Mechanical and structural factors

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21.10.1 Diabetes mellitus and the kidney 4977 type 1 diabetes, although this distinction is not absolute. What is certain is that progression of nephropathy is much faster in patients with higher systemic blood pressure. Haemodynamic factors The glomerular filtration rate (GFR) is increased in newly diagnosed type 1 and type 2 diabetic patients. This phenomenon has been termed hyperfiltration and is thought to be due to a relative vasodila- tation of the afferent glomerular arteriole, which leads to an increase in intraglomerular capillary pressure (Fig. 21.10.1.1) and thereby glomerulosclerosis. Hyperfiltration and raised intraglomerular ca- pillary pressure are thought to be caused in part by activation of the local renin–angiotensin system, leading to an excess production of angiotensin II and thereby relative vasoconstriction of the efferent glomerular arteriole. The evidence for a causative role of hyperfiltration for nephrop- athy in humans is conflicting and not helped by differing definitions of an abnormally high GFR and the difficulty of obtaining an esti- mate of intraglomerular capillary pressure. It appears that the rate of decline of GFR in hyperfiltering type 1 patients with a normal UAER is greater than that seen in age-matched and duration- matched controls. A meta-analysis has demonstrated a link between hyperfiltration and subsequent development of moderately in- creased albuminuria in type 1 diabetes but could not exclude a con- founding effect of hyperglycaemia. Recent data suggest that there is a link between hyperfiltration and later development of moderately increased albuminuria in adolescents, and a positive relationship between GFR and glomerular basement membrane thickening in younger adults. Pima Indians show an increase in GFR at or shortly after the development of type 2 diabetes, but their baseline values are not linked to the subsequent development of nephropathy. Growth factors In experimental animals, an initial increase in kidney size ob- served in diabetes is preceded by an increase in renal production of insulin-like growth factor 1, and there are reports of increased circulating and urinary levels in people with diabetes. Other growth factors listed in Box 21.10.1.1 have been linked to matrix accumulation and development of proteinuria in experimental diabetes. Increased whole kidney volume is also a feature of newly diag- nosed type 1 diabetes in humans, but there is no conclusive link to subsequent development of nephropathy. Several of the growth factors listed in Box 21.10.1.1 have been found to have an in- creased production or gene expression in biopsies from patients with diabetes compared to those from nondiabetic patients. It is unclear whether these changes are causative. There are recent data linking the serum

concentration of circulating tumour ne- crosis factor receptors 1 and 2 and fibroblast growth factor to subsequent development of nephropathy, but these results re- quire confirmation and there are problems with standardizing the assays. Mechanical and structural factors Along with whole kidney volume, glomerular size is also increased at diagnosis of type 1 diabetes and is a feature of established clinical proteinuria in both type 1 and type 2 diabetes. These changes may be secondary to haemodynamic alterations in early nephropathy or represent an adaptive response to loss of filtration surface in estab- lished glomerulopathy. A link between glomerular size and subse- quent progression to sclerosis has been described in patients with minimal-change nephropathy, but the connection in diabetes is not proven. Reductions of heparan sulphate proteoglycan in the extracellular matrix of diabetic patients and the glomerular basement membrane of those with moderately and severely increased albuminuria have been reported. This finding has formed the basis of the so-called Steno hypothesis, which proposes that these alterations underpin the pathophysiology of nephropathy. More recently there has been a focus on changes in the composition of the endothelial glycocalyx as an explanation of increasing albuminuria in diabetes, and it may be that changes in heparan sulphate proteoglycan in this struc- ture, rather than the GBM, are more important in terms of protein permselectivity. In vitro studies of mechanical stretch on cultured human mesangial cells and podocytes have demonstrated increased pro- duction of cytokines and growth factors associated with extracellular matrix accumulation. These studies provide a plausible mechanism whereby changes in intraglomerular capillary pressure may lead to glomerulosclerosis. The discovery of glomerular epithelial cells (podocytes) in the urine of patients with proteinuria has led to extensive research into their possible role in progressive nephropathies, including diabetes. Reduced numbers of podocytes have been found in human diabetic glomeruli from patients with diabetic nephrop- athy, but it remains unclear whether these changes precede or result from developing glomerulopathy. There is a significant negative relationship between the numbers of podocytes per glomerulus and increasing albuminuria in patients with estab- lished diabetic nephropathy. Glomerulus: Glomerular capillaries Glomerular filtrate Proximal tubule Bowman’s capsule Afferent arteriole Efferent arteriole Mesangium Fig. 21.10.1.1 Schematic of a glomerulus. In diabetes, there is relative afferent arteriolar dilatation and angiotensin II-induced efferent arteriolar constriction. This leads to increased glomerular capillary flow and pressure resulting in elevated GFR (hyperfiltration) and increased albumin filtration. Blockade of the renin–angiotensin system dilates the efferent arteriole and reduces GFR and capillary pressure.

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