



Analysis of the Development of Kidney Disease in Diabetes Mellitus

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Editorial

Progressive kidney failure is an unfortunately common complication of Type 1 (T1DM) and Type 2 (T2DM) diabetes. At least 20% of patients with diabetes will progress to ESRD usually within 20 years of onset of the disease [1]. This makes diabetes the most common cause of ESRD in the USA at somewhat less than 50% of the existing affected population. In addition more than 40% of T1DM and T2DM patients will have some evidence of significant kidney involvement. Since the medical and financial impacts of kidney involvement in diabetes are significant it is important to understand the factors in the diabetic phenotype that contribute to this high incidence of kidney dysfunction. There are at least three clinical phenotypes which correlate with an increased incidence of the development of significant and progressive kidney failure: these are glomerular hyperfiltration, kidney hypertrophy and at least moderate hyperglycemia indicating poor glycemic control [2-5].

Diabetic patients exhibiting early glomerular hyperfiltration and increased kidney size appear to be overrepresented in the population who suffer some progressive kidney failure over the next 10-20 years of disease [2,6,7]. First, we must understand how the increase in glomerular filtration rate occurs. Early studies using glomerular hemodynamic measurements suggested that increases in single nephron plasma flow (snpf) and increased glomerular capillary hydrostatic pressure gradient (delta P) produced a major increase in nephron glomerular filtration rate (sngfr) and whole kidney GFR [8]. It was tempting to suggest that increased glomerular capillary hydrostatic pressure may have been a major factor in producing glomerular injury. However later studies from our group have shown that glomerular capillary pressure is not elevated in early diabetes in rodents if volume status is maintained and plasma glucose is only moderately increased [3,9]. However delta P is modestly increased because Bowman's space pressure is reduced by a few mm Hg, thereby increasing this contribution to the increase in GFR and sngfr. It is of interest that the effects of insulin administration are quite different in control non diabetic rats and diabetic animals, the latter of whom who exhibit hyperfiltration. Insulin administration in large doses always increases SNGFR and GFR in normal, non-diabetic rats, but the same insulin doses decreases SNGFR and GFR in hyperfiltering diabetic rodents, to values after insulin that are similar in control and diabetic animals [10]. Therefore it is clear that vasodilation is the mechanism whereby hyperfiltration occurs, but what is the more pertinent question is what is the stimulus perceived in the early diabetic condition which leads to vasodilation?

For many years it has been assumed that the vasodilation observed early in diabetes is a primary event affecting the diabetic vasculature [2,7,9,11]. If that were the case, then glomerulo-tubular balance would dictate downstream responses which include modest reductions in fractional re-absorption in the proximal and more distal tubules and an increase in the Na, Cl and K content in tubular fluid in the macular densa (MD) segment in the early distal tubule. Our micropuncture assessments in control rats revealed MD Na, Cl⁻ and K⁺ concentrations of 21, 20 and 1.2 mM respectively. These values in the hyperfiltering streptozotocin (STZ)-diabetic rat were reduced by 20-28% as was the absolute rate of tubular fluid delivery. Had the increase in SNGFR been a primary glomerular event, we would have predicted an increase in electrolyte concentrations at the MD of approximately 30-40% [9,11-13]. These results suggest that there is a major increase in proximal tubular re-absorption in the early hyperfiltering diabetic kidney to explain these collective results [4,5,14,15]. These results obtained by micropuncture then fit with other clearance studies utilizing lithium clearance which came to the same conclusion that proximal tubular re-absorption was substantially increased in the early stages of diabetes [16,17]. In addition the major reduction in MD electrolyte concentration and fluid delivery must be leading to a relaxation response of the tubuloglomerular feedback (TGF) system which then causes functional vasodilation of the glomerular vessels and a major increase in SNGFR and GFR. These results then suggest that hyperfiltration is not a primary glomerular event,

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but rather that major increases in proximal tubular re-absorption, possibly linked to hyperglycemia and diabetes, was the basis for the hyperfiltration response by decreasing the delivery of electrolytes and tubular fluid flow to the macula densa segment in the early distal tubule [18-20].

Earlier studies from our laboratory tended to support the above formulation suggesting primary increases in tubular re-absorption as the basis for glomerular hyperfiltration, via an interaction with an intact tubuloglomerular feedback mechanism [13,18,20]. We used micropuncture to examine the SNGFR and proximal tubular responses to phlorizin, a non-selective inhibitor of SGLT Na⁺/Glucose transporters, which acts in the proximal tubule to inhibit both sodium glucose linked transporter 2 (SGLT2), acting primarily as well at the intestinal glucose transport mechanism [13]. We examined the acute responses in control, non-diabetic, and early diabetic rats with regard to proximal tubular re-absorption, SNGFR and the MD electrolyte content. In control rats, proximal tubular re-absorption decreased by only 5% and the SNGFR was unchanged immediately after administration of phlorizin. However, in early diabetic rats, proximal tubular re-absorption decreased by approximately 24% and the SNGFR decreased significantly by over 20%. MD electrolyte content and flow rates changed as one might predict with increases in Na and Cl and flow rates in the diabetic rats after phlorizin but no changes were seen in the control animals. These results also suggest that the early diabetic animal has increased proximal tubular re-absorption and that this increase is largely the result of increased Na⁺/glucose transporters, SGLT2 and SGLT1 which resulted in reductions in delivery of fluid to the MD segment and functional TGF responses resulting in increased SNGFR or glomerular hyperfiltration. Other studies have shown that SGLT2 expression is increased within a few days after the induction of STZ diabetes as a basis for the enhanced re-absorption, and increases in the size of proximal tubules early after diabetes [21-25].

In normal rats, GFR is relatively insensitive to wide changes in NaCl intake or may move slightly in the same general direction as changes in dietary NaCl [20,26]. Early studies from our group in 1995 examined the response to marked NaCl restriction in early diabetic male rats and found increased renal blood flow, GFR and kidney weight [27]. In contrast and of interest, marked increases in NaCl intake in early and later phases of diabetes caused marked renal vasoconstriction, reduced GFR and sngfr [28]. This inverse relationship between NaCl intake and GFR is counterintuitive and we termed this physiologic finding in diabetes the "salt paradox" of diabetes. This salt paradox was also observed in diabetic mice and rats with type II diabetes mellitus (T2DM) [29,30] and in young children with diabetes wherein NaCl restriction to 20 mM/day markedly increased renal plasma flow and GFR [31]. Micropuncture studies established that the salt paradox occurs because diabetes causes proximal tubule re-absorption to become markedly sensitive to changes in dietary NaCl such that eating more NaCl leads to greater suppression of proximal tubule re-absorption and greater MD electrolyte concentrations, and vice versa for a low-NaCl diet, with secondary consequences on GFR via tubuloglomerular feedback [20]. As predicted the salt paradox is absent in the diabetic mice without tubuloglomerular feedback, A1R ^{-/-} mice [29]. Therefore control non-diabetic rats respond to variations in NaCl intake by altering distal tubular NaCl reabsorption, whereas the diabetic rat varies re-absorption primarily in the proximal nephron and by changing GFR [20].

Increases in proximal tubular re-absorption in diabetes associated strongly with growth of the proximal tubule, initially associated with senescence and later hypertrophy. We observed that inhibition of ODC with DFMO prevented kidney hypertrophy and also prevented glomerular hyperfiltration [32]. ODC inhibition also prevented expression of the salt paradox [33]. In parallel NaCl intake does modify the kidney size by influencing growth of the proximal tubule in diabetes. ODC is selectively expressed in the distal tubules of diabetic kidneys associated with increased generation of polyamines [34]. The responsive cell is the proximal tubular cell suggesting that this is a paracrine system with distal tubules generating agents which contribute to proximal tubular growth [34]. Inhibition of proximal tubular re-absorption with SGLT2 inhibitors does prevent hyperfiltration but does not always prevent kidney hypertrophy unless plasma glucose concentrations are also normalized. The salt paradox is also absent in animals without tubuloglomerular feedback activity. Chronic SGLT2 inhibition continues to prevent glomerular hyperfiltration [35]. Recent studies in large numbers of humans also suggest that SGLT2 inhibition largely prevents worsening of diabetic nephropathy and reduces the rate of doubling of serum creatinine by at least 50% as well as reducing the frequency of onset of ESRD, but with no change in albuminuria [36].

The mechanisms whereby progressive damage to the kidney is mediated are not as yet clear. However, changes in hyperfiltration and kidney size appear important and may be predictive and involved in the development of other adverse disease phenotypes such as intrarenal hypoxia and relatively inefficient metabolic activity linked to NaCl re-absorption [37]. In addition these findings are also closely associated with the development of renal fibrosis and inflammation characteristic of renal involvement later in the diabetic kidney [38]. Therefore the development of agents such as SGLT2 inhibitors may prove highly successful in partially preventing or at least delaying the onset of progressive kidney disease [36].

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