Management of Hypertension in Diabetes Mellitus

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INTRODUCTION

Hypertension in diabetes mellitus represents an important health problem as the combination of the two disorders is common and carries significant morbidity and mortality rate. Both disorders are significant independent risk factors for cardiovascular, cerebral, renal and peripheral atherosclerotic vascular disease [1]. The major causes of increased morbidity and mortality in diabetes mellitus have been the long-term (chronic) complications, both microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (cardiovascular, cerebrovascular and peripheral vascular disease); the prevention and amelioration of these complications have been the major goals of recent research. In insulin-dependent diabetes mellitus (IDDM), the Diabetes Control and Complication Trails (DCCT) provided incontrovertible evidence that intensive insulin therapy and strict glycaemic control effectively delays the onset and slows the progression of diabetic nephropathy, retinopathy and neuropathy with a likely reduction in risk factors for macrovascular disease[2].

The prevalence of hypertension in diabetic patients (30-50%) is approximately twice as that in the non-diabetic population (15-20%) [1,3,4]. Diabetes is associated with increased cardiovascular (macrovascular) risk; the presence of hypertension accelerates mortality and morbidity four-to-five-fold [1,3,4,5]. Associations have been found between elevated blood pressure and the development and progression of diabetic nephropathy and retinopathy (microvascular disease) [1,3,4,5,6]. Furthermore, there is evidence that anti hypertensive treatment is beneficial with respect to the evolution (progression) of diabetic nephropathy [4,5,7,8].

Since hypertension is a major determinant of morbidity and mortality in diabetes, it should be detected and treated early and aggressively. However, despite improvements in detection treatment and control of hypertension over the past decade, uncontrolled hypertension in diabetes is still a major problem.

To emphasise the importance of detection and management of hypertension in diabetes, the American Diabetes Association (ADA) held a Consensus Development Conference in 1993 and from this, a consensus statement regarding the treatment of hypertention in diabetes was derived[1]. The issues addressed included epidemiology, pathophysiology, goals of therapy and therapeutic modalities. An attempt was made to provide some perspectives on the consensus statement with particular reference to the treatment of hypertension in diabetes.

I Hypertension in Diabetes Mellitus

Hypertention (HT) in diabetes may be due to one on the following reasons[9]

a) secondary to complications of diabetes (nephropathy, renal scarring following repeated urinary tract infects, isolated systolic hypertension due to atherosclerosis).
b) Metabolic syndrome (insulin resistance – hypertension, NIDDM, obesity, atherosclerosis, dyslipidaemia.
c) Coincidental (essential hypertension, isolated systolic hypertension) (IDDM, NIDDM).
d) endocrine disorders and drugs

The time course and natural history of HT differs markedly between Type 1 (IDDM) and Type 2 (NIDDM) diabetes. In IDDM, the BP is usually nor-

Table 1
Natural History of Diabetic Nephropathy in Insulin-dependent diabetes mellitus (IDDM)

Stage	Designation	Functional changes*		Clinical features			Structural changes
		UAE	GFR	Diabetes duration (yrs)	Blood pressure	Diabetic retinopathy	
I	Glomerular hyperfiltration	normal	increased	onset	normal	--	Glomerular hypertrophy
II	Silent stage	normal high normal	increased	2-3	normal	--	Glomerulosclerosis
III	Incipient diabetic nephropathy	microalbuminuria+	increased	>5	mild increase	--	Glomerulosclerosis
IV	Overt/established diabetic nephropathy	clinical proteinuria #	decreasing γ	10 (10-13)	hypertension	present	Glomerulosclerosis
V	End-stage renal disease (ESRD)	decreasing albuminuria	low**	20-40	hypertension	present	Glomerulosclerosis

* UAE = urinary albumin excretion: GFR = Glomerular filtration rate + UAE = > 30 - <300 µg/24hr; >20 - < 200 µg/min
# UAE : ≥ 300 µg/24 hr; ≥ 200 µg/min γ "normal" to advanced reduction
** associated with elevated serum creatinine

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mal at presentation and remains so for the first 5-10 years. HT is clearly a function of diabetic nephropathy (Table1).

The BP rises shortly after the onset of incipient nephropathy (microalbuminuria) and increases further at the stage of established/overt nephropathy (proteinuria) and with end-stage renal disease [4,10,11,12,13]. HT is found in 50% of patients with IDDM of greater than 30-yr duration and this comprises largely the subgroup with diabetic nephropathy (DN). Conversely, long-term survivors of diabetes (>30 yr) who have not developed DN are rarely found HT.

By contrast, in NIDDM patients, hypertension maybe discovered before or at the time of diagnosis or may develop during nephropathy[4]. HT occurs in approximately 40% of patients with NIDDM[14].

a) Insulin resistance and the associate hyperinsulinaemia have been proposed as a potential link between the metabolic (diabetes, obesity, dyslipidemia) and cardiovascular (HT, atherosclerosis) disorders [15,16,17].
b) The natural history of diabetic nephropathy and the contribution of impaired renal function to development of HT in NIDDM is less well defined [10].
c) Isolated systolic HT is common in NIDDM and is attributed to macrovascular disease.

About one-third of IDDM patients and 10-20% of NIDDM patients develop diabetic nephropathy[18]. The pathophysiological mechanisms underlying the association of hypertension and diabetes involves a complex interaction between hereditary and acquired disturbances[4].

II Definition of Hypertension in Diabetes

Although the optimal BP in diabetic patients is unknown, the current consensus of the American Diabetes Association (ADA)[1] recommends that the classification of blood pressure and hypertension in diabetes can be based on the Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC-V)[19].

The JNC-V classification for adults (> 18 yr) defines hypertension as an average BP > -140 mmHg systolic or > 90 mmHg diastolic, based on repeated measurements: hypertension is further classification into stage 1-4 (mild – very severe) (Table 2). Moreover, there should be an evaluation for the presence of target organ damage caused by hypertension, the complications of diabetes and modifiable cardiovascular risk factors.

Table 2

Classification of blood pressure for adults (≥18 yr) (JNC-V, 1993)*

	Blood Pressure (mmHg)	
Category	Systolic	Diastolic
Normal	< 30	< 85
High normal	130 – 139	85 – 89
Hypertension :		
Stage 1 (mild)	140 –159	90 – 99
Stage 2 (moderate)	160 –179	100 – 109
Stage 3 (severe)	180 – 209	110 – 119
Stage 4 (very severe)	≥ 210	≥ 120

*Reference 19

Young diabetic patients should be considered hypertensive if there is a persistent elevation of BP greater than the 95th percentile for age.

III Goals of Therapy – Hypertension in Diabetes

The board goal of therapy is to prevent morbidity and mortality associated with hypertension with the least disturbance to quality of life.

The Consensus Statement of the ADA[1] recommends that the goal of blood pressure therapy for non-pregnant diabetic is to reduce and maintain BP < 130mmHg systolic and <85mmHg diastolic (i.e. JNC-V classification of normal BP); moreover, that the BP may be reduced even further if done with caution and if well tolerated. In younger patients, age-related normal blood pressures should be used as targets for treatment. Antihypertensive therapy should not worsen glycaemic control, lipid levels or concomitant disorders e.g. peripheral vascular disease, chronic airways disease and gout.

It must be noted that there have been no large, population-based, randomised trials of hypertension treatment in patients with diabetes. Thus the efficacy of antihypertensive therapy and the exact target levels of BP remain unclear[22]. The lack of diabetes-specific results have led to extrapolation of BP treatment strategic from the non-diabetic population.

The recent ADA recommendations[1] for early detection and aggressive treatment of hypertension in

diabetes is supported by recent evidence for the beneficial effect of antihypertensive therapy in hypertensive and normotensive IDDM and NIDDM patients with incipient and overt diabetic nephropathy.

The ADA also recommends that a major goal of therapy is a treatment plan that can be followed easily, and for the long-term, considers the patients socioeconomic status along with the patients educational, cultural and ethic background.

IV Therapeutic Modalities for Hypertension in Diabetes

A. Lifestyle Modications

These include weight management, dietary modification, increased physical actively, moderation of alcohol ingestion and cessation of smoking. The significance of lifestyle modifications cannot be over-emphasised and are cornerstones in management of birth, diabetes and hypertension. Lifestyle modification may be used as definitive or adjunctive therapy, in addition to lowering BP, and hyperglycaemia, they have an added potential benefit of reducing other cardiovascular risk factors (e.g. dyslipidaemia. Obesity, physical inactivity) and may reduce the cost and side effects of drug therapy. There is insufficient current evidence to justify dietary supplementation of potassium, magnesium and calcium in the absence of documented deficiency[1].

B. Pharmacologic Treatment

Pharmacological therapy is initiated when life-style modifications fail to control hypertension (target BP < 130/85) : for stage 1 and 2, after 2-3 mth of lifestyle modifications; for stage 3 and 4, at the time of diagnosis. Further substitutions and additions should be based JNC_V recommendations until control is achieved[1,19].

While all classes of antihypertensive drugs are equally effective in controlling blood pressure in diabetic patients, five classes are effective for single agent therapy. These include thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitor, calcium antagonists, alpha-1 receptor antagonists and beta-blockers[1]. However, until evidence from large scale studies in diabetes is available, the therapeutic choice must be based on current understanding of the pathophysiology of hypertension in diabetes and the known pharmacological action and side effects of the various groups.

No consensus was reached regarding the use of any single class of antihypertensive drugs over others in the initial stages of treatment of hypertension in diabetes in the absence of nephropathy.

Table 3 outlines the current consensus of the ADA regarding antihypertensive therapy in diabetes[1]. Since class has potential advantages and disadvantages, a brief outline will be provided regarding the five major classes of antihypertensive drugs.

Table 3
Antihyertensive therapy for patients with diabetes (ADA consensus statement, 1993)*

Agents that may have a special advantage
• ACE- inhibitors
• α -1 receptor blockers
• Calcium antagonists
• Thiazide diuretics in small doses.
Agents that should be used with caution
• α and β-blockers
• β-blockers
• Centrally acting a $_2$-agonists
• Sympatholytic agents
Agents whose use is uninfluenced by the pressure of diabetes
• Direct vasodilators
• Loop diuretic

* Reference 1

Thiazide diuretics

i. In small doses (12.5-25 mg) are effective in lowering BP.
ii. Reduce the expanded plasma volume associated with HT in diabetes.
iii. In non-diabetes, help to decrease cardiovascular morbidity and mortality in large population based studies.

Disadvantages, which are minimised at low doses, include dyslipidaemia, altered carbohydrate metabolism, hypokalemia, hyperinsulinaemia, hypomagnesaemia and hyperuricaemia.

Angiotensin-converting enzyme (ACE) inhibitors have no adverse effect on lipid or glycaemic control and can improve insulin sensitivity[4]. Side effects include hyperkalemia in patients with impaired renal function and/or hyporeninaemic hypoaldoseronism and in patients on potassium-sparing diuretics and supplements; cough which is class-specific; rapid deterioration of renal function in patients with bilateral renal artery stenosis. ACE inhibitors are contra-indicated in pregnancy and have been shown to reduce microalbuminuria and proteinuria and delay or retard diabetic nephropathy in both normotensive and hypertensive diabetes patients (vide infra).

Calcium Antagonists have no adverse effect on lipid, carbohydrate or potassium metabolism. |n a few studies, some calcium antagonists were shown to reduce microalbuminuria and proteinuria, but their long-term reno-potective effect is unknown. Side-effects include headache, flushing, peripheral oedema and constipation.

Alpha- 1 receptor blockers have a beneficial effect on lipid metabolism and improve insulin sensitivity. They may cause orthostatic hypotension in patients with autonomic neuropathy.

Beta-blockers without intrinsic sympathomimetic activity (ISA) have unfavourable effects on glucose and lipid metabolism and interfere with the awareness and recovery of hypoglycaemia. Cardioselective beta-blockers with ISA appear to have less metabolic sideeffects. By reducing peripheral blood flow, claudication and vasospasm may be worsened. In large, population-based studies in non-diabetics, betablockers have been shown to reduce cardiovascular mortality and morbidity; studies have shown that they have a cardioprotective effect following myocardial infarction.

Other antihypertensive agents and special situations. Potassium-sparing agents should be used with caution because of the greater potential for hyperkalemia in the diabetic patient. Sympatholytic agents have many side effects including orthostatic hypotension and impotence. Centrally acting alpha 2-agonist (e.g. clonidine) may cause drowsiness, dryness of the mouth, postural hypotension and depression. Alpha-Beta blockers have similar metabolic side effects as beta-blockers, have no cardioprotective effect and have to be taken twice a day. Loop diuretics and direct vasodilators have no special advantages or precautions in diabetic patients; loop diuretics should replace thiazides if serum creatinine is elevated > 2mg/dl or 177 mol/l). Hypertensive emergencies should be managed as in non-diabetics[19], except that diazoxide is contraindicated because it can exacerbate hyperglycaemia.

Step-down therapy: After 6 months of good blood pressure control by life style modification and drug therapy, the dose and number of drugs may be reduced.

V Protecting Renal function in Diabetes

In order to understand the retionale behind the current recommendations of the ADA[1] regarding the choice of antithypertensive class to protect renal function in diabetes, it is important to provide an outline of the impact of diabetic nephropathy and of the studies which have examined the role of antithypertensive drugs.

A. Diabetic Nephropathy

Diabetic nephropathy (DN) is characterised by proteinuria and declining glomerular filtration rate (GFR). One of the major aims in management of diabetes is to prevent or delay the onset and/or progression of the long-term complications which are the major causes of increased morbidity and mortality[2]. About one-third of IDDM patients[21] and 10-20% of NIDDM patients[18] develop nephropathy. Diabetes is a common cause of end-statge renal disease (ESRD) accounting for approximately 30% of ESRD in most centres.

B. Natural History of diabetic Nephropathy

Much is now known about the natural history of DN in IDDM [10, 18, 22] (Table 1). Following an initial phase of glomerular hyperfiltration (GFR > 120ml/ min/1.7m2) and after 5-10 yrs of diabetes, some patients develop microalbuminuria (incipient DN) (urine albumin excretion 30-300 mg/24 hrs or 20-200 ug/min). In the majority (approx. 80%), if untreated, established (overt) DN will develop over the succeeding 5-15 yrs and is characterised by proteinuria (urine albumin excretion > 300 mg/24hr or > 200 ug/min) and declining GFR, at a rate of 1 ml per minute per month. Hypertension invariably develops during this period. With worsening proteinuria, hypertension and declining GFR, there is a relentless downhill course with ultimate development of ESRO. After the onset of proteinuria, ESRD will develop in virtually all patients within 10-20 yrs.

C. Glycaemic and Blood Pressure Control

Several factors, in particular glycaemic and blood pressure control, have been found to influence the development and progression of DN[1-8, 18,22,23].

Several smaller studies suggested that glycaemic control reduced DN[18] and now the DCCT[2] has shown inconclusively that intensive glycaemic control prevents the onset (microalbuminuria) and delays the progression (microalbuminuria, proteinuria) in IDDM patients. However, there is no evidence from long-term studies that glycaemic control influences the progression from established nephropathy (proteinuria) to ESRD.

Regarding the role of blood pressure, hypertension has been shown to increase the risk of both, the development and progression of DN[1]. Randomised clinical trials indicated that antihypertensive drugs are beneficial in slowing the progression of DN in IDDM by

a) decreasing microalbuminuria or proteinuria,

b) retarding progression from incipient (microalbuminuria) to established (proteninuria) DN and
c) slowing the decline in GFR in patients with established DN[1,6,7,8,13,18,22].

D. Impact of antithypertensive therapy

From the earliest studies over a decade ago, it was shown that conventional antithypertensive therapy (with beta-blockers, diuretics and hydralazine) was able to decrease urinary albumin excretion and decrease the rate of decline in GFR in IDDM patients with DN. Such early studies confirmed for the first time that aggressive anti-hypertensive therapy may be useful in delaying progression of DN[7,8].

Subsequently, from animal studies, there was evidence that ACE-inhibitors were superior to other antihypertensive drugs in regarding the progression of renal disease [4,18,23]. ACE-inhibitors but not other agents, decrease intraglomerular capillary pressure (glomerular hypertension) by preferential dilatation of efferent glomerular arterioles.

The information regarding calcium antogonists in DN is incomplete [4,5]. Results from some animal studies indicate that they decrease glomerular damage and proteinuria. In humans, trials with calcium antagonists have produced variable and often conflicting results. Some studies have shown equal efficacy of calcium antagonist (nifedipine) and ACE-inhibitors (perindopril) in decreasing microabuminuria [24,5]; nifedipine was shown to have no adverse effect on GFR in one prospective study[5]. Other studies have shown that some calcium antagonists e.g. nifedipine Worsens proteinuria in DN by selective afferent glomerular vasodilation, a factor which may antagonise a blood pressure dependent anti proteinuric effect [4]. However, in one study, there was a suggestion of increased proteinuria even with verapamil[5]. Although the general feeling is that calcium antagonists are inferior to ACE-inhibitors with respect to proteinuria, it must be borne in mind that the various calcium blockers act differently[5,25].

For the past decade, there has been an explosion of data on the effect of various antihypertensive agents on proteinuria and renal function in diabetic patients, but with conflicting results. This was so because of the wide variability in the therapeutic classes, study groups and study designs, making it difficult to synthesise the results. In this regard, two meta analyses [26,27] deserve comment. In a meta-analysis of about 100 controlled and uncontrolled studies, Kasiske et al[26] examined the effects of several classes of antihypertensive agents on blood pressure (BP), GFT and protein/albumin excretion (UPE/UAE). The results indicated that the effects on BP and GFR were similar for all classes and that a BP reduction of 10mmHg was associated with a GFR increase of 3.7ml/min. with respect to reduction UPE/UAE, ACE-inhibitors reduced proteinuria independent of changes in BP, treatment duration, type of diabetes or stage of DN. On the other hand, with other classes of drugs, any decreases in proteinuria was related to BP reduction. Moreover, ACE-inhibitors had an added favourable affect on GFR independent of BP changes. The conclusion was that in patients with diabetes, ACE-inhibitors can decrease proteinuria and preserve GFR independent of changes in systemic BP.

Weidmann et al[4,27] reported on a meta analysis of studies in patients with microalbuminuria (incipeint DN) or proteinuria (established DN) who were treated for at least four weeks with ACE-inhibitors, calcium antagonists or conventional therapy (diuretic and/or beta-blockers). The analysis showed that the reduction in proteinuria or microalbuminuria was greater with ACE-inhibitors that with the other classes of drugs, and that proteinuria tended to increase with nifedipine despite similar reduction in BP. A distinct antiproteinuric effect was noted with BP reduction by 10-15% with ACE-inhibitors, conventional therapy and calcium antagonists excluding nifedipine. However, at unchanged or slightly decreased BP, ACE-inhibitors were superior in reducing proteinuria.

Recently, in a randomised study in IDDM patients with established DN, Lewis et al[23] showed that when compared with a placebo, treatment with ACE-inhibitor (captopril) was associated with a 50% reduction in the risk of deterioration of renal function, mortality, dialysis and/or transplantation; moreover, these beneficial effect were independent of BP reduction.

E. Recommendations from ADA Consensus Statement[1]

a) in hypertensive diabetic patients with albuminuria (>30mg/24hr), ACE-inhibitors should be the first choice class of drugs (when economically feasible and not contraindicated).
b) in normotensive patients with albuminuria, ACE-inhibitors may also be beneficial, but the evidence is less clear.
c) when ACE-inhibitors are contraindicated or ineffective, other anti-hypertensive agents should be used.

CONCLUSION

Hypertension is a common problem in diabetes mellitus and is a major determinant of mortality and morbidity of both, microvascular and Macrovascular complications. Hypertension accelerates the

development and progression of such microvascular complications as diabetic nephropathy and there is evidence that anthihypertensive therapy is beneficial in its genesis and progression. It is, therefore, imperative that hypertension should be detected and treated early and aggressively.

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