Interfaces between medical specialties

The diabetic patient with hypertension

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Summary

Hypertension and diabetes co-exist more commonly than would be expected from their individual prevalences. Elevated blood pressure is most commonly due to coexisting essential hypertension, or diabetic renal disease. Early stages of diabetic renal disease can be identified by detecting microalbuminuria. Standard measures of blood pressure are not necessarily raised, but 24-hour ambulatory measures frequently identify a loss of nocturnal drop in blood pressure. Treating hypertension aggressively is important in slowing the inexorable decline in glomerular filtration rate. In diabetes there appears to be no 'J'-shaped relationship between blood pressure and cardiovascular events, thus removing any concern about attaining low blood pressures as long as the patient is asymptomatic. Morbidity and mortality in these patients is usually associated with cardiovascular events, and it is important to assess the effect of drugs on left ventricular hypertrophy and metabolic parameters. Many drugs are effective at lowering blood pressure, but angiotensin-converting enzyme inhibitors may have an additional renoprotective action. α -Adrenergic antagonists may improve lipid profiles and calcium antagonists are probably lipid neutral, making these drugs useful alternatives. Dihydropyridine calcium antagonists (eg, nifedipine) may augment protein-uria, and hence non-dihydropyridine calcium antagonists (eg, verapamil, diltiazem) would be preferred. β -Blockers and thiazide diuretics have the disadvantage of causing a deterioration in glycaemic and lipid profiles, but can be useful on occasions.

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Hypertension is associated with increased cardiovascular mortality, and an increased risk of microvascular complications in patients with diabetes. The overall incidence of hypertension in patients with diabetes is approximately twice that of non-diabetic controls,¹ although in patients with uncomplicated insulin-dependent diabetes (IDDM) it is no greater than the background population (box 1). In noninsulin dependent diabetes (NIDDM), however, the incidence of hypertension is markedly increased. It is also noted that patients with essential hypertension are more likely to develop type 2 diabetes. Hypertension and insulin resistance are commonly associated, forming part of the so-called 'Syndrome X' or 'Reaven Syndrome'.² Syndrome X is characteristic of many patients with NIDDM, but the mechanisms underlying it are not clearly understood. Insulin is known to have vasoactive properties,^{3,4} and it can influence the activity of other vasoactive agents, eg, noradrenaline⁵ although the exact *in vivo* role of insulin in diabetic patients is uncertain.

Once diabetic renal disease develops, hypertension nearly always follows, and causes further deterioration in renal function. In recent years much work has focussed on the role of systemic blood pressure in the progression of diabetic renal disease.⁶ Diabetic renal disease is unusual in IDDM patients who have had diabetes for less than five years, but NIDDM can be present for many years before diagnosis, such that diabetic nephropathy can be a feature at presentation. The development of diabetic nephropathy itself is usually associated with hypertension in both IDDM and NIDDM, but patients can be 'normotensive' by clinical measurements during the early stages of diabetic renal disease. It is reasonable to assume a diagnosis of diabetic nephropathy in patients who have persistent proteinuria (albumin excretion of >350 mg/day) without haematuria, in the presence of diabetic retinopathy and in patients who lack clinical biochemical features suggestive of other secondary causes,⁷ although renal biopsy is required to be absolutely certain of the diagnosis (box 2).

Early stages of diabetic renal disease are associated with mildly increased urinary albumin excretion (microalbuminuria, 30–300 mg/day). In clinical practice, persistent microalbuminuria is established by demonstrating two abnormal early morning albumin: creatinine ratios, and an abnormal timed overnight albumin excretion. These criteria are necessary because of the variability in measuring urinary albumin concentrations. The presence of persistent microalbuminuria is associated with an increased risk of overt diabetic nephropathy and cardiovascular mortality in both IDDM and NIDDM. In IDDM microalbuminuria has a predictive value of 70–80% for the development of nephropathy over the subsequent 10 years, whilst in NIDDM it is about 20–50% (box 3). The lower predictive value in NIDDM may be because there is a greater incidence of cardiovascular death in NIDDM patients with microalbuminuria, than in IDDM, and hence patients may not live long enough to develop nephropathy. Indeed, in NIDDM microalbuminuria is a strong predictor of vascular morbidity and mortality even at urinary albumin excretion rates as low as 10.6 $\mu\text{g}/\text{min}$,⁸ and deaths due to vascular causes are much more common than deaths due to renal causes in microalbuminuric patients.

Patients with diabetes may also have secondary causes of hypertension (eg, Conn's syndrome, pheochromocytoma) and, as in non-diabetic patients, these should be sought, particularly in patients who are young, have difficulty controlling their hypertension, or who have distinctive clinical or biochemical features.

Pathogenesis of hypertension and renal disease in diabetes

Studies in patients reveal that total body sodium is increased by around 10% in patients with diabetes, resulting in intravascular expansion which predisposes subjects to hypertension. With the development of renal disease, total body sodium rises even further and blood pressure becomes increasingly sensitive to

Coexistence of diabetes and hypertension

- incidence of hypertension in diabetic patients is twice control population
- incidence of hypertension in uncomplicated IDDM is normal, but incidence in NIDDM is increased
- patients with essential hypertension are more likely to develop NIDDM
- in the absence of nephropathy, secondary causes of hypertension should be sought in young diabetics

Box 1

Indications for renal biopsy in a diabetic patient with proteinuria

- Not following the usual natural history, eg,
- duration of diabetes less than 5 years (IDDM)
 - haematuria (with no lower urinary tract cause)
 - no evidence of diabetic retinopathy

Box 2

Predictive value of microalbuminuria

- IDDM: 70–80% of patients develop nephropathy over the next 10 years
- NIDDM: 20–50% of patients develop nephropathy over the next 10 years
- NIDDM: microalbuminuria is a strong predictor of macrovascular events, eg, myocardial infarction

Box 3

Features associated with hypertension in diabetes

- sodium retention (increased by 10%)
- increased vasomotor tone
- relatively increased activity of renin-angiotensin aldosterone pathway

Box 4

Putative renoprotective mechanism of action of ACE inhibitors

- reduce efferent glomerular arteriolar tone, resulting in reduced capillary hydrostatic pressure
- inhibition of mesangial growth factors, eg, angiotensin II
- altered trans-capillary permeability to protein

Box 5

total body sodium concentration.⁹ Hyperglycaemia and hyperinsulinaemia both act directly on the renal tubule to inhibit sodium excretion,¹⁰ and there is also an increase in activity of the renin-angiotensin aldosterone pathway which further exacerbates sodium retention.⁹ As mentioned previously the increased vasomotor activity mediated either directly or indirectly by insulin, may also contribute to raised blood pressure (box 4).

The understanding of the pathophysiology of hypertension in patients with diabetic nephropathy has been generally extrapolated from information obtained from experimental models examining hypertension in the absence of specific renal disease. Although this is the best information available, the extrapolation may not be valid. In diabetic nephropathy it is believed that the glomerular efferent arteriole is constricted to a greater degree than the afferent arteriole,¹¹ with the result that there is an increase in glomerular capillary hydraulic pressure with increased glomerular filtration. Associated with this is mesangial expansion which is partially stimulated by growth factors such as angiotensin II, noradrenaline, endothelin and others.¹² Hyperfiltration may also be stimulated by a number of other mediators.

The results of some experimental work have suggested that angiotensin-converting enzyme (ACE) inhibitors may have specific renoprotective effects in addition to their hypotensive activity.¹³ ACE inhibitors may improve intrarenal haemodynamics by relaxing glomerular efferent arteriolar tone to a greater extent than afferent arteriolar tone, thus decreasing glomerular capillary hydrostatic pressure.¹³ In addition, ACE inhibitors may decrease glomerular permeability for proteins and inhibit mesangial proliferation (box 5).¹⁴

Defining hypertension

The WHO guidelines on hypertension¹⁵ suggest aiming for a target blood pressure of 160/95 mmHg in non-diabetic patients with primary hypertension (box 6). The British Hypertension Society guidelines are very similar, providing a clear consensus in the management of hypertension.¹⁶ Diabetes is a further risk factor for arteriosclerosis, especially if associated with dyslipidemia, and it was suggested that in such patients a more aggressive target blood pressure of 140/90 mmHg should be achieved. Target blood pressures of 160/90 mmHg or less are suggested for patients over 60 years old. Mild elevations in blood pressure can be sufficient to accelerate the decline in glomerular filtration rate, and reduction of diastolic pressure below the level of 90 mmHg can further arrest this decline.¹⁷ In addition, many diabetic patients who appear to be normotensive on standard blood pressure checks do not demonstrate the normal decline in nocturnal blood pressure when 24-hour ambulatory blood pressure (AMBP) monitoring is used.^{18,19} Thus, diabetic patients, especially those with microalbuminuria, may be exposed to excessive blood pressure load during the night, which can result in continuing renal damage. This may be marked by a steady rise in urinary albumin excretion rate within the microalbuminuric range. The progressive rise in albuminuria in normotensive microalbuminuric patients is limited when a mean arterial pressure of less than 100 mmHg is achieved,^{20,21} although it appears that further benefit was observed when a mean arterial pressure of 90–95 mmHg was achieved,²² or a mean diastolic pressure of 80 mmHg in IDDM.²³

It is important to note that there appears to be no so-called ‘J-shaped’ relationship between blood pressure and cardiovascular events in patients with diabetes. There is an ongoing trial which compares the effects of different blood pressure thresholds on the progression of renal disease in NIDDM,²⁴ the results of which are awaited with interest.

Nonpharmacological options for diabetic patients with hypertension

A number of lifestyle changes can have an impact on blood pressure control, the effect of these, however, are generally less impressive in patients with overt nephropathy (box 7). Significant weight reduction, especially if maintained, can have a significant beneficial impact on blood pressure²⁵ and this may be because it improves insulin resistance. A salt-restricted diet²⁶ and moderation of alcohol intake²⁷ can also improve control of hypertension. Regular exercise can enhance the number and activity of glucose transporters, which may be the mechanism of improved insulin sensitivity. This may partly explain the lowering of blood pressure associated with regular physical training.²⁸

Blood pressure levels to start drug therapy (WHO/ISH guidelines¹³)

- non-diabetic without cardiovascular risk factors: 160–180/95–100 mmHg if persistent for 6 months
- non-diabetic with cardiovascular risk factors: 160–180/95–100 mmHg if persistent for 3 months
- diabetic or with cardiovascular risk factors: 140–160/90–95 mmHg if persistent for 6 months

Box 6**Nonpharmacological interventions for hypertension**

- weight reduction
- low salt diet
- increase isotonic exercise
- moderation of alcohol intake
- low protein diet for patients with nephropathy

Box 7**Guidelines for treatment of uncomplicated hypertension in diabetes***First line drugs*

- ACE inhibitors: captopril 6.25–50 mg bid, enalapril 5–40 mg daily, lisinopril 5–40 mg daily
- calcium channel blockers: verapamil SR 120–480 mg daily, diltiazem SR 120–360 mg daily, amlodipine 5–10 mg daily
- α_1 -adrenergic antagonists: doxazosin 1–16 mg daily
- β -blockers: atenolol 50–100 mg daily, metoprolol 100–200 mg daily
- thiazide diuretics: bendrofluazide 1.25–2.5 mg daily

Second line drugs

- centrally acting drugs and vasodilators: α -methyl dopa 250 mg–1 g tid, hydralazine 25–50 mg bid

The specific drugs mentioned are only provided as examples

Box 8**Pharmacological agents to treat hypertension in diabetes**

There are a large number of pharmacological agents available for use. As with all hypertensive patients, the efficacy and side-effects of each drug need to be considered before making a choice. However, in diabetic patients, in addition, it is especially important to consider the effects of the drug on glycaemic control, serum lipid profile and kidney function, especially the haemodynamic effects in patients with diabetic renal disease (boxes 8 and 9).

Thiazide diuretics help to promote sodium excretion by inhibiting sodium reabsorption in the distal convoluted tubule. These drugs are effective and cheap. They exert most of their hypotensive activity at doses as low as 1.25 mg (bendrofluazide²⁹), thus in most cases reducing the need for higher doses at which side-effects are more common. In high doses thiazide diuretics have an adverse effect on glycaemic control. It is commonly, but not universally, believed that thiazide diuretics increase low-density lipoprotein (LDL) cholesterol concentrations and reduce high-density lipoprotein (HDL) cholesterol concentrations,³⁰ thus increasing the risk of atherogenesis. These changes in lipid profiles may partly explain the higher cardiovascular mortality observed in hypertensive diabetic patients treated with thiazide diuretics when compared to no treatment or treatment with other agents.³¹ Although thiazides are cheap and effective at lowering blood pressure, there is concern about their use in patients with diabetes, because of their adverse side-effect profile such as deranged lipid profiles, hyperglycaemia, impotence, hyperuricaemia and others.

β -Blockers antagonise the effects of noradrenaline and adrenaline on β receptors in the heart and peripheral blood vessels (depending on the selectivity), and are effective hypotensive agents. Unfortunately β -blockers prevent symptoms such as tremor and palpitations, which are common warning symptoms of hypoglycaemia, and thus the risks of hypoglycaemia unawareness are increased. Even cardioselective agents can prevent palpitations, and may have some effect on the peripheral symptoms associated with adrenaline released during hypoglycaemia. Diabetes is generally associated with increased hepatic triglyceride production, and this can be further exacerbated by β -blockers.³² Finally, non-selective β -blockers can reduce insulin secretion³³ and sensitivity,³⁴ which may act to worsen overall glycaemic control. For all these reasons other agents may be more appropriate when considering global risk factors in patients with diabetes, but β -blockers may still be useful, especially when ischaemic heart disease also exists, eg, in patients with NIDDM.

Calcium channel blockers are either dihydropyridine derivatives (eg, nifedipine, nitrendipine, nicaldipine), or non-dihydropyridine derivatives (eg, diltiazem, verapamil). These agents are vasodilators and are thought to promote renal sodium excretion. They have no effect on glycaemic control or lipid profiles.³⁵ There has been some concern that dihydropyridine derivatives (eg, nifedipine) may not reduce proteinuria to the same degree as other agents even though they are equally effective at lowering blood pressure.³⁶ This is of concern because proteinuria itself may contribute towards glomerular damage.³⁷ Not all studies have demonstrated this adverse effect of nifedipine.³⁸ After one-year follow-up there was no difference in urinary albumin excretion between patients treated with nifedipine compared to those given perindopril, although more recent data from this cohort of patients suggest that there may be a difference after five years follow-up.

ACE inhibitors are increasingly being used as first-line treatments for hypertension in patients with diabetes, as a number of trials have indicated that they may have a specific renoprotective effect in addition to their hypotensive action. In hypertensive patients with established nephropathy (urinary albuminuric excretion greater than 200 μ g/min or 300 mg/day), ACE inhibitors reduced urinary albuminuric excretion more than calcium channel blockers in some^{39,40} but not all⁴¹ studies, although no differences in decline in glomerular filtration rate or increase in serum creatinine was detected. In such patients with NIDDM, ACE inhibitors have been shown to reduce albuminuria more than β -blockers,⁴² and in IDDM patients they have been shown to be superior to β -blockers in preserving glomerular filtration rate.⁴³ In a recent study in nephropathic IDDM patients with well-controlled hypertension, the effect of adding captopril to the treatment regimen was analysed. Despite no overall significant fall in blood pressure there was a 48% reduction in the risk of doubling serum creatinine concentrations in the active compared to the placebo group.⁴⁴ Although there was no significant drop in blood pressure in the treated group, these patients did have a marginally lower blood pressure, and the placebo group had marginally higher 24-hour urine protein excretion at baseline suggesting that they may have had more advanced disease to start with. Despite these problems, however, further trials, including a recent meta-

Guidelines for treatment of hypertension associated with incipient or frank nephropathy

First line drugs

- ACE inhibitors

Second line drugs

- non-dihydropyridine calcium channel blockers
- α_1 -adrenergic antagonists

Third line drugs

- thiazide diuretics
- β -blockers

Fourth line drugs

- centrally acting drugs and vasodilators

Box 9

Figure Histological changes of diabetic glomerulosclerosis

analysis, demonstrate that overall ACE inhibitors probably exert a significant additional renal protective effect compared to other hypertensive agents in both IDDM and NIDDM patients.^{45,46} In the trial by Lewis *et al*⁴⁴ it was interesting to note that the patients with higher serum creatinine benefited more than those with a lower serum creatinine, suggesting that the ACE inhibitors were particularly beneficial for those with more advanced nephropathy.

Much attention has been focused on the role of ACE inhibitors in normotensive diabetic patients with microalbuminuria. Bearing in mind the earlier comments on AMBP monitoring, these patients may not be 'truly normotensive'. In these patients ACE inhibitors have been shown to reduce urinary albumin excretion and also reduce the instance of overt nephropathy in both IDDM^{47,48} and NIDDM⁴⁹ patients.

Hyperkalaemia and irritant cough can be associated with ACE inhibitors, but the main cause of concern is the risk of acute renal failure in patients with renal artery stenosis. In autopsy studies the prevalence of renal artery stenosis has been as high as 8%,⁵⁰ although these results may have been biased towards an older population, and it is probably an overestimate. Also, anatomical renal artery stenosis does not necessarily relate to functionally important renal artery stenosis. In clinical studies the prevalence of renal artery stenosis in diabetic patients with hypertension was identical to that found in non-diabetic hypertensive patients.⁵¹ Intravascular depletion (eg, secondary diuretics) can increase the risk of deterioration in renal function, but it appears that where renal function did deteriorate, cessation of medication resulted in return of previous renal function in around 80% of cases.⁵² In contrast to these adverse effects ACE inhibitors can have beneficial metabolic effects, with improvements in lipid profile,⁴⁹ although initial reports of improved glycaemic control have not been borne out in longer term follow-up.⁵³

The potential impact on resources mean that it is not practically possible to perform screening for renal artery stenosis in all patients with hypertension, or even all diabetic patients with hypertension. In patients who have no evidence of arteriosclerosis, especially peripheral vascular disease, and do not have renal bruits, one practical solution is to check baseline serum potassium and creatinine and to re-check them about three days after starting ACE inhibitors. If there is a deterioration in serum creatinine then the ACE inhibitors should be stopped. We would limit specific screening for renal artery stenosis (eg, isotope renogram) to patients who are showing a rise in creatinine with ACE inhibitors or patients with widespread arteriosclerotic disease, especially major peripheral vascular disease. Losartan is a specific angiotensin II receptor antagonist and is now available for general use. Its efficacy and exact role in clinical practice, particularly in diabetes, will require further evaluation.

α_1 -Adrenergic antagonists cause vasodilation and decrease peripheral resistance, and have been shown to be effective antihypertensive agents in patients with diabetes⁵⁴; they are relatively safe in patients with renal failure. α_1 -Blockers can reduce LDL-cholesterol and triglyceride concentrations and increase HDL-cholesterol concentrations.⁵⁵ The mechanism underlying the hypolipidaemic effect of doxazosin is not clearly understood. Doxazosin may inhibit intracellular cholesterol synthesis resulting in increased LDL receptor activity, causing improved clearance of LDL-cholesterol from the blood. In addition, there may be increased fatty acid oxidation resulting in decreased hepatic triglyceride output.⁵⁵ α -Adrenergic antagonists may also improve insulin sensitivity. The main drawback with these agents is that they can cause first-dose hypotension, but this is avoided by starting with low doses and by giving them at night, and is less troublesome with the newer agents, eg, doxazosin. There has also been some concern that tolerance can develop to prazosin, although this is probably an individual effect rather than a class effect. Further work requires to be done on specific effects of α_1 -blockers on kidney function in early and late diabetic renal disease.

Centrally acting drugs such as α -methyl dopa, clonidine, and peripheral vasodilators, eg, hydralazine and minoxidil, can be very effective at lowering blood pressure and can be particularly useful for patients with resistant hypertension such as in established diabetic nephropathy. Unfortunately they can have significant side-effects which limit their general use.

Guidelines for treatment

In non-diabetic hypertensive patients, thiazide diuretics and β -blockers are advocated as first-line agents because they have been demonstrated to reduce morbidity and mortality in long-term outcome trials. Newer agents have not been tested in such trials, but they are as effective at lowering blood pressure. It

Summary points

- hypertension is twice as common in diabetic patients
- increased incidence of diabetes in patients with essential hypertension
- microalbuminuria (30–300 mg/day) predicts nephropathy in IDDM and predicts nephropathy and cardiovascular disease in NIDDM
- diabetic nephropathy is usually associated with proteinuria, no haematuria, pre-existing diabetic retinopathy, and diabetes duration of more than 5 years (in IDDM)
- when renal disease is evident (microalbuminuria or nephropathy) hypertension should be treated aggressively to slow the decline in renal function and glomerular filtration rate
- ACE inhibitors appear to offer a renoprotective effect in addition to their hypotensive activity. Captopril now has a license for normotensive microalbuminuric diabetic patients
- ACE inhibitors are the first line choice for hypertension in diabetes. Calcium channel blockers and α -adrenergic blockers are second line choice for patients unable to take ACE inhibitors

Box 10

Table Metabolic profiles of different antihypertensive drugs (chol= cholesterol, TG=triglycerides)

Drug class	Effect on glycaemic control	Effect on lipid profile	Comments
Thiazides	↑ glucose	↑ LDL-chol ↓ HDL-chol	
β -Blockers	(↑) glucose	↑ TGs	Decrease awareness of hypoglycaemia
Calcium channel blockers	Neutral	Neutral	Dihydropyridines may increase proteinuria
ACE inhibitors	Probably neutral, but possibly ↓ glucose	Neutral	Probably has specific reno-protective effect in nephropathy and microalbuminuria
α -Adrenergic blockers	Neutral	↑ HDL-chol ↓ LDL-chol	

has been recommended that calcium channel blockers, ACE inhibitors and α_1 -adrenergic antagonists should be considered as alternative first-line agents in diabetes, where thiazides and β -blockers can cause adverse metabolic side-effects. In hypertensive IDDM patients with microalbuminuria or nephropathy, an ACE inhibitor should be the drug of choice unless the patient has evidence of renal artery stenosis or untoward side-effects. There is also increasing evidence that ACE inhibitors may benefit patients with NIDDM. Furthermore, captopril has recently been licensed for use in normotensive IDDM patients with microalbuminuria. Non-dihydropyridine calcium channel blockers and α_1 -adrenergic blockers would be second line drugs in patients with incipient or frank nephropathy.

Last year a working party on ‘Blood pressure and diabetes: everyone’s concern’ was established under the chairmanship of Professor Harry Keen. A total of 1390 diabetologists, nephrologists, endocrinologists, general practitioners with an interest in diabetes and Family Health Service advisers were circulated with a questionnaire. The order of preference of which antihypertensive to use in diabetic patients with hypertension was identical for all specialist subgroups, and was as follows: ACE inhibitors, calcium channel blockers, α_1 -adrenergic blockers, β -blockers, and thiazide diuretics. Our own preference would be broadly similar, except that we would prefer to avoid using dihydropyridine calcium channel blockers.

Benefits of antihypertensives

The risks of cardiovascular mortality in diabetic patients are increased two- to seven-fold if hypertension is present,⁵⁶ and 37-fold if nephropathy is also present.⁵⁷ Hyperlipidaemia is a frequent co-existent problem which is thought to increase the risk of cardiovascular system mortality further. Left ventricular hypertrophy, identified on chest X-ray and/or electrocardiogram, is associated with a particularly poor outcome in diabetic patients with hypertension. Hence the goal of antihypertensive therapy is to lower blood pressure and reduce left ventricular hypertrophy. The comparative effect of different hypotensive drugs on reducing left ventricular hypertrophy in diabetic patients has not been well studied, but in non-diabetic subjects, ACE inhibitors, α_1 -blockers, non-dihydropyridine calcium channel blockers (eg, verapamil) and methyl-dopa, appeared to be more effective than thiazide diuretics, β -blockers and dihydropyridine calcium channel blockers (eg, nifedipine).^{58,59}

Appendix

A national working party on hypertension and diabetes has met recently. Our views are in agreement with the recommendations of this working party. Further information can be obtained from: Rhys Roberts Associates, Wildmoor House, Wildmoor, Sherfield on Loddon, Basingstoke, RG 27 0HD, UK

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