Clinical Queries: Nephrology 4 (2015) 9–14

Contents lists available at ScienceDirect

Clinical Queries: Nephrology

journal homepage: www.elsevier.com/locate/cqn

Review Article

Updates in the management of diabetic nephropathy

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ARTICLE INFO

Article history:
Received 27 April 2015
Accepted 18 November 2015

Keywords:
Diabetic nephropathy
RAS blockade
Non-proteinuric diabetic nephropathy
Incretin system
Glycaemic control

ABSTRACT

Diabetic nephropathy is the most frequent cause of end stage renal disease (ESRD) worldwide. Current treatments consisting of glycaemic and blood pressure control, and efficient anti-proteinuric effects of RAS blockade are not sufficient to prevent progression of ESRD in a substantial proportion of patients. This finding is consistent with the hypothesis that key pathogenic mechanisms leading to progression of renal disease in diabetic patients are not modified or inactivated by current therapeutic approaches. Despite extensive research in molecular signalling mechanism and a number of high-profile clinical trials of potentially nephroprotective agents, the pathogenetic mechanisms underlying the diabetic nephropathy are not fully understood. Currently, only one trial (atrasentan) that seems to have a potentially renoprotective effect is underway. Further research into the potential nephroprotective effects of novel glucose lowering agents is needed.

Introduction

Diabetic nephropathy (DN) is the most common cause of chronic kidney disease (CKD) worldwide. Between 20% and 40% of patients with diabetes develop diabetic nephropathy, although the reasons why not all diabetic patients develop this complication is not known. The current therapy of diabetic nephropathy includes control of hypertension, glycaemic status and using ACEi/ARB to reduce albuminuria and to retard progressive loss of renal function. However, this approach fails to fully prevent diabetic nephropathy. Recently, abnormalities of oxygen biology, such as hypoxia, oxidative stress (OS) and dyserythropoiesis, have been implicated in the pathogenesis of DN.[1] The newer approaches targeting oxygen biology may offer new treatment in the management of diabetic nephropathy.[2] This review will focus on the recent advances in the pathogenesis and management of diabetic nephropathy and will be presented under the following headings:

1. Progression of diabetic nephropathy
2. Oxygen biology in pathogenesis of DN
3. Potential future therapies targeting O_2 biology
4. Current standard therapy
5. Limitations of current therapy
6. Novel approaches
7. Preclinical studies
8. Conclusions

1. Progression of diabetic nephropathy

The classic pattern of diabetic nephropathy involves initial microalbuminuria that progresses to macroalbuminuria and is followed by a progressive decrease in renal function leading to ESRD.[3] Around 25–35% of patients with diabetes and decreased renal function have normoalbuminuria or microalbuminuria.[4,5] Decreased renal function in the absence of substantial proteinuria was observed even before RAS blockade become the standard therapy for diabetic kidney disease.[6] The exact mechanisms of progressive loss of renal function in diabetic patients with normoalbuminuria or microalbuminuria are not known. However, the proposed potential mechanism for progression of DKD in these patients includes: (1) Systemic and local inflammation; (2) High uric acid levels; (3) Vascular diseases; (4) Tubular injury as a result of high glucose level; (5) Repeated haemodynamically mediated episodes of acute kidney injury and (6) Comorbid renal disease. Non-proteinuric diabetic kidney disease has been reported in both type 1 and type 2 diabetes mellitus.[4,7] Biopsy studies showed classic change of DKD in 22/23 patients with microalbuminuria or macroalbuminuria, but only in 3/8 patients with normoalbuminuria.[8] This report illustrates the occurrence of pathological change of DKD in the absence of albuminuria (non-proteinuric diabetic nephropathy).

2. Oxygen biology in pathogenesis of DN

Besides haemodynamic and metabolic abnormalities, a broad range of abnormalities associated with oxygen biology, such as

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http://dx.doi.org/10.1016/j.cqn.2015.11.001

hypoxia, oxidative stress (OS) and dyserythropoiesis, have provided new insight in our understanding of diabetic nephropathy. The cellular mechanism associated with oxygen biology and their role on the genesis of DN is discussed below:

(a) Oxidative stress (OS)
(b) Hypoxia
(c) Dyserythropoiesis
(d) Erythropoiesis and renal fibrosis

2.1. Oxidative stress (OS)

OS results from the accumulation of ROS and disrupts cellular function. A "Local" OS is demonstrated in the Human diabetic kidney.[9,10] The primary cause of local OS in DN remains debated as ROS are generated by numerous enzymatic and non-enzymatic pathways,[11–14] for example the activation of the renin-angiotensin system, of NADPH oxidase, of nitric oxide synthase. A newer pathway of OS has recently emerged, the prolylhydroxylase-1 (PHP)-hypoxia-inducible factor (HIF) system.[15]

2.2. Hypoxia

Renal tissue hypoxia remains difficult to document directly from blood or urine analyses; however, recently, molecular imaging technologies have allowed an evaluation of renal oxygen levels.[16,17] The causes of chronic hypoxia in DN are heterogenous.[18–21] Lesions in efferent arterioles, dyserythropoiesis and anaemia of CKD contribute to poor oxygen supply in DN. Hypoxia not only causes local OS in DN, but also affects various biological reactions linked to oxygen metabolism.[1,22,23] The consequence of hypoxia plays a pivotal role in the genesis and progression of DN. Therapies interfering with it may prove clinically useful.

2.3. Dyserythropoesis

EPO production occurs mainly in the kidney and is reduced in CKD patients with an eventual anaemia.[18] Recent studies have indicated that EPO administration improves kidney function in CKD, either directly or indirectly.[24] The therapeutic benefits of EPO beyond the correction of anaemia are still debated. It is noteworthy that, recently, evidence has been published on the pleiotropic effects of EPO on the central nervous and cardiovascular systems, as well as on the kidney.[25,26] Renal EPO-producing (REP) cells, originating from neural crests, but not fibroblast from injured tubular epithelial cells, transdifferentiated into myofibroblast and contribute to renal fibrosis.[27]

2.4. Erythropoiesis and renal fibrosis

The peritubular interstial fibroblastic cells are renal erythropoietin-producing (REP) cells and are widely distributed in the interstitium of cortex and outer medulla.[28,29] During CKD progression, myofibroblasts emerge in the peritubular interstitium and their expansion eventually leads to the ESRD.[18] The myofibroblasts in renal fibrosis were initially thought to originate from a variety of cell types, including tubular epithelial cells (TECs) and vascular smooth muscle cells.[18,30] However, recent studies have shown that this is not the case.[27] The REP cells transdifferentiated to myofibroblast under inflammatory signals in CKD and deteriorate their EPO-producing ability. In the early phase of renal fibrosis, REP cells may recover their initial nature through the correction of the inflammatory milieu. However, during prolonged CKD progression, the transformed REP cells are no longer able to regain their EPO-producing ability and finally contribute to renal fibrosis and end-stage renal failure (ESRD).

3. Potential future therapies targeting O_2 biology

3.1. PHD inhibitor

Oral PHD inhibitor stimulates HIF activity in various organs of experimental animals. Locally, they induce angiogenesis in a mouse sponge assay. HIF activation potentially corrects tissue hypoxia and provides pleiotropic effects, such as anti-inflammatory, anti-oxidative stress and oxygen-independent energy production.

Unfortunately, non-specific inhibition of HIF-α degradation also augments vascular endothelial growth factor and EPO production, both of which have proven detrimental for proliferative diabetic retinopathy in humans.[31] A phase II clinical trial of a PHD inhibitor, FG-4592, is currently underway in patients with stage 3–4 CKD to alleviate anaemia, hypertension and hyperlipidaemia, all of which are independent risk factors not only for cardiovascular events but also CKD.[32] Although clinically available PHD inhibitors, such as FG-4592, are not specific for distinct PHD subtype, they mainly inhibit PHD_2. A specific PHD1 inhibitor has not yet been reported but it should protect hypoxic tissues through a reduced OS without affecting angiogenesis and/or erythropoiesis. It might be suitable for the treatment of DN and other types of CKD where chronic hypoxic renal injury is concomitant.

3.2. Nrf_2 activator/$Keap_1$ inhibitor

Bardoxolone methyl, derived from a natural product oleanolic acid, is a potent inducer of Nrf_2.[33] In phase II clinical trial, known as BEAM, in patients with advanced CKD and type 2 diabetes, Bardoxolone improved renal function with only mild side effects, such as muscle spasm, weight loss and hypomagnesaemia.[34] Unfortunately, a subsequent phase III BEACON trial in patients with CKD and type 2 diabetes has to be terminated on 18 November 2012 because of serious adverse events (www.clinicaltrials.gov/ct2/show/NCT01351675).

No effective $Keep_1$ inhibitor is currently available. Sulforaphane, a natural product present in broccoli sprouts, modulates $Keap_1$.[35] Sulforaphane ameliorates renal injury in mouse model of streptozotocin-induced DN.[36]

3.3. REP modulating agents

EPO production in the liver is significantly larger in foetus than in adult,[37] hence, the idea to treat renal anaemia through the induction of EPO production in the liver. EPO production is activated through the PHD–HIF pathway in the liver as well as in the kidney under hypoxic condition.[38] Hopefully, the development of PHD inhibitors (mainly PHD2) might stimulates EPO production in the liver instead of the damaged kidney.[18,37,39] Reverse transformation of the myofibroblast in CKD may be expected. An experimental study demonstrated that the attenuated EPO production by differentiated REP cells was restored and the prevention of renal fibrosis was achieved by the administration of neuroprotective agents, dexamethasone and neutrophins in agreement with the neural crest origin of REP cells.[22]

3.4. Summary of O_2 biology

The meticulous correction of obesity, blood pressure, serum glucose or lipid level is still unable to fully avoid the renal consequence of diabetes mellitus. This failure points towards a need for better understanding of newer mechanisms of DN and requires the consideration of newer pathophysiological culprits.