Natural History of Diabetic Microangiopathies

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Diabetic microangiopathy is better called diabetic microcirculatory disease, because it is characterized by as well dysfunction of small vessels and as increased capillary basal membrane thickness. Its role for the development of tissue damage is not fully understood and might vary in different organs. Therefore, the two diabetic complications which are assumed to be typical manifestations of the diabetic micro-circulatory disease like retinopathy and nephropathy have to be described separately.

We have studied the natural history of diabetic retinopathy and nephropathy only in insulin-dependent diabetics. This was done because micro-vessel disease is more common in this type of diabetes than in patients with non-insulin-dependent diabetes mellitus. Also the onset of diabetes is usually more well-known in IDDM than in NIDDM. Only young insulin-dependent diabetics were studied in order to avoid confusion from age-related complications.

First some epidemiological facts about retinopathy which indicate the severity of the problem. The prevalence of legal blindness in a diabetic population living in a limited geographic area of Denmark was shown by Vesti Nielsen¹⁾ to be 7.9 percent in insulin-dependent diabetics and 4.6 percent in orally treated non-insulin-dependent diabetics. Seventy-five percent of the blind insulin-dependent diabetics were blind from retinopathy, whereas only 40 percent of blind non-insulin-dependent diabetics were blind from retinopathy. The cumulative incidence of blindness in a population of 264 juvenile insulin-dependent diabetics followed for more than 40 years was 16 percent²⁾. In a further 15 percent vision became so much reduced that the patients were unable to read the newspaper without magnifying glass²⁾. Thus, diabetic retinopathy is the most common cause of acquired blindness among professionally active persons in Denmark. This is also the case in the United States. It is hoped that the prognosis for vision will improve significantly after the introduction of photocoagulation treatment and vitrectomy in the treatment of diabetic retinopathy.

A precise description of the natural history of diabetic retinopathy has been difficult until now, because of the lack of quantitative measurements of pathological changes of the retina. Today, however, retinal function can be studied quantitatively by fluophotometry where the leakage of fluorescein from retinal capillaries and pigment epithelium to the posterior vitreous body can be measured

indicating a break-down of the blood/retinal barrier. Another quantitative evaluation of retinal function can be made by measuring the oscillatory potential of the ERG which has been elaborated by Japanese workers and has been further developed in Denmark by Dr. Simonsen. A decrease of the oscillatory potential probably indicates dysfunction of the Müller cell and/or amacrine cells. Also the quantitative evaluation of retinal morphology is easier now since Japanese scientists have developed a wide-angle fundus camera allowing the photography of a large part of the retina in one picture. These methods should be used in the future. At the onset of diabetes, no morphological changes can be found: fluorescein angiography and fundus photos are normal: no microaneurysms, bleedings or exudates are seen. Fluophotometry⁵⁾ is also normal; by ERG, however, a small but significant reduction of the oscillatory potential is seen⁶⁾. These changes are normalized after 7-11 days of insulin treatment. After some years of diabetes a decrease of oscillatory potential and an increase of leakage measured by fluophotometry is seen^{3,4,5)}. The first morphologic sign of diabetic retinopathy is the red dot, a microaneurysm, best seen by angiography. It might be difficult to differentiate between small degenerative defects of retinal pigment or drusen and microaneurysms by angiography and this may lead to some confusion which can be overcome by stereophotography. We have only seldom seen microaneurysms before 5 years of diabetes duration in young insulin-dependent diabetics⁷⁾. After 5 years of diabetes the incidence of retinopathy increases to a maximum after about 10 years of diabetes. The cumulative incidence after 40 years of diabetes is about 100 percent. After microaneurysms have been formed, small bleedings may occur as well in the outer layer of the retina, seen as blot haemorrhages, in the inner nerve fibre layer as flame-shaped haemorrhages or just behind the vitreous body as boat-shaped preretinal haemorrhages. Cotton wool exudates might appear later on. They represent infarctions in the inner retinal layer. Hard wax-like exudates are more common. They are deposits of lipids and hyaline material in the outer layer of the retina. These exudates might lead to impaired vision if accumulated in the macular area or complicated by edema in the macular area. Due to hypoxia new vessel formation may take place. This is a bad sign if it happens around the optic disc. Five years later 50 percent of these patients will become blind⁸⁾. The cause of blindness in these cases are bleedings from the thin new vessels and growth of connective tissue into the vitreous body. If only peripheral proliferations are seen, the prognosis is much better⁸⁾.

Several factors might accelerate the progression of retinopathy, the most important being nephropathy⁸⁾. Also pregnancy⁹⁾, hypertension¹⁰⁾, and possibly puberty⁷⁾ might lead to progression of retinopathy. We therefore treat elevated blood pressure very carefully in these patients and try to persuade pregnant long-term diabetics to interrupt the pregnancy if proliferative retinopathy or severe maculopathy is found.

The pathogenesis of diabetic retinopathy is not understood in every detail (for review see 11). Several factors seem to be of importance: 1: haemodynamic factors as flow¹²⁾, pressure, and extravasation of fluid and proteins. 2: metabolic factors such as sorbitol and water accumulation in retinal cells, 2-3 DPG accumulation in erythrocytes, increase of von Willebrandt factor in retinal endothelium¹³⁾ and increase of plasma HGH¹⁴⁾ and 3: rheological alterations as increased thrombocyte aggregation and changes in viscosity. All these factors contribute to the process which leads to focal occlusion of retinal micro-circulation i.e. capillaries and arterioles. Consequently, pericapillary tissue (Müller cell¹⁵⁾, amacrine cells, pericytes, nerve fibers) may suffer leading to the formation of cotton wool exudate^{16,17)}, focal capillary distension (microaneurysm) or arteriolar rupture (haemorrhages and exudates). To compensate hypoxia new vessel formation takes place.

As well microaneurysms, bleedings, exudates and proliferations are reversible in diabetic retinopathy, and sometimes spontaneous improvement of retinopathy is seen, but until now we do not know which mechanisms are active in these cases. Whether meticulous diabetic control-for instance near-normalization of blood glucose by insulin pumps-might be of any benefit in established cases of diabetic retinopathy is not quite clear. In our experiments¹⁸⁾, we found impairment of retinal morphology in spite of functional improvement after one year of near-normalization of blood glucose in insulin-dependent diabetics.

The most severe micro-circulatory complication in diabetes is nephropathy¹⁹⁾. Diabetic nephropathy was defined as persistent proteinuria (protein excretion > 0.5 g per 24 hrs) in at least four consecutive samples of 24 hr urine with an interval of at least one month in patients without renal infection or heart insufficiency. The clinical term diabetic nephropathy must not be confused with the morphological term glomerulosclerosis. The cumulative incidence of glomerulosclerosis in insulin-dependent diabetics is about 100 percent, however, only a minority of patients will ever develop diabetic nephropathy and only about 30 percent will have clinical symptoms from this disease. Thus, glomerulosclerosis seems to be a necessary, but not a sufficient precondition for the development of diabetic nephropathy. This is also seen from a morphometric study of renal tissue performed by Frøkjær Thomsen in our group¹⁹⁾. A new process seems to be added to glomerulosclerosis in those patients who develop diabetic nephropathy. However, we do not know the nature of this new process. By morphometric measurements of the kidneys it cannot be decided which kidney belongs to a patient with diabetic nephropathy and which kidney only belongs to a patient with glomerulosclerosis but without diabetic nephropathy.

The cumulative incidence of diabetic nephropathy is 45 percent¹⁹⁾. The incidence curve shows two peaks. This indicates heterogeneity of diabetic nephropathy.

That diabetic nephropathy is one of the most severe complications of juvenile

insulin-dependent diabetes is seen from an analysis of survival data showing the survival of juvenile diabetics to be very much dependent on whether diabetic nephropathy develops or not¹⁹⁾. Compared to non-diabetics, the relative survival of patients who do not develop diabetic nephropathy is only 200 percent whereas the relative survival of patients developing diabetic nephropathy is more than 1000 percent.

During the last years we have studied the development of diabetic nephropathy in detail. Normal urinary albumin excretion rate (U-alb-V) is $<20 \mu\text{g}/\text{min}$. In insulin-dependent diabetics U-alb-V is increased, dependent on the metabolic regulation state. Also GFR is increased but blood pressure is normal. During near-normalization of blood glucose, GFR and U-alb-V can be reduced, but not normalized. These abnormalities are found independent of the duration of diabetes and the presence of glomerulosclerosis. In patients developing diabetic nephropathy however, the U-alb-V will increase from 200 to 1000 percent of normal. This increase can be followed by sensitive immunologic determination of urinary albumin and takes place before the urine becomes albustix-positive. This increase is seen before GFR declines and blood pressure increases. When U-alb-V increases further to albustix-positive levels, GFR will decline from the supernormal level to normal level. At the same time a slight, but significant increase of blood pressure is seen¹⁹⁾.

Elevated blood pressure is thus an early symptom of diabetic nephropathy. As soon as U-alb-V has reached the albustix-positive level, the steady decline of GFR begins. The decline rate is very variable and blood pressure plays an important role. When GFR is about 50 percent of normal, serum-creatinine begins to rise. Seven years after the onset of proteinuria, 50 percent of patients have died, and one year after serum-creatinine has reached 5 mg/100 ml, 70 percent of patients are dead²⁰⁾. The cause of death in patients developing persisting proteinuria is uremia (66%) and ischemic heart disease (19%)²¹⁾.

Near-normalization of blood glucose does not seem to influence the decline rate of GFR in patients with diabetic nephropathy²²⁾. However, reduction of blood pressure does²³⁾. It is, however, possible that initial diabetic nephropathy is reversible by meticulous control of blood glucose.

In conclusion the cumulative incidence of diabetic retinopathy and glomerulosclerosis is about 100 percent in insulin-dependent diabetics of juvenile onset. But only about 30 percent of the patients will develop visual disturbances and only 30 percent will suffer from symptoms of renal insufficiency. As well the prevalence of retinopathy and glomerulosclerosis increase with diabetes duration, the first sign being seen after 5-15 years of diabetes duration, retinopathy 5 years earlier than nephropathy. In order to improve the prognosis of vision, proliferative retinopathy and maculopathy should be treated with argonlaser treatment and patients with beginning proteinuria should have their blood pressure controlled vigorously. Primary prevention of retinopathy and diabetic nephropathy

by strict metabolic control should be examined in a prospective randomized way.

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