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# Renal Angiotensinogen Gene Expression and Tubular Atrophy in Diabetic Nephropathy

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## 1. Introduction

The growing incidence of diabetes mellitus, with predicted rises in prevalence from 285 to 380 million cases in 2025, then 438 million by 2030, is a major public health burden in both developing and developed countries. Type 1 and type 2 diabetes increase the risk of microvascular complications, which cause significant morbidity and mortality. Diabetic nephropathy (DN) and retinopathy represent the major causes of end-stage renal disease and blindness (1-2) in developed countries. DN is associated with an increased risk of hypertension, adverse cardiovascular events (3), chronic kidney diseases and haemodialysis (4). Efforts are therefore being made to find ways of preventing and/or slowing down the progression of DN worldwide.

DN is initiated by glomerular changes, namely hypertrophy, then thickening of the basement membrane with subsequent expansion of the mesangial matrix and glomerulosclerosis (5). This is associated not only with microalbuminuria, an early clinically detectable lesion, but also with tubulointerstitial fibrosis and tubular atrophy (5-6). Oxidative stress, hyperglycemia and renin-angiotensin system (RAS) dysfunction have been linked to the development of these lesions (5-6). Although albuminuria is a useful clinical marker, tubulointerstitial fibrosis and tubular atrophy represent a better predictor of nephropathy progression because of their close association with declining renal function (5). Many randomized controlled trials have shown the efficacy of optimal glycemic control and RAS blockade in the primary and secondary prevention of DN (4, 7-9). The former is easily understood, as decreased "glucotoxicity" reduces end-organ damage. However, the mechanisms underlying the protective action of RAS inhibition, notably angiotensin II (Ang II) receptor blockade, are not well understood. In this review, we present the recent results of studies aiming to understand the consequences of RAS blockade at the molecular level, with an emphasis on tubular lesions in DN.

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## 2. The renin-angiotensin system in diabetic nephropathy

### 2.1 Clinical findings on the implications of RAS blockade in diabetic nephropathy

The benefits of RAS inhibition on end-organ protection in diabetic patients are well established. One of the early clinical trials on diabetic patients was performed with captopril, an angiotensin-converting enzyme inhibitor (ACE-I), and showed a reduction in the risks of death, dialysis and transplantation (10). Other trials initially used monotherapy with ACE-I, but also angiotensin receptor blockers (ARB) (11-12). Dual blockade was proposed after one of the largest clinical trials, the Candesartan And Lisinopril Microalbuminuria (CALM) Study, showed reduced albuminuria with dual therapy compared to monotherapy (13). Further clinical trials with larger sample sizes, however, have failed to confirm the superiority of dual RAS blockade compared to monotherapy; multicentric clinical trials are ongoing to resolve this issue (14).

### 2.2 Background on the roles of angiotensin II in the kidney

Despite controversies over the efficacy of dual or simple RAS blockade, the importance of Ang II in diabetic nephropathy development is well accepted. Ang II, an octapeptide discovered in the 1930s in the United States and characterized in Switzerland, was initially named for its first-known function: contraction of blood vessels (15). It is the most powerful biologically active peptide of the RAS, with vasoconstriction but also nonhemodynamic effects, such as electrolyte reabsorption, renal hypertrophy and tubular apoptosis in the kidneys (15).

#### 2.2.1 Receptors

It is well established that Ang II mediates its effects mainly via binding to two G protein-coupled receptors: AT<sub>1</sub>R (which has 2 subtypes in rodents, namely AT<sub>1a</sub> and AT<sub>1b</sub>) and AT<sub>2</sub>R. AT<sub>1</sub>R, a seven-transmembrane domain receptor, is the main known mediator of Ang II actions (16); its action is summarized in **Table 1**. Ang II stimulation leads to upregulation of AT<sub>1</sub>R in the tubular compartment but downregulation of the same receptors in the glomerular compartment (17). The role of AT<sub>2</sub>R in kidneys is still not fully understood: upon stimulation by Ang II, it can counteract the effects of AT<sub>1</sub>R (18) but also activate inflammation (cf **Table 1**). In animal models of kidney damage, de novo expression of AT<sub>2</sub>R in glomeruli and vessels was induced by Ang II together with upregulation of AT<sub>2</sub>R in tubular cells (19).

Recent studies have shown the importance of 2 other receptors, the Ang1-7 or Mas receptors and the AT<sub>4</sub> receptor (20). The latter is still under investigation and has been proven to be linked to memory. However, it is also present in vessels and kidneys (proximal and distal tubules); it increases intracellular Ca<sup>2+</sup> levels and activates Erk and MAPK signalling (21).

#### 2.2.2 Actions

Ang II stimulates glomerular cell proliferation and causes accumulation of extracellular matrix material by stimulating transforming growth factor  $\beta_1$  (TGF- $\beta_1$ ), which leads to increased protein synthesis. TGF- $\beta_1$  decreases protein degradation by stimulating matrix metalloproteinases, mainly MMP-2, but also plasminogen activators inhibitor-1 (PAI-1) (22-23).

AT <sub>1</sub> R		AT <sub>2</sub> R		Mas receptors	
Activation	Inhibition	Activation	Inhibition	Activation	Inhibition
Phospholipase A2	Adenyl cyclase	iNOs/L-arginine/O <sub>2</sub>	PKC (MAPK)	p38MAPK, SHIP-1 (PI3K)	TGF-β <sub>1</sub>
Jak/STAT		+NADPH		Erk 1/2	
IITP		(NO&cGMP)		Bradykinines	
Ca <sup>2+</sup>		NF-kappa B		COX	
p21ras, C-Src				(Prostaglandins),	
PKC (MAPK&TGF-β <sub>1</sub> )				NO	
NADPH (ROS)					

Table 1. Signalling pathways stimulated by AT<sub>1</sub>, AT<sub>2</sub> and Mas receptors

It has been demonstrated that high glucose, together with Ang II, is involved in tubular lesions seen in DN (5, 24). Indeed, high glucose and Ang II enhance angiotensinogen (Agt, the sole precursor of all angiotensins) gene expression, both in vitro in rat immortalized renal proximal tubular cells (iRPTC) (25, 26) and in vivo in streptozotocin-treated mice (a model of diabetic mice) proximal tubules (5, 24). This turns into a vicious circle, increasing tubular atrophy, as Agt is the sole substrate of the RAS and is used for synthesis of Ang II.

### 2.3 From angiotensinogen to angiotensin II

The importance of the systemic RAS in blood pressure control and sodium homeostasis has been well accepted and Ang II has been recognized as a cardinal parameter in the development of both hypertension and kidney injury (5, 13, 15, 27). Overactivation of AT<sub>1</sub> R by Ang II therefore represents a target for treatment, but as Ang II has many other paracrine effects (induction of inflammation, mitogenesis, cell growth, apoptosis, differentiation, migration, etc.), current therapies are not sufficient to reverse the consequences of Ang II hyperaction. Of note, local RAS have been unravelled in some organs, notably the kidneys, with luminal fluid levels of Ang II being at least 1,000-fold higher than in the plasma (28). This local RAS could also play an important role in sodium retention and blood pressure regulation and hypertension, representing both a cause and a consequence of kidney injury. Complex interactions between diabetes and hypertension due to similar etiologies of both conditions, together with the stimulating effect of hyperglycemia on Ang II production in vitro, point to an important role for local RAS in DN.

#### 2.3.1 Synthesis and degradation of angiotensin II

The classic components of the RAS are all found in renal proximal tubules, including Agt and the enzymes (prorenin/renin, ACE, angiotensin-converting enzyme 2 (Ace2), aminopeptidases and carboxy peptidases). Upon cleavage of the prorenin into a proteolytic enzyme, renin will cleave Agt into a decapeptide: angiotensin I (Ang I). Then the dipeptidyl peptidase ACE will remove 2 amino acids from the latter and generate Ang II. Ang II is further metabolized into smaller fragments, such as Ang 1-7 and Ang III, Ang IV and Ang V, by various peptidases. Among those peptidases, Ace2 is a human homologue to ACE (42% similarity) that was discovered in 2000; it cleaves Ang I into Ang 1-9 / Ang II to Ang 1-7, both having hemodynamic properties (29). While ACE is present in most tissues, Ace2 is specifically expressed in the kidney, and less in the testes and heart, with neither ARB nor

ACE-I, which can inhibit its activities (29). Ace2 levels in glomerules and proximal tubules are decreased in patients with chronic kidney disease and DN (30).

The following diagram illustrates the pathway for the synthesis and degradation of Ang II.

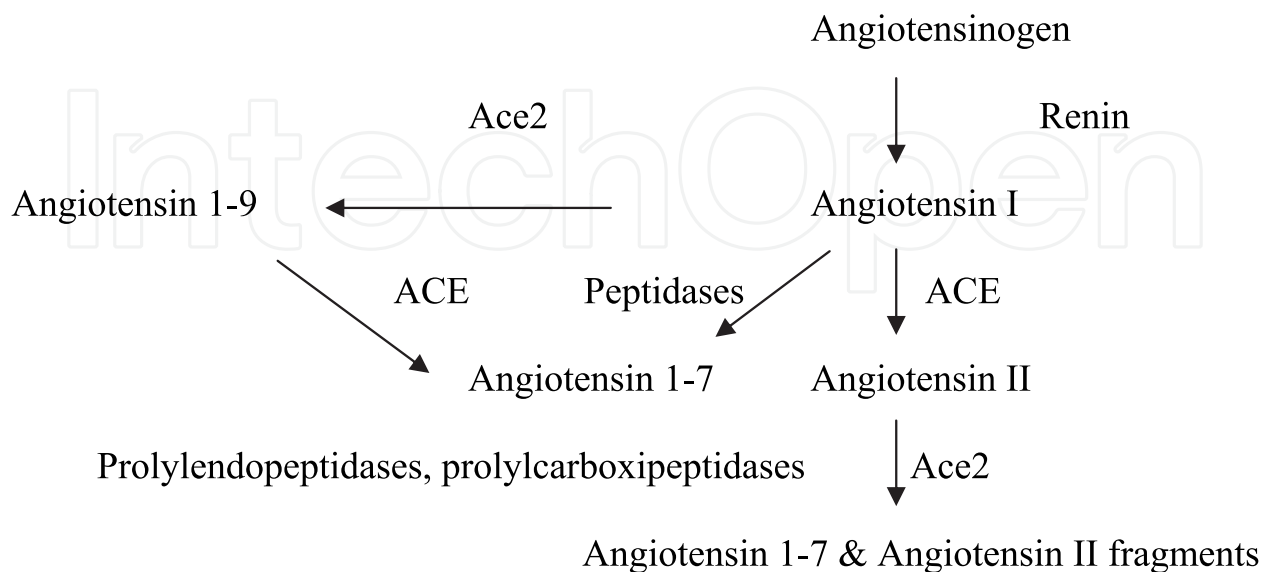


Fig. 1. Synthesis and degradation of Ang II

When Ace2 null mice were bred with the Akita model of type 1 diabetes, the obtained Ace2(-/y) Ins2(WT/C96Y) mice exhibited increased mesangial matrix scores, urinary albumin excretion rates and glomerular basement membrane thicknesses compared to Ace2(+/y)Ins2(WT/C96Y) with the same blood glucose levels (31). This highlights once more the role of RAS in the development of kidney injury in cases of chronic hyperglycemia.

### 2.3.2 Importance of angiotensinogen in diabetic nephropathy

Our laboratory has previously demonstrated that both ARB and ACE-I block Agt gene expression and induction of hypertrophy stimulated by high glucose levels in immortalized rat RPTCs and that renal Ang II acts in an autocrine manner to stimulate TGF- $\beta$ 1 expression and, subsequently, TGF- $\beta$ 1 enhances cellular hypertrophy and collagen  $\alpha$ <sub>1</sub> (type IV) expression in RPTCs (32). Our experiments on RPTCs have shown that high glucose stimulates Agt gene expression via at least 4 pathways:

- Protein Kinase C via de novo synthesis of diacylglycerol;
- p38 MAP Kinase;
- Hexosamine biosynthesis;
- ROS.

The latter have been extensively studied within the frame of elucidating the molecular mechanisms of hyperglycemia action in DN. It is now accepted that elevated glucose levels enhance PKC activation, augment membrane lipid peroxidation in glomeruli and induce Agt gene expression in rat RPTCs via ROS generation (25). Excessive intracellular accumulation of glucose (seen in chronic hyperglycemia) leads to disturbances at the level of the TriCarboxylic Acid (TCA) pathway, followed by the formation of high quantities of

electron donors (NADH, H<sup>+</sup> and FADH<sub>2</sub>) and mitochondrial superoxide overproduction (33). Increased mitochondrial superoxide production activates three main pathways: the polyol/protein kinase C pathway, the hexosamine biosynthesis pathway, and increased production of advanced glycated end products (AGE) and its receptor, RAGE (33). Our transgenic (Tg) mice overexpressing rat catalase (CAT) in their RPTCs exhibit attenuated ROS generation, Agt gene expression and RPTC injury in streptozotocin (STZ)-induced diabetes in vivo (5), unequivocally demonstrating the importance of ROS in mediating Agt gene expression and in the development of DN.

## 2.4 Recent findings on diabetic nephropathy using transgenic mouse models

In order to elucidate in vivo the importance of local intrarenal RAS, at least two systems could be used: targeted renal expression of RAS in knock out mice for any component of RAS and targeted renal overexpression of one component of the RAS in wild type mice. Our laboratory has been using the latter approach to elucidate the role of intrarenal RAS in DN.

### 2.4.1 The angiotensinogen transgenic mouse model

To obtain specific overexpression of the rat Agt gene (rAgt) in RPTC, our laboratory used the Kidney-specific Androgen regulated Promoter 2 (KAP2) (34, 35). The cDNA encoding full-length rAgt fused with HA-tag at the carboxyl terminal and NotI restriction enzyme site attached at both 5'- and 3'-termini was thus inserted into the KAP2 promoter and thereafter microinjected into one-cell fertilized mouse embryos as shown below:

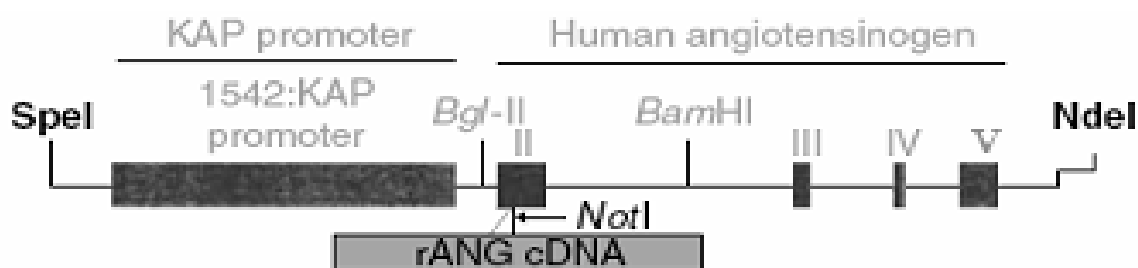


Fig. 2. Schematic map of the kidney androgen-regulated promoter (KAP2)-rat Agt construct

Studies using this rAgt-transgenic (Tg) mice model have demonstrated that overexpression of renal rAgt alone induces hypertension and albuminuria and that RAS blockade reverses these abnormalities (34). Thereafter the same model was used to assess a possible synergistic deleterious action of local RAS overactivity and high glucose on RPTCs, which could contribute to the pathophysiology of DN and help unravel new protective mechanisms.

### 2.4.2 Tubular apoptosis in diabetic angiotensinogen transgenic mice

STZ was used to induce diabetes in non-transgenic (non-Tg) and Tg mice. As far as systemic hypertension is concerned, neither STZ-induced diabetes nor insulin treatment changed the blood pressure levels of Tg mice or non-Tg mice. STZ administration led, four weeks later, to diabetes, increased kidney/body weight and albuminuria, and were normalized by insulin treatment. RAS blockers did not affect glucose levels but reversed

the deleterious effects of rAgt-overexpression in diabetic mice. Renal injury found in Tg mice was more severe in STZ-treated Tg mice, with loss of brush borders in RPTC and marked tubular luminal dilatation. In addition, glomerular and RPTC hypertrophy and increased tubular luminal area were markedly attenuated by insulin and RAS blockers in Tg and non-Tg STZ-treated mice, while a combination of both treatments completely reversed these abnormalities. Apoptotic assays (TUNEL) and immunohistochemistry using caspase-3 antibody showed increased levels of apoptosis in RPTC of Tg mice compared to non-Tg, the latter having higher levels than non-STZ treated mice. Investigations of the molecular pathways involved reveal an increased level of Bax and concomitant downregulation of Bcl-xL. One hypothesis could therefore be that hyperglycemia enhanced tubular apoptosis by increasing the Bax/Bcl-xL ratio, thus having a pro-apoptotic effect. STZ-induced diabetes leads to apoptosis in RPTCs and to a lesser degree in distal tubules, but not in the glomeruli, confirming previous findings of a pro-apoptotic effect of diabetes on RPTCs (36). Treatment with insulin and/or RAS blockers leads to an almost complete absence of apoptosis in kidneys of non Tg and Tg mice. Another salient finding in Agt-Tg mice is the persistent kidney injury despite hydralazine treatment. In fact, hydralazine treatment markedly reduced systemic blood pressure but did not affect albuminuria and tubular apoptosis. Further investigations into the underlying mechanism of high glucose and Ang II action were performed on Tg mice overexpressing catalase (CAT-Tg) in their RPTCs. STZ-induced diabetic CAT-Tg mice exhibited attenuated ROS generation and tubular apoptosis (5). Furthermore, in double Tg mice having Agt and CAT specifically expressed in their RPTCs, ROS generation, NADPH activity and levels of hemoxygenase 1 (HO-1) were significantly lowered by CAT overactivity compared to Agt-Tg mice. Levels of collagen type IV, monocyte chemotactic protein-1 (MCP-1), TGF- $\beta_1$  and plasminogen activator inhibitor-1 were also lowered by CAT overexpression in double Tg mice compared to Agt Tg mice (37). Thus, CAT overexpression alleviates oxidative stress in RPTC and reduces the toxicity of Ang II and chronic hyperglycemia on the kidneys.

### 3. Conclusion and perspectives

Agt and chronic hyperglycemia act together at the level of the RPTC, leading to tubular atrophy due to pro-apoptotic activities and interstitial fibrosis. This unravels the importance of the local RAS in the development of DN. Both *in vitro* and *in vivo* experiments of overexpression of Agt indicate that the latter stimulates RPTC hypertrophy and apoptosis, but significant effects on the glomeruli remain to be determined. However, because tubular atrophy seems to be a better predictor of disease progression than glomeruli lesions, this finding may be considered of significant clinical importance, as therapeutics reproducing the effects of CAT may be specifically developed to impede or even stop the progression of DN.

Further directions include studying the effect of the local RAS on glomeruli and deciphering the molecular pathways by which Agt and chronic hyperglycemia induce RPTC apoptosis. One important clue is the role of ROS, which is induced by both intrarenal RAS overactivity and chronic hyperglycemia. Indeed, we have reported an increase of apoptotic cells in RPTCs of db/db mice (type II diabetic mouse model) and normalization by overexpression of catalase (CAT) in their RPTCs (db/db CAT-Tg mice) (38) as shown below:

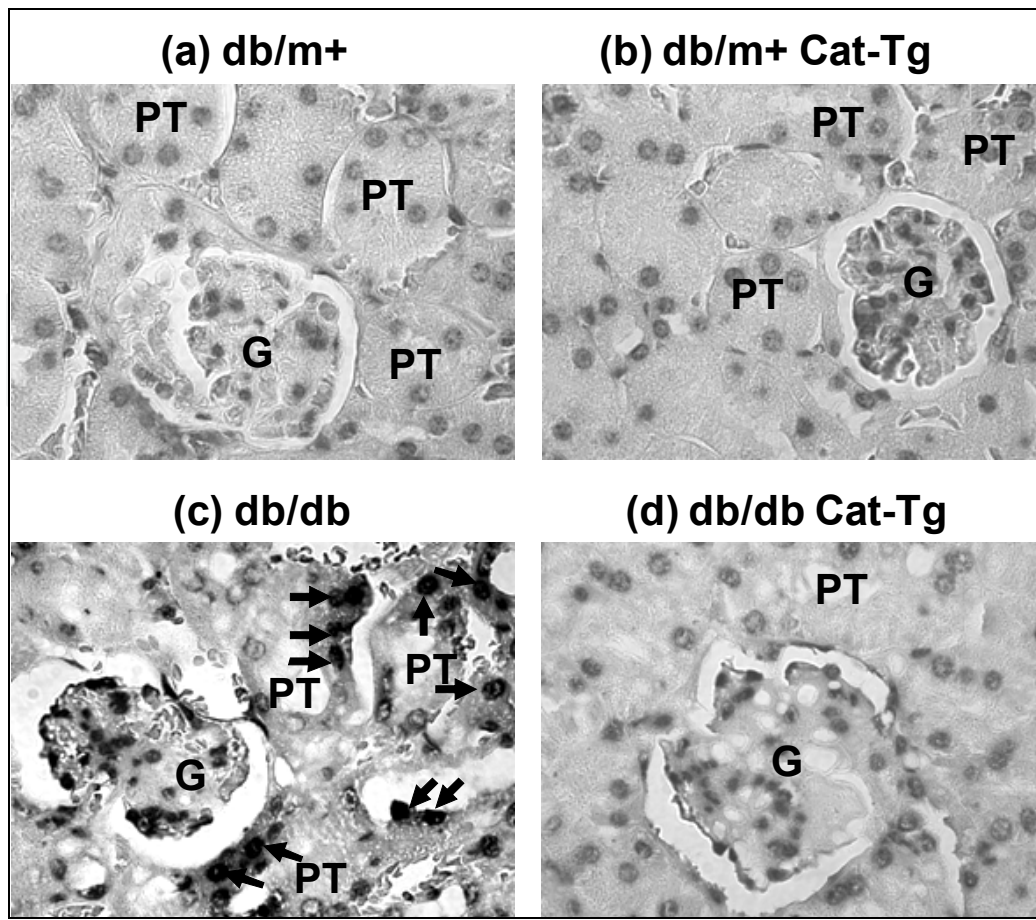


Fig. 3. Apoptosis in male non-Tg and Tg mouse kidneys at week 20, analyzed by TUNEL staining. Arrows indicate apoptotic cells. G, glomerulus; PT, proximal tubule. Magnification x600.

Using DNA chip microarrays technology, our laboratory recently identified 2 pro-apoptotic genes, Bcl-2 modifying factor (*Bmf*) and *Caspase-12*, which are differentially upregulated in renal proximal tubules of db/db mice but normalized in db/db CAT-Tg mice (39) as shown below:

Probe Set ID	Gene Title	Fold-change (db/db vs db/m+)	p-value (db/db vs db/m+)	Fold-change (db/db vs db/db-CAT Tg)	p-value (db/db vs db/db-CAT Tg)
1450231_a_at	baculoviral IAP repeat-containing 4	1.28	0.0039	1.29	0.0038
1454880_s_at	Bcl2-modifying factor	3.07	0.0099	3.07	0.0098
1449297_at	caspase 12	1.82	0.0069	1.81	0.0070
1431875_a_at	E2F transcription factor 1	1.19	0.0065	1.19	0.0064
1423602_at	Tnf receptor-associated factor 1	1.99	0.0073	1.97	0.0074
1445452_at					

Fig. 4. List of genes up-regulated in microarray chips of db/db vs db/m+ and db/db vs db/db CAT-Tg mice



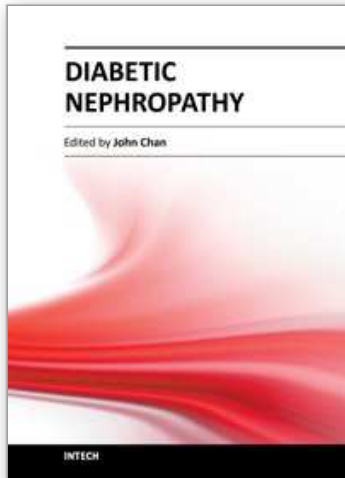
One hypothesis that needs further examination is whether intrarenal RAS overactivation and chronic hyperglycemia may act synergistically to induce ROS generation and subsequently induce endoplasmic reticulum (ER) stress in RPTCs and enhance ER-stress gene expression such as caspase-12, glucose-regulated protein 78 (GRP78)/immunoglobulin-heavy-chain-binding protein (BiP), and CCAAT/enhancer-binding protein homologous protein (CHOP) expression and activation, triggering the initiation and amplification of the apoptotic cascade leading to tubular apoptosis.

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## **Diabetic Nephropathy**

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Internationally renowned experts have provided data on their own studies, and discuss the relative usefulness of their work in relation to diabetic nephropathy. The first section describes the novel role of intrarenal renin-angiotensin-aldosterone system (RAAS) and oxidative stress in the development of diabetic nephropathy and discusses the current and novel pharmacological interventions in the treatment of diabetic nephropathy. The second section discusses other important contributors outside of the RAAS in the pathogenesis of diabetic nephropathy including AGE/RAGE, epithelial-mesenchymal-transition (EMT) and immune cytokines. Features: Provides novel information on various pathophysiological determinants in the development of diabetic nephropathy Provides novel information on various pharmacological interventions of diabetic nephropathy

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