Perspectives in Diabetes
Role of Postglomerular Microvessels in Pathophysiology of Diabetic Nephropathy
Assessment and Hypothesis
G.G. PINTER AND J.L. ATKINS

Although glomerular damage plays a well-established and important role in the pathomechanism of diabetic nephropathy, it alone does not fully explain the progression of renal complications in long-term diabetes mellitus. We discuss experimental evidence showing involvement of the postglomerular microvessels (peritubular capillaries and venules) in diabetic microangiopathy. This involvement is manifest in increased permeability of these vessels to plasma proteins and in highly augmented lymphatic drainage of the extravasated proteins from the renal interstitium. We suggest that in the advanced phase of diabetic nephropathy, proteinuria (corresponding to excess leakage of proteins through the glomerular capillary wall) indicates the probability that postglomerular microvessels have also allowed leakage of plasma proteins. As long as lymphatic drainage is capable of removing the increased quantity of extravasated plasma proteins from the interstitium, renal function should not be deleteriously affected. However, if the excess amount of extravasated proteins exceeds the capacity of lymphatic drainage, increases in interstitial volume and pressure are unavoidable with detrimental consequences for glomerular filtration and tubular reabsorption. Under these conditions, a potential positive-feedback loop can be visualized that involves increased extravasation of plasma proteins leading to increased interstitial pressure that through dilation of the afferent and efferent arterioles results in a further increase in protein extravasation. These conditions combined with glomerular damage should lead to the eventual collapse of renal function. Diabetes 40:791–95, 1991

Insulin-dependent diabetes mellitus (IDDM) has profound effects on the circulatory system. In the early phase of the disease, the extracellular fluid volume is expanded. In the late phase, complications affecting blood vessels, i.e., macroangiopathy and microangiopathy, cause severe disturbances in the function of various organs. An important consequence of the microangiopathy is increased permeability (1,2), and a prominent target of late diabetic complications is the kidney.

Convincing evidence has accumulated indicating that in diabetic patients albuminuria is an unfavorable sign that predicts progressive nephropathy. Approximately 33% of the IDDM population is subject to the typical progression from a normal albumin excretion rate (<17 µg/min or ~20 mg/24 h) to microalbuminuria (extending from normal rate to 200 µg/min or ~300 mg/24 h) and progressing further to overt macroalbuminuria (>300 mg/24 h) (3). The progression of diabetic nephropathy is often precipitated by poor glycemic and blood pressure control. Without therapeutic intervention, there is a progressive decline of glomerular filtration rate of ~1 ml/min (3). In an epidemiological study of 1475 IDDM patients, 49% survived for 7 yr after the onset of persistent proteinuria (4).

Despite clear evidence for a correlation between albuminuria and renal failure in diabetic patients, the pathophysiological causative links that connect increased albumin excretion to progressive renal failure remain elusive.

Albuminuria is generally interpreted as a manifestation of glomerular abnormality, either functional (hypertension in the glomerular capillaries) or structural (altered permeability accompanying morphological changes of the glomerular filtering membrane), and the search for the pathomechanism of end-stage diabetic nephropathy has focused primarily on the glomerular abnormality. However, there are indications that glomerular damage may not be the single causative factor in diabetic nephropathy because similar morphological changes of the glomeruli have often been seen in
diabetic patients both with and without clinical nephropathy (5). Moreover, the diabetic kidney shows consistent abnormalities in addition to glomerular damage, which have not been fully incorporated into an integrated picture of the pathophysiology of progressive diabetic nephropathy. Such consistent abnormalities are 1) that the renal interstitium tends to enlarge in advanced diabetic nephropathy (6–8) and 2) that, in an experimental model of diabetes, we observed a substantial increase of renal lymph flow and plasma protein drainage from the kidney through the lymph after 5–6 mo of the disease (9,10). Further increases occurred at 8–9 mo (9,10).

This study attempted to fit these additional findings together with the glomerular abnormality into a coherent hypothesis. This hypothesis is based on the observation in experimental diabetes of increased plasma protein leakage from the postglomerular microvessels, i.e., peritubular capillaries and small venules. We also suggest that increased proteinuria, which indicates protein leakage from the glomerular capillaries, signals a similar increase of protein efflux also from the peritubular capillaries. Our hypothesis further attempts to explain how the increased protein efflux from the peritubular capillaries leads to pathophysiological changes in renal interstitial volume and pressure and eventually to deterioration of kidney function.

PLASMA PROTEIN CIRCULATION THROUGH KIDNEY CORTICAL INTERSTITIUM

Normal conditions. In extrapolating from rat and dog data (11,12), it is estimated that, in a normal human kidney, ~3–5 mg/min of plasma albumin crosses the wall of the postglomerular microvessels into the interstitium. This rate is ~300 times the urinary excretion rates of proteins generally considered normal. The high surface area of the postglomerular microvessels and structural differences between these vessels and glomerular capillaries readily account for the relatively high protein leakage from the postglomerular microvessels (13).

The flows of tubular reabsorbate and plasma proteins through the kidney-cortical interstitium constitute a complex pattern. The kidney cortical interstitium consists of narrow and wide regions (14). Fenestrations and fully open channels of the peritubular capillary wall are not evenly distributed; they appear in clusters, and fenestrations preferentially face the narrow interstitial regions (14,15). These clustered regions occupy only a limited surface area of the peritubular capillary wall (14,15). We have suggested that plasma proteins leak out through these limited regions of the peritubular capillary wall, distinct from the reabsorbing surfaces that comprise the major part of the capillary wall where the bulk of the tubular reabsorbate enters the capillary (16). We have further estimated that, under normal conditions, the reflexion coefficient of the reabsorbing surfaces is high (>0.99) and that virtually none of the extravasated protein caught up in the reabsorbative stream would reenter the capillaries; almost all of the extravasated plasma proteins would drain from the interstitium through the lymph (11).

Although the concentration of plasma proteins in the renal interstitium has not been directly determined, in the absence of evidence to the contrary, it is usually assumed that the lymphatic concentration is equal to the effective concentration in the interstitium, which is ~25 or 33% of the plasma concentration in young individuals. Under normal conditions, the outward-directed hydrostatic pressure difference between the postglomerular microvessels and the interstitium is exceeded by the inward-directed difference in colloid osmotic pressure (COP) throughout the entire length of these vessels. Therefore, the COP difference is the dominant component of the driving force for the uptake of the tubular reabsorbate from the interstitium into the postglomerular microvessels.

Experimental diabetes. The normal conditions are substantially disturbed in the streptozocin-administered rat model of diabetes. In anima’s exposed to diabetes over 5–6 mo, both plasma albumin leakage from the postglomerular microvessels and albumin drainage through a cannulated lymph vessel increased by a factor of 3.5–4.0 (9). After 8–9 mo of exposure, average plasma albumin leakage from the postglomerular microvessels increased nearly 10-fold, and albumin drainage through a cannulated lymphatic vessel increased ~5-fold (9). This great discrepancy does not necessarily indicate an imbalance of similar magnitude between protein inflow into and outflow from the interstitium, because, in chronic stress, new lymphatic pathways may have opened. Moreover, in contrast to the normal condition, the convective flow of tubular reabsorbate could wash back proteins into the postglomerular microvessels, provided that the permeability changes affected both the fenestrated regions and the reabsorbing surfaces. However, these compensatory mechanisms did not appear to be sufficient, and interstitial volume and pressure increased. In our studies, a slight expansion of the extravascular albumin pool in the kidney cortex occurred at 5–6 mo, whereas at 8–9 mo, the extravascular albumin pool was enlarged to ~3-fold of the normal value found in control age-matched rats (9,10, and unpublished observations). Increases of interstitial pressure were evidenced by increasing lymph flow rates noted above. Data concerning renal lymphatic drainage in diabetic patients are not available. Even though rats do not show full-blown diabetic nephropathy in this experimental model, interstitial enlargement is a consistent finding in human diabetic kidneys, suggesting the general applicability of these findings to the human condition.

Interstitial enlargement in diabetic nephropathy has been demonstrated with morphometric analysis in human population by Bader et al. (7) and Thomsen et al. (8). Both groups of investigators concluded that interstitial volume increase was one of the consistent features of nephropathy along with other interstitial changes, i.e., increased fibrosis. Both groups found a highly significant positive correlation between the fractional volume of the cortical interstitium and plasma creatinine concentration, indicating that as interstitial enlarged, renal function proportionately declined (7,8).

In our studies in the streptozocin-administered diabetic rat model, enlargement of the interstitium in the kidney cortex was indicated by an increased quantity of extravasated albumin in the interstitium (6,9,10). Because the lymphatic concentration and presumably the interstitial concentration of albumin have not increased or only slightly increased, we infer that the larger amount of albumin was distributed in an expanded interstitial volume. In the rat model, which may represent an early phase of the human condition, we have
seen no change in the interstitial albumin pool at 3 wk after streptozocin administration (6,9,10). Other investigators have observed even earlier increased protein leakage from kidney microvessels (17).

**HYPOTHETICAL MECHANISM**

Incipient accumulation of extravasated albumin in the interstitium tends to diminish the COP difference between capillary and interstitium and slow the uptake of tubular reabsorbate into the postglomerular microvessels. The consequence is an incipient expansion of interstitial volume with only a slight change in the interstitial protein concentration. Because the kidney is enclosed in a fibrous capsule, even a slight expansion of the interstitial volume should bring about an increase in the interstitial hydrostatic pressure. In the early phase, a slight increase in interstitial pressure causes increased lymph flow and protein drainage through lymph. The slightly increased interstitial hydrostatic pressure can also compensate for the somewhat diminished COP difference across the peritubular capillary wall in moving fluid into the peritubular capillaries. Therefore, in the early phase of increased plasma protein leakage from the peritubular capillaries, there should be few if any deleterious consequences affecting renal function.

If plasma protein leakage from the peritubular capillaries continues to increase, a limit might be reached when the lymphatic drainage can no longer cope with the large quantity of extravasated plasma proteins. Under these conditions, greater increases of interstitial volume and pressure should give rise to several detrimental consequences. Although the tubular basement membrane provides a degree of rigidity to the tubules, increased interstitial hydrostatic pressure at some point may lead to tubular compression and thus to an increase in tubular pressure opposing filtration in the glomeruli. It may also deform and compress the peritubular capillaries.

**Positive feedback and decline of renal function.** The detrimental consequences of increased hydrostatic pressure in the interstitium include a decrease of both preglomerular and postglomerular resistances and a subsequent increase of blood pressure in the peritubular capillaries. This can occur as a result of an apparent tendency for keeping the circumferential tension of the arteriolar wall at a nearly constant level. Laplace's law, as applied to elastic cylindrical tubes, describes the relationship between the radius of the tube (r), the transmural pressure difference across the wall (ΔP), and the circumferential tension of the tube (T). In a simplified form, the following relationship holds: $T = \Delta P \cdot r$. After an initial change in ΔP or r that causes a shift in T, when the vascular smooth muscle readjusts the circumferential tension of the wall toward its original value, a reciprocal change will occur in the other variable. Thus, after a decrease in ΔP, the readjustment leads to an increase of r (dilation of the vessel). An experimental demonstration of this phenomenon is a decrease of total kidney resistance when the ureter is occluded and interstitial pressure rises (18,19).

In applying this mechanism to the kidney in advanced diabetes, when interstitial hydrostatic pressure rises, the transmural pressure across the afferent and efferent arteriolar walls decreases, and subsequently the vessels dilate. Thus, a high-resistance site is removed from the entrance to the postglomerular microvessels, and the ensuing rise in peritubular capillary pressure should help keep these ves-

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**FIG. 1.** Diabetic microvascular kidney disease. Hypothetical sequence of events arising from increased protein extravasation from postglomerular microvessels. Resulting increase of interstitial pressure potentially induces formation of both negative- and positive-feedback loops. Dilation of afferent and efferent arterioles is explained by tendency of circumferential wall tension of these vessels to remain relatively constant (see text).
sels open. However, an increase in peritubular capillary pressure should bring about a further increase in interstitial pressure. The proposed mechanism is that an increase of peritubular capillary pressure has at least two direct consequences. 1) slowing down the uptake of tubular reabsorbed into the capillary and 2) enhancing net protein movement from the postglomerular vessels into the interstitium. Such increased protein extravasation has been demonstrated after elevation of renal venous pressure (20). These events should result in further reduction of the COP difference between capillary and interstitium and yet another increase in interstitial hydrostatic pressure. Thus, a positive-feedback mechanism should be set in motion under these circumstances. Although glomerular filtration rate and, consequently, fluid input into the interstitium are diminished in advanced diabetic nephropathy, increased entry of plasma proteins will nevertheless upset the normal finely tuned balance between fluid input and capillary uptake. Fluid accumulation in the interstitium should thus continue with continued activation of the positive-feedback loop. Figure 1 shows a schematic representation of these events.

This highly simplified scheme clearly cannot describe the comprehensive mechanisms that take place in diabetic nephropathy; between two successive events on Fig. 1, the connecting arrow may actually stand for a cascade of occurrences. For example, we anticipate that vasoactive substances may also modulate the vasodilatation and the positive-feedback loop.

Interaction between increased interstitial pressure and glomerular filtration rate. We indicated that increased interstitial pressure will lead to a dilation of the afferent and efferent arterioles, although not necessarily to the same degree. The result is an increase in glomerular blood flow. Another consequence of increased interstitial pressure is that when transmitted through Bowman's capsule, it should reduce the effective filtration pressure across the glomerular capillary wall. Thus, two different potential determinants of glomerular filtration should be affected in opposing directions (21). In the presence of other changes in the glomeruli, i.e., hypertrophy and thickening of the capillary basement membrane, it is impossible to predict what short-term change will occur in the glomerular filtration rate. However, the net effect of all these simultaneous changes should eventually be detrimental, because under these conditions glomerular filtration would occur at higher than normal blood pressure and higher than normal glomerular blood flow. One or both of these may perpetuate the glomerular structural abnormalities.

The hypothesis presented here fully appreciates the well-established and important role of glomerular damage in diabetic nephropathy, which includes changes in the capillary basement membrane structure and the filtering surface (22–24). We emphasize rather that all microvessels in the kidney are involved in the pathological changes. In particular, we expound how changes in postglomerular microvessels may contribute to the pathophysiology of diabetic nephropathy.

CONCLUSION

A consistent enlargement of the interstitial space seen in human and experimental diabetes suggests that other factors besides glomerular damage may play a role in the pathomechanism of human diabetic nephropathy. If the increased leakiness of the postglomerular microvessels to proteins we observed in an animal model of IDDM also occurs in human diabetes, it could explain the increase in interstitial volume. We hypothesize that excess extravasation of plasma proteins should lead to increased interstitial volume and pressure in the kidney and thus evoke various mechanisms, which, working in tandem with glomerular damage, could contribute to the progressive decline of kidney function. Some of these mechanisms are, at least in the short run, potentially protective, i.e., they tend to restore a balance to the processes of filtration and reabsorption. However, other mechanisms result in a positive-feedback loop and accelerate the eventual collapse of kidney function.

REFERENCES

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