Choice of Drugs in the Treatment of Hypertension in Diabetes

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In treating hypertension (HT) associated with diabetes mellitus (DM), certain factors must be taken into consideration.

Hypertension occurs in diabetes twice more frequently than in non-diabetics. The time, course and natural history of HT markedly differs between the insulin-dependent diabetes mellitus(IDDM) and the non-insulin dependent diabetes mellitus (NIDDM).

The types of HT seen in DM are listed in Table 1. HT in IDDM is closely related to nephropathy. The earliest ,manifestation of the letter is in the form of microalbuminuria. Microalbuminuria is absent in the first 5-10 years, increases by 15-40% annually and overt nephropathy was noted in the past after 9-12 years of diabetes. However, presently it is on the decline. HT in IDDM preceeds or parallels microalbuminuria. It is seldom more than 160/95mm Hg. In those with DM of around 30 years duration, frequency of HT is 50 percent. HT is rare without nephropathy. Familial HT is 4 times more common in those with HT and nephropathy.

Table 1
Hypertension in Diabetes

Renal
Essential
Isolated Systolic
Supine Hypertension
with Orthostatic Hypotension
Surgically Curable

In NIDDM, microalbuminuria preceeds development of nephropathy. Renal function declines often at this stage. Microalbuminuria in NIDDM, however, is not always due to nephropathy and therefore lacks correlation to HT. Urinary tract infection, non-diabetic renal failure, congestive cardiac failure may also contribute individually or collectively to microalbuminuria. HT is present in 20-50% of NIDDM's at the time of diagnosis of DM. In twenty years time, another 20-40% develop hypertension. HT in NIDDM may be present without microalbuminuria and has features of essential HT. Isolated systolic pressure(160/90 mm Hg) is mainly seen in NIDDM, particularly so in those with impaired glucose tolerance (IGT). Thus, HT in NIDDM may be related to hyperinsulinaemia (HI) and insulin resistance (IR). It also correlates to body mass index (BMI), inactivity, advancing age and duration of diabetes.

All those IDDM and NIDDM patients with macroalbuminuria have HT.

Supine hypertension with orthostatic hypotension may also be encountered in IDDM patients with nephropathy. Surgically curable HT like in renal artery stenosis is less common in diabetics.

The Pathogenesis of HT in Diabetes

Whether HT causes nephropathy or vice versa is not well established. However, it is known that hypertension can worsen nephropathy and vice versa. Various factors related to pathogenesis are listed in Table 2. The role of HI and IR in causing HT is debatable (because of racial ethnic differences – no relation of HI and HT is seen in Afro Americans and Pima Indians while it is so in Caucasians and lack of definite relation to BMI – Lean HT individual being more IR than normotensive people) as nearly 50% of IDDM and 30% of NIDDM remain normotensive despite HI and IR. This suggests that HI and IR can make HT manifest only in those who have genetic risk factors for HT (Table 3). This is further supported by a family history of HT in those NIDD's having HT.

Table 2
Pathogenesis of Hypertension

Nephropathy Hypertension
Expanded Plasma Volume
Increased Exchangeable Sodium
Peripheral Vascular Resistance
Low Levels of ANP and Prostaglandin
Low Plasma Renin Activity
Increased Endothelin
Hyperinsulinaemia
Increased Sympathetic Nervous Activity

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Table 3
Hypertension Associated with insulin Resistance

Determining Factors
Genetic Risk
Positive Family History of HT
Increased Na^{+}-Li^{+} counter transport across RBC
Enhanced Responsiveness to Insulin
Stimulated Sympathetic Nervous Activity
Resistance to Vasodilatory Effect of Insulin

Treatment of HT

In the absence of a large population-based randomised trials of treatment of HT in diabetic patients, the present day management of HT is based only on clinical experience.

The goals of treatment of HT are:
Prevention/decreased mortality and morbidity, improved quality of life
and reversal of risk factors.

In treating HT, one should appreciate the fact that the optimal blood pressure (BP) levels in diabetic patients is not known. The Joint National Committee defines HT as an average BP of > 140 mm Hg systolic or > 90 mm Hg diastolic. High BP are staged 1 through 4 as mild to very severe (Table 4).

Table 4
Classification of Blood Pressure for Adults > 18 years of Age[#] [5]

Category	*Systolic Blood Pressure (mm Hg)*	*Diastolic Blood ressure (mm Hg)*
Normal	130	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

The function of target organs and modifiable risk factors should be evaluated. The target level aimed in therapy is a BP of ≤ 130/85mm Hg.

HT therapy should not worsen glucose tolerance, lipid levels, peripheral vascular disease, coronary blood flow, chronic airway obstruction and precipitate gout.

Non-Drug Therapy in HT

In mild hypertensive NIDDM patients, advice should be on relaxation techniques and non-drug therapy as listed in Table 5.

Table 5
Non-drug Therapeutic Recommendations for Hypertension

Stop smoking (for cardiovascular health)
Lose weight, particularly upper body obesity
Reduce sodium intake (2g or 88 mmol/day)
Moderate alcohol intake (not more than 2 small drinks/day i.e. 60 ml alcohol)
Do regular aerobic, isotonic exercise
Relax and relieve stress
Use less saturated fat, more fish oils
Maintain adequate potassium, calcium and magnesium intake

Pharmacological treatment of HT

Table 6 lists the drugs used presently in the order of preference; their advantages and disadvantages. One may start with a single agent and set up therapy by increasing the dosage and/or adding additional agents till the BP reaches optimal levels. If the BP continues to be satisfactory for about six months, one should consider reducing the number of drugs or their dosage by careful and frequent monitoring of not only BP but also renal and cardiovascular status.

Management of hypertensive crisis in diabetic patients is the same as in non-diabetics. This includes the use of

1. sublingual nifedipine frequently,
2. infusion of nitroprusside and
3. Diazoxide.

Table 6
Antihypertensive Drugs for patients with Diabetes

Drugs	Advantages	Disadvantages/Caution
ACE inhibitors	Reduce micro/macroalbuminuria, delay nephropathy in NT/HT. No adverse effect on glucose tolerance and lipids. Increase insulin sensitivity.	Increases K^+ in RF, hyporeninaemic hypertension, renal artery stenosis, cough, angioedema. Renal function monitoring required.
Calcium channel blockers	No adverse effect on lipids and glucose control. Decrease mircro/ macroalbuminuria, but less efficient compared to ACE inhibitors.	Constipation, peripheral oedema.
Alpha receptor blockers	Beneficial effect on lipids, increase insulin sensitivity.	No cardioprotection. Orthostatic hypotension.
Thiazide diuretics in small doses	Decrease cardiovascular mortality and morbidity. Decrease expanded plasma volume.	Dislipidaemia, glucose intolerance, hyperinsulinaemia, low K^+ and Mg^+, hyperuricaemia.
Beta-blockers without intrinsic sympathometric activity	Reduce cardiovascular mortality prevent recurrent MI and sudden death.	Glucose intolerance, increase in lipids, impaired glucose recovery, left ventricular dysfunction. Decreased peripheral blood flow.

Other drugs -- Loop diuretics can replace thiazides. If serum creatinine is more than 2.0 mg%, potassium sparing diuretics should not be used. Sympatholytic drugs worsen orthostatic hypotension and are therefore better avoided. Clonidine – useful often in resistance cases.

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