Nephropathy

Reduction of albuminuria in type 1 diabetes does not mean reduction in cardio-renal risk

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Once again, the priceless resource that is the DCCT/EDIC study has been used to shed light on a vexed question in diabetic nephropathy research. The association between increasing albuminuria and cardio-renal risk was established in the 1980s, and was confirmed in people without diabetes in recent meta-analyses (Fox et al, 2012). Broadly speaking, cardiovascular mortality is doubled in those with moderately increased albuminuria (≥30 mg/day; previously known as microalbuminuria) and at least doubled again in those with severe albuminuria (≥300 mg/day; previously known as macroalbuminuria or clinical nephropathy).

The risks for end-stage renal disease (ESRD) are even greater with increasing albuminuria, although many die of cardiovascular disease before reaching ESRD. Both improved glycaemic and blood pressure control (mainly with renin–angiotensin system [RAS]-blocking agents) have been shown to reduce cardio-renal risk (Maione et al, 2011; Fullerton et al, 2014), although the results are relatively modest and take many years to become apparent.

Post hoc analyses of these studies have shown that the greatest benefit is seen in those with (mainly) severe albuminuria, who show the greatest reduction following therapeutic intervention (Heerspink et al, 2015). This has led some to call for reduction in albuminuria to be an accepted surrogate endpoint for intervention trials. This proposition has been debated for many years, and has been the subject of editorials and conferences (Levey et al, 2009). So far, regulatory authorities have been unwilling to adopt the proposal. Does this latest analysis from the DCCT/EDIC Research Group help in any way?

The frontline results from the study are summarised alongside. Essentially, in an original cohort of 1441 people with type 1 diabetes, 355 developed moderate (micro) albuminuria; 171 remitted to normoalbuminuria (normo) and, subsequently, 43 reverted back to moderate. 157 progressed from moderate to severe (macro), 22 from normo, and 1 from remitted moderate to severe. Cardiovascular event rates were no different from those with sustained or remitted moderate albuminuria, with about a two-fold increase in hazard ratio (HR) compared to patients with normoalbuminuria.

Similarly, HRs for a reduced eGFR of ≤60 mL/min/1.73 m^2 were the same for sustained and remitted moderate albuminuria, at around 3 compared to normoalbuminuria. Predictably, severe albuminuria had a much higher HR of 25.5 for reduced eGFR (these results being lower than those reported in the abstract as they relate to a fully adjusted model taking into account smoking status, RAS blocker use and achieved HbA_{1c}).

The strengths of this analysis are the comprehensive and complete dataset, as well as the long duration of follow-up (>27 000 person-years at risk). The main weaknesses are the relatively low number of events (although these rates are consistent with recently published data from other cohorts; Groop et al, 2009), and the limitation to type 1 diabetes. In addition, the analysis concentrated on a categorical change in albuminuria status. This means that a person could be classed as remitting if albumin excretion rate (AER) fell from 31 to 29 mg/day, but not if it reduced from 299 to 31 mg/day. Moreover, the definition of normoalbuminuria is arbitrary and historic; there is a near linear relationship between AER 10–30 mg/day and cardiovascular risk (Fox et al, 2012). It would, therefore, be interesting to repeat the analysis using percent change rather than categorical change in AER.

For practical and ethical reasons, there is unlikely to be a prospective trial with different levels of AER as an outcome. So, we are limited to *post hoc* analyses of intervention trials, and even those as thorough as DCCT/EDIC can never provide a definitive answer. As a result, this analysis does not support the concept of a reduction of AER as a valid surrogate outcome measure of cardio-renal benefit, at least in type 1 diabetes. The diabetes and nephrology communities need to come up with novel strategies to resolve this question. ■

References on following page

Clin J Am Soc Nephrol

Albuminuria changes: Clinical outcomes

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 This investigation examined how progression or remission of microalbuminuria is associated with long-term risks of adverse cardiovascular (CV) and renal outcomes.

2 The study cohort of 1441 people with T1D were from the DCCT/EDIC study. Albumin excretion rates were measured regularly for up to 30 years. At each urine collection, the participant's status was reclassified as normoalbuminuria, sustained microalbuminuria, macroalbuminuria or remitted microalbuminuria.

3 During follow-up, 355 participants with normoalbuminuria at baseline developed persistent microalbuminuria, 171 with persistent microalbuminuria regressed to persistent normoalbuminuria, and 180 developed macroalbuminuria.

4 Sustained microalbuminuria, remitted microalbuminuria and macroalbuminuria were each associated with a higher risk of CV events and reduced eGFR compared with normoalbuminuria.

5 Sustained normoalbuminuria was not associated with a reduced risk of CV events or reduced eGFR compared with sustained microalbuminuria.

6 After further adjustment for renin–angiotensin system (RAS) inhibitor use, remitted microalbuminuria and macroalbuminuria were associated with significantly higher CV risk, but sustained microalbuminuria was not.

7 This supports the prevention of the development of microalbuminuria and its progression to macroalbuminuria through interventions such as RAS inhibition. However, achieving remission of established microalbuminuria does not appear to improve outcomes.

de Boer IH, Gao X, Cleary PA (2016) Albuminuria changes and cardiovascular and renal outcomes in type 1 diabetes: the DCCT/EDIC Study. *Clin J Am Soc Nephrol* **11**: 1969–77

Diabetes Care

Linear eGFR decline prior to end-stage renal disease in T1D

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 These authors set out to characterise the trajectories of renal function decline that precede the onset of end-stage renal disease (ESRD) in people with T1D.

2 This observational study involved 364 people without kidney disease at baseline who subsequently developed ESRD while attending a diabetes clinic between 1991 and 2013.

3 Serum creatinine measurements made prior to the onset of ESRD were retrieved and used to estimate eGFR. Individual trajectories of eGFR over time were characterised for 257 individuals.

4 The rate of eGFR decline per year ranged widely, but was rapid in most individuals. Trajectories, as characterised by linear regression-based spline models, were linear or nearly so for 87% of individuals. Acceleration or deceleration was observed in a small minority. Smoothed trajectories followed a linear fit in 76% of participants.

5 Renal decline appears to be linear in the early stage of the process and just before ESRD. Deviations from linearity are small and have little effect on time to ESRD.

6 This suggests that decline is determined by a single disease process that continues with the same intensity from its initiation until ESRD.

7 Because of the linearity of renal decline, the authors suggest that effective interventions at an early stage aimed at reducing eGFR slopes could postpone the onset of ESRD by years.

Skupien J, Warram JH, Smiles AM et al (2016) Patterns of estimated glomerular filtration rate decline leading to end-stage renal disease in type 1 diabetes. *Diabetes Care* **39**: 2262–9

Diabet Med

Socio-economic factors and ESRD

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 The causes of end-stage renal disease (ESRD), a complication of T1D, are multifactorial, but metabolic control has been identified as being of major importance. Parental socio-economic status (SES) has been associated with metabolic control in children with T1D.

2 This nationwide, longitudinal study investigated how parental and personal education levels and SES influence the development of ESRD caused by T1D.

3 The Swedish Childhood Diabetes Registry identified 9299 people with T1D of >14 years' duration who were, therefore, at risk of developing ESRD. SES data on these participants was retrieved from a different national registry. Statistical analyses included 154 people with ESRD resulting from diabetes.

4 Low maternal education (≥12 years) increased the risk of developing ESRD (hazard ratio [HR], 2.9) compared to those with a university degree. Low paternal education had less effect on the risk (HR, 2.2), but was still significant. The highest impact was seen in those with a low personal educational level (HR, 5.7).

5 If either parent had ever received income support, the risk of developing ESRD was increased (HR, 2.6). More than half of the people with ESRD had received income support, but this may have been an effect of ESRD rather than a cause.

6 Individual and parental SES factors influence the development of ESRD in T1D. Socially deprived people should receive special attention during childhood and in adult life.

Toppe C, Möllsten A, Schön S, Dahlquist G (2016) Socio-economic factors influencing the development of end-stage renal disease in people with type 1 diabetes – a longitudinal population study. *Diabet Med* 18 Nov [Epub ahead of print]

Diabetes Care

T1D diagnosis and emerging adults

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 This Norwegian, population-based study retrospectively assessed mortality, causes of death and incidence of end-stage renal disease (ESRD) in a cohort diagnosed with T1D between the ages of 15 and 29 years. This period is associated with increased-risk behaviours and transition to adult care.

2 The cohort, diagnosed from 1978–82 (n=719), was followed for a mean duration of 29.6 years. National death and renal registries provided information on causes of death and presence of ESRD.

3 Causes of death were reviewed by a committee. Standardised mortality ratios (SMRs) were calculated for comparison with the background population.

4 During follow-up, 20.6% (n=148; 106 men, 42 women) of the cohort died. The SMR was 4.4. Cumulative mortality by years since diagnosis was 6.0%, 12.2% and 18.4% at 10, 20 and 30 years, respectively.

5 The cumulative incidence of ESRD owing to diabetic nephropathy was low (4.6%; n=33). The mean time from T1D diagnosis to ESRD was 23.6 years.

6 SMRs in younger age bands were higher than those in the older age bands. The high mortality rate at 20 years after diagnosis was mainly caused by violent death and acute complications. Mortality related to alcohol was five to seven times higher than in the general population.

7 The results draw attention to the vulnerability of people in diagnosed with T1D in this age group.

Gagnum V, Stene LC, Leivestad T et al (2017) Long-term mortality and end-stage renal disease in a type 1 diabetes population diagnosed at age 15–29 years in Norway. *Diabetes Care* **40**: 38–45

"Individual and parental socio-economic status factors influence the development of end-stage renal disease in T1D."

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