Nephropathy

Progression and regression of microalbuminuria in type 1 diabetes

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Around one-third of people with type 1 diabetes will develop microalbuminuria and for some this heralds the progression to macroalbuminuria and ultimately end-stage renal failure. However, regression of microalbuminuria will occur in a significant number (Perkins et al, 2003).

Data on 325 people in the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) cohort (de Boer at al, 2011; summarised alongside) who developed persistent microalbuminuria during the study period shows that regression to normoalbuminuria occurred in 40% of participants. Regression was associated with better glucose control and lower blood pressure and was as often independent of the use of renin–angiotensin–aldosterone system (RAAS) inhibitors.

Renal outcomes for people developing microalbuminuria during the DCCT – rather than EDIC follow-up – were better for those initially in the intensive treatment arm of the study, with a 35% lower progression to both macroalbuminuria and impaired glomerular filtration rate (estimated glomerular filtration rate <60 mL/min/1.73 m^2 at two consecutive study visits) and a two-fold increase in the likelihood of regression to normoalbuminuria, suggesting that improved glycaemic control can still impart an important effect at this stage. Lower HbA_{1c} levels at or following the diagnosis of microalbuminuria were associated with a greater likelihood of regression to normoalbuminuria, and late regression, after >10 years of microalbuminuria, occurred in 17 people. Mean HbA_{1c} level at the time of late regression was 7.7% (61 mmol/mol) and mean blood pressure 121/77 mmHg with, again, <50% taking a RAAS inhibitor at the time.

> *"Progression and regression of microalbuminuria are common in type 1 diabetes and the diagnosis of microalbuminuria provides a valuable opportunity for targeted intervention ..."*

Progression and regression of microalbuminuria are common in type 1 diabetes and the diagnosis of microalbuminuria provides a valuable opportunity for targeted intervention by improving glycaemic control and blood pressure therapies with RAAS inhibitors.

Perkins BA, Ficociello LH, Silva KH et al (2003) Regression of microalbuminuria in type 1 diabetes. *N Engl J Med* **348**: 2285–93

NEJM

Olmesartan delays onset of microalbuminuria

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

1 In this randomised, double-blind, multicenter, controlled trial, 4447 people with T2D received olmesartan (40 mg once daily) or placebo for a median of 3.2 years.

2 The primary outcome was the time to first onset of microalbuminuria.

3 The blood pressure target was achieved in almost 80% of participants taking olmesartan and in 71% taking placebo; blood pressure measured was 3.1/1.9 mmHg lower in the olmesartan group than in controls.

4 Microalbuminuria developed in 8.2% of those receiving olmesartan and 9.8% of controls; time to the onset of microalbuminuria was increased by 23% with olmesartan (hazard ratio, 0.77; P=0.01).

5 The authors concluded that olmesartan was associated with a delayed onset of microalbuminuria.

Haller H, Ito S, Izzo JL Jr et al (2011) Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med* **364**: 907–17

ARCHIVES OF INTERNAL MEDICINE

Regression of microalbuminuria in T1D following intensive glycaemic and BP lowering

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

1 Microalbuminuria is a common complication of T1D, the long-term outcomes of which are variable.

2 The authors sought to determine the incidence of, and clinical factors associated with, long-term renal outcomes after the development of microalbuminuria in the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) study.

3 The DCCT randomly assigned 1441 people with T1D to intensive or conventional diabetes therapy; participants were followed-up (median 13 years) in the observational EDIC study, during which 325 participants developed incident persistent microalbuminuria (albumin excretion rate ≥30 mg/24 hours at two consecutive study visits).

4 Ten-year cumulative incidences of progression to macroalbuminuria and regression to normoalbuminuria were 28% and 40%, respectively.

5 Intensive diabetes therapy conveyed more favourable albuminuria outcomes; as did lower HbA_{1c} level, absence of retinopathy, female sex, lower blood pressure (BP), and lower LDL-cholesterol and triglycerides.

6 Microalbuminuria outcomes are variable in T1D, but the authors concluded that intensive glycaemic control, lower BP, and a more favourable lipid profile are associated with improved outcomes.

de Boer IH, Rue TC, Cleary PA et al (2011) Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. *Arch Intern Med* **171**: 412–20

DIABETOLOGIA

Genetic associations in DM nephropathy

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

1 In this meta-analysis, the authors sought to assess the pooled effect of each genetic variant reproducibly associated with diabetic nephropathy.

2 A literature search of PubMed, EMBASE and Web of Science was undertaken; all genetic variants statistically associated with diabetic nephropathy in an initial study, then independently reproduced in at least one additional study, were included (diabetic nephropathy was defined as macroalbuminuria/proteinuria or end-stage renal disease [ESRD]).

3 Associations between the variants discovered in the literature search and diabetic nephropathy were calculated at the allele level. The primary measure of effect was a pooled odds ratio, and prespecified subgroup analyses were undertaken to stratify T1D/T2D, proteinuria/ESRD and ethnicity.

4 The literature search yielded 3455 citations, of which 671 were genetic association studies investigating diabetic nephropathy; from these, 34 replicated genetic variants were found and 21 of these remained significantly associated with diabetic nephropathy in a random-effects meta-analysis.

5 The odds ratios of associated genetic variants ranged from 0.48 to 1.70 and additional variants were detected in subgroup analyses for people of Asian ethnicity and those with T2D.

6 The authors found a total of 24 genetic variants associated with diabetic nephropathy and suggest that the relative contribution of these genes in the pathogenesis of diabetic nephropathy should be the focus of future studies.

Mooyaart AL, Valk EJ, van Es LA et al (2011) Genetic associations in diabetic nephropathy: a meta-analysis. *Diabetologia* **54**: 544–53

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Atrasentan effective in reducing residual albuminuria in T2D

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

1 Endothelin-receptor antagonists reduce albuminuria but are associated with fluid retention.

2 In the present study, the authors examined the effect of atrasentan, a selective endothelin A receptor antagonist, on albuminuria in a randomised, double-blind, placebo-controlled trial of people with diabetic nephropathy already receiving stable doses of renin–angiotensin system inhibitors.

3 Eighty-nine people with estimated glomerular filtration rates >20 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio (UACR) of 100:3000 mg/g were randomised to placebo or atrasentan (0.25, 0.75, or 1.75 mg daily) for 8 weeks.

4 Atrasentan significantly reduced UACR compared with placebo in the 0.75- and 1.75-mg groups (both $<P=0.011$).

5 In the placebo group, 17% of participants achieved ≥40% reduction in UACR from baseline compared with 30, 50, and 38% in the 0.25-, 0.75-, and 1.75-mg atrasentan groups, respectively ($P=0.029$ for 0.75 mg vs placebo).

6 Peripheral oedema occurred in 9% of controls and in 14, 18, and 46% of those receiving 0.25, 0.5, and 1.75 mg atrasentan, respectively ($P=0.007$ for 1.75 mg vs placebo).

7 The authors concluded that atrasentan at the tested doses was generally well-tolerated, effective in reducing residual albuminuria and may improve renal outcomes in people with T2D and nephropathy.

Kohan DE, Pritchett Y, Molitch M et al (2011) Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. *J Am Soc Nephrol* **22**: 763–72