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Diabetes and hypertension

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Hypertension is about twice as common in diabetics as in non-diabetics. The increased prevalence may relate to insulin resistance and its sequelae. Hypertension is a major risk factor for both large and small vessel disease, contributing to accelerated atherogenesis and progression of diabetic nephropathy and retinopathy. Treating raised blood pressure in diabetics is beneficial in the context of large vessel disease and in slowing progression of overt nephropathy. There is controversy as to whether antihypertensives, and particularly ACE inhibitor drugs, will prevent progression from incipient to overt nephropathy.

All the major classes of antihypertensives can be used in diabetics, but the thiazide diuretics and β-blockers have metabolic side-effects which make them less appropriate as first line agents. The calcium antagonists and ACE inhibitors have better metabolic profiles and the latter reduce insulin resistance. ACE inhibitors may also have a renal protective effect in incipient nephropathy although the studies have been fairly short-term and with small patient numbers. Although ACE inhibitors and calcium antagonists are suitable as first line antihypertensives in diabetics, evidence is still lacking that these drugs reduce morbidity and mortality over and above that seen with other antihypertensives.

The isolation of insulin in 1922 was for many diabetics life saving and for others health preserving. It was soon realised, however, that those people whose lives were being saved by insulin were starting to succumb to the long-term vascular complications of the disease. 70 years later diabetes is still a major health problem. Coronary artery disease, stroke and peripheral vascular disease are significantly more common in diabetics than non-diabetics.[1] Diabetic small vessel disease (microangiopathy) leading to eye and kidney damage also accounts for much morbidity and mortality.[1]

Hypertension is a major risk factor for large vessel disease in diabetics as in non-diabetics and is also a risk factor for microangiopathy, particularly in speeding progression of nephropathy.[1]

This article will consider the relationship between hypertension and diabetes including its prevalence, aetiology and association with large and small vessel disease together with management regimes.

PREVALENCE OF HYPERTENSION IN DIABETES

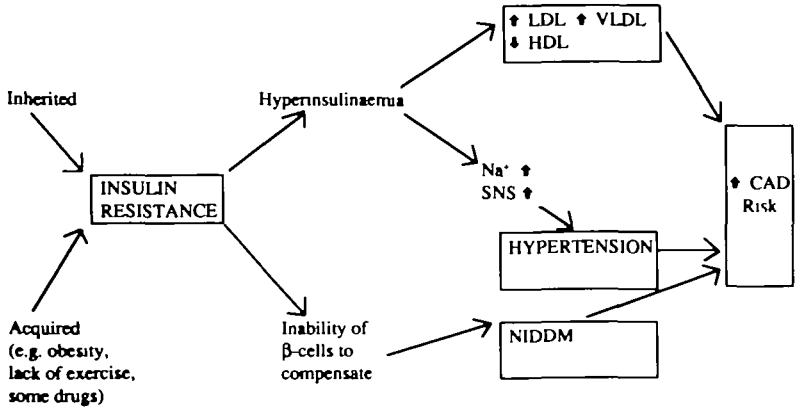
Epidemiological data suggest that the prevalence of hypertension in diabetes is significantly higher than in non-diabetics – perhaps twice as common, occurring in up to 50% of Type 2 diabetics.[2,3] A recent report from the Diabetes Intervention Study demonstrated a striking excess of hypertension in newly diagnosed Type 2 diabetics together with an excess of other recognised risk factors.[4] These data are supported by both hospital diabetic clinics and community based population studies, although few have differentiated between Type 1 and Type 2 disease.[2]

REASONS FOR THE INCREASED PREVALENCE OF HYPERTENSION IN DIABETES

Various hypotheses have been suggested to account for the increased prevalence of hypertension particularly in Type 2 diabetics. It may be related, in part, to obesity and increased sympathetic nervous system stimulation and catecholamine production seen in diabetics.[2] Part of the excess may also relate to diabetic nephropathy, although this cannot account for the great excess seen in the general diabetic population.

Several cardiovascular risk factors (such as hypertension, lipid abnormalities and glucose intolerance) may co-occur in the same patient. In 1988 Reaven suggested that these risk factors might relate to insulin resistance as the primary feature – 'Syndrome X' hypothesis.[5] Insulin resistance itself might be inherited or acquired – eg due to obesity, dietary factors, lack of exercise and some drugs (Fig. 1).

Reaven proposed that insulin resistance would lead to hyperinsulinaemia which is associated with increased LDL and reduced HDL concentrations. Insulin resistance could also cause development of impaired glucose tolerance or frank Type 2 diabetes in those genetically predisposed to the disease. Insulin resistance and consequent hyperinsulinaemia might also be causally related to the development of hypertension (Fig. 2). Insulin may, for example, cause retention of sodium at the proximal renal tubule[6] and is also associated with increased catecholamine output and sympathetic nervous system stimulation.[7,8] There is evidence that Type 2 diabetics have an increase in total body sodium[9] and this has also been demonstrated in those with essential



SNS = Sympathetic nervous system
VLDL = Very low density lipoproteins
LDL = Low density lipoproteins
HDL = High density lipoproteins
NIDDM = Non insulin dependent diabetes
CAD = Coronary Artery Disease

Fig. 1 Illustrates the 'Syndrome X' hypothesis. Insulin resistance, which may be inherited or acquired, leads to hyperinsulinaemia, abnormalities of the lipid profile, glucose intolerance and hypertension.

hypertension. Epidemiological data also relate essential hypertension to the later development of Type 2 diabetes.[10] Acute loading studies have suggested that even non-diabetic patients with essential hypertension have significantly increased glucose and insulin levels compared with matched normotensive subjects.[11]

The 'Syndrome X' hypothesis is the subject of much controversy.[12] If correct, it has potentially important therapeutic implications, particularly for the management of hypertension.

HYPERTENSION AS A RISK FACTOR FOR LARGE VESSEL (MACROVASCULAR) DISEASE

Major risk factors for atherosclerosis in both the diabetic and the non-diabetic include hypertension, hyperlipidaemia, positive family history and cigarette smoking with an independent effect from diabetes itself.[13–16] The incidence of large vessel disease is dramatically increased in both Type 1 and Type 2 diabetics and is the major cause of morbidity and premature death.[13,15,17–21] The atherosclerotic process appears to be identical in diabetics and non-diabetics except that it is

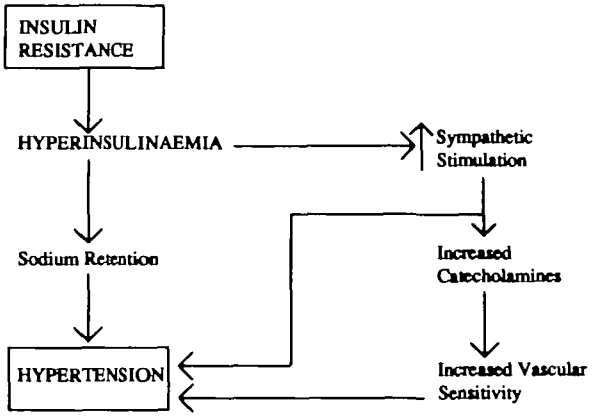


Fig. 2 Possible interactions relating insulin resistance to development of hypertension.

accelerated ie occurs at an earlier age and with greater frequency. Thus, diabetics have a 2-fold increased risk of coronary heart disease,[3,22] 2–6-fold increased risk of stroke[23–25] and a dramatically increased risk of peripheral vascular disease.[26,27]

Alterations in endothelial cell platelet interactions and lipid and lipoprotein metabolism have been implicated in the accelerated atherogenesis in diabetic patients. Hyperglycaemia and increased levels of low density (LDL) and very low density (VLDL) lipoproteins may adversely affect vascular endothelium.[28] Hypertension may increase the risk of vascular endothelial injury with subsequent macrophage and platelet aggregation, release of growth factors that stimulate the proliferation of smooth muscle cells and the deposition of lipid laden foam cells.

HYPERTENSION AS A RISK FACTOR FOR SMALL VESSEL DISEASE (MICROANGIOPATHY)

Microangiopathy may affect all of the small blood vessels in the body, but is clinically most apparent in the eyes (retinopathy) and in the kidneys (nephropathy). Retinopathy is still the commonest cause of blindness in the UK and nephropathy accounts for about 20% of deaths in diabetics below the age of 50 years.[17–19] Nephropathy is also associated with a significantly increased risk of cardiovascular disease.[29]

There is some evidence that hypertension may be a risk factor for retinopathy, particularly its progression. One long-term prospective study of retinopathy looked at the incidence of retinal exudates

in diabetics over a 5-year period.[30] Systolic pressures greater than 145 mmHg were associated with more than twice the number of retinal exudates compared with those patients with systolic pressures below 125 mmHg. Cross sectional data also supports a role for hypertension in retinopathy.[31]

The mechanisms through which hypertension might contribute to the evolution of retinopathy is unknown, although increased capillary leakage may be a factor.[32]

Hypertension is a significant risk factor for diabetic nephropathy – accelerating its progression in both animal models[33] and in man,[34] and perhaps even initiating the problem. Recent data suggest that the genetic predisposition to hypertension is associated with diabetic nephropathy even when systemic blood pressure is not raised. The presence of hypertension in a parent trebles the risk of nephropathy in a diabetic.[35]

IS TREATING HYPERTENSION IN THE DIABETIC OF BENEFIT?

No large prospective studies to determine whether treatment of hypertension lessens the risk of large vessel disease have been carried out in diabetic patients. Since the pathology of atheroma formation appears identical in diabetics and non-diabetics (albeit accelerated) it seems reasonable to extrapolate data from the large multicentre studies in the general hypertensive population. These have reported significant reduction in risk of stroke and congestive heart failure, but have been disappointing from the point of view of coronary artery disease risk (*see* pp 272–298, *this issue*).[36,37] Various hypotheses have been suggested to explain the paradox that hypertension appears to be a major risk factor for coronary artery disease and yet lowering blood pressure may not reduce that risk. It has been argued that antihypertensives may have been started too late or that the wrong drugs might have been used due to adverse cardiovascular effects.

From the point of view of diabetic retinopathy the prospective trial already alluded to demonstrated that reduction in blood pressure significantly reduced the incidence of retinal exudates.[30] Further studies are awaited with interest.

The data for diabetic nephropathy is particularly convincing. Control of even mild to moderate hypertension significantly reduces albumin excretion rate (AER) and slows the decline in renal function in established nephropathy.[38–40] Blood pressure control, however, does not reverse the process and once established progression to renal failure is inevitable.

More controversial is whether patients with incipient nephropathy can be prevented from progressing to overt nephropathy by agents such

as ACE inhibitors. Incipient nephropathy is defined on the basis of microalbuminuria[29] – an albumin excretion rate above the normal range but below the level of 'Albustix' detection (in practice 20–200 μg/min). Microalbuminuria has an 80% predictive power for those who will later go on to develop overt disease.[29] Several short-term trials with relatively small patient numbers have suggested that ACE inhibitors may cause a significant reduction in AER and may have a renal protective effect (see later). This may relate to reports from animal data suggesting that raised intraglomerular pressure is important in the development of diabetic nephropathy perhaps secondary to efferent arteriolar constriction.[29] ACE inhibitors may act by causing relaxation of the efferent arteriole with consequent reduction in intraglomerular pressure in those with incipient nephropathy, even in the context of normal systemic blood pressure. Longer term trials with larger patient numbers are required, however, to answer the point about renal protection.

WHEN SHOULD HYPERTENSION BE TREATED IN THE DIABETIC PATIENT?

It is difficult to give firm guidelines on treatment over and above those already produced for the management of hypertension in the non-diabetic population. Approaches to the management of, for example, a young Type 1 diabetic patient with microalbuminuria and a blood pressure of 150/90 mmHg would be different to those taken with an elderly uncomplicated Type 2 diabetic. Current data, however, suggests that screening for hypertension in diabetes needs to be aggressive and it is my impression that there is a reduction in the threshold for treating blood pressure in many specialist diabetic clinics.

THERAPIES OF HYPERTENSION IN DIABETES

As in non-diabetics the finding of a raised blood pressure should be confirmed on several occasions before commencing therapy. This should be accompanied by a full clinical assessment and basic investigations, and is not further discussed in this article.

An obese Type 2 diabetic with mild to moderate hypertension may benefit primarily from non-pharmacological measures. These include: weight reduction, reduction of alcohol intake if excessive, a diet high in fibre, low in fat and sodium, and exercise.[41] These manoeuvres may also reduce insulin resistance.

Where antihypertensive agents are necessary careful consideration should be given to the most appropriate agent in diabetic patients. The Table provides a summary of the metabolic side-effects that may be associated with each of the main classes of antihypertensives. The

thiazide diuretics may have adverse effects on the glycaemic profile and can be associated with deterioration in the lipid profile, electrolyte imbalance and they increase insulin resistance.[37] They also commonly cause impotence in males. Diabetes itself may be associated with a prevalence of male impotence of up to 50%. Most of the early trials on these agents were done using high doses and few data are available on the currently used lower doses. Indapamide, a non-thiazide diuretic, does not appear to have deleterious side-effects on diabetic control or serum lipids.[37]

Table Metabolic profiles of commonly used antihypertensives

	Thiazides	Beta-blockers	Calcium antagonist	ACE I
Glycaemia	↑	↑	—	(↓)
Lipids	↑	(↑)	—	(↓)
Electrolyte profile	↑	—	—	—
Insulin resistance	↑	↑	(↓)	↓

Thiazides and beta-blockers may also cause erectile impotence. ACE I = Angiotensin Converting Enzyme Inhibitors; ↑ = Deterioration; ↓ = Improvement; — = Neutral effect.

Similarly, beta-blockers may be associated with deterioration in glycaemia, adverse effects on the lipid profile (this is disputed)[37] and they increase insulin resistance.[42] They may also precipitate erectile impotence in males.

Calcium antagonists and ACE inhibitors are either neutral or may actually improve glycaemia and lipid profiles.[37] More recently the selective alpha-blockers have come on the market. These have not been included in the Table since there is not such an extensive literature on this class of drugs in diabetic patients. They also appear not to worsen metabolic control or adversely affect plasma lipids. There is also evidence that ACE inhibitors may reduce insulin resistance and thereby increase insulin sensitivity whilst at the same time having apparently beneficial effects on lipid and glycaemic profiles.[43,44] These observations in the context of the Syndrome X hypothesis might be of benefit, although no long-term studies have been done to see if this is the case.

Based on efficacy and side-effect profiles the ACE inhibitors and calcium antagonists have established themselves as first line agents for the management of hypertension in diabetes. The ACE inhibitors, in

particular, have theoretical advantages over the other antihypertensives, but whether they actually prolong life or reduce morbidity over and above other antihypertensives is not known.

TREATMENT OF HYPERTENSION IN DIABETIC NEPHROPATHY

Diabetics may have increased exchangeable body sodium and it is sensible to reduce dietary sodium intake together with encouraging obese patients to lose weight.

Pharmacological measures include loop diuretics which because of increased body sodium levels often achieve an initial good response. These drugs may, however, cause a deterioration in diabetic control, thus requiring an adjustment in insulin dose (see earlier). Beta blocking drugs have also been used and indeed virtually all trials of antihypertensive agents have demonstrated a significant reduction in rate of decline of renal function in those with established nephropathy.[38–40,45]

There is presently great interest in the possible role of ACE inhibitors in renal protection. They may have a specific protective effect by causing relaxation of the efferent arteriole thereby reducing intraglomerular pressure.[46] This might be beneficial in diabetic nephropathy over and above effects on systemic blood pressure.[47–50]

Several studies have also reported a possible renal protective effect of ACE inhibitors in normotensive microproteinuric diabetics.[51,52] The studies have been short-term and with small patient numbers, but support the idea that these drugs may prevent progression from microalbuminuria to overt proteinuria.

My own group has just completed a 1 year prospective, double blind, randomised single centre study of 27 Type 1 and Type 2 diabetic patients with albumin excretion rate in the microalbuminuric range comparing an ACE inhibitor with placebo.[53] Only ACE inhibition was associated with a significant fall in AER, but no significant changes in renal haemodynamics within or between the groups were found. 5 of the 12 patients in the active group remained microalbuminuric and 7 became normoalbuminuric. 9 of the 15 patients in the placebo group remained microalbuminuric, 3 became normoalbuminuric and 3 became frankly macroalbuminuric, ie developed overt nephropathy. We concluded that ACE inhibition may be associated with a renal protective effect, but with the caveat that small numbers of patients were studied with relatively short study duration. It is still not clear whether these effects are due to lowering of systemic blood pressure or are related to specific intrarenal effects.

The above is a potentially very important therapeutic area and it is clear that large long-term prospective randomised double blind comparisons of treatments are now required.

CONCLUSIONS

Hypertension and diabetes commonly co-exist and the reasons for this are the subject of much controversy. It is clear that hypertension is a major risk factor for small and large vessel disease in diabetics, and that treatment of raised blood pressure is of benefit. There is, however, still controversy concerning the levels at which blood pressure should be treated, although a consensus is emerging that particularly for younger patients and those with incipient or overt nephropathy there should be a lower threshold for treatment.

The full range of antihypertensive agents are available for the management of hypertension in diabetes. There are, however, potential disadvantages of using thiazides and beta-blockers which may make some of the more modern agents (such as ACE inhibitors and calcium antagonists) preferable as first line drugs. In this context the role of ACE inhibitors may be important since preliminary short-term studies suggest that they may have a specific renal protective effect. Certainly ACE inhibitors and calcium antagonists are suitable first line antihypertensive agents in diabetics based on efficacy and side-effect profiles which in many cases appear to be superior to the older more established drugs. Evidence is still lacking, however, that these drugs reduce morbidity or mortality over and above that seen with other antihypertensive agents.

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