Diabetic kidney disease: impact of puberty

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Lane, Pascale H. Diabetic kidney disease: impact of puberty. Am J Physiol Renal Physiol 283: F589–F600, 2002; 10.1152/ajprenal.00368.2001.—Puberty accelerates microvascular complications of diabetes mellitus, including nephropathy. Animal studies confirm a different renal hypertrophic response to diabetes before and after puberty, probably due to differences in the production of transforming growth factor-β (TGF-β). Many of the complex physiological changes during puberty could affect potentially pathogenic mechanisms of diabetic kidney disease. Increased blood pressure, activation of the growth hormone-insulin-like growth factor I axis, and production of sex steroids could all play a role in pubertal susceptibility to diabetic renal hypertrophy and nephropathy. These factors may influence the effects of hyperglycemia and several systems that ultimately control TGF-β production, including the renin-angiotensin system, cellular redox systems, the polyol pathway, and protein kinase C. These phenomena may also explain gender differences in kidney function and incidence of end-stage renal disease. Normal changes during puberty, when coupled with diabetes and superimposed on a genetically susceptible milieu, are capable of accelerating diabetic hypertrophy and microvascular lesions. A better understanding of these processes may lead to new treatments to prevent renal failure in diabetes mellitus.

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complications of diabetes, but prepubertal years of hyperglycemia appear to contribute to their development (141, 145). Clinically, the first detectable sign of diabetic nephropathy is microalbuminuria, the excretion of levels of albumin above those seen in normal individuals but less than those detectable by protein dipsticks (108). Once microalbuminuria is present, patients have established glomerular and tubulointerstitial lesions of DM (18, 92). Renal structural changes include glomerular hypertrophy and glomerular fibrosis, thickening of basement membranes, hyalinosis of arterioles, expansion of the interstitium, tubular atrophy, and global glomerulosclerosis (93).

Biopsy studies of children confirm development of basement membrane thickening and mesangial expansion in the kidney before microalbuminuria (34, 40, 102, 128, 142, 143). The process of mesangial expansion may differ in adults and children. Drummond (33) compared patients with onset of DM1 early in life with those with onset after puberty. Patients were matched for duration of DM1 and mesangial expansion. The density of the peripheral glomerular basement membrane, the presumed filtration surface, was significantly greater in the prepubertal patients. The capillary network was thus able to compensate for mesangial expansion in the early-onset group but not in those with onset after puberty. Ellis et al. (40) also studied biopsies from young diabetic patients and found that peripheral capillary surface in the glomerulus correlated with renal functional tests, independent of mesangial expansion. These studies suggest that the relationship between mesangial expansion and glomerular capillary area before puberty is not as close as that reported in the adult diabetic population (39).

**Experimental Studies**

Structure-function relationships are more difficult to study in animal models of diabetes. In rats, sexual maturity is achieved by 13 wk of age (155). The maximal duration of prepubertal diabetes is only a few weeks, an insufficient period in which to study the classic lesions of DM1, such as mesangial expansion and glomerular surface area. Earlier structural changes must serve as end points, including renal and glomerular hypertrophy. The processes that promote renal hypertrophy and diabetic kidney disease are intricately linked (172). Therapies effective in treating progressive nephropathies also generally block renal and glomerular hypertrophy as well (49), making hypertrophy an acceptable end point for experimental studies. Renal and glomerular hypertrophy and diabetic lesions all involve the accumulation of extracellular matrix materials, so it is not surprising that these processes share common mechanisms.

In animal models, the kidney shows an age-related structural response to DM. Bach and Jerums (7) first showed that prepubertal rats injected with streptozotocin did not develop renal hypertrophy as adult rats did. Our group and others have confirmed this phenomenon (41, 91).

In the kidney, the critical response to DM ultimately seems to be production of transforming growth factor-β (TGF-β). This growth factor has three mammalian isoforms, all of which are secreted as dimeric proteins noncovalently associated with a cleaved propeptide that confers latency (55). Unlike other cytokines, TGF-β must undergo activation before it can interact with its receptor system (55, 173). After activation and receptor binding, TGF-β generally results in signal transmission via the SMAD system (20, 130). TGF-β generally acts in an autocrine or paracrine fashion; however, free TGF-β may also circulate in the plasma (58). The production and disposal of this “systemic” cytokine are not completely elucidated, although the kidney appears to be a major determinant of its balance (154).

TGF-β promotes production and diminishes breakdown of extracellular matrix in mesangial and tubular cells, as well as mediating hypertrophy of the kidneys. Its central role in DM and other progressive kidney diseases has been reviewed extensively (13, 63). Many therapeutic targets in diabetic kidney disease promote activity of this growth factor, including changes in cellular function (Fig. 1) and alterations in hemodynamic responses (Fig. 2).

Because TGF-β is a major factor implicated in diabetic renal hypertrophy, we investigated whether it played a role in postpubertal renal hypertrophy. Male rats were given streptozotocin at 4 or 14 wk of age (90). Mature animals developed significant renal enlargement in association with elevated expression of TGF-β1 mRNA as previously described. Kidney weight was not significantly increased in rats with prepubertal onset of DM, and TGF-β1 mRNA and protein did not increase. Age of onset also affected tissue activity of this
growth factor. TGF-β-inducible gene H3 is an extracellular matrix component also called MP78/70 or RGF-CAP (53, 127, 158). Its expression is induced in renal tubular cells by isoforms 1 and 2 of TGF-β but not IGF-I or epidermal growth factor (54). Expression of this marker of TGF-β activity was elevated only in postpubertal animals in our study (90). Given the central role of TGF-β in diabetic kidney disease, it would be surprising if this growth factor did not play a role in these phenomena (172).

Implicating renal TGF-β clinically has been a challenge. Renal excretion of TGF-β1 has been used as a surrogate measure of renal levels of this growth factor, although interpretation of these levels is controversial because the relationship of urine and renal levels has not been clearly established in humans. The degree of correlation in rat models is variable, but in our laboratory it is never a close relationship (correlation coefficients vary from 0.15 to 0.30), and the correlation may be inverse depending on experimental conditions (Fig. 3).

In adults with type 2 DM (DM2) and coronary artery disease, Sharma et al. (154) showed that the kidney becomes a net producer of TGF-β. In their study, age-matched nondiabetic patients had a net renal extraction of circulating TGF-β. In addition to renal contributions to circulating TGF-β in diabetic patients, these individuals had significantly elevated urinary excretion of the growth factor as well (154). Similar studies have not been performed in children or in patients with DM1; only peripherally circulating blood levels and urinary excretion of this growth factor have been assessed. In children and adolescents with DM, elevated urinary excretion of TGF-β was associated with renal hypertrophy (24). Its excretion was not related to gender, glycated hemoglobin, or albumin excretion rate. Another study found increased TGF-β1 in the urine of a similar patient population in association with α1-microglobulin, a marker of tubular injury (81). None of these studies examined urinary TGF-β longitudinally during puberty, so the time course and significance of these data are not yet known.

Given these considerations, it appears that some change accompanying puberty allows mesangial matrix accumulation to compromise the glomerular filtration surface. The intention of this article is to review the potential impact of puberty on the primary mechanisms contributing to diabetic kidney disease.

**PUBERTY AND THE KIDNEY**

Striking changes in normal physiology occur at puberty, including the acceleration and cessation of somatic growth, the development of secondary sexual characteristics, and onset of reproductive capacity. These phenomena are under the control of the hypothalamic-pituitary axis (112, 168). Many changes in neuroendocrine physiology are potential modulators of renal growth and TGF-β activity during puberty, including gonadotropins, activins, inhibins, growth hormone (GH), IGF-I, leptin, and other hormones. Functional changes such as increasing blood pressure could contribute as well. Any or all of these may be dysregulated by DM.

**Hemodynamic Mechanisms**

One of the first treatments to show efficacy in delaying the course of diabetic kidney disease was control of high blood pressure (107). Antihypertensive therapies have also been shown to slow progression of glomerular lesions in adolescents with DM1 (128, 143). Glomerular micropuncture studies have confirmed elevation of blood pressure and TGF-β and their effect on renal hemodynamics. The relationship between these factors and glomerular function is summarized in Fig. 2.

![Fig. 2. Interrelationships among diabetes, intrarenal hemodynamic forces, and TGF-β. All parameters have been documented in animal models of diabetes. Direct effects of renin-angiotensin system (RAS) and shear stress on TGF-β have also been documented in vitro. RAS, blood pressure (Bp), and insulin-like growth factor-I (IGF-I) have been studied directly in patients as well. PGC: glomerular capillary pressure; SNGFR, single-nephron glomerular filtration rate.](image)
intraglomerular pressures as well as systemic blood pressure in experimental animals. A variety of mechanisms induced by hyperglycemia may produce increased glomerular pressure and shear stress as well as glomerular hyperfiltration. Ultimately, these hemodynamic perturbations have all been shown to induce TGF-β (Fig. 2) (76).

Blood pressure in childhood. Blood pressure increases with age in normal children, as shown repeatedly in large national task-force studies (121, 161). While idiopathic hypertension may develop during puberty, most children with microalbuminuria remain normotensive (38, 40, 128, 144). It is possible that some critical, lower level of mean arterial pressure is necessary for microalbuminuria to develop. Recent work by the International Diabetic Nephropathy Study Group showed a correlation between higher blood pressures within the normal range and mesangial expansion in normoalbuminuric patients with DM1 (34, 102). Such subtle increases in arterial pressure may be of clinical importance in a condition like DM that results in abnormal autoregulation of pressure and flow in the kidney (101, 125). Higher systolic blood pressure has been recognized as a risk factor for progression of microalbuminuria in adolescents (141). Another study found no difference in blood pressures between prepubertal and pubertal patients with DM, even though postpubertal patients were older and some had microalbuminuria (40). Lawson et al. (94) examined Na+/Li+ countertransport throughout puberty and found no developmental differences in this marker of essential hypertension, even in postpubertal patients developing microalbuminuria.

Inherited predisposition to hypertension and cardiovascular disease. Even if elevated blood pressure is not the mechanism of microalbuminuria during puberty, it may be a marker of genes or other factors that promote diabetic nephropathy. Reducing blood pressure was the first successful treatment for diabetic nephropathy (107). Risk of macro- or microvascular disease in DM is reduced more by tight blood pressure control than by tight glucose control (8). The possibility that a genetic predisposition to hypertension incurred nephropathy risk has been considered. Using blood pressure in first-degree relatives and Na+/Li+ countertransport as markers of essential hypertension, many groups have demonstrated an increased risk of nephropathy associated with a familial tendency toward hypertension (9, 45, 48, 80, 88, 137, 159, 165). A family history of other cardiovascular risk factors is also associated with an increased risk of nephropathy (30).

One gene family that may influence blood pressure and cardiovascular risk is the renin-angiotensin system (RAS). This system may also be important at the tissue level in mediating cellular responses to the diabetic state. Given the superiority of anti-angiotensin therapy in DM, it is not surprising that this gene family is being targeted for investigation (8, 96). The first widely explored polymorphism in this system involved an insertion/deletion that accounted for much of the variability in measured plasma angiotensin-converting enzyme activity. Many reports have found that the deletion polymorphism places people at greater risk of hypertension, myocardial infarction, and diabetic kidney disease (16, 37, 135, 136, 140, 163, 167). Other gene polymorphisms that may confer risk involve the angiotensin II type 1 receptor and the angiotensinogen gene (32, 106).

Hyperglycemia During Puberty

Since the Diabetes Control and Complications Trial, the relationship between hyperglycemia and complications cannot be dismissed (162). The higher a given patient’s glucose level, the greater is the risk of development or progression of microalbuminuria. Hyperglycemia has been shown to stimulate a number of intracellular events implicated in diabetic nephropathy and culminating in the final common path of TGF-β production (summarized in Fig. 1) (62, 87, 109, 164).

Hyperglycemia also produces nonenzymatic glycation of proteins that may alter their functions (15). Structural proteins may turn over more slowly, messenger molecules may act aberrantly, and enzymes may function abnormally. Advanced glycation end products (AGEs) may also interact with receptors that alter cellular function and promote diabetic complications. Administration of AGEs manufactured in vitro to otherwise normal mice results in renal lesions similar to those seen in DM, along with increased expression of genes implicated in this disorder (177). These lesions are accompanied by increased production of TGF-β and extracellular matrix components, as described in other diabetic models. Dietary intake of preformed AGEs may be another pathogenic factor for diabetic complications (82).

Adolescents tend to have worse glycemic control than younger children or adults with DM (111). While some of this may be due to “adolescent rebellion,” physiological reasons also exist to explain this phenomenon. Several studies have demonstrated that insulin sensitivity decreases early in puberty in nondiabetic children and in patients with DM (3, 12, 23, 57, 110, 131). This begins between Tanner stage 1 (prepuberty) and Tanner stage 2, the earliest stage of puberty detectable on physical examination (breast buds, fine pubic hair, and testicular enlargement). Insulin sensitivity returns to normal once somatic growth and sexual maturation are complete. Body fat increases early in puberty, but the body mass index does not correlate with insulin sensitivity in these adolescents. Sex steroids also seem unlikely to be the cause, because these hormones are at even higher levels in adults when insulin sensitivity improves. Several studies have found a relationship between insulin sensitivity and the GH-IGF-I axis, suggesting an increased tissue GH effect as the cause of this phenomenon (12, 23). It is unlikely that IGF-I itself causes insulin resistance, because it may react with the insulin receptor and have hypoglycemic effects (46). A trial involving recombinant IGF-I in adolescents with DM1 showed improved glycemic control (36). The authors hypothesized that
administration of IGF-I may suppress GH and its adverse consequences on tissue insulin sensitivity.

**GH-IGF Axis and Diabetic Nephropathy**

One major manifestation of puberty is the acceleration and completion of somatic growth. This process is controlled by GH, which exerts most of its tissue influences via production of IGF. This system includes a number of factors, binding proteins, and receptors (47). GH-IGF has classic endocrine effects as well as paracrine effects, with all components of the IGF system expressed in the kidney. IGF-I has been implicated in the early hypertrophy seen in rats in the kidney. IGF-I has been shown to increase glomerular filtration rate in nondiabetic humans (59, 60), and experimental diabetes shows increased renal binding of IGF to its receptors during hyperfiltration (170). IGF-I could promote diabetic nephropathy through direct hypertrophic effects as well as hemodynamic effects (Fig. 2). While relationships between circulating levels of IGF-I and glomerular filtration rate may be demonstrated, the relationship of this growth factor to tissue-level effects in diabetic patients, including hyperfiltration, remains speculative (6, 73).

Clinical studies have been mixed on the relationship among GH, IGF-I, and diabetic nephropathy during puberty. One found a significant association with both renal hypertrophy and microalbuminuria (25), while another did not confirm this observation (153). Once again, these studies remain problematic because they examine serum and urine levels of growth factor rather than tissue-level effects.

While clinical and experimental evidence support a possible role of GH and IGF-I in diabetic hyperglycemia and renal hypertrophy (46, 47, 172), it seems unlikely that these are the key mediators of postpubertal acceleration of nephropathy. Activity of this hormonal system peaks during puberty, then declines in adulthood (112), while postpubertal susceptibility to nephropathy is sustained throughout adulthood (89).

**Sex Steroids and Diabetic Kidney Disease**

**Sex and the kidney.** If sex steroids drive postpubertal acceleration of diabetic nephropathy, then kidney function might be expected to be different between the sexes. In normal humans, gender has been shown to influence the renal response to angiotensin II (52, 67, 104). The RAS also varies during the normal menstrual cycle, with increased circulating RAS components but blunted tissue effects during the luteal phase (19, 129). The RAS is activated by oral contraceptives, probably via an estrogen response element present in the promoter region of angiotensinogen (74). Oral contraceptives may also increase creatinine clearance (14).

Men have higher plasma renin activity than age-matched women (72), as well as higher blood pressures (121, 161). Animal data suggest that this difference is androgen dependent (133, 134).

Sex hormone-mediated differences in renal function have been confirmed in animal models as well. While mean arterial pressures did not differ, the acute pressure-diuresis/natriuresis response was blunted in female rabbits (43). A number of studies suggest significant relationships between sex and the nitric oxide system in the systemic and renal vasculature (61, 65, 66, 123, 175). These relationships are not surprising, given that estrogen receptor-α and nitric oxide synthase III (endothelial nitric oxide synthase) colocalize to caveolae, where they form a functional signaling module (17). Cardiovascular and renal effects of estrogens have been reviewed recently (35).

Androgens also influence cardiovascular and renal function. Higher levels of renin activity and blood pressure are present in male animals, and castration or anti-androgen treatments block these phenomena (132–134, 138). These hormones activate the intrarenal RAS, ultimately resulting in a number of potentially detrimental effects discussed in detail in the following sections (42).

**Sex and kidney disease.** Men with end-stage renal disease due to any cause outnumber women (157). Most nondiabetic renal diseases clearly increase the risk of kidney failure in men (122, 151). The results for diabetes are less clear, as reviewed by Seliger et al. (151). This results in part from different patient mixes and different definitions of diabetic nephropathy. Recent data from Japan show a striking sexual dimorphism in age of onset of end-stage renal disease in DM, with younger women relatively protected (69). When Caucasians with diabetes are examined in the US, there is a slight male predominance (157). In African-Americans with diabetes, there is a slightly excess risk for women; however, this may be due to the occurrence of DM2 after menopause, when any protection from gender might be minimized (157). There may also be competing mortality in men that reduces the risk of occurrence.

The effects of sex hormones are evident in animal models of renal diseases as well. Age, sex, and hormonal status influence compensatory renal hypertrophy in rats (114–120). Sex and hormonal status of both donor and recipient affect a model of chronic transplant nephropathy in rats (113). Glomerulosclerosis of normal aging occurs primarily in male rats (10, 51), although these gender differences may not be present in aging humans (124). As in humans, data from diabetic models are less clear. Sexual differences have been demonstrated in two models of DM2. Renal lesions in the Cohen diabetic rat are minimized by gonadectomy in both sexes (21, 139, 169) and by estrogen antagonism in females (22). In another model of DM2, results from spontaneously hypertensive rats (SHR) given streptozotocin in the neonatal period also show sexual differences. In this model, ovariectomy has no effects on blood pressure, kidney function, or renal hypertrophy, but orchietomy shows significantly beneficial effects (70). The major model of DM1, the streptozotocin-treated rat, has not been characterized for
sexual differences in the renal response to the diabetic state.

A number of potentially pathogenic pathways for diabetic nephropathy may be influenced by sex steroids. Sexual differences in blood pressure have been discussed above; the following sections will examine intracellular pathways of importance in diabetic complications and renal hypertrophy.

**PKC and Sex Steroids**

One major cellular system that is dysregulated in diabetes is PKC (Fig. 1) (87). Hyperglycemia increases production of diacylglycerol (DAG), which stimulates PKC (87). PKC may in turn stimulate MAPK, which may lead to production of growth factors that ultimately promote accumulation of extracellular matrix materials in the glomerular mesangium and tubulointerstitium (164). Both estrogens and androgens induce PKC activity in certain tissues, including breast cancer cell lines and male reproductive organs (11, 29, 98). Sakabe et al. (147) described PKC activation in cultured thymic epithelial cells exposed to androgen or progesterone; estrogen had no effect in this model. Kidney cells have not been studied for sex steroid effects on PKC.

Adult male control rats treated with an oral PKC-β inhibitor showed no difference in kidney weight from untreated controls; however, renal growth was virtually complete at initiation of this study (86). This does not rule out a role for PKC and sex steroids in normal renal growth. Takahara et al. (160) reported data from mice overexpressing PKC-β2 in the vasculature; at 4 mo of age, male mice demonstrated a 25% increase in renal weight compared with controls and females. PKC-β inhibitors have been shown to prevent mesangial expansion in the diabetic db/db mouse, a model of DM2 (85).

**Polyol Pathway and Sex Steroids**

All cells have the capability to convert glucose to sorbitol via oxidation of NAD(P)H with the enzyme aldose reductase (176). Cells in which glucose uptake is not insulin dependent will have an excess of substrate and typically accumulate sorbitol in DM. This process can produce several effects. First, the osmotic balance of the tissue is disturbed because of the accumulation of sorbitol. Second, consumption of NAD(P)H in these reactions may alter the redox potential of the cell, making it less able to deal with oxidant stress. Third, sorbitol may then be converted to fructose, which promotes nonenzymatic glycation of proteins and accumulation of advanced glycation end products. All of these effects of the polyol pathway are capable of stimulating processes that ultimately produce TGF-β (Fig. 1).

In 1986, diabetes-induced changes in polyol metabolism and collagen cross-linking were shown to be prevented by castration in streptozotocin rats, linking this metabolic pathway to androgens (171). The mechanism of this link remains unclear. Members of the aldo-keto reductase superfamily contain androgen response elements (99, 126). Many of these gene products are important in reproductive function. Androgen-mediated expression of one of these enzymes, mouse vas deferens-specific aldose reductase-like protein, is potentiated by PKC activity (44).

The human aldose reductase promoter region contains a sequence similar to this consensus androgen response element, although studies show that this region is not normally under androgen control; however, point mutations would be sufficient to result in androgen responsiveness (146). Genetic polymorphisms in this promoter region are associated with increased risk of diabetic nephropathy, although the functional nature of these polymorphisms is not yet known (105).

Other sex hormones may regulate this gene superfamily as well. Aldose reductase activity in the adult ovary varies during the estrous cycle and is regulated by human chorionic gonadotropin, although its exact role in female reproduction remains poorly defined (71).

**Oxidative Stress and Sex Steroids**

The diabetic state is associated with increases in the production of reactive oxygen molecules as well as alterations in the redox potential of cells (78, 103). In the kidney, generation of excess superoxide anion in this setting leads to nitric oxide consumption and protein tyrosine nitration (68). These changes may further alter cellular function, through both altered function of the affected proteins and diminished nitric oxide bioavailability, with resulting consequences to vascular and epithelial function. Oxidative stress also activates PKC, which in turn produces increased TGF-β production (Fig. 1).

Interrelationships between sex hormones and oxidative stress have been described best in SHR. Both male and female SHR develop hypertension, but blood pressures are much higher in adult males than females (133). This increased pressure is due to androgen-
mediated activation of the RAS with resultant oxidative stress (50, 133, 138).

Some androgens may actually have antioxidant effects. Dehydroepiandrosterone (DHEA) has been reported to have variable effects, depending on the protocol and dose. This adrenal androgen has recently been shown to have antioxidant effects in male streptozotocin DM rats during 3 wk without insulin treatment (4). It is possible that males (with higher testosterone levels) are more prone to oxidative injury, whereas females (with lower testosterone but equivalent DHEA) are relatively protected.

TGF-β and Sex Steroids

The direct interrelationships of sex steroids and TGF-β are more complex. Most studies to date have characterized specialized tissues, such as bone, uterus, breast, prostate, and tumors. The primary adrenal androgen, DHEA, induces transcription of TGF-β in macrophages (174). Estrogen accelerates wound healing in conjunction with an increase in TGF-β1 in the wound (5). In contrast, estrogen-replacement therapy in ovariectomized sheep prevents neointimal hyperplasia and TGF-β1 accumulation in the aorta (152). In addition to effects on the production of the growth factor, estrogen may also oppose its effects at the transcriptional level, as shown in murine mesangial cells (95, 156). This occurs when estrogen-receptor complexes in the cytoplasm associate with Smad 3, making it less available for TGF-β signal transduction (100), or when the ligand-receptor complex blocks activation and translocation of casein kinase 2, an important step in TGF-β-mediated collagen transcription (178). Androgens also interact with TGF-β signaling pathways. The androgen receptor binds to Smad 3 with or without androgen. This receptor-Smad 3 complex then binds to androgen response elements to promote transcription.

The presence of androgens accelerates this process, increasing transcriptional activity (75).

CONCLUSIONS

Puberty is a complex period of changing physiology. Many of these normal physiological changes may interact with the diabetic state to produce increased susceptibility or acceleration of diabetic nephropathy during and after maturation. Hyperglycemia, while necessary for the development of diabetic nephropathy, is not sufficient for this complication to develop. It has long been recognized that many patients with relatively poor control are spared from nephropathy, while some with good control still develop this complication. Seaquist et al. (150) first demonstrated familial clustering of nephropathy in DM1. Since that time, many studies have examined potential genetic factors that may influence individual patient susceptibility to diabetic complications. Medline searches reveal that 27 articles on the genetics of diabetic nephropathy were published in 1991–1992. This number has increased recently, with 86 publications in the 1998–1999 period. These include genes in many pathways previously implicated in the pathogenesis of this disorder. More candidate genes will emerge with completion of the human genome map.

The normal changes during puberty, when coupled with DM and superimposed on a genetically susceptible milieu, may increase potentially pathogenic mechanisms of diabetic nephropathy, especially the production and activity of TGF-β (summarized in Fig. 4). By better understanding the nature of these interactions, we may be able to develop treatments to slow or prevent the progression of diabetic nephropathy, the most common cause of end-stage renal disease (166).

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