Nephropathy

Targeting inflammation in diabetic nephropathy

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Haemodynamic factors involved in the pathogenesis of diabetic nephropathy can be ameliorated, in part, by blockade of the renin–angiotensin–aldosterone system (RAAS), but progressive structural damage, characterised by mesangial matrix accumulation and fibrosis, ultimately leads to renal failure. Although RAAS blockade is useful in slowing the progression of diabetic nephropathy, novel approaches are required to arrest – or even reverse – the natural history of the disease.

Oxidative stress, inflammation and fibrosis appear to be intimately related to matrix accumulation in diabetic nephropathy (Navarro-González et al, 2011), giving potential therapeutic roles for modulators of profibrotic cytokines (e.g. transforming growth factor [TGF]-beta) and vascular growth factors (e.g. vascular endothelial growth factor [VEGF]).

> ***"Oxidative stress, inflammation and fibrosis appear to be intimately related to matrix accumulation in diabetic nephropathy, giving potential therapeutic roles for modulators of profibrotic cytokines and vascular growth factors."***

Two recent studies summarised here (Pergola et al, 2011 [summarised alongside]; Sharma et al, 2011 [summarised overpage]) provide insights into attempts to target inflammation in diabetic nephropathy.

Bardoxolone methyl, a derivative of oleanolic acid, is an oral antioxidant that upregulates a number of cytoprotective genes resulting in amelioration of inflammation. Pergola and colleagues (2011) studied the effect of step-wise increases in bardoxolone methyl dose on estimated glomerular filtration rate (eGFR) over 52 weeks in individuals with type 2 diabetes and nephropathy.

Active treatment was associated with an early overall improvement in eGFR at 4 weeks that was maintained for the study period. The effect appeared to be greatest with the 75 mg daily dose, with no additional benefit apparent at 150 mg. More participants experienced a fall in eGFR in the placebo group than in the bardoxolone methyl groups (54% vs 20–25%), with 13% treated with placebo experiencing a >25% fall in eGFR at 24 weeks, compared with only 2% in the bardoxolone methyl group. Adverse effects of treatment included muscle spasms, gastrointestinal (GI) symptoms and significant elevations in hepatic transaminases in 10% of participants. Interestingly, no beneficial effect on albumin excretion was seen with active treatment.

Pirfenidone, an oral inhibitor of TGF-beta production, has been reported to inhibit matrix deposition in lung and kidney disease, and has shown some promise in slowing eGFR decline in those with refractory focal segmental glomerulosclerosis (Cho et al, 2007). Sharma and colleagues (2011) evaluated the effect of pirfenidone on a group of individuals with type 1 or 2 diabetes and nephropathy in a small, exploratory study.

eGFR improvement was seen in the pirfenidone group and declined in the placebo group. However, treatment withdrawals were frequent, particularly in the higher dose group (44%) as a result of adverse GI events. Plasma biomarkers did not appear to correlate with the eGFR response and, as in Pergola et al's investigation of bardoxolone methyl, there was no beneficial effect on albuminuria seen in the cohort treated with pirfenidone.

Although these studies represent relatively small steps on the road to new treatment options in diabetic nephropathy, there is, nonetheless, reason to be encouraged.

Note to the reader

This is my final commentary for *Diabetes Digest.* I would like to thank those of you who have read this column over the years. I hope you have found it of interest.

Cho ME et al (2007) *Clin J Am Soc Nephrol* **2**: 906–13
Navarro-González JF et al (2011) *Nat Rev Nephrol* **7**: 327–40

NEJM

Bardoxolone methyl associated with eGFR improvement in T2D with CKD

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓✓

1 Bardoxolone methyl is an oral antioxidant inflammation modulator and previous short-term studies have shown the efficacy of this agent among people with chronic kidney disease (CKD) and T2D.

2 The authors undertook a double-blind, randomised, placebo-controlled trial to determine the change from baseline in the estimated glomerular filtration rate (eGFR) with bardoxolone methyl, as compared with placebo, at 24 weeks and at 52 weeks in people with CKD and T2D (i.e. eGFR of 20–45 mL/min/1.73 m^2 of body surface area).

3 Adults (n=227) in a 1:1:1:1 ratio to receive placebo or bardoxolone methyl at a target dose of 25, 75, or 150 mg once daily.

4 Participants receiving bardoxolone methyl had significant increases in mean eGFR compared with placebo at 24 weeks (P<0.001), which was maintained through to week 52.

5 The most frequent adverse event in the treatment arms were muscle spasms; the authors described these events as generally mild and being dose-related.

6 The authors concluded that bardoxolone methyl therapy was associated with improvement in eGFR in those with advanced CKD and T2D, which suggests that bardoxolone methyl may have promise for the treatment of CKD in this population.

Pergola PE, Raskin P, Toto RD et al (2011) Bardoxolone methyl and kidney function in CKD with type 2 diabetes. *N Engl J Med* **365**: 327–36

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Possible role for pirfenidone in slowing diabetic nephropathy

Readability	✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓

1 Animal studies suggest that pirfenidone is an effective oral antifibrotic agent in the treatment of diabetic nephropathy; its effects in human diabetic nephropathy was assessed in the current study.

2 A randomised, double-blind, placebo-controlled study was undertaken; 77 people with diabetic nephropathy (elevated albuminuria; reduced estimated glomerular filtration rate [eGFR; 20–75 mL/min/1.73 m²) were enrolled and received placebo or 1200 mg or 2400 mg of pirfenidone per day.

3 Primary outcome was a change in eGFR after 1 year of therapy.

4 Fifty-two people completed the study; mean eGFR increased in the pirfenidone 1200 mg/d group (+3.3±8.5 mL/min/1.73 m²), and significantly decreased in the placebo group by comparison (–2.2±4.8 mL/min/1.73 m²; P=0.026). The 2400 mg/day pirfenidone group dropout rate was high (11 of 25).

5 Four people receiving placebo, one person receiving 2400 mg/day pirfenidone and no people in the pirfenidone 1200 mg/d group initiated haemodialysis (P=0.25).

6 Baseline levels of plasma biomarkers of inflammation and fibrosis significantly correlated with baseline eGFR but did not predict response to therapy.

7 The authors concluded that pirfenidone is a promising agent for the management of overt nephropathy in people with diabetes.

Sharma K, Ix JH, Mathew AV et al (2011) Pirfenidone for diabetic nephropathy. *J Am Soc Nephrol* **22**: 1144–51

HYPERTENSION

SUA modifies risk of renal disease

Readability	✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The authors sought to determine whether reductions in serum uric acid (SUA) during losartan therapy are associated with renoprotection

2 A *post hoc* analysis of 1342 people with T2D and nephropathy participating in the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan Trial was undertaken to determined the relationship between month 6 change in SUA and renal endpoints.

3 Mean baseline SUA was 6.7 mg/dL in both groups; by study end SUA in the losartan group was lowered by –0.16 mg/dL (P=0.031) compared with placebo.

4 The authors concluded that approximately one-fifth of losartan's renoprotective effect was attributable to its effect on SUA, which supports SUA as a modifiable risk factor for renal disease.

Miao Y, Ottenbros SA, Laverman GD et al (2011) Effect of a reduction in uric acid on renal outcomes during losartan treatment: a post hoc analysis of the reduction of endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan Trial. *Hypertension* **58**: 2–7

DIABETES, OBESITY & METABOLISM

Saxagliptin is well-tolerated by people with T2D and renal impairment

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 In this multicentre, randomised, parallel-group, double-blind, placebo-controlled study, participants (n=170) with HbA_{1c} levels 7–11% (53–97 mmol/mol) and creatinine clearance <50 mL/min were stratified by baseline renal impairment (moderate, severe, haemodialysis), and randomised (1:1) to saxagliptin 2.5 mg once daily or placebo for 12 weeks. Oral and injectable antidiabetes regimens were continued.

2 The adjusted mean decrease from baseline to week 12 in HbA_{1c} was statistically significantly greater in the saxagliptin group than in the placebo group (–0.42%; P= 0.007). Saxagliptin was generally well tolerated; adverse and hypoglycaemic events were similar in the treatment and placebo arms.

3 The authors concluded that saxagliptin 2.5 mg once daily is a well-tolerated treatment option for people with inadequately controlled T2D and renal impairment.

Nowicki M, Rychlik I, Haller H et al (2011) Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment. *Diabetes Obes Metab* **13**: 523–32

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Rosuvastatin in T2D with ESRD reduces risk of CV events

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 In this *post hoc* study of a subset of the AURORA Trail, 731 participants with T2D on dialysis were assessed.

2 Among those randomised to receive rosuvastatin, a non-significant 16.2% reduction in risk for the AURORA Trial's composite primary endpoint (cardiac death, non-fatal myocardial infarct, fatal or non-fatal stroke) was found; however, rosuvastatin therapy significantly reduced the rate of cardiac events (–32%) among people with T2D (hazard ratio, 0.68; 95% confidence interval, 0.51–0.90).

3 The authors concluded that among people on dialysis with T2D, rosuvastatin therapy might reduce the risk of fatal and non-fatal cardiac events.

Holdaas H, Holme I, Schmieder RE et al (2011) Rosuvastatin in diabetic hemodialysis patients. *J Am Soc Nephrol* **22**: 1335–41

"... approximately one-fifth of losartan's renoprotective effect was attributable to its effect on serum uric acid, which supports serum uric acid as a modifiable risk factor for renal disease."