DIABETIC CONTROL AND RETINOPATHY

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Diabetic retinopathy is an important cause of blindness. According to a local community survey in 1975, retinopathy occurs in about 8.5% of patients with diabetes in Singapore. However, in the preinsulin era, diabetics had a high mortality mainly from ketoacidosis and infections, and retinopathy was hardly a clinical problem. The patients simply did not live long enough to develop this and other microvascular complications. With the advent of methods for controlling blood sugar, patients live longer but life is frequently marred by impaired vision, renal failure and neuropathy. It seems ironical that in prolonging our patients' lives, we have brought about certain very distressing problems for them, and these problems might indeed be regarded as iatrogenic. The truth of the matter of course, as alluded to earlier, is that retinopathy like other microvascular lesions of diabetes is a function of the duration of diabetes itself, and our ability to control blood sugar and prevent early death has as it were made it possible for retinopathy to manifest itself. It would therefore appear that the degree of diabetic control sufficient to prolong life is not adequate to prevent the development of retinopathy clinically. Two questions pertaining to this problem are usually asked. Firstly, is retinopathy a direct consequence of diabetes? Secondly, can better control of hyperglycaemia of diabetes prevent or alleviate retinopathy? These are clearly important questions on which data have gradually accumulated over the years. This article reviews some of the more recent findings.

Retinal and other microvascular lesions resembling those of diabetes mellitus in man have been found in dogs made diabetic with alloxan and allowed to remain hyperglycaemic for years[1] . Similar observations have been made in rats and other animals with experiementally-induced diabetes. These observations lend support to the hypothesis that the vascular abnormalities are initiated by deficient insulin activity and are not the manifestation of some hereditary defects associated with diabetes. The development of diabetic vascular lesions in normal kidneys transplanted into patients with diabetes mellitus (in the management of advanced diabetic nephropathy)[2] provides incontrovertible evidence that the microvascular lesions of diabetes are indeed complications of diabetes. It clearly establishes the fact that microvascular lesions can be induced in a normal organ exposed to the diabetic environment. This observation has also been made in rats[3]

How diabetes mellitus leads to retinopathy is however still far from clear. An important role has been assigned to retinal ischaemia or hypoxia consequent to diabetes. There is allegedly deficient 2, 3-

diphosphoglycerate (a product of glucose metabolism), probably resulting from insulin deficiency, which causes the oxygen dissociation curve to shift to the left, leading to less oxygen being made available to tissues[4]. There is an increased amount of Hb AIC (as a result of chronic hyperglycaemia)[5] which reduces the oxygen-releasing potential of 2, 3-DPG and which possibly reduces the deformability of the erythrocytes resulting in damage to the endothelium. It is also believed that chronic hyperglycaemia by causing an accumulation of intracellular sorbitol[6] damages the endothelial cells and pericytes of the capillaries, leading to increased leakiness of the capillaries which is present even before ophthalmoscopic or angiographic evidence of retinopathy[7] and which is reduced in streptozotocin-induced diabetic rats, on normalisation of blood sugar. The thickened basement membrane of the capillaries is thought to be the consequence of capillary leak.[8]

The next question clearly centres around the relationship between control of diabetes and the development of retinopathy. In this respect it is salutory to remind ourselves that the metabolic abnormalities of diabetes mellitus are not confined simply to hyperglycaemia. Because blood glucose is clinically convenient to measure, it has been used as a measure of severity of the disease and as an index for monitoring response to treatment. Even depending on blood glucose level alone in assessing diabetic control, evidence has accumulated which indicates that good control can prevent, delay and even reverse the dreaded complication of retinopathy. The earlier evidence was however retrospective in which retinopathy was found to be decreased or delayed as blood glucose levels were brought towards the normal range[9 10]. The University Group Diabetes Project[11] was an attempt at prospective study of the relationship between diabetic control and diabetic complications but although the five forms of therapy adopted failed to demonstrate any effect on microvascular lesions, the study was not really pertinent because it was based on mild diabetics with minimal initial hyperglycaemia and the reduction in blood sugar with treatment was small. Furthermore the study, in using fixed dosage of medication for individual patients throughout the period of observation, differs from the situation in clinical practice where optimal control is often attainable only with judicious adjustment of dosage of medication. The past few years have seen numerous studies in animals especially in dogs and rats, in which reduction of hyperglycaemia (of experimentally-induced diabetes) prevents or minimises microvascular diseases. Engerman and his colleagues[12] showed in alloxandiabetic dogs that microvascular complications are preventable and may be inhibited by control of the metabolic disorder. They randomly distributed the diabetic dogs into two prospective treatment groups, one for inadequate and the other for good control regime, using insulin. Better control was found to reduce significantly the incidence and severity of retinopathy. Other workers had similar findings with experimentally-induced diabetic rats. An important prospective study in patients is that by Job and his colleagues[13]. Forty-two diabetic patients who had been on insulin once a day were randomly assigned to one of two kinds of insulin regimen. One group received once-a-day insulin injections while the other had multiple injections of insulin in a day. Retinal changes were quantitatively estimated by counting the microaneurysms observed on fluorescein angiograms at the posterior pole of the more diseased eye. Base-line characteristics of the 2 groups were not significantly different in terms of duration of diabetes, age at diagnosis, daily dose of insulin, fasting blood sugar and number of microaneurysms. During the 3-year follow-up, the mean yearly increase in the number of microaneurysms was significantly less in the multiple than in the single-injection group. This study shows that the use of divided daily insulin injections was effective in improving diabetic control and delaying retinal changes. Walford and associates[14] have reported that with conscientious application of recently developed self-monitoring technique, which involved drawing 11 blood specimens throughout the day and measuring blood glucose with a reflectance photometer on enzyme strips enabled a better control of hyperglycaemia. This was associated with reversal of some microvascular complications. A case was cited of a 19-year old boy whose florid retinopathy showed regression of new vessels after 10 months of self-monitoring. Mauer[3] treated experimentally-induced diabetes in rats with islet-cell transplantation and documented improvement in the microvascular lesions of the kidney although the improvement was seen only in the earlier period of treatment. These observations strongly indicate that the microvascular lesions of diabetes are not only preventable but also capable of regression in some instances, with strict control of blood sugar alone. Thus, it might be extrapolated that if physiological control of blood sugar can be simulated with treatment, retinopathy could cease to be a problem.

However, control of diabetes in the ordinary clinical setting does not reproduce the physiological situation with respect to blood glucose, let alone other more abstruse metabolic parameters. Even the multiple insulin injection regime cannot be compared to the physiological state in which occurs moment-to-moment regulation, by the ambient blood glucose level, of secretion of insulin into the portal circulation. (Note that in treatment, injected insulin is introduced into the systemic circulation). Thus blood glucose profile of treated diabetics shows frequent hyperglycaemias and gross fluctuations, compared to the physiological state where blood glucose is kept normal within narrow limits all the time. Fluctuations in blood glucose are probably as damaging to the retina as hyperglycaemia. There are measures which can alleviate blood glucose fluctuation. One, which is well-known, but not widely practised, is spreading the daily food intake more evenly throughout the day. Eating habits and inconvenience of frequent eating however militate against this practice. Increasing the vegetable-fibre content of food is another way of avoiding blood glucose fluctuations. Adding fibre preparation to low-fibre content diet may be another way of alleviating blood glucose fluctuations[15]. Finally the nearest to physiological restoration of blood sugar would appear to lie in either the artificial pancreas or islet-cell transplantation. When these methods of treatment become clinically available, we can confidently expect that retinopathy and other microvascular lesions will no longer plague the life of our diabetic patients.

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