous system, increased renal tubular sodium retention, elevated intracellular calcium concentration and vascular smooth muscle cell proliferation and atherosclerosis, and impaired NO metabolism in skeletal muscle.7,20–35 Another mechanism is the upregulation of vascular AT1R by post-transcriptional mechanisms enhancing the
vasoconstrictive and volume-expanding actions of the RAAS. Some studies even suggest that excess levels of insulin can interfere with compliance of the great vessels and decrease the ability of the aorta to reflect aortic waves. Therapy targeted at insulin resistance, such as aerobic exercise or thiazolidinedione drugs, results in a decrease in BP.

Management

In patients with diabetes, the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends a target BP of <130/80mmHg in order to prevent death and disability associated with high BP. Once hypertension is detected both pharmacological and non-pharmacological interventions should be implemented. Instituting lifestyle modifications is paramount, along with medical therapy at the earliest detection of the pre-hypertensive patient.

Lifestyle Changes

The first objective in any hypertensive diabetic should be to initiate lifestyle changes. These changes should include an improved diet, regular physical activity, weight management and cessation of smoking. Weight loss has shown to be an effective therapy in hypertension management. Moreover, studies have shown that modest weight loss can lower or even eliminate the need for antihypertensive medication. Patients should be advised to adopt the Dietary Approach to Stop Hypertension (DASH) eating plan, consisting of a low sodium, high potassium, low calorie (800–1,500kcal/day) and high fibre diet, as it is shown to be effective in lowering BP. Coupled with diet, increased physical activity, such as walking for 30–45 minutes three to five days a week, has been shown to improve lipid profiles, BP and insulin resistance.

Pharmacotherapy

The JNC 7 recommendations are consistent with guidelines from the American Diabetes Association (ADA), which has also recommended that BP in diabetics be controlled to levels of 130/80mmHg or lower. Whatever the goal level, rigorous control of BP is paramount for reducing CVD mortality and morbidity. To achieve goal BP in diabetics, two or more drugs are usually required. There is convincing evidence regarding a certain class of drugs that seems to offer certain beneficial effects over others in hypertensive diabetics.

ACE-I

There is significant evidence that interruption of the RAAS can provide cardio-protective properties. Data from several large studies, such as the Captopril Prevention Project (CAPPP) and the Micro-HOPE, a sub-study of the Heart Outcomes Prevention Evaluation (HOPE) trial, have demonstrated the cardiovascular benefits of ACE-I. ACE-I are also known to improve insulin sensitivity, retard the progression of diabetes and even prevent the development of diabetes in hypertensive patients by inhibiting RAAS. Most notably, ACE-I have also demonstrated the ability to slow progression of nephropathy in microalbuminuric, normotensive type 2 diabetes compared with other antihypertensives. After initiation of therapy with ACE-I or angiotensin receptor blockers (ARBs), monitoring of renal function and potassium is imperative.

ARBs

Other medications receiving considerable attention in recent years are the ARBs. The antihypertensive action of ARBs is roughly equivalent to ACE-I, but does have an improved side effect profile when compared with ACE-I. Similar to ACE-I, ARBs have beneficial effects in reducing the progression of diabetes and carry other cardiovascular and renal benefits noticed in ACE-I, by virtue of its RAAS blockade.

Several clinical trials demonstrate that ARBs also have beneficial effects on glucose metabolism that are likely independent of bradykinin-mediated mechanisms. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, losartan reduced the relative risk of developing type 2 diabetes by 25% when compared with the beta-blocker atenolol. Similarly, reduction in the relative risk of developing diabetes was noted in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) studies.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial demonstrated the advantage of an ARB, valsartan, over a calcium channel blocker (CCB), amlodipine, in reducing the relative risk of new onset diabetes by 23% in patients with hypertension aged 50 years or older.

The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) is another double-blind multicentre study set up to investigate the role of an ARB and an ACE-I, alone or in combination, in the prevention the incidence of type 2 diabetes as a secondary end-point. ACE-I/ARB studies so far have assessed the incidence of type 2 diabetes as a secondary end-point. The consistent and promising results noted from these studies resulted in initiation of studies to...
clarify the extent by which the inhibition of RAAS can reduce the incidence of new onset diabetes. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medications (DREAM) trial is a large international multicentre randomised, prospective double-blind controlled trial involving 4,000 people, randomised to receive either ramipril and/or rosiglitazone using a 2x2 factorial design and assessed for new onset diabetes. Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) is another study that evaluates the effects of an oral antidiabetic drug, nateglinide, and an ARB, valsartan, on prevention of type 2 diabetes in patients with impaired glucose tolerance. This study is similar to DREAM, but is a larger trial (7,500 subjects compared with 4,000) and investigates the effects of antidiabetic/antihypertensive therapy on the development of CVD in people with impaired glucose tolerance.

Collectively, these on-going studies are expected to clarify the extent to which inhibition of the RAAS can reduce the incidence of new onset diabetes in patients with impaired glucose tolerance, a group that includes many Americans with essential hypertension.

**Beta-blockers**

Beta-blockers can be effective antihypertensive agents in the diabetic population as part of a multi-drug regimen. Beta-blockers also find their use in diabetes patients with concomitant evidence of coronary artery disease (CAD) such as anginal symptoms, including anginal equivalents, or post-myocardial infarction (MI). The effectiveness was demonstrated in the UK Prospective Diabetes Study Group (UKPDS), where atenolol was comparable with captopril in reduction of CVD outcomes. Although these agents have been associated with adverse effects on glucose and lipid profiles and implicated in new onset diabetes in obese patients, they are not absolute contraindication for use in diabetic patients. In fact, carvedilol, which has both α- and β-receptor blocking properties, has been shown to induce vasodilatation and improve insulin sensitivity.

**Thiazide Diuretics**

Thiazides have been shown to cause electrolyte imbalances, metabolic changes and volume contraction. Nevertheless, in the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which compared a thiazide (chlorothalidone) with a calcium channel blocker (CCB) (amlodipine) or an ACE-I (lisinopril), found that the thiazide was less expensive and superior to the ACE-I or CCB in lowering the incidence of CVD in hypertensive populations. Therefore, ALLHAT suggests that thiazides could be considered as a first-line therapy for many diabetic patients with hypertension, despite the fact that they may adversely affect insulin resistance and potassium balance in some individuals. Indeed, utilising a thiazide diuretic in the antihypertensive repertoire has consistently been shown to improve cardiovascular outcomes, even in those with diabetes. Treating volume expansion with thiazide diuretics can increase the activity of the RAAS. Thus, combining a diuretic with an ACE-I or an ARB can be an effective BP-lowering combination.

**CCB**

It has been shown that non-dihydropyridine (ND) CCBs, such as verapamil and diltiazem, decrease proteinuria in diabetics. Not to the degree of ACE-I alone, but in combination therapy, NDCCBs and ACE-I have been shown to have additive effects in reducing albuminuria. The Syst-Eur trial with netrendipine demonstrated that intensive antihypertensive therapy for older patients with type 2 diabetes and isolated systolic hypertension eliminated the additional risk for CVD events and stroke associated with diabetes.

In the Hypertension Optimal Treatment (HOT) trial, there was a reduction in major CVD events with diastolic BP control in patients with diabetes when felodipine was used as first-line therapy.

Thus, CCBs are not harmful or contraindicated in hypertensive patients with diabetes and the combination of an ACE-I and a calcium antagonist is effective for the management of hypertension in diabetic patients.

**Summary**

Diabetes is a growing epidemic in both the developing and developed world and more so in the former. It places an enormous burden on already sparse resources. Diabetes is known to be associated with hypertension. The presence of one increases the risk of having the other. This close relationship between diabetes and hypertension suggests a possible common genetic or pathophysiological process or both. Hypertension and diabetes are associated with increased risk of CVD and renal disease. The risk is exacerbated when both are present. It is therefore imperative that hypertension is controlled rigorously to prevent or decrease the risk of CVD and renal disease. Insulin resistance, RAAS, endothelial dysfunction, and autonomic nervous system dysfunction play an important part in the pathogenesis of hypertension and diabetes.
Therapy aimed at improving insulin sensitivity and RAAS blockade seems to offer survival benefits to diabetics with hypertension. Further work in identifying the mechanism of hypertension, diabetes and insulin resistance would shed more light on the missing link that connects these seemingly different disease processes.

References


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