Renal complications

Linking cardiovascular disease and nephropathy in type 1 diabetes

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Diabetes is characterised by increased risk of cardiovascular disease (CVD), and the association between increased CVD morbidity and mortality, and nephropathy, in type 1 diabetes has been recognised for over 25 years. Microalbuminuria emerged as a strong predictor of CVD events in the Pittsburgh Epidemiology of Diabetes Complications follow-up study (Prince et al, 2007).

The role of inflammation in the pathogenesis of atherosclerosis and coronary artery disease has emerged in the past decade. T-cells and macrophages dominate early atherosclerotic lesions. Endothelial activation by cholesterol and, subsequently, platelets, leads to the expression of leucocyte adhesion molecules, which result in attraction and inward migration of lymphocytes and monocytes, triggering the processes that eventually lead to plaque rupture and thrombosis.

Biomarkers of this inflammation – high sensitivity C-reactive protein, soluble tumour necrosis factor-alpha receptor-1, soluble intercellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) – have been associated with elevated urinary albumin excretion in a few cross-sectional studies in type 1 diabetes.

In the study summarised alongside, Lin and colleagues set out to explore the relationship between these biomarkers and the development of nephropathy in the DCCT (Diabetes Control and Complications Trial) patient cohort. They found an association between elevated baseline levels of sICAM-1 and increasing urinary albumin excretion over time, with those patients in the highest tertile of sICAM-1 having an almost two-fold increased risk of developing sustained microalbuminuria. This association was greater in the secondary prevention group, who already had evidence of microvascular disease (retinopathy). The authors concluded that sICAM-1 may be a mediator of progressive microvascular disease and a key molecule in the pathway of inflammation and injury, leading to the development of albuminuria and renal disease in diabetes.

"Inflammation and endothelial cell dysfunction appear to play important roles in the progression of nephropathy in type 1 diabetes."

The association with sICAM-1 rather than VCAM-1 may reflect differing characteristics of the two molecules, with sICAM-1 reflecting systemic endothelial cell dysfunction and VCAM-1 more central to the initiation of atherosclerosis. Poor glycaemic control has also been associated with increased expression of sICAM-1 and, interestingly, individuals in the DCCT intensive control group experienced reductions in both sICAM-1 and VCAM-1, and a lower risk of developing progressive albuminuria.

Inflammation and endothelial cell dysfunction appear to play important roles in the progression of nephropathy in type 1 diabetes. sICAM-1 may emerge as an important early biomarker that will help to stratify people at increased risk of developing nephropathy in type 1 diabetes and permit earlier intervention.

Prince CT, Becker DJ, Costacou T et al (2007) Changes in glycaemic control and risk of coronary artery disease in type 1 diabetes mellitus: findings from the Pittsburgh Epidemiology of Diabetes Complications Study (EDC). *Diabetologia* **50**: 2280–8

DIABETES CARE

Inflammation and progressive nephropathy

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

1 Kidney disease and cardiovascular disease are significant complications for people with type 1 diabetes, with progressive nephropathy causing substantial morbidity and mortality.

2 The authors evaluated the hypothesis that, if inflammation contributes to nephropathy development, then it could potentially be used as therapeutic marker for slowing the development of vascular complications in diabetes.

3 The study was a prospective analysis of biomarkers and change in urinary albumin excretion rate (AER) over time in 1441 people with type 1 diabetes. Data were gathered from stored blood samples from the Diabetes Control and Complications Trial.

4 Baseline levels of four biomarkers were measured: high-sensitivity C-reactive protein, soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1, and soluble tumour necrosis factor-alpha receptor-1).

5 A significantly higher increase in AER was observed in people in the highest tertile of baseline sICAM-1 compared with those in the lowest tertile (P=0.04), after adjustments for age, sex, duration of diabetes, HbA_{1c} and randomised treatment assignment.

6 The results show that higher baseline levels of sICAM-1 are associated with an elevated risk of progressive nephropathy in people with type 1 diabetes and may represent a therapeutic target for slowing the development of vascular complications.

Lin J, Glynn RJ, Rifai N et al (2008) Inflammation and progressive nephropathy in type 1 diabetes in the diabetes control and complications trial. *Diabetes Care* **31**: 2338–43

CURRENT MEDICAL RESEARCH AND OPINIONS

CKD and long-standing type 1 diabetes

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

1 Evidence suggests that microalbuminuria and nephropathy may progress more slowly in people with type 1 diabetes of long duration (>20 years).

2 To explore this, the authors investigated the characteristics of chronic kidney disease (CKD) in 400 people with type 1 diabetes of >50 years' duration in the UK.

3 Measurements were taken of HbA_{1c}, lipids, creatinine and urinary albumin:creatinine ratio (ACR).

4 Mean age was 69 years and mean duration of diabetes was 55 years; nine per cent of participants had macroalbuminuria and 27% micro-albuminuria; no one had stage 5 CKD.

5 Microalbuminuria was significantly associated with increased duration of diabetes (P=0.02), male sex (P=0.02), smoking (P=0.002), higher HbA_{1c} (P<0.0001), raised triglycerides (P=0.04) and peripheral vascular disease (PVD) (P<0.0001).

6 Macroalbuminuria was significantly associated with smoking (P=0.02), raised triglycerides (P=0.01), raised creatinine (P=0.02), PVD (P=0.01) and hypertension (P=0.01).

7 The results suggest that a relatively typical spectrum of proteinuric CKD exists in type 1 diabetes of long duration.

8 The authors concluded that microalbuminuria and CKD are common, even in type 1 diabetes of long duration (>50 years), and have similar characteristics and associations as those with shorter disease duration.

Gill GV, Daousi C, Barnett AH et al (2009) Chronic kidney disease in long duration type 1 diabetes lasting more than 50 years. *Curr Med Res Opin* **25**: 395–400

DIABETOLIGIA

Lisinopril and renoprotection

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

1 Angiotensin converting enzyme inhibitors are now considered first-line therapy in people with type 1 diabetes (T1DM) and diabetic nephropathy (DN).

2 This study aimed to determine the optimal renoprotective dose of lisinopril in this population, assessed by short-term changes in urinary albumin excretion rate (UAER).

3 Forty-nine people with T1DM and DN were randomised to receive lisinopril 20, 40 or 60 mg once-daily over three 2-month treatment periods; all 49 completed all three treatment periods.

4 All doses of lisinopril significantly reduced UAER, 24-hour ambulatory blood pressure (BP) and estimated glomerular filtration rate from baseline (P<0.05).

5 Reductions in albuminuria and BP were most pronounced with lisinopril 40 mg. No further beneficial effects on albuminuria and BP were observed by increasing the dosage to 60 mg.

Schjoedt KJ, Astrup AS, Persson F et al (2009) Optimal dose of lisinopril for renoprotection in type 1 diabetic patients with diabetic nephropathy: a randomised crossover trial. *Diabetologia* **52**: 46–9

DIABETES CARE

Improved pregnancy with intensive anti-hypertensive therapy

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

1 This study investigated pregnancy outcomes in 117 women with type 1 diabetes (T1DM) according to their level of albuminuria after implementation of intensified antihypertensive therapy.

2 The therapy was given to 14 of 100 women with normoalbuminuria, 5 of 10 with microalbuminuria, and all seven with nephropathy. Mean systolic blood pressure (BP) during pregnancy was 120 mmHg, 122 mmHg and 135 mmHg, respectively (P=0.0095); no between-group differences in diastolic BP or HbA_{1c} were observed.

3 No preeclampsia was observed in women with microalbuminuria. Frequency of preterm delivery in women with normoalbuminuria or microalbuminuria was 20%, compared with 71% in women with diabetic nephropathy (P<0.01).

4 Comparable pregnancy outcomes were observed in women with T1DM with either microalbuminuria or normoalbuminuria following intensified antihypertensive therapy.

Nielsen LR, Damm P, Mathiesen ER (2009) Improved pregnancy outcome in type 1 diabetic women with microalbuminuria or diabetic nephropathy: effect of intensified antihypertensive therapy? *Diabetes Care* **32**: 38–44

DIABETOLOGIA

Hyperfiltration associated with risk of nephropathy

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

1 A systemic review and meta-analysis was undertaken to evaluate whether glomerular hyperfiltration predicts future development of nephropathy in people with type 1 diabetes (T1DM).

2 Ten studies following 780 people with T1DM were included; 130 people developed nephropathy.

3 Those with hyperfiltration had a pooled odds of progression to a minimum of microalbuminuria 2.71 times that of those with normofiltration (95% confidence interval 1.20–6.11).

4 The authors concluded that, in the studies reviewed, people with glomerular hyperfiltration had an increased risk of developing nephropathy.

Magee GM, Bilous RW, Cardwell CR et al (2009) Is hyperfiltration associated with the future risk of developing diabetic nephropathy? A meta-analysis. *Diabetologia* **52**:691–7

"Comparable pregnancy outcomes were observed in women with type 1 diabetes with either microalbuminuria or normoalbuminuria following intensified antihypertensive therapy."