Editorial Comment

Nephropathy and coronary death—the fatal twins in diabetes mellitus

Torsten Deckert
Gentofte, Denmark

Is albuminuria only a marker for renal involvement? Clinical nephropathy in patients with insulin-dependent diabetes mellitus is defined by persistent albuminuria of >300 mg/24 h in otherwise healthy patients. Before this advanced stage of nephropathy is reached, urinary albumin excretion increases slowly from the normal range (1–30 mg/24 h) to a range of albumin excretion designated as ‘microalbuminuria’, i.e. 30–300 mg/24 h. Persistent microalbuminuria is referred to as ‘incipient nephropathy’. Recent longitudinal studies have demonstrated that persistently increased urinary albumin excretion is not only an early marker of renal disease and decrease in glomerular filtration rate, but also a marker for an increased risk of cardiovascular morbidity and mortality. Six years after the onset of clinical nephropathy in patients with insulin-dependent diabetes mellitus the cumulative incidence of coronary heart disease is 8 times higher than in diabetics with normal urinary albumin excretion matched for age, duration of diabetes and sex [1]. After 25 years of diabetes at age 40–45, cardiovascular mortality in albuminuric patients is 50 times higher than in the background population and 10 times higher than in a comparable group of diabetic patients without clinical nephropathy [2]. Consequently, microalbuminuria is a novel and potent marker of cardiovascular risk. This is true not only in patients with insulin-dependent diabetes mellitus, but also in patients with non-insulin-dependent diabetes (NIDDM) and even in healthy individuals without diabetes. The reasons for such association between albuminuria and cardiovascular risk are not totally clear, but some concepts have recently emerged.

Why is albuminuria a predictor of cardiovascular risk?

One reason might be that metabolic, rheologic and hemodynamic abnormalities, e.g. hyperlipidemia, hyperfibrinogenemia and hypertension frequently coexist in patients with incipient nephropathy and clinical nephropathy [3]. However, an increase in plasma cholesterol by 20–25%, in fibrinogen by 20% and mean blood pressure by 10–15%, as seen in diabetic patients with nephropathy, will certainly increase the risk, but cannot fully account for the 10-fold higher cardiovascular mortality in such patients. This discrepancy points to the action of additional factors. One such factor might be a simultaneous development of structural defects within the extracellular matrix of the glomeruli and of large vessel walls [4]. This hypothesis—the Steno hypothesis—is supported by the coincidence of albuminuria and clinical events like declining glomerular filtration rate and coronary heart disease, by the coincidence of albuminuria and signs of endothelial dysfunction and last but not least by the simultaneous development of albuminuria and generalized vascular hyperpermeability. The key event for increased glomerular and generalized vascular hyperpermeability for macromolecules seems to be a structural defect of the extracellular matrix, not only increased intravascular pressure. Several structural defects of the extracellular matrix can be demonstrated in insulin-dependent diabetes mellitus patients with albuminuria. Besides non-enzymatic glycation of the components of ECM the most interesting alteration seems to be a decreased concentration and/or sulphation of heparan sulphate.

Is heparan sulphate a culprit?

Heparan sulphate proteoglycan contributes to the structural stability and the negative charge of the extracellular matrix. When the concentration of heparan sulphate in the glomerular basement membrane is reduced in experimental animals, albuminuria will appear instantaneously [5]. In nephropathy of patients with insulin-dependent diabetes mellitus the concentration of heparan sulphate proteoglycan in the glomerular basement membrane is reduced by about 50% [6] and, a negative correlation has recently been found between the content of heparan sulphate in the glomerular basement membrane and albuminuria [7]. In addition, the number of anionic sites within the glomerular basement membrane [8] and renal charge selectivity [9] are negatively-correlated to albuminuria in these patients. Furthermore, treatment with heparin can prevent albuminuria and the reduction of glomerular anionic sites induced by diabetes in experimental animals [10]. Thus, decreased concentration of heparan
sulphate within the extracellular matrix of the glomerulus is probably causally involved in the development of albuminuria as well. It is interesting, that heparan sulphate also strongly inhibits mesangial expansion [11] and that decreased concentration of heparan sulphate within the mesangium is expected to contribute to the mesangial expansion and increased formation of extracellular matrix seen in diabetics with albuminuria.

Is there a link between the glomerular and the coronary lesion?

According to the hypothesis proposed by our group, i.e. the Steno hypothesis, alterations within the intima and media of large vessels resembling those in the glomerular microcirculation might be responsible for premature atherosclerosis seen in albuminuric diabetics. Heparan sulphate is involved in the pathogenesis of atherosclerosis in several ways [12]: decreased concentration of heparan sulphate within the matrix of large vessel walls will increase transudation of plasma macromolecules including lipoproteins into the vessel wall; furthermore, a strong negative correlation is seen in human aortas between the concentration of heparan sulphate and atherosclerosis [13]. In aortas of diabetic patients a decreased ratio of heparan sulphate to dermatan sulphate has recently been demonstrated [14]. Thus, decreased concentration of heparan sulphate within the extracellular matrix could be the reason for the association between increased urinary albumin excretion and premature atherosclerosis.

How could diabetes affect heparan sulphate metabolism?

Diabetes affects the concentration of the core protein and the degree of sulphation of heparan sulphate within the extracellular matrix in several ways. Hyperglycemia leads to dyscoordinated gene expression and secretion of extracellular matrix components, resulting in a significantly decreased heparan sulphate/collagen IV ratio [15]. In addition, the activity of N-deacetylasel, the key enzyme for sulphation of heparan sulphate is decreased in diabetic animals and humans. This will result in a decrease of the degree of sulphation of heparan sulphate [16]. Binding of heparan sulphate proteoglycan to other components of the extracellular matrix is decreased by non-enzymatic glycation of laminin and collagen IV, thereby contributing to a reduced concentration of heparan sulphate in the extracellular matrix [17]. Since not all diabetics with poor metabolic control develop vascular lesions, genetic factors, e.g. polymorphism of perlecan and/or N-deacetylasel genes might also play a role and influence the remodelling of extracellular matrix.

Summary

In summary, the decreased concentration of heparan sulphate within the extracellular matrix of patients with insulin-dependent diabetes mellitus is caused by a combination of genetic factors and poor metabolic control. Decreased concentrations of heparan sulphate are seen in patients with diabetes mellitus and proteinuria and this might be the explanation for the proteinuria as well as the expansion of the mesangium and the intimal dysfunction, including increased permeability of the vessel wall to macromolecules, which is present in such patients. Thus, the effective remodelling of extracellular matrix might explain coincidence of proteinuria, decline in renal function and premature atherosclerosis in patients with diabetes mellitus.

References

14. Wasty F, Alavi MZ, Moore S. Distribution of glycosaminoglyc-

