Moving closer to an understanding of the hyperfiltration of type 2 diabetes mellitus

Donald E. Wesson

Departments of Internal Medicine and Physiology, Texas Tech University Health Sciences Center, Lubbock, Texas

THE NEPHROPATHY OF TYPE 2 diabetes mellitus (DM2) is the single largest cause of complete kidney failure requiring replacement therapy (stage 5 kidney disease) in industrialized countries (13). It has long been suspected that the elevated glomerular filtration rate (GFR) of early diabetic nephropathy contributes to the progressive nephropathy with subsequent GFR decline experienced by some DM2 patients (5). Identifying mechanisms(s) for this so-called hyperfiltration of early DM2 nephropathy might help identify mechanisms of nephropathy progression and lead to therapeutic strategies that prevent this most common cause of complete kidney failure. Nevertheless, most insights into the disturbed hemodynamics of diabetic nephropathy have been derived through study of human (2) and experimental (3, 12) models of the nephropathy of type 1 diabetes mellitus (DM1). Experimental models of early DM1 nephropathy show increased single nephron GFR (SNGFR) and suggest that this is mediated through increased proximal tubule fluid reabsorption combined with decreased sensitivity of tubuloglomerular feedback (TGF) (12). In addition, nearly all of the models used to study the kidney hemodynamics of early DM1 nephropathy were created by injection of streptozotocin, a potentially nephrotoxic compound that might have effects on the kidney separate from those of diabetes (10). Like the early nephropathy of DM1, humans with the early nephropathy of DM2 have increased GFR and renal plasma flow (9), as well as increased glomerular size (6).

Determining the mechanism(s) for hyperfiltration in early DM2 nephropathy, however, has been hindered by the lack of a good animal model in which to study this issue.

In this issue, Levine et al. (8) report data regarding mechanisms for the hyperfiltration of early DM2 nephropathy using micropuncture techniques in the classic db/db mouse model of DM2. This model exhibits many characteristics of human DM2 and is considered to be a good animal counterpart of the human syndrome (1). Although these diabetic mice do not develop kidney failure (1), like some humans with DM2, Levine et al. (8), as well as earlier investigators (10), report glomerular pathology in this model that is nearly identical to the human DM2 nephropathy. Importantly, Levine et al. (8) report that these diabetic mice also have increased whole kidney GFR compared with wild-type mice, like the human counterpart (3). They show that this increased whole kidney GFR is associated with increased SNGFR in this model of early DM2 nephropathy, and their data support that this is mediated by increased proximal tubule fluid reabsorption combined with reduced sensitivity of TGF (8). These data are similar to those described earlier in experimental models of early DM1 nephropathy in the rat (12). These important studies of Levine et al. (8) add importantly to our understanding of the disturbed hemodynamics of early DM2 nephropathy and should lead the way to additional studies that will help decipher the contributors to the progression of DM2 nephropathy.

The in vivo micropuncture technique has been done classically in the rat, and nearly all published kidney hemodynamic data of diabetic nephropathy were obtained in diabetic models of this animal. Adapting this technique to the mouse model presented a significant technical challenge as detailed by other investigators (11). In addition, the marked fluid losses characteristic of the diabetic state required the authors to develop a fluid replacement protocol to establish a stable micropuncture preparation that was reasonably euvolemic so as to avoid the confounding contributions of volume depletion or expansion on their hemodynamic data. The authors must be commended for their careful attention to this important detail and for their apparent success at having achieved a stable model from which their data can be reasonably interpreted as representative of the in situ state.

The authors convincingly show that SNGFR is increased in this model of early DM2 nephropathy. This parameter was higher whether measured at the proximal or distal tubule, the latter likely being more reflective of the in situ value because its determination is least stimulatory to TGF. Determination of SNGFR through collection of proximal tubule fluid leads to TGF stimulation because this method interrupts fluid flow past the macula densa and thereby can artifically increase SNGFR (11), supporting the importance of the determination made at the distal compared with the proximal tubule. The proportional increase in whole kidney GFR was higher than the proportional increase in SNGFR of cortical nephrons that are the nephrons most accessible by the micropuncture technique. These data suggest that this model of early DM2 nephropathy has a higher proportional SNGFR increase in the less accessible juxtaglomerular nephrons, sampling from which always stimulates TGF. The authors show that this higher SNGFR was associated with increased fluid reabsorption and suggesting that this increased reabsorption mediated, at least in part, the increased SNGFR, as suggested by earlier investigators (12).

The authors used the difference between SNGFR at the proximal and distal tubules, done in paired fashion, to measure TGF activity. Given that the percent difference in these determinations is similar in euvolemic diabetic and wild-type animals despite tubule fluid flows being higher in the diabetic animals, the authors reasonably conclude that TGF sensitivity is reduced in this early DM2 nephropathy model. In addition, the proximal minus distal SNGFR difference of the diabetic animals widened when fluid replacement insufficiently replaced fluid losses (consistent with volume depletion) and narrowed when fluid replacement exceeded these losses (consistent with volume expansion). These data are consistent with increased TGF sensitivity with volume depletion and decreased sensitivity with volume expansion in the animals with early
DM2 nephropathy, a phenomenon seen in normal mice (11). Because this apparently normal qualitative TFG responsiveness to altered volume status in the diabetic animals occurs in a setting of higher baseline tubule fluid flows than in wild-type animals, these data support that the TGF flow-response curve of the diabetic animals is shifted to the right. If so, this would allow for SNGFR in the diabetic animals to remain elevated, despite increased fluid flows that otherwise would have decreased SNGFR through stimulated TGF if the flow-response curve were not shifted to the right. Loop perfusion studies would be necessary to better clarify this point as stated by the authors.

Studies in humans with early DM2 nephropathy suggest increased nitric oxide (NO) activity in humans with early DM2 nephropathy and suggest that this increased activity mediates hyperfiltration in these subjects (4). Data from other investigators suggest increased NO activity in the streptozotocin-induced rat model of DM1 nephropathy (7). Although Levine et al. (8) did not report renal NO activity in their DM2 model, they do show that SNGFR can be reduced by inhibition of NO synthase, supporting a role for increased NO activity in mediating the hyperfiltration in this animal model of early DM2 nephropathy. Studies in a rat model of DM1 nephropathy suggest that increased NO activity contributes to hyperfiltration in this setting by increasing glomerular plasma flow and/or by influencing TGF (4, 7). The studies of Levine et al. (8) support that NO contributes to the hyperfiltration of early DM nephropathy in this mouse model, consistent with a role for NO suggested in the human studies described.

Together, these ground-breaking studies by Levine et al. (8) show in this experimental model of early DM2 that SNGFR is increased with decreased TGF sensitivity and that hyperfiltration can be reduced with inhibition of NO synthase. The studies adapt the powerful micropuncture technique to an important experimental model of this common disease and have laid a foundation for future studies to examine not only the hemodynamic but also the transport disturbances that characterize human DM2 nephropathy. In addition, such studies will provide direction for further human studies that will increase understanding of the mechanisms for the most common cause of complete kidney failure in the industrialized world.

REFERENCES