THE EFFECT OF DIABETIC CONTROL ON DIABETIC RETINOPATHY

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SUMMARY

Poor diabetic control is associated with an increased risk of diabetic retinopathy, and there is a particularly increased risk in insulin-dependent (type 1) patients for the development of proliferative diabetic retinopathy. There is good evidence that hyperperfusion is an important factor in the evolution of diabetic retinopathy. This hyperperfusion is worse in those with poor diabetic control. The increased blood flow associated with high glucose interferes with autoregulation, and this further increases flow, damaging the endothelial lining of the blood vessels and leading to worsening of the retinopathy.

There are over 800 publications in the world literature relating diabetic control to diabetic retinopathy. None of these suggests that good control is bad for diabetic retinopathy, and there are only a few which indicate that retinopathy is not related to the degree of diabetic control. There are many problems with most of the studies: they are small, retrospective, not controlled, not randomised, and worst of all the assessment of the quality of control is not reliable. Until the late 1970s it was impossible to determine accurately the level of diabetic control achieved, as there were no adequate methods of estimating it. It was the introduction of the measurement of glycated haemoglobin (HbA1)[1] which allowed for the first time the estimation of diabetic control over a prolonged period of 8–12 weeks. It was also not possible for insulin-dependent (type 1) diabetic patients to determine their day-to-day control accurately until home monitoring of blood glucose became possible.[2]

Small randomised studies soon appeared in the literature on using intensified diabetic management by continuous subcutaneous insulin infusion or multiple insulin injections.[3–5] These studies suggested that in the first few months after initiating strict diabetic control in previously poorly controlled patients with mild diabetic retinopathy the retinopathy tended to deteriorate, and cotton wool spots, haemorrhages, multiple microaneurysms and venous abnormalities developed. These abnormalities only rarely progressed to proliferative retinopathy, and usually regressed by 12–18 months.[6,7]

There are now two large studies in progress which in the next 3 years will clearly establish the relationship between diabetic control and complications. The first of these is the Diabetic Control and Complications Study (DCCT)[8,9] for insulin-dependent diabetic patients in the United States; the other is the United Kingdom Prospective Diabetes Study (UKPDS)[10] for non-insulin-dependent (type 2) patients. Until these studies are completed the best evidence for the effect of control comes from the large Wisconsin epidemiological study of Klein and his co-workers.[11–14]

FINDINGS OF THE WISCONSIN STUDY

The initial examination of patients in the Wisconsin study was done between 1980 and 1982.[11,12] It was found that young-onset diabetic patients (diagnosed before their thirtieth year, and presumed insulin-dependent) had almost no retinopathy until 5 years after diagnosis, and then a rapid increase in prevalence reaching 97% by 15–20 years duration of the disease. Proliferative retinopathy also increased from about year 10 of diabetes to year 25, when it reached 60%. In the older-onset patients retinopathy was present in over 20% at the time of their first examination. In those on insulin, prevalence increased to levels similar to those in the young-onset patients, while those not treated by insulin had a lower level of retinopathy. Proliferative retinopathy was also less common in these patients. A maximum of 40% of those on insulin had proliferative lesions, and 20% of those not on insulin. There were a number of risk factors for the presence of retinopathy and proliferative retinopathy. These included duration of diabetes, age of onset, raised blood pressure, worse diabetic control and albuminuria.

More interesting was the result of the 4-year follow-up examination, and the study of the relationship of diabetic control at baseline to the incidence, progression, and pro-

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gression to proliferative retinopathy in these patients. The patients were divided into quartiles on the basis of their HbA1 level. In the young-onset patients the lowest quartile had an incidence of retinopathy of 45%, while the highest had an incidence of over 80%. In the older-onset group on insulin the incidence was 40% and 50% respectively, but the difference between the lower three groups was small. In those not on insulin the lowest quartile had an incidence of only 15%, compared with 50% in the highest quartile. Similar differences were present in the progression of retinopathy in those who already had retinal lesions at baseline. For the incidence of progression to proliferative retinopathy the greatest difference was in the young-onset patients: the lowest quartile had only a 1% incidence of new proliferative lesions while in the highest quartile it was 24%.[13,14] Klein felt that if the mean HbA1 could be reduced by just 2% from its value of 11% the incidence of new proliferative retinopathy would decrease by 50% in the whole group.

It therefore appears that poor diabetic control is bad for retinopathy. The question is why this is so.

RETINAL BLOOD FLOW IN DIABETIC RETINOPATHY

High blood glucose is associated with increased retinal blood flow. This was found by Atherton *et al.* in cats[15] and Sullivan *et al.* in minipigs.[16] Atherton, using cine fluorescein angiograms, found that there was a marked rise in volume flow following a bolus injection of glucose, and that this was maintained during continuous infusion of glucose. Similar molar concentrations of mannitol or saline did not have this effect. The Hammersmith group,[16] using laser Doppler velocimetry (LDV), found that bolus injection of glucose or slow infusion raised blood flow to a similar degree provided the blood glucose level was the same. Urea in equiosmolar concentration did not have this effect. In humans too high a glucose concentration seems to increase blood flow. Thus using the mean transit time of fluorescein Kohner *et al.* found reduced transit time in patients with mild background retinopathy and newly diagnosed diabetes, and also in those with moderate diabetic retinopathy. Effective pituitary ablation and photocoagulation both increased the mean transit time, suggesting reduced blood flow in these eyes.[17] More recently Grunwald and co-workers found that after instituting strict diabetic control in previously poorly controlled diabetics blood flow at 5 days could predict progression of retinopathy. Those in whom blood flow increased were the ones who at 6 months showed deterioration of diabetic retinopathy, while those in whom at 5 days blood flow was reduced showed no change or an improvement.[18] The largest of the studies, and the most convincing, was from the Hammersmith group, using LDV.[19] In this study 24 normal volunteers and 76 diabetic patients were studied, of whom 13 had no retinopathy, 27 had background retinopathy, 12 had preproliferative retinopathy, 12 proliferative retinopathy and 12 had proliferative retinopathy successfully treated by panretinal photocoagulation. Fig. 1 shows the results. There was no difference between the normal controls and diabetics without retinopathy. Those with mild background retinopathy had a 30% increase in blood flow, those with preproliferative and proliferative retinopathy 50% and 66% increases in flow respectively. After successful photocoagulation flow was reduced by 60% compared with those without retinopathy.

WHY DOES THE INCREASED FLOW MATTER?

The retinal blood vessels do not have an autonomic innervation, thus blood flow is controlled largely by autoregulation. Autoregulation in the retinal circulation is usually tested by oxygen breathing. This causes a significant reduction in vessel calibre and a reduction in blood flow. Grunwald *et al.* found a 60% reduction of flow in normal subjects breathing 100% oxygen; this was reduced in diabetics, most markedly in those with proliferative retinopathy, to 25%.[20] When they studied poorly controlled non-insulin-dependent diabetics they found an increased retinal blood flow and reduced oxygen reactivity. Infusing insulin to bring the glucose down to normal levels resulted in decreased blood flow and improved oxygen reactivity.[21] Using 60% oxygen our group has found a 43% reduction in blood flow in normal controls, and only a 25% reduction in poorly controlled diabetics, while in the same patients when the blood glucose was below 10 mmol/l it was 30%. Thus high glucose interferes with autoregulation, and allows a constantly high blood glucose to cause a constantly high blood flow.

Increased blood flow results in an increased shear stress, since shear stress is directly related to volume flow and viscosity. In poorly controlled diabetics both are increased. The increased shear stress and circumferential stress result in damage to the endothelial cells, the key factor in diabetic retinopathy. Of course there are other factors involved: high glucose damages the pericytes,

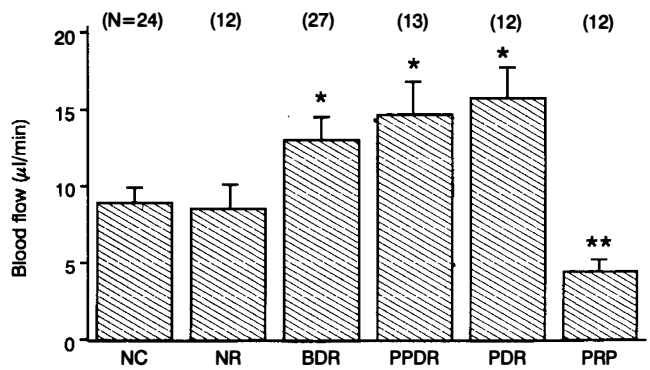

Fig. 1. *Mean blood flow (and SD) in superior temporal vessel in normal controls and diabetic patients. Numbers in brackets indicate numbers of patients in that group. NC, normal control; NR, no retinopathy; BDR, background diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, post-panretinal photocoagulation. *p<0.05 compared with normal controls; **p<0.01 compared with normal controls.*

probably through glycation of proteins, there are changes in endothelin production and endothelin response in endothelial cells and pericytes, all of which contribute to the evolution of retinopathy. It is likely that hypertension is also very damaging to diabetic retinopathy because if glucose is high then autoregulation in that condition cannot protect the endothelial lining from the increased shear stress and circumferential stress resulting from the increased retinal blood flow.

Key words: Diabetic control, Diabetic retinopathy, Retinal blood flow.

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