

PERSPECTIVE

Hypertension and diabetic retinopathy—what's the story?

J T Gillow, J M Gibson, P M Dodson

Improved understanding of the role of hypertension in the pathogenesis of diabetic retinopathy presents both a challenge and an opportunity for ophthalmologists and other diabetic healthcare professionals to improve patient care. Around 40% of patients with type 2 diabetes are hypertensive, the proportion increasing to 60% by the age of 75.¹ Recent reports from the United Kingdom Prospective Diabetes Study (UKPDS) have focused attention on the links between hypertension and sight loss in diabetes.^{1,2} These reports in type 2 diabetes accord with previous observational studies in type 1 diabetes^{3,4} and demonstrate both hypertension as a risk factor for diabetic retinopathy and the beneficial effects of tight blood pressure control. This review summarises recent papers, including the UKPDS reports, and discusses the implications for management of people with diabetes.

Prevalence of hypertension in diabetes

Diabetes and hypertension are among the commonest diseases in developed countries, and the frequency of both diseases rises with age. In the Wisconsin study examining patients with type 1 diabetes, hypertension was defined by current antihypertensive treatment or a mean blood pressure $\geq 160/95$ (or $\geq 140/90$ in those under 25 years). The prevalence of hypertension at baseline was 17.3%, and the 10 year incidence was 25.9%.⁵ Hypertension is more common in type 2 diabetes, and in the UKPDS 38% of newly diagnosed patients with type 2 diabetes had hypertension defined as repeated blood pressure $\geq 160/90$ (or $\geq 150/85$ in those on antihypertensive medication).⁶ In the years after diagnosis of type 2 diabetes the incidence of hypertension is higher than in the age matched general population.

In type 1 diabetes the development of diabetic nephropathy may play a major role in the subsequent development of hypertension since microalbuminuria is present in about 80% of type 1 diabetic subjects before the onset of hypertension.⁷ The pathogenesis of hypertension in type 2 diabetes is not so clear, with a lesser significance

for nephropathy, with microalbuminuria predating hypertension in approximately 25% of type 2 diabetic subjects with hypertension.⁷ Other relevant factors in type 2 diabetes are decreased baroreceptor sensitivity, increased peripheral vascular resistance from enhanced smooth muscle contractility, and vascular structural changes including protein glycosylation and increased type IV collagen.⁸ Additionally, hyperglycaemia causes increased function of the sodium/glucose proximal convoluted tubule co-transporter leading to sodium retention. Over and above the action of hyperglycaemia, other factors including insulin resistance and hyperinsulinaemia may be aetiologically important in the development of hypertension in type 2 diabetes as insulin itself has sodium retaining properties. Reaven's syndrome (also known as the metabolic syndrome or syndrome X) describes this association of hyperinsulinaemia, insulin resistance, obesity, hypertension, and hyperlipidaemia in type 2 diabetes.⁹

Hypertension in the pathogenesis of diabetic retinopathy

Diabetic retinopathy does not occur in the absence of diabetes, and glucose toxicity is the key initial trigger for diabetic retinopathy. Diabetic retinopathy is a microvascular disorder in which the endothelial cells malfunction owing to chronic exposure to high levels of glucose and other factors. The resulting lesions include thickened capillary basement membrane, defects in the blood-retinal barrier, and pericyte loss.

Hyperglycaemia also impairs the regulation of retinal perfusion,^{10,11} leading to increased susceptibility to injury from systemic hypertension (Fig 1). Autoregulation is defined as the ability of blood vessels to keep blood flow constant under varying perfusion pressure. Normal retinal autoregulation protects the eye from systemic hypertension, and in non-diabetic patients blood flow stays constant or increases only slightly until the rise in mean arterial pressure is about 40%.¹²

Retinal hyperperfusion is a key source of injury in diabetic retinopathy associated with shearing damage to capillaries. Increased retinal blood flow is found with conditions that worsen diabetic retinopathy; these include hypertension, hyperglycaemia, pregnancy, and autonomic neuropathy. In contrast, conditions that reduce retinal blood flow tend to protect from advancing retinopathy; these include moderate carotid artery stenosis and raised intraocular pressure.¹¹

The metabolic and haemodynamic factors tend to interact in the evolution of diabetic retinopathy. The DCCT and UKPDS have shown that poor control of diabetes hastens the development and progression of retinopathy.^{13,14} In experimental animals high glucose concentration results in a considerable increase in retinal blood flow.¹⁰ In humans with mild diabetic retinopathy improvement in metabolic control usually results in a prompt reduction in retinal blood flow.¹¹

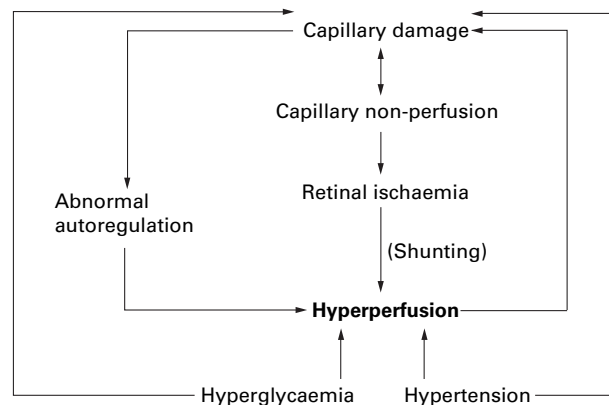


Figure 1 Role of retinal hyperperfusion in diabetic retinopathy.

It is now established that hypertension is a risk factor both for the development of retinopathy and also for the progression of retinopathy.^{15 16} If blood pressure is important in the aetiology of diabetic retinopathy levels below the hypertensive range must be considered. Testa and colleagues found, in type 1 diabetes, that retinopathy was more likely to progress in subjects whose blood pressure was higher but still within the normal range than in subjects with lower blood pressure.¹⁷ This has been confirmed in another study in type 1 diabetes where raised diastolic blood pressure alone (>90th centile, but <90 mm Hg) correlated significantly with presence of retinopathy in a young diabetic population.¹⁸ In the same study raised systolic blood pressure, but ≤ 140 mm Hg, also correlated with the presence of retinopathy.

Does treating hypertension reduce progression of diabetic eye complications?

The epidemiological association between hypertension and retinopathy has been demonstrated, but studies were needed to show that hypertension is not just a risk marker for retinopathy and that treatment of hypertension is beneficial. The results of controlled prospective studies using antihypertensive agents to prevent the development of diabetic retinopathy have been awaited with interest. Until 1998 at least in type 2 diabetes the likely benefits of treatment of hypertension has been assumed from extrapolation of large treatment trials in non-diabetic subjects. Several recently reported randomised control trials or subgroup analyses of diabetic hypertensive subjects have now reported. These trials have mostly concentrated on macrovascular disease and cardiovascular outcomes, with the UKPDS confirming their findings, but with exciting outcome data on microvascular disease, and in particular, diabetic retinopathy.

The UKPDS is the first report in patients with type 2 diabetes to show conclusively that tight blood pressure control reduces the risk of clinical complications from diabetic eye disease. This was a multicentre randomised control trial comparing tight (blood pressure <150/85 mm Hg) with less tight blood pressure control (<180/105 mm Hg). The less tight control group (n=390) were treated with antihypertensive drugs, avoiding angiotensin converting enzyme (ACE) inhibitors or β blocking agents. The tight control group were further randomised to either captopril (n=400) or atenolol (n=358), and other agents were added if control was inadequate. Mean blood pressure during follow up was 144/82 mm Hg in the tight control group and 154/87 mm Hg in the less tight control group (p<0.0001). After 7 years' follow up with the 10 mm Hg reduction in systolic blood pressure and 5 mm Hg reduction in diastolic blood pressure there was a 34% reduction in the proportion of patients with deterioration of retinopathy by two steps on the ETDRS scale (p=0.004). At 9 years there was a 47% reduction in risk of a decrease in vision by three or more lines in both eyes measured with an ETDRS chart (p=0.004). Photocoagulation was reduced by 35% in the tight control group (p=0.023) with the majority likely to be from reduced requirement for macular photocoagulation, which accounted for 78% of laser treatments performed. The bulk of the reduction in visual loss will probably be accounted for by reduced macular oedema, since macular oedema is the main cause of visual impairment in type 2 diabetes. The number of patients who needed intensive treatment of blood pressure over 10 years to prevent one patient developing any complication was low at 6 and to prevent death from a cause related to diabetes was 15.

The recently reported Steno 2 study in type 2 diabetes with microalbuminuria has similarly provided evidence

that intensive control of multiple factors including hypertension has a beneficial effect on retinopathy. The study compared intensive (n=73) with standard (n=76) control of hypertension, hyperglycaemia, and hypercholesterolaemia.¹⁹ ACE inhibitors were used irrespective of blood pressure in the intensively treated group, but restricted to hypertensive patients with standard therapy, and additionally aspirin was used more liberally in the intensively treated group. After 4 years one patient in the intensively treated group became blind in one eye compared with seven in the standard group (p=0.03). There was a 0.45 relative risk of retinopathy progression in one eye by one level on the EURODIAB scale with intensive compared with standard treatment at 4 years (p=0.04).

There is the suggestion that at least in type 1 diabetes antihypertensive drugs could be useful even in the presence of normotension. The EUCLID study²⁰ involved randomisation of predominantly normotensive normoalbuminuric type 1 diabetic patients to placebo (n=166) or an ACE inhibitor (n=159). At 2 years ACE inhibition was associated with a statistically significant 50% reduction in progression of retinopathy by at least one EURODIAB level (p=0.02), and the odds ratio for proliferative retinopathy was 0.18 with lisinopril treatment (p=0.03).²¹ The effect could not be wholly accounted for by the 3 mm Hg reduction in diastolic blood pressure in the lisinopril treated group. Caution must be applied to the study since the placebo group had a significantly higher mean glycosylated haemoglobin than the treated group, and even though this was accounted for at the time of statistical analysis some reservations must remain about the study conclusions. Nevertheless, meta-analysis of other studies on ACE inhibitors in normotensive diabetics has also produced evidence of a beneficial effect on retinopathy.²¹

What is the threshold for treatment and what is the appropriate target blood pressure?

Doctors and patients should now be more interested in the absolute rather than the relative reductions in risk produced by treatment. The World Health Organisation/International Society of Hypertension 1999 guidelines use a systolic blood pressure criterion of >140 mm Hg or a diastolic blood pressure of >90 mm Hg for definition of hypertension, and suggest that decision to treat should be based on cardiovascular risk assessment, using the Framingham equation.²² Since diabetes is a major risk factor for coronary heart disease (CHD) the treatment thresholds and targets in diabetes will be lower than for non-diabetic patients. This raises the historic controversy that excessive lowering of blood pressure could lead to an increase in cardiovascular mortality rather than a reduction, the so called J-shaped curve.²³ However, the recently published results from the Hypertension Optimal Treatment (HOT) study²⁴ have dispelled this concern. The study was based on the hypothesis that treated hypertensive patients have a higher cardiovascular mortality than matched normotensive patients as a result of inadequate antihypertensive therapy. A large subgroup of diabetic subjects in the HOT study was also available for analysis (n=1501). In the diabetic group randomised to ≥ 80 mm Hg (equating to a mean systolic pressure of 139.7 mm Hg and a mean diastolic pressure of 81.1 mm Hg) the number of cardiovascular events was half that observed in the group randomised to ≥ 90 mm Hg. The trial was not designed to assess retinopathy outcome, but a microvascular end point benefit was shown by the reduction in albuminuria, demonstrating that intensive control of blood

Table 1 Joint British Societies' recommendations for treatment of hypertension in diabetes²⁵

| Type 1 diabetes | | | |
|-----------------|--------------------------------|-----|---|
| Threshold | ≥130 systolic | or | ≥80 diastolic |
| Target | <130 systolic <125 systolic | and | <80 diastolic <75 diastolic if proteinuria |
| Type 2 diabetes | | | |
| Threshold | ≥160 systolic ≥140 systolic | or | ≥90 diastolic ≥90 diastolic if target organ damage, microvascular or macrovascular complications or absolute coronary risk ≥15% over 10 years |
| Target | <130 systolic | and | <80 diastolic |

pressure is appropriate, and will not in practice produce a J-shaped curve.

The Joint British Societies' recommendations²⁵ have incorporated recent trial evidence in diabetes. In type 1 diabetes target blood pressure should be <130 mm Hg systolic and <80 mm Hg diastolic (and <125 mm Hg systolic and <75 mm Hg diastolic when there is proteinuria). The recommended threshold for blood pressure treatment for type 1 diabetic subjects is ≥130 mm Hg systolic or ≥80 mm Hg diastolic. The same message is given for type 2 diabetes, with the treatment target of <130 systolic and <80 diastolic, and recommended threshold for treatment of ≥160 mm Hg systolic or ≥90 mm Hg diastolic. In the presence of macrovascular or microvascular disease, coronary risk ≥15% over 10 years, or target organ damage the threshold for treatment should be reduced further to 140/90 mm Hg (Table 1). These target levels for diabetes constitute a formidable challenge, demonstrated by the UKPDS which found that 29% of the tight control group required three or more antihypertensive medications, and 60% needed at least dual antihypertensive therapy after 9 years of follow up.

White coat hypertension is a concern that can delay intervention particularly because many patients are aware of the phenomenon, and may question the need to intervene.²⁶ Self measurement of blood pressure at home may be required, and is a reasonable alternative to the less convenient and more expensive ambulatory blood pressure monitoring.²⁷ Communication between all health personnel involved in the care of the diabetic patient makes monitoring easier, and both community diabetes nurses and shared care records can contribute effectively.

Which antihypertensive drugs should be used in diabetic subjects?

There remains some controversy in the choice of antihypertensive therapy in diabetic subjects. Newer agents such as ACE inhibitors and calcium channel blockers appear to be metabolically neutral for glycaemic control and insulin resistance, and the effects of these two groups of agents have now been extensively studied in a number of recent trials. β Blocking agents and to a lesser extent thiazide diuretics may both adversely affect the metabolic status in diabetes mellitus, but remain important agents.^{28 29} α Receptor antagonists are appropriate second line medications particularly since some, such as doxazosin, can have beneficial metabolic effects in type 2 diabetes. The angiotensin II receptor antagonists provide a useful sixth major class of agents for use in treatment of diabetic hypertension. In practice, many patients require combinations of treatments from different classes.

Recent reports of adverse effects from calcium channel blockers in type 2 diabetes have caused some concern. This is on the basis of retrospective analysis of trial data where a higher incidence of coronary artery disease has

been suggested.³⁰ In diabetic subjects three large studies raised concern regarding excess cardiovascular morbidity from calcium antagonist therapies. The Appropriate Blood Pressure Control in Diabetes (ABCD) study³¹ and the Fosinopril versus Amlodipine Cardiovascular Events Randomised Trial (FACET)³² compared an ACE inhibitor with calcium antagonist therapy. The third study, the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS)³³ compared a calcium antagonist (isradipine) with a diuretic (hydrochlorothiazide). All three trials had significantly more cardiovascular events in the calcium antagonist treated diabetic patients compared with the other treatments, but were not designed to assess retinopathy outcomes, although the total number of events in all three studies was small.

In contrast with these findings, analysis of a diabetic subgroup of the Syst-Eur trial³⁴ has found no excess in cardiovascular deaths in the calcium antagonist treated groups compared with placebo. Further evidence that calcium antagonist therapy is not harmful in diabetic subjects is given by the results of the HOT study. These studies examined almost 2000 diabetic patients, and provide considerable reassurance that calcium antagonists reduce rather than increase cardiovascular mortality. It seems likely that ACE inhibitor drugs may be more beneficial than calcium antagonists, particularly in type 1 diabetes, but the latter drugs are also protective against cardiovascular disease in diabetic subjects with systolic hypertension.

In type 2 diabetes, the UKPDS not only examined the effect of tight versus less tight blood pressure control, but also compared the efficacy of captopril, a short acting ACE inhibitor, with atenolol, a β blocker. Both drugs were effective in reducing blood pressure to a mean of 144/83 and 141/81 mm Hg respectively, and were equally effective in reducing cardiovascular and microvascular end points. These data suggest that in type 2 diabetes it is the blood pressure lowering that is important, rather than the choice of agent. It should be noted however that more patients on atenolol stopped the therapy before the end of the study as a result of side effects compared with those on captopril and needed more hypoglycaemic therapy.

It has been suggested that the ACE inhibitors and the angiotensin II blockers may carry a specific advantage not related to the degree with which they lower systemic blood pressure. Possible theoretical advantages for ACE inhibitors in retinopathy include postulated direct effects on retinal blood flow via vascular endothelial ACE receptors, and the role of the renin-angiotensin system in angiogenesis.³⁵ In the context of retinopathy, and for other systemic reasons (particularly renal), the ACE inhibitors are favoured as first line treatment, especially in type 1 diabetes, but it is recognised that many patients (60% in type 2 diabetes) will require the addition of at least a second agent.

Impact of recent research on ophthalmic practice

The prevalence of both type 1 and 2 diabetes is increasing worldwide; according to recent projections, it will affect 239 million people by 2010—a doubling of prevalence since 1994.³⁶ Without taking into account changes in diagnostic criteria,³⁷ the prevalence of both type 1 and 2 diabetes is also increasing in the UK and, thus, diabetic retinopathy will present an increasing public health challenge both in the UK and elsewhere. Despite the rising prevalence of diabetes, blind registrations for diabetic eye disease have fallen presumably as a result of successful treatment.^{38 39} However, diabetes remains a major source of blindness in the community. Official blind registration data are known to be incomplete, although underregistration is

greater for the partially sighted than for the blind. The most direct estimate of underregistration in a representative population estimated that 90% of eligible blind people were registered.⁴⁰ In 1990–1, diabetes (diabetes and diabetic retinopathy, ICD 250 and ICD 362.0 categories respectively) accounted for 4% of all blind registrations, well behind the leading causes of macular degeneration at 49% and glaucoma at 12%, but in the working age group of 16–64 years, diabetes was the most important single cause of blindness, with 12% attributed to diabetic retinopathy. In 1990–1 in England and Wales there were 558 newly registered cases of blindness due to diabetes.³⁹ This figure is significantly below the 721 cases for England alone in 1980–81,³⁸ but it still represents a major avoidable source of blindness in the community.

Tight control of blood pressure markedly reduces sight loss in diabetic retinopathy. In the UKPDS a 10 mm Hg fall in systolic blood pressure and a 5 mm Hg fall in diastolic blood pressure was associated with a 47% reduction in risk of doubling of visual angle at 9 years. There are also significant renal and cardiovascular benefits. This benefit is additional to the benefits achieved by retinopathy screening and laser treatment. Given the known major gains from tighter blood pressure control, and the documented failure to deliver this care on a population basis, strategies for managing the care of the diabetic population need to be reviewed. Following the publication of the UKPDS the UK Department of Health has called for more frequent monitoring and more intensive treatment of patients with diabetes.⁴¹

The UKPDS has finally and conclusively demonstrated for the first time that tight glycaemic control and tight hypertension control slows the progression of retinopathy in type 2 diabetes. The challenge for the medical profession is to translate this research finding into effective care. Tighter metabolic control and effective treatment of hypertension has the potential to reduce significantly requirements for laser treatment and ultimately visual impairment from diabetic retinopathy. The favourable impact on visual disability in the population is likely to be sustained since the risk reduction from both tighter metabolic and blood pressure control is greater for microvascular end points than cardiovascular end points, and hence could lead to a reduction in the burden of microvascular morbidity, particularly from diabetic retinopathy.

Maculopathy is the major reason for laser treatment in ophthalmology departments in the UK. The Royal College of Ophthalmologists study found nearly twice as many macular first laser treatments were performed compared with pan-retinal photocoagulation.^{42–45} Maculopathy, particularly ischaemic maculopathy, is the type of sight threatening retinopathy least responsive to laser treatment. There is some evidence that ischaemic and exudative maculopathies have different cardiovascular profiles with hypertension as a striking factor in the ischaemic type. It has been suggested that the majority of non-correctable visual impairment from diabetes in UK hospital practice is due to ischaemic maculopathy and also retinal vein occlusions associated with diabetic hypertension (Dodson PM, personal communication). The failure of laser as a treatment modality for ischaemic maculopathy makes the prevention of maculopathy, especially ischaemic maculopathy, by tight blood pressure control a particularly important approach to preventing visual loss in diabetes.

Ophthalmologists will need to ensure that diabetic eye care involves both medical treatment and laser photocoagulation. There is a good rationale for blood pressure to be measured at ophthalmology assessments provided the results are acted upon by the ophthalmologist or made available for the patient's physician. The finding that 29%

of the UKPDS tight blood pressure control group required three or more antihypertensive medications shows that a major commitment is needed, and requires a significant increase in medical effort and resources. Intensive medical treatment brings the hope that ischaemic maculopathy which cannot be treated with laser may be controlled. A population approach to tight blood pressure control in the diabetic population may reduce the incidence of sight threatening retinopathy with a favourable impact on the lives of diabetic patients.

Conclusions

Epidemiological evidence has given insight into the role of hypertension in the progression of diabetic retinopathy. Recent clinical trial evidence has demonstrated beyond question the value of tight blood pressure control in diabetic eye disease. Diabetes mellitus and hypertension in combination multiply the risk of macrovascular and microvascular disease, yet in current UK clinical practice the tight control of blood pressure has not been achieved in the population with diabetic retinopathy. Diabetic retinopathy remains the leading cause of blindness in working age people in the UK despite the introduction of screening programmes and the wide availability of laser treatment. Strategies to lower blood pressure in patients with diabetic retinopathy need encouragement for a further reduction of sight loss in diabetes.

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