Diabetic Retinopathy and High Blood Pressure: Defining the Risk

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Over the last 20 years, photocoagulation has proved to be effective in preventing blindness in patients with diabetic retinopathy. Even so, many patients with diabetes still become blind. This is because they have a more rapidly progressive form of retinopathy—in fact, the disease progresses in some patients despite photocoagulation treatment. It is therefore important to identify those patients who are at special risk for rapidly advancing retinopathy.

The duration of diabetes is probably the best known risk factor for existing retinopathy and for the development of retinopathy. Blood glucose control is now recognized as important in reducing the risk of progression of already existing retinopathy, at least in patients with insulin-dependent diabetes (IDDM). Good control can also delay the appearance of retinopathy in patients who do not already have it. High blood pressure is another risk factor, but its role is not as clearly established as is the duration of hypoglycemia and glycemic control.

In this communication, three aspects of hypertension as a risk factor for diabetic retinopathy are discussed: 1) What evidence is there that hypertension is detrimental to diabetic retinopathy? 2) Why is hypertension detrimental? and 3) Are there hypertensive drugs with a beneficial effect in diabetic retinopathy?

EVIDENCE FOR HYPERTENSION BEING DETRIMENTAL TO DIABETIC RETINOPATHY

The role of hypertension in the incidence and progression of retinopathy is not clearly established. The reason for this is primarily that many of the published studies are relatively small, and often the methods used to establish the presence and severity of retinopathy are not sensitive. Most of the positive studies relating to this topic are cross-sectional. Thus Knowler et al. found more retinopathy in diabetic Pima Indians who had higher blood pressure than in Pima Indians who had a lower blood pressure. Similarly, in a survey of patients with type II non-insulin-dependent diabetes mellitus (NIDDM), Janka et al. considered hypertension to be an important risk factor for diabetic retinopathy. The most important studies are the Wisconsin epidemiological studies. In these, Klein and coworkers found that hypertension was significantly associated with the presence and severity of diabetic retinopathy in both IDDM and NIDDM. The most important study of NIDDM in this respect is the United Kingdom Prospective Diabetes Study (UKPDS). This study showed that within 6 months of diagnosis both the presence and severity of retinopathy were associated with high blood pressure (unpublished results).

There are few valid studies of the relationship between blood pressure and progression of retinopathy. In the Wisconsin epidemiological study, systolic blood pressure was a significant predictor of the incidence of retinopathy and diastolic blood pressure a significant indicator of the progression of retinopathy in patients with IDDM at 4 years. In patients with NIDDM (“older onset” in the Wisconsin study), blood pressure had no effect on either the incidence or the progression of diabetic retinopathy. The UKPDS reported significantly different results. In this study, the 6-year incidence and progression of retinopathy were both significantly related to blood. Klein suggests that the variability of the results concerning blood pressure is because blood pressure is not so much a risk factor as a risk indicator but this is unlikely in view of the UKPDS results. The difference between the Wisconsin study and UKPDS is that, in the latter, patients were...
seen at the time of diagnosis of diabetes and the effect was studied at 6 years rather than 4 years. Thus, at present, it is probable that blood pressure is important in the incidence and progression of diabetic retinopathy. Why should this be?

**WHY IS HYPERTENSION DETRIMENTAL TO DIABETIC RETINOPATHY?**

It has been shown by Patel et al that diabetic retinopathy is associated with hyperperfusion. These workers found that retinal blood flow was similar in diabetic patients with no retinopathy and in nondiabetic patients, but that blood flow increased with increasing severity of retinopathy. That increased blood flow can be damaging is shown by the fact that conditions associated with increased blood flow, such as pregnancy and poor diabetic control, are associated with worsening retinopathy, whereas conditions such as increased intraocular pressure and a mild degree of carotid stenosis, which reduce blood flow, are protective. Hyperperfusion is damaging because it increases shear stress, which damages the endothelial lining of the small vessels of the retina.

The retinal vessels, in contrast to most vessels in the circulation, do not possess a functional sympathetic innervation. Blood flow is therefore controlled by autoregulation; that is, blood vessels keep blood flow constant even though perfusion pressure varies. It has been established that high blood glucose, as well as low blood glucose, increases blood flow in nondiabetic experimental animals. High blood pressure increases perfusion pressure. Autoregulation should normally overcome this, at least when the rise in blood pressure is not excessive. However, when blood glucose is elevated, the increased blood flow will inhibit the autoregulatory adaptation of vessels. This was shown in a series of experiments in which blood pressure was raised by infusion of tyramine, a naturally occurring sympathomimetic amine. Ten healthy volunteers and 12 normotensive patients with IDDM were studied. The diabetics were studied twice, once with normal blood glucose (under 10 mmol/L) and once when their blood glucose was high (above 15 mmol/L). Blood flow was measured when the mean arterial pressure (MAP) was at baseline, and again when it rose to 15%, 30%, and 40% above baseline. Even at baseline the diabetic subjects had a somewhat higher blood flow than the nondiabetic subjects. In the nondiabetic subjects, blood flow increased only slightly until the MAP reached 40%, whereas in the well-controlled diabetic subjects it was already significantly increased when the MAP rose by 30%. When blood glucose was elevated in the same diabetic subjects, there was no evidence of any autoregulation, even when the rise in blood pressure was only mild (that is, 15% above baseline).

Further evidence for hypertension being associated with increased blood flow came from a study of mildly hypertensive nondiabetic and diabetic patients. In these patients, autoregulation could only be tested by studying the patients twice: once when their blood pressure was raised, and once when it had been lowered for at least 3 months. In these patients, oxygen reactivity was measured again as an autoregulatory mechanism. These studies showed that, as in normotensive diabetic subjects, high blood glucose increased retinal blood flow and reduced oxygen reactivity. To bring oxygen reactivity to the levels of normotensive diabetic subjects requires bringing both blood pressure and blood glucose under control.

The blood flow changes in these diabetic subjects are truly horrendous, and it is therefore not amazing that shear stress is increased. Increased shear stress has many effects: it alters the balance of mediators that control vascular tone, hemostasis, matrix production, and vascular cell growth; it increases the production of vasodilators such as nitric oxide and vasodilator prostaglandins; and it deceases the production of vasoconstrictors such as endothelin-1.

It is effects of an increased blood flow, together with the direct toxic effect of high glucose on pericytes and endothelial cells, that result in the occlusion of capillaries and dilatation and leakage of vessels. Capillary occlusion leads to the formation of microaneurysms, the nonperfusion of capillary beds, which has severe consequences, and the formation of new vessels.

**ARE THERE HYPOTENSIVE DRUGS WITH A BENEFICIAL EFFECT ON DIABETIC RETINOPATHY?**

The most important point is to prevent high blood pressure early on in diabetes. Even when blood pressure is within the normal range, young diabetic subjects with slightly higher blood pressure are more likely to have more advanced diabetic retinopathy. For example, Testa and colleagues found that retinopathy was more likely to progress in subjects whose blood pressure was slightly higher but still within the normal range than it was in subjects with a lower blood pressure. Among the first 12 patients with mild diabetic retinopathy treated with intensive insulin therapy, blood flow was related to the deterioration of retinopathy at 6 months in those patients whose blood flow did not decrease with improvement of diabetic control. These patients also had a higher MAP at the time of entry into the study, although it was within the normal range.

There are few long-term studies on blood pressure control in diabetic patients. There is the UKPDS for NIDDM patients, which has a hypertensive arm. In this study, both strict and less strict control of blood pressure are achieved with a number of different ther-
apeutic agents; however, it will be another 2 years before we will see any results from this study. In 1988, Teuscher and coworkers reported on the treatment of hypertension in diabetic patients. They found that retinopathy advanced less in patients whose blood pressure was more effectively controlled. Patel and coworkers carried out a pilot study in which they compared an angiotensin converting enzyme (ACE) inhibitor with a β-blocker in diabetic patients with early diabetic retinopathy and a slight elevation of blood pressure. They found that, after 1 year, blood pressure control and retinopathy were similar in the two groups. However, when blood flow changes were compared between the two groups of patients, it was found that the patients who received the ACE inhibitor fared significantly better than did the patients who received the β-blocker.

This pilot study is not by itself an indicator that ACE inhibitors might be the drug of choice for diabetic retinopathy, in spite of the study by Parving et al, which also suggested this. It rather indicates that long-term studies of diabetic patients with hypertension are needed to test whether certain drugs have a particularly beneficial effect.

REFERENCES