Cellular and molecular mechanisms of diabetic glomerulopathy

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Abstract
The epidemic of diabetic kidney disease is predicted to rise significantly in the next decade and will continue to represent the leading cause of end-stage renal failure. The interaction between metabolic and haemodynamic insults represents an important driver of the relentless decline in renal function that we observe in patients with diabetes. Studies have described different cellular pathophysiological mechanisms of diabetic glomerulopathy; increased oxidative stress appears to be the major alteration that drives the activation of many other cellular pathways which in turn will result in the phenotypic alterations seen in diabetic glomerulopathy. The glomerulus should be seen as a delicate network of cells that interact closely with one another in regulating the process of water and small solute filtration. In diabetes, this equilibrium is disrupted and its correction should aim at reinstating the balanced equilibrium as seen in physiology. Future therapeutic challenges will be represented by a tissue-specific personalized ‘ad hoc’ therapeutical approach which will depend on patients’ characteristic and stage/progression of disease.

Keywords: blood pressure; diabetes; kidney disease; metabolism; proteinuria

Introduction
Management of the diabetes epidemic and the burden of diabetes renal complications are a huge global challenge: the number of patients with diabetes worldwide is believed to be ∼180 million and is set to increase to 350 million in the next two decades [1]. Patients with Type 2 diabetes will account for 90% of all cases, and we expect an increase in new cases of diabetic nephropathy (DN) within the predicted 30–40% prevalence of renal disease in this population. DN is the leading cause of end-stage renal failure and accounts for 30% of individuals entering renal replacement programmes (United States Renal Data System 2010, www.renalreg.com).

In diabetes, metabolic (hyperglycaemia) and haemodynamic perturbations (hypertension) are the two major insults that, by modulation of different cellular pathways, drive the relentless decline in renal function [2, 3].

Discussed in this review are the major cellular pathways involved in the pathophysiology of diabetic glomerulopathy with particular focus on the interactions between glomerular cells [4], further emphasis is put on potential novel treatment for patients with diabetic chronic kidney disease.

Diabetic glomerulopathy: pathophysiological cellular alterations

One of the earliest signs of diabetic glomerulopathy is an alteration of the permselective properties of the glomerular filtration barrier to protein with increased amount of protein in the urine, defined as ‘albuminuria’. In the early stage of disease, albuminuria is usually quantitatively of small magnitude and intermittent, while, as the disease progresses, it becomes more persistent and of greater amount until it reaches the stage of ‘clinical proteinuria’ known as an important predictor for renal disease progression and end-stage renal disease [5].

In diabetes, albuminuria is considered to arise from defects of the glomerular filtration barrier [6]. The glomerulus is a complex structure that relies, for its physiological function, on the co-operative interaction of several cell types (endothelial, mesangial cell and podocytes) and the glomerular basement membrane (GBM).

Diabetes significantly affects all glomerular cells. Glomerular endothelial cells become swollen and structurally immature with loss of the endothelial glycocalyx [7]. In studies with glomerular endothelial cells in vitro, high glucose exposure of cells is paralleled by damage of the glycocalyx, with secondary increased albumin permeability through the glomerular endothelial cell monolayer [8]; similarly, in patients with Type 1 diabetes, the decreased thickness of the endothelial cells’ glycocalyx layer correlates with the severity of albuminuria [7].

The podocytes play a key role in preserving glomerular capillary integrity, regulating synthesis of extracellular matrix (ECM) protein of the GBM and contribute to the physiological function of the glomerular capillary barrier with the interdigitation of their foot processes and the slit diaphragm [9]. In diabetes, podocyte function and structure are disrupted leading to excessive ECM deposition (GBM thickening), podocyte architectural changes (foot
process fusion) and detachment from GBM, all alterations seen in patients with both Type 1 and Type 2 diabetes [10].

Mesangial cells, that constitute the backbone of the glomerular capillary tuft, contribute to the progressive diabetes-mediated accumulation of ECM which leads to progressive glomerulosclerosis [3, 6, 10].

The chronology of diabetes-induced glomerular lesions is still not fully understood and there has been little insight into the interactions and role of different resident cell types in the processes leading to glomerular damage.

In various experimental animal models of diabetes, podocyte loss is followed by remaining podocytes trying to cover a larger GBM surface area; this is followed by podocyte foot processes widening, proteinuria and at a later stage, progressive glomerulosclerosis [11, 12]. Specifically, it has been observed that early glomerular changes in experimental animal models of diabetes are characterized by podocyte injury without evidence of mesangial expansion [11–13].

In humans, it has been difficult to stage the morphological changes that occur during the early phases of diabetic glomerulopathy but that loss of podocytes and formation of areas of bare GBM could represent a starting point for glomerular injury [14].

**Diabetic glomerulopathy: metabolic and haemodynamic perturbations-mediated effects**

Metabolic and haemodynamic perturbations, and importantly their interaction, are key players in the pathophysiology of diabetic glomerulopathy [3] (Figure 1). Importantly, it appears that epigenetic changes, likely mediated by chronic hyperglycaemia, could play an important role in pathophysiology of DN in humans [15].

Metabolic–haemodynamic interaction was first postulated by Hostetter [16] who described a hyperglycaemia-mediated alteration of glomerular capillaries autoregulation, thereby reducing the afferent and, to a much lesser degree, efferent arteriolar tone, resulted in higher glomerular hydraulic pressure and secondary glomerular lesions.

The mechanisms at the basis of hyperglycaemia-mediated disruption of capillary vasoregulation are complex. Hyperglycaemia-mediated activation of the local tissue renin–angiotensin–aldosterone system (RAAS) resulting in excess of angiotensin-2 [17], leads to an increase in reactive oxygen species (ROS) production and transforming growth factor β1 (TGF-β1) expression, both implicated in vasodilatation of both afferent and efferent glomerular arterioles [6, 18]. The documented higher sensitivity of the efferent (versus the afferent) glomerular arteriole to the vasoconstrictive action of angiotensin-2 contributes to the imbalance in arteriolar tone which results in higher glomerular capillary pressure [19], resulting in glomerular cells mechanical elongation and activation of those cellular mechanisms that lead to glomerular damage [20].

The increased glomerular capillary pressure [3] and the consequent elongation of mesangial cells, in direct continuous with the glomerular capillaries, results in a TGF-β1 autocrine/paracrine-mediated effect with up-regulation of the facilitative glucose transporter Glut-1 which further enhances the chronic transport of glucose molecules across the cells’ membrane with secondary excess in glucose metabolism and ECM deposition [3]. In line with these observations, an increased expression of cortical Glut-1 has been observed in experimental animal models of diabetes [3].

The excess in cellular glucose transport and metabolism and the parallel haemodynamic perturbation (increased glomerular capillary pressure) determine an increase in ROS production [2] that results in activation of a series of common stress-activated signalling pathways, such as nuclear factor-kappaB (NF-κB), p38 mitogen-activated protein kinase (MAPK) and Jun N-terminal kinases/stress-activated protein kinases [2], that lead to the outset of different intracellular metabolic pathways, such as the polyol and hexosamine pathway, increased production of advanced glycation end products (AGEs), increase diacylglycerol levels and activation of protein kinase C (PKC) [2].

High glucose/mechanical stretch-mediated increased in ROS production is central to the pathogenesis of DN [2, 21] and secondary excess in angiotensin-2, increased PKC activation and TGF-β1 expression have, in turn, been implicated as important pro-oxidative stress stimulants. The increased oxidative stress is mainly mediated by up-regulation of NAPH oxidase protein Nox4 as seen in renal cortex of experimental animal models of diabetes. In line with the Brownlee central hypothesis of chronic complications in diabetes [2], Nox4 has been localized mainly to mitochondria and its down-regulation in isolated mitochondria in vitro is paralleled by a reduction in NADPH oxidase activity and inhibition of glucose-mediated ROS production [22]. Alterations in antioxidant defence also appears to contribute to the pathophysiology of diabetic kidney disease: studies conducted in skin fibroblast of
patients with Type 1 diabetes with nephropathy showed an impaired high glucose-mediated antioxidant response when compared to cells obtained from non-diabetic individuals and patients with Type 1 diabetes without complications who retained, on the contrary, an intact antioxidant response to glucose-induced oxidative stress [23]. Recently, activators of NF-E2-related factor-2 (Nrf2), a transcription factor involved in antioxidant response, have been proposed as potential treatments for DN in humans. Early work in humans with the Nrf2 activator Bardoxolone suggests a significant improvement in estimated glomerular filtration rate (eGFR) in patients with Type 2 diabetes and chronic kidney disease [24]. The Bardoxolone-mediated effects on eGFR reverted to baseline value when the medication was stopped suggesting a likely haemodynamic effect on glomerular capillary filtration, a hypothesis also supported by the parallel increase in albuminuria; clinical trials currently under way will provide more information on the potential therapeutic effect of this drug in DN.

Excess ROS production is paralleled by activation of NF-κB and inflammatory cytokines, important in the pathogenesis of diabetic kidney disease. Renal lymphomonocyte infiltrates have been described in human and experimental animal models of diabetes. Modulation/inhibition of monocyte chemotactic protein-1 activation, of its receptor chemokine (C-C motif) receptor-2 [25] and intercellular adhesion molecule-1 [26] have been shown to retain anti-proteinuric and renoprotective effects in diabetic mice. In this respect, there is evidence, in humans and experimental settings, that both peroxisome proliferator-activated receptors (PPAR)-γ (glitazones) and PPAR-α (fibrates) agonists, through their anti-inflammatory effect, provide renal protection in diabetes. Studies in search of agonists with a better side effects profile are ongoing [27, 28].

The excess entry of glucose into the cells leads to glucose conversion to sorbitol by aldose reductase and sorbitol accumulation has been observed in glomerular cells in diabetes. Sorbitol cellular accumulation determines alteration in cellular osmolality and biochemical changes leading to increased oxidative stress and non-enzymatic glycation of protein. The role of the polyclonal pathway in DN has been investigated using specific aldose reductase inhibitors but the results to date have not provided a definitive answer [21].

Enzymatic and non-enzymatic protein glycosylation occur respectively mainly via the activation of the hexosamine pathway and formation of AGEs. Flux through the hexosamine pathway has been implicated in diabetic glomerulopathy [29]. Under normal physiological conditions, a small percentage (1–3%) of glucose transported into the cells is metabolized through the hexosamine pathway. The rate-limiting enzyme glucosamine:fructose-6-phosphate amidotransferase converts fructose-6-phosphate to glucosamine-6-phosphate favouring the accumulation of uridine diphosphate N-acetylglycosamine, substrate for O- and N-protein glycosylation. In mesangial cells, the flux of glucose through the hexosamine pathway has been implicated in activation of p38MAPK, increased expression of TGF-β1 and NF-κB activation [29, 30].

AGEs represent a heterogeneous group of proteins, lipids and nucleic acids, irreversibly cross-linked with reducing sugars that directly or via receptor-mediated mechanisms (receptor for AGEs—RAGE) determine alteration in gene expression and activation of cellular signalling proteins that results in increase oxidative stress, increase inflammation and cytokines release. Blockade of RAGE in experimental animal models of diabetes ameliorates both functional (albuminuria) and structural diabetes-mediated renal alterations (glomerulosclerosis). Similarly, studies in RAGE null mice support a key role for RAGE in glomerular perturbations in diabetes [31]. In kidney biopsies obtained from patients with diabetes, AGE accumulation is primarily found in renal basement membranes, and its accumulation is paralleled by up-regulation of RAGE in podocytes. Inhibitors of AGEs, such as blockade of AGE formation, AGE breakers and AGE blockers or scavengers (such as soluble RAGE), are currently being tested for clinical application. Importantly, these treatments should be started in the early phase of the disease in order to prevent the tissue accumulation of AGEs seen in diabetes [31].

The clinical evidence and knowledge of insulin resistance being an important player in the pathophysiology of diabetic glomerulopathy [32] has recently been explored with an experimental animal model where the insulin receptor (IR) was deleted in a podocyte-specific manner [33]. Podocyte IR null mice are characterized by glomerular lesions similar to those seen in experimental animal models of diabetes [33]. Importantly, podocytes, but not glomerular endothelial cells, have been found to be insulinresponsive and able to increase glucose uptake after insulin stimulation. Nephrin, an important component of the slit diaphragm, appears to be necessary for podocyte response to insulin and down-regulation of nephrin expression in wild-type podocytes or up-regulation of nephrin expression in otherwise nephrin-deficient podocytes, respectively, reduces or rescues insulin-mediated glucose transport [34, 35].

Nephrin and other slit diaphragm protein such as CD2-associated protein (CD2AP) and podocin have been involved in the regulation of podocyte cytoskeleton [36], and their dysregulation, as seen in diabetes, leads to podocyte foot process fusion, effacement and detachment from the GBM. The role of nephrin in cytoskeleton regulation appears to be at the basis of podocyte reduced insulin response in diabetes [35], but whether this is part of and/or relates to a systemic ‘insulin resistance status’ that predisposes to kidney disease will need to be addressed in future studies.

Another important player in diabetic glomerulopathy is PKC; of the many PKC isoforms, PKC-β1/β2 and PKC-ε have been involved in the pathophysiology of diabetic renal complications in experimental animal models of diabetes. Animals with PKC-β1 and of PKC-α deletion results in an amelioration of diabetes-mediated lesion with a reduction in diabetes-mediated increased expression of the profibrotic cytokines TGF-β1, resulting in reduced ECM synthesis, reduced oxidative stress and preservation of nephrin expression and integrity of the glomerular filtration barrier. Conversely, TGF-β1
expression and activity is up-regulated in mice with deletion of PKC-ε, suggesting that activation of PKC-ε in diabetes may translate in renal protection rather than a mediator of renal injury [37]. Future studies will need to promote the translation of these observations to the clinical setting.

Excess substrate availability such as high circulating glucose level (glucose toxicity) will trigger the cellular machinery that links the nutrient availability and the cellular response; the most studied pathways include the Sirtuins (Sirt) and the mammalian target of rapamycin (mTOR). Predisposition for renal microvascular complications is associated with insulin resistance paralleled by elevated glucose circulating levels and ‘excess substrate availability’ [38], a condition characterised by decreased Sirt1 expression [39] and increased mTOR pathway activation [40].

Sirt [41] are ubiquitously expressed NAD+-dependent deacetylases and deacetylate many transcription factors (PPARγ, PPARγ coactivator-1α, NF-κB and forkhead box class O proteins) all of which are associated with vascular dysfunction in diabetes. In vitro, Sirt1 is protective against high glucose-induced endothelial cell damage [42]. Sirt1 is down-regulated in the kidney of diabetic rats against high glucose-induced endothelial cell damage [38], a condition characterised by decreased Sirt1 expression [39] and increased mTOR pathway activation [40].

Sirt1 up-regulation and amelioration of DN [40, 45].

mTOR forms two functional complexes, termed mTOR complex-1 (mTORC1) and mTORC2. mTOR regulates a wide array of cellular processes including cell growth, proliferation, inflammation and autophagy in response to excess in nutrients availability such as glucose and growth factors. Recently, podocyte-specific activation of mTOR has resulted in a DN-like phenotype, while the genetic reduction of mTORC1 activity significantly prevented renal disease in experimental animal models of diabetes [46, 47].

Future studies will have to translate the potential role of Sirt1 agonist or mTOR antagonist in the pathophysiology of DN in humans.

Links and interactions between cells: cytokines and growth factors

The metabolic and haemodynamic insults driving the diabetes-mediated glomerular functional/structural alterations result in a sustained dysregulation of cytokines/growth factors, constitutively expressed by glomerular cells, that exert their action in an autocrine/paracrine manner leading to renal disease development and progression.

A close interaction has been described between endothelial cells and podocytes, mesangial cells and endothelial cells and mesangial cells and podocytes [48]. Communications between cells do occur between podocytes and endothelial cells or area of limited filtration such as areas of contact with mesangial cells, basement membrane and podocytes, where cytokines/growth factors move across in either direction by diffusion following a gradient. Further direct interaction between cells occur when cells are in close proximity through gap junctions, such as interdigitating mesangial and endothelial cells in the paramesangial region of the capillary loop.

These existing connections highlight how podocytes, glomerular endothelial cells and mesangial cells interact and depend on each other in the regulation of glomerular physiology and that phenotypic alteration of any of these cells would likely result in secondary changes to neighbouring cells.

One of the growth factors involved in the maintenance of normal glomerular physiology vascular endothelial growth factor (VEGF)-A has been implicated in diabetic glomerulopathy. In healthy kidneys, VEGF-A is constitutively expressed in podocytes, while its receptors VEGFR-1 and VEGFR-2 are localized on the glomerular endothelial cells, mesangial cells and podocytes [49, 50], although for the latter, data is still not definitive [51].

In diabetes, glomerular damage is associated with early up-regulation of the VEGF-A/VEGF receptor system [52], and data on primary over-expression of VEGF-A specifically in the podocytes result in diabetic-like glomerular abnormalities [53], while inhibition of VEGF-A or its receptors in diabetic animal results in prevention of proteinuria and glomerular damage [50]. Importantly, treatments should be directed at normalization of VEGF-A levels, as excess inhibition of VEGF-A could per se lead to glomerular disease [54], a concept in line with the described reduced VEGF-A expression, as seen in advanced diabetic kidney disease in humans [55].

Angiopoietins (Ang) are another important vascular growth factor involved in the pathophysiology of DN. Ang are involved in angiogenesis and vasculogenesis [56] and Ang-1 and Ang-2, respectively, activate or inhibit their receptor Tie-2, expressed on glomerular endothelial cells and podocytes [57]. In the healthy animal, Ang-1 is constitutively expressed in the podocyte and promotes cell survival and vascular stability and inhibits vascular permeability by maintaining the anatomic functional properties of the glomerular vasculature [57].

In diabetes, the balance between Ang-1 and Ang-2 in the glomerulus is disrupted leading to an excess of Ang-2 over Ang-1. In rats administered with streptozotocin, whole-kidney Ang-1 and Ang-2 levels rise in parallel in the early phase of disease, while as the disease progress, Ang-1 levels diminishes, while Ang-2 remains elevated [57]. Similar findings have been observed in patients with Type 2 diabetes who present with increased circulating Ang-2 levels [57]. Transgenic mice with podocyte-specific inducible over-expression of Ang-2 had significant increases in albuminuria and glomerular endothelial apoptosis, with a decrease in expression of both VEGF-A and nephrin [58]. Furthermore, animals with Ang-1 deletion in the glomeruli showed accelerated diabetes-mediated glomerular damage suggesting that Ang-1 expression could potentially confer microvascular protection [59].

Endothelin-1, the predominant isoform of the endothelin peptide family, is a potent vasoactive peptide and is widely expressed in all cells of the glomerulus and
vasculature [60]. Endothelin-1 binds to two receptors, \( \text{ET}_\alpha \) which has vasoconstrictor functions and \( \text{ET}_\beta \) which mediates vasodilatation [60]. In glomeruli from diabetic mice, endothelin-1 is up-regulated [61] and administration of \( \text{ET}_\alpha \) selective antagonists ameliorates diabetes-mediated glomerular albumin permeability which is paralleled by reduced ROS production, reduction in pro-inflammatory cytokines, amelioration of fibrosis and prevention of nephrin loss in podocytes [62]. In humans, \( \text{ET}_\alpha \) receptor antagonist is associated with a significant attenuation of proteinuria on top of RAAS inhibition therapy, but unfavourable side effects have, to date, prevented their use in clinical practice [63].

TGF-\( \beta \), a potent prosclerotic cytokine, is mainly expressed in mesangial cells, while its receptor is present in all glomerular cells. TGF-\( \beta \) is an important mediator of the haemodynamic and metabolic-mediated perturbations in the glomeruli and promotes up-regulation of VEGF-A, the secreted ECM-associated protein connective tissue growth factor and increased ROS production which mediated and amplified its prosclerotic effects [21, 64–66].

Interventions inhibiting TGF-\( \beta \) action with neutralizing antibodies (conducted in experimental animal models) have resulted in beneficial effects mainly on diabetes-mediated glomerulosclerosis with little or no effect on albuminuria [67]. More recently, Pirfenidone, an oral anti-fibrotic agent, has demonstrated a promising anti-fibrotic effect both in the experimental setting [68] and in patients with diabetes [69].

Recently, microRNAs (miRs), a family of short non-coding RNAs, have been identified as important players in gene expression regulation and have been proposed as potential targets for treatment of DN. Specifically, miR-192, miR-200b/c, miR-200a and miR-141, expressed in the kidney, have been identified as an important modulator of metabolic and TGF-\( \beta \)-mediated effect in diabetic kidney disease both in vitro and in vivo. Further deletion of Dicer, a key enzyme involved in miRs biogenesis, in podocytes results in proteinuria and severe kidney disease in mice [70–73]. Future work will need to translate these observations to potential new treatments approaches.

Nitric oxide (NO) is a free radical that has been implicated in the cellular mechanism of diabetic glomerulopathy. Chronic diabetes-mediated perturbations are paralleled by uncoupling of endothelial nitric oxide synthase (eNOS) with secondary decrease in NO availability and increased ROS production [74]. In animal models of diabetes, renal NO levels are reduced alongside diminished eNOS expression levels [75] while mice lacking eNOS develop accelerated diabetic kidney disease [76]. The combination of low NO bioavailability along with high VEGF-A expression has been proposed as a major driver of glomerular alterations in diabetes [74]; the availability of NO seems to regulate the beneficial or non-beneficial role of VEGF-A on the vasculature. In normal physiology, VEGF-A stimulates NO production promoting vascular integrity. The reduction in NO as seen in the diabetic kidney results in an NO-independent VEGF-A action that results in progressive vascular damage and increased vascular permeability [77].

Activation of the local renin–angiotensin system (leading to an excess in angiotensin-2) in diabetic glomerulopathy not only affects haemodynamic changes within the glomerular capillaries but also plays a significant role in the events leading to glomerular inflammation [78] and increased oxidative stress [34]. Inhibition of RAAS has been shown to ameliorate the development and progression of DN. Importantly, RAAS inhibition promotes, in parallel to reduction of angiotensin-2, an increase in the synthesis of vasodilator peptides such as angiotensin-(1–7) [79]. Angiotensin-(1–7) is synthesized as a result of ACE2 (expressed in podocytes)-mediated degradation of angiotensin-1 to angiotensin-(1–9) and angiotensin-2 to the vasodilator angiotensin-(1–7) substrate [80]. In experimental animal models of DN, over-expression of ACE2 ameliorates glomerular injury [81], therefore drugs targeting this pathway could also lead to potential treatment for diabetic kidney disease.

**Clinical perspectives and conclusions**

Poor glycaemic and blood pressure control have been recognized as the major determinants of chronic kidney disease in diabetes.

Prospective randomized controlled trials such as the Diabetes Control Complications Trial and its follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, in patients with Type 1 diabetes demonstrated that improved glycaemic control resulted in significant reduction of micro/macro-albuminuria [82] and that early sustained intensive glycaemic treatment provides long-term beneficial effects on renal disease progression [83–85].

In parallel, studies in patients with Type 2 diabetes (United Kingdom Prospective Diabetes Study—UKPDS) also demonstrated that better glycaemic control reduced the risk for the development of albuminuria [86], and similarly to the EDIC study, showed significant prevention of microvascular events during 10 years of post-trial follow-up [87].

The ACCORD [88], ADVANCE [89] and the VADT [90] studies were three clinical trials enrolling patients with Type 2 diabetes with \( \sim 10 \) years duration of disease, poor glycaemic control (HbA1c \( \sim 9\% \)) and at high vascular risk, asking whether intensive glycaemic control for \( \sim 4–6 \) years had any effect on micro and macrovascular disease [91, 92]. The results demonstrated a positive effect on renal microvascular complications only in the ADVANCE trial [93] but showed an overall failure on micro and macrovascular outcomes, possibly reflecting a poor ‘metabolic memory’ in the diabetic population studied.

Intervention studies on blood pressure lowering have demonstrated a beneficial reduction of the speed of kidney disease progression and a significant reduction in albuminuria in patients with both Type 1 and Type 2 diabetes [94, 95].

In the UKPDS, the effect of tighter blood pressure control in patients with Type 2 diabetes and hypertension reduced the occurrence of microalbuminuria, but
Conversely to glycaemic control, no legacy effect has been observed for blood pressure, and therefore good blood pressure control must be continued if the benefits are to be maintained [96].

Blood pressure control with RAAS inhibition is considered an important intervention in DN [3], but recent studies have challenged the benefit of RAAS inhibition in normotensive diabetic patients before the onset of albuminuria [97], and in patients with Type 1 diabetes, the use of RAAS inhibitors failed to prevent or slow the progression of the early histological lesions of DN [98]. Similarly, the Diabetic Retinopathy Candesartan Trials (DIRECT) failed to demonstrate any effect of the angiotensin receptor blocker candesartan on development of microalbuminuria in patients with both Type 1 and Type 2 diabetes [99]. Conversely, the Bergamo Nephropathy Diabetes Complications Trial (BENEDICT) found that the risk of developing microalbuminuria was reduced by RAAS inhibition but not by calcium antagonist for equivalent blood pressure reduction in hypertensive patients with Type 2 diabetes and normoalbuminuria [100].

It would appear that a potential positive effect of RAAS inhibition is mainly seen in hypertensive populations and less in normotensive and less ‘at risk’ normoalbuminuric diabetic patients in the early phase of disease.

The future challenges would reside in targeting and correcting the diabetes-mediated renal dysfunction in specifically different phases of renal disease progression (early, progressive and late), and as clinicians, we should consider personalized ‘ad hoc’ therapeutical approaches.

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References


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