REVIEW ARTICLE

Arterial hypertension in diabetes mellitus: from theory to clinical practice

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Abstract

Diabetes mellitus and arterial hypertension are two common diseases that often coexist. Patients with diabetes have much higher rate of hypertension than that in general population. The co-existence of these disorders appears to accelerate microvascular and macrovascular complications and greatly increases the cardiovascular risk, risk of stroke and end stage renal disease. Arterial hypertension is clearly related to nephropathy in subjects with type 1 diabetes. In patients with type 2 diabetes insulin resistance seems to play a pivotal role in the pathogenesis of hypertension. Several well designed randomized controlled trials have provided evidence that patients with diabetes will benefit from a more aggressive treatment of hypertension. This benefit is seen at blood pressure level < 130/80 mmHg. Mopreover, most diabetic patients with hypertension require combination therapy to achieve optimal blood pressure goals. Angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, β-adrenoreceptor blockers and calcium- channel blockers are all effective antihypertensive agents in type 2 diabetes mellitus and no comparative trial showed the superiority of any particular class in either lowering blood pressure or reducing cardiovascular morbidity and mortality.

On the basis of experimental arguments and clinical observations that have shown their apparent superiority in slowing diabetic nephropathy, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers are preferred as the first choice alone or in combination with diuretics. Second choice should be long-acting calcium-channel blockers or cardioselective β blockers. Clinicians should be aware of the need for aggressive treatment of hypertension and spend more time in order to provide maximal benefit to the treatment of diabetes mellitus and hypertension. Hippokratia 2008; 12 (2): 74-80

Key words: arterial hypertension diabetes mellitus

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Diabetes mellitus and arterial hypertension are common chronic disorders that often coexist. Large epidemiologic studies showed that diabetes is associated with increased cardiovascular mortality and that hypertension accelerates morbidity and mortality markedly in these patients[1]. Also, cardiovascular events are more than twice as likely in patients with diabetes and hypertension than patients with either disease alone[2].

The prevalence of hypertension in diabetic patients is approximately twice that of the non diabetic population[1]. The incidence of diabetes mellitus is rapidly rising and will soon affect 300 million people worldwide while more than half of them will be hypertensives[2].

Moreover, diabetes mellitus is the most common cause of end stage renal disease in the Western world[3]. In the past two decades according to the U.S. Renal Data System[4], there has been continual increase in the incidence of end-stage renal disease among patients with diabetes, predominantly of those with type 2 diabetes.

Recent reports from the United States have shown that almost two thirds of adult diabetic population use antihypertensive therapy or have blood pressure >130/80 mm Hg[5].

Many attempts have been made to elucidate the mechanism of the coexistence of diabetes and hypertension. It has been suggested genetic predisposition as possible mechanism even in the presence of insulin resistance, gene alterations, membrane cation transport abnormalities, altered adrenoreceptor responsiveness, increased sodium sensitivity of the vasculature and neurohumoral changes[6]. Unfortunately, up to now, no hypothesis has been able to elucidate the mechanism of the development of hypertension in patients with diabetes.

Among patients with type 1 diabetes mellitus the prevalence of hypertension is similar to that of the general population and becomes more frequent when nephropathy occurs[7]. Although early hemodynamic changes are similar in both types of diabetes, in type 2 diabetes hypertension seems to antedate these changes[8,9]. There is convincing evidence that the pathogenesis of hypertension in persons with diabetes mellitus is multifactorial and that

this pathogenesis could not be explained by one simple hypothesis.

Arterial hypertension and type 1 diabetes mellitus

In patients with type 1 diabetes mellitus the development of arterial hypertension is clearly related to microalbuminuria[10]. Recent studies, using ambulatory blood pressure monitoring, have shown that subjects with type 1 diabetes mellitus and microalbuminuria have higher nocturnal blood pressure than either subjects with type 1 diabetes and normal urinary albumin excretion or age-matched controls[10,11].

Lurbe et al[12] studied 75 adolescents and young adults who had type 1 diabetes with normal urinary albumin excretion and blood pressure for more than five years and concluded that in patients with type 1 diabetes an increase in systolic blood pressure during sleep precedes the development of microalbuminuria. In those whose blood pressure during sleep decreased normally, the progression from normoalbuminuria to microalbuminuria was less likely. They suggested that an evaluation of the risk of nephropathy at an early stage of type 1 diabetes would provide the best basis for choosing therapies designed to prevent the progression to microalbuminuria e.g. angiotensin-converting-enzyme inhibitors (ACE-I) or angiotensin II-receptor blockers (ARBs). On the other hand documentation of normal nocturnal blood pressure might suggest that there is no need for early therapeutic interventions other than those designed to provide optimal glycemic control.

The results of recent studies have shown that a predisposition to essential hypertension increases the risk of diabetic nephropathy. This concept has been based on studies showing that parents of patients with type 1 diabetes have a higher prevalence of hypertension than that of general population[13].

In type 1 diabetes the onset of hypertension seems to be associated with microalbuminuria and appears to be a consequence rather than a cause of renal disease. Moreover it has been shown that there is an increased activity of sodium-lithium exchanger[14] and of sodium-hydrogen exchanger[15] in both subjects with essential hypertension and those with type 1 diabetes mellitus and nephropathy[16]. In type 1 diabetes mellitus hypertension is often secondary to overt nephropathy[17]. Elevated blood pressure in turn exacerbates nephropathy; thus these comorbid states reinforce each other[18].

Arterial hypertension and type 2 diabetes mellitus

Many large, well designed multicentre, studies have shown that arterial hypertension and type 2 diabetes appear to be associated clinically as a syndrome involving also other conditions such as dyslipidemia, central obesity, hyperuricemia and accelerated atherosclerosis[19,20]. This syndrome has been described as insulin resistance syndrome[27], metabolic syndrome[20] or "syndrome X"[21]. Although underlying explanation for this constellation of clinical features remains unexplained, insulin resistance seems to play a pivotal role[20].

Insulin resistance is a metabolic disorder, manifested by a reduction of glucose utilization in peripheral skeletal muscle[22]. The result of this disorder is that larger amounts of insulin are needed to achieve normoglycemia. In untreated patients with essential hypertension, fasting and postprandial insulin levels are higher than in normotensive controls, regardless of the body mass index, with a direct correlation between plasma insulin concentrations and blood pressure level[23]. A genetic predisposition to insulin resistance and hypertension is present in patients with type 2 diabetes mellitus[24]. In addition to the genetic predisposition, insulin resistance / hyperinsulinemia is incriminated in the development of hypertension through abnormalities in insulin signalling and associated cardiovascular and metabolic derangements[17,24,25]. These would include cell membrane ion exchange, enhanced sympathetic and renin-angiotensin-aldosterone system activity (RAAS) as well as suppressed atrial natriuretic peptide activity, sodium retention with consequent volume expansion, progressive renal disease, cardiac hyperactivity, left ventricular hypertrophy, dyslipidemia, chronic hyperglycemia and increased oxidative stress[26] (Figure 1).

The role of hyperinsulinemia in the pathogenesis of arterial hypertension is still debated. For example, patients with insulinoma do not appear to have increased arterial blood pressure[27]. In the insulin-resistant state, there is inhibition of several insulin signalling pathways, thus contributing to vasoconstriction[25]. Insulin resistance is often present in persons with impaired fasting glucose levels and represents a risk factor for cardiovascular disease even in the absence of significant hyperglycemia[20].

Hyperinsulinemia may contribute to the genesis of hypertension through its effect on sodium homeostasis

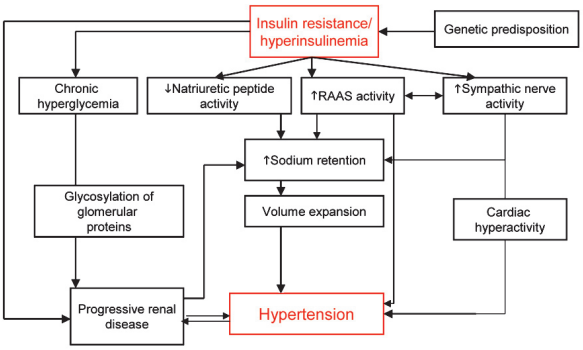

Figure 1. Insulin resistance/hyperinsulinemia seems to play a pivotal role in the pathogenesis of hypertension in genetically predisposed people. Chronic hyperglycemia contributes to progressive renal damage via glycosylation of glomerular proteins. Reduced atrial natriuretic peptide activity, enhanced RAAS activity and sympathic nerve activity as a consequence of insulin resistance/hyperinsulinemia are also involved in the pathogenesis of hypertension. Hypertension exacerbates renal damage and these comorbid states reinforce each other.

and enhanced responsiveness of the sympathetic nervous system. Both experimental and clinical studies suggest that increased sympathetic nervous system activity is an important mediator of insulin resistance via stimulating renal sodium reabsorption and subsequent volume expansion[28]. Obesity is a well established risk factor for development of type 2 diabetes mellitus and hypertension[29]. Almost ninety percent of the patients with type 2 diabetes are obese. Although the obese individuals uniformly develop insulin resistance, not all of them develop type 2 diabetes mellitus or arterial hypertension.

Nephropathy in patients with diabetes mellitus and arterial hypertension

Hypertension plays a major role in the development and progression of nephropathy in both type 1 and type 2 diabetes mellitus. Although hypertension often develops after the onset of nephropathy, up to 50% of patients with type 2 diabetes have hypertension at the time of diagnosis[30]. The prevalence of hypertension in type 2 diabetes is high. The rate of hypertension is already twice as high in patients with impaired glucose tolerance as compared to normal controls[31] and the risk of nephropathy with progression to end-stage renal disease is similar in both types of diabetes[32].

Both the prevalence and the incidence of end-stage renal disease are approximately twice than that 10 years ago[33]. Unfortunately hypertension is controlled in less than 25% of the hypertensive population[34] and a target blood pressure of less than 130/80 mmHg is achieved only in a minority of type 2 diabetes patients. The risk of end-stage renal disease is particularly high in patients with hypertension and diabetes, almost five to six times higher than in patients with hypertension without diabetes[35]. Therefore more aggressive treatment of hypertension in patients with type 2 diabetes is mandatory.

The issue is if the progress in understanding the mechanisms involved in the genesis of nephropathy in patients with diabetes and hypertension could be translated adequately into clinical practice.

The Captopril Collaborative Study Group[36] demonstrated a significant risk reduction nephropathy progression in patients with type 1 diabetes treated with captopril. A meta analysis of 12 trials in 698 type 1 diabetic patients with microalbuminuria[37] revealed that the treatment with ACE inhibitor for two years was associated with a 60% reduction in progression to macroalbuminuria and in threefold increase in regression to normoalbuminuria in comparison with placebo. In addition the 2-year urinary albumin excretion was 50% lower in the ACE inhibitor than in placebo group. Recently in a randomized controlled trial ACE inhibitor has been shown to prevent progression from normoalbuminuria to overt nephropathy and that these drugs have long lasting (eight years) beneficial renoprotective effect[38].

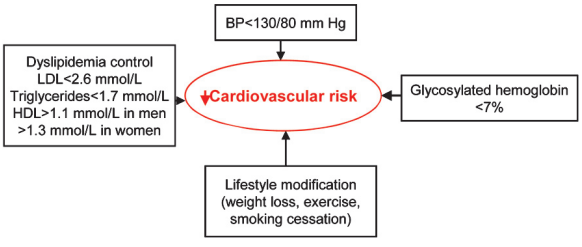

Figure 2. Target levels for the modifiable risk factors in patients with diabetes mellitus

A number of meta-analyses have suggested that for the same reduction in blood pressure ACE inhibitors are more effective in decreasing albuminuria than other antihypertensive drugs[39]. This has been supported by the findings of the Microalbuminuria, Cardiovascular and Renal Outcomes – Heart Outcomes Prevention Evaluation (MICRO-HOPE) study[40] showing that overt nephropathy was reduced by 24% in the ramipril treated group resulting in significant protection against cardiovascular events. Therefore this study provides a rationale for using ACE inhibitors in patients with type 2 diabetes, nephropathy and other cardiovascular risk factors.

Three multicentre randomized double-blind placebo controlled studies with ABRs have provided recently convincing evidence that these drugs have renoprotective effect in patients with type 2 diabetes mellitus and nephropathy[41-43]. Parving et al[41] administered irbesartan to 590 hypertensive patients with type 2 diabetes and microalbuminuria at a dose of 150 mg daily or 300 mg daily and followed them for 2 years. They concluded that irbesartan had a renoprotective effect that was independent of its blood pressure lowering effect. Furthermore in this study (IRMA II) the restoration of normoalbuminuria was more evident in the group receiving irbesartan at a dose of 300 mg daily. Two other studies, IDNT[42] and RENAAL[43] also used ARBs, but they enrolled patients with higher grade of proteinuria and established renal insufficiency. In patients whose disease was at this more advanced phase, the use of ARBs led to lower levels of proteinuria, lower rates of decline in the glomerular filtration rate and later onset of end-stage renal disease than the use of control medications.

Patients with diabetes often require combination therapy to achieve blood pressure target detailed in various international guidelines. The Candesartan and Lisinopril Microalbuminuria (CALM) study[44] has investigated the role of the combination of the ACE-I lisinopril and the ARB candesartan in hypertensive type 2 diabetic subjects with microalbuminuria. This combination showed that candesartan was as effective as lisinopril in reducing blood pressure and microalbuminuria and that combination therapy was well tolerated and was more effective in reducing blood pressure. Recently the CALM II study[73] has been published with the longest follow-up regarding dual blockade in diabetic patients. The conclusion of this study was that there was no statistically significant difference between lisinopril 40 mg once daily and lisinopril 20 mg in combination with 16 mg candesartan once daily in reducing systolic blood pressure in hypertensive patients with diabetes. However, in two recently published stud-

ies[46,47] where dual blockade was added to maximal recommended dose of ACE inhibitor, significant additional effects on blood pressure and proteinuria were obtained in both patients with type 1 and type 2 diabetes mellitus.

The DETAIL Study[48] a prospective, multicenter, double blind, five-year study compared angiotensin II-receptor blocker telmisartan 80 mg once daily with ACE inhibitor enalapril 20 mg once daily in 250 subjects with type 2 diabetes and early nephropathy. This study showed that telmisartan was not inferior to enalapril in providing long-term renoprotection in patients with type 2 diabetes and supported that ABRs and ACE inhibitors are clinically equivalent in patients that place them at high risk for cardiovascular events.

The combination of an ACE inhibitor and a calcium channel blocker seems to be also effective in reducing blood pressure and proteinuria. In the BENEDICT Study[49], a multicenter, double-blind, randomized study 1204 subjects with type 2 diabetes and hypertension but with normoalbuminuria were randomly assigned to the treatment with trandolapril at a dose 2 mg daily plus verapamil at a dose 180 mg daily or trandolapril alone 2 mg daily, verapamil alone at a dose 240 mg daily or placebo for at least three years. The target blood pressure was 120/80 mm Hg. The primary end-point was the development of persistent microalbuminuria. This study showed that the combination of trandolapril with verapamil, was no superior than trandolapril in reducing of the incidence of microalbuminuria and that the effect of verapamil was similar to that of placebo.

Diabetes mellitus, arterial hypertension and cardiovascular risk

Cardiovascular disease is the leading cause of death in patients with both types of diabetes and the mortality in these patients is two or three times increased compared to nondiabetic population[2]. In a population-based study in Finland, Haffner et al[50] have shown, that the incidence of fatal myocardial infarction was 18.8% for nondiabetic individuals with a history of myocardial infarction and 3.5% for those without prior infarction. In patients with diabetes mellitus, the incidence of myocardial infarction was 45% for those with prior myocardial infarction and 20.2% for those without.

Randomized controlled trials provided conclusive evidence for the benefits of blood pressure reduction below 130/80 mm Hg. In the United Kingdom Prospective Diabetes Study (UKPDS)[51] patients assigned to a tight blood pressure control had a 37% reduction in the risk of developing microvascular end points compared with those assigned to less tight blood pressure control. Moreover this tight blood pressure control resulted in a significant 32% reduction of diabetes related mortality, 44% strokes and 24% of all diabetes-related endpoints. This study showed that the relative benefit of cardiovascular disease reduction conferred far more potently by intensive blood pressure reduction than by intensive blood glucose control[51,52].

In the Hypertension Optimal Treatment (HOT)[53] study 1051 diabetic patients with hypertension were randomly assigned to achieve diastolic blood pressure of less than 90, 85 or 80 mm Hg while taking the dihydropyridine calcium-channel blocker felodipine, often with the addition of one or two other drugs. The conclusion based on this study was that the risk of major cardiovascular events was 50% lower among patients with type 2 diabetes whose target diastolic blood pressure was set at 80 mm Hg than among patients whose target diastolic blood pressure was set at 90 mm Hg[53,54].

The significance of systolic blood pressure control has been noted in many studies. These studies have provided convincing evidence that after the age of 50 years systolic blood pressure is more valid measure of cardiovascular risk and even the pulse pressure assumes increasing importance with higher systolic blood pressure in correlating with cardiovascular morbidity and mortality[55].

Consequently, many clinical studies have focused on defining optimal levels of blood pressure as well as the class and the dose of drug needed to achieve this goal. Grossman et al [58] compared the effectiveness of the different classes of antihypertensive drugs and supported that intensive blood pressure control reduced cardiovascular morbidity and mortality in patients with diabetes regardless of whether low-dose diuretics, β-blockers, angiotensin-converting enzyme inhibitors, or calcium antagonists were used as the first-line treatment.

The metabolic effects of antihypertensive medications aroused a great concern because these drugs are used by more than 20 million adults in the United States alone[59]. Initially, short-term metabolic studies of thiazide diuretics aroused concern about the diabetogenic potential of these drugs[60]. Subsequently, the results of some epidemiologic studies and clinical trials suggested a causal link between the use of β-blockers or thiazide diuretics and subsequent development of type 2 diabetes[61].

Traditionally the use of β-blockers has been discouraged in patients with diabetes because they were associated with adverse effect such as weight gain, reduced peripheral blood flow, pronounced hypoglycemia and nightmares. Cardioselective β-blockers are preferred to the nonselective type because they are associated with less blunting of hypoglycemia awareness and less elevation of lipid and glucose levels. On the other hand drugs that interrupt the renin-angiotensin system have beneficial effect on glucose metabolism[40,62] (Table 1).

Table 1. Risk reduction of new onset diabetes mellitus

Trial	Group				Relative Risk (95% CI)	P value
HOPE	Ramipril (n=4645)		Placebo (n=4652)		0.66 (0.51-0.85)	<0.001
	New DM	%	New DM	%		
	102	3.6	155	5.4		
LIFE	Losartan (n=4605)		Atenolol (n=4588)		0.75 (0.63-0.88)	0.001
	New DM	%	New DM	%		
	241	6.0	319	8.0		

Arterial hypertension, diabetes mellitus and stroke

Stroke is a major public health problem and an important cause of morbidity and mortality. Epidemiological data from the United States showed that stroke is the third leading cause of death and the leading cause of disability[63,64]. Both arterial hypertension and diabetes mellitus are independent risk factors for stroke and when these disorders coexist the risk of stroke is further increased. Silent cerebral infarcts are often incidentally detected on imaging techniques in the elderly population with hypertension and diabetes and occur without localized neurological symptoms. Recently Eguchi et al[65] studied the impact of hypertension and diabetes on silent cerebral infarcts in 360 asymptomatic hypertensive patients with or without diabetes. This study showed that the presence of diabetes mellitus was the most powerful determinant of silent cerebral infarcts in patients with hypertension. Large randomized clinical trials with diabetic population have clearly demonstrated that adequate blood pressure control improves the cardiovascular disease risk, particularly for stroke[40,51,56,66-68]. There are nonmodifiable, and modifiable risk factors for stroke. In the diabetic hypertensive population, among the most important modifiable risk factors is elevated blood pressure. Lowering blood pressure to <130/80 mm Hg is strongly recommended for the primary and secondary stroke prevention[69].

Arterial hypertension in diabetic patients: from guidelines to clinical practice

The Seventh Report of the Joint National Committee on Prevention, Detection Evaluation and Treatment of High Blood Pressure (JNC 7)[70] and American Diabetes Association[71] have recognized the patients with diabetes as a population at particular high risk and have recommended that blood pressure should be decreased to less than 130/80 mm Hg in these patients (Table 2) and in the presence of renal impairment or of significant proteinuria > 1 gr/24 hours the recommended treatment target is <125/75 mm Hg[72]. There is evidence that intensive reduction in blood pressure to this level will reduce microvascular and macrovascular complications in patients with diabetes. Lifestyle modification is a part of therapy in patients with diabetes and hypertension. In obese patients with diabetes and mild hypertension, body weight reduction, increased physical activity, decrease in dietary sodium intake and avoidance of alcohol ingestion should be encouraged[73].

Table 2. Blood pressure control in patients with diabetes mellitus – Current recommendations

Joint National Committee 7*	**<130/80**	**ACE I**
American Diabetes Association**	**<130/80**	**ACE I or ABR**

*The 7th report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The JNC report, *JAMA 2003;289:2560-2572*

** ADA Standards of medical care for pts with diabetes mellitus, *Diabetes Care 2003; 26(suppl1)539-550*

All patients with diabetes and hypertension should be treated with a regimen that includes an ACE inhibitor or an angiotensin receptor blocker as a first-line therapy. To achieve the desired reduction in blood pressure (<130/80 mm Hg) most diabetic patients will require therapy with three to five antihypertensive drugs[74]. Patients with diabetes retain sodium and their hypertension is volume-sensitive. Therefore diuretic therapy with thiazide diuretic or loop diuretic if renal failure is present (creatinine >1.8 mg/dl) is often required[75] in combination with ACE inhibitors or ARBs. If additional therapy is required a calcium channel blocker, selective β- blocker or α-blocker may be used[76].

The elderly patients with diabetes have often vascular disease. Therefore these patients should be examined carefully to rule out the presence of stenotic lesions. The blood pressure should be lowered slowly in these patients because their ability of the cerebral and renal autoregulation is reduced[77]. Moreover renal function and potassium levels should be monitored in patients with diabetes treated with ACE inhibitors or ARBs because of potential risk of hyperkalemia or unrecognised renal-artery stenosis. In addition, the possibility of orthostatic hypotension that is often seen in patients with longstanding diabetes as a consequence of autonomic neuropathy should be examined.

Comparative trials have failed to show definite superiority of any particular class in either lowering blood pressure or reducing cardiovascular morbidity and mortality up to now[78]. The control of blood pressure to level <130/80 mm Hg is strongly recommended, but only a small proportion of the patients with diabetes achieves this target. The reasons for poor rates of control of hypertension have been discussed extensively and they have been attributed to patients-related factors, such as lack of awareness and knowledge of hypertension, lack of access to health care, low literacy rates, poor adherence to prescribed treatment and clinical visits, and the cost of drugs[79,80]. Other factors include decreased time for interaction between patients and health care practitioners and the environment or setting where interaction occurs. Guidelines can be effectively translated into clinical practice only if clinicians have the will to implement what is already known[81]. However, multifactorial intervention[82] directed towards modifiable risk factors that include blood pressure control, glycemic control, lipid control and lifestyle modification is the most appropriate strategy that would provide maximal benefit to patients with diabetes mellitus.

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