Nephropathy

SEARCH uncovers significantly higher rates of nephropathy in young people with type 2 diabetes

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Although the absolute numbers remain low, incidence rates of young people (YP) with type 2 diabetes (T2D) in some ethnic groups are similar to those seen for type 1 diabetes (T1D) in white (Europid) populations (Mayer-Davis et al, 2017). These data from the SEARCH investigators in the US confirm an increase in the annual incidence rate of 1.4% for T1D, but a five-fold greater increase for T2D from 2002/3 to 2011/12. In the study summarised alongside, the same investigators report the rate of microvascular and other complications in YP with diabetes.

SEARCH recruited 2018 newly diagnosed YP (1746 with T1D and 272 with T2D) aged <20 years from five diabetes registries. A subset with a diabetes duration of >5 years (mean, 7.9 years) were reviewed for the presence of nephropathy (defined as a single albumin:creatinine ratio measurement of ≥30 mg/g [~3 mg/mmol]); retinopathy (graded mild, moderate or proliferative from digital photography); or neuropathy (defined as a score >2 using the Michigan Screening Instrument). Cardiac autonomic neuropathy, arterial stiffness and hypertension were also assessed.

The age-adjusted prevalence of nephropathy was almost four times higher in those with T2D (19.9% vs 5.8%; $P<0.001$). The differences were less for retinopathy and neuropathy, but the overall odds ratios for YP with T2D were 2.58, 2.24 and 2.53, respectively. The odds ratios were not significant for autonomic neuropathy, arterial stiffness or hypertension. Overall, 72% of those with T2D had at least one diabetes complication, compared to 32% with T1D.

For T1D, the rates are similar to the 2003 DCCT/EDIC study (DCCT/EDIC Research Group, 2003). This is disappointing but not surprising as the mean HbA_{1c} at the time of review was 77 mmol/mol (9.2%), almost identical to the conventional control arm of the DCCT. For T2D, the data are more worrying. In the UKPDS, the prevalence of nephropathy 15 years after diagnosis was 28% (Bilous, 2008). SEARCH has a rate of nearly 20% after 7.9 years.

What might explain this disparity? Of the clinical features associated with nephropathy development, YP with T2D were more overweight; had higher blood pressures; were more likely to be black, Hispanic or Native American; and more likely to come from poorer socioeconomic backgrounds. Obviously, all of those with T1D were on insulin, but only half of those with T2D were, and 27% were on no blood glucose-lowering therapy. Despite these differences, HbA_{1c} levels were similar.

There are some caveats. First, the numbers with T2D were relatively low and these individuals may represent a particularly vulnerable population. It may not be possible to extend the results to all YP with T2D globally. Second, albuminuria was assessed only once and there is a recognised large day-to-day variability. Moreover, the albumin:creatinine ratio is increased in obese people and in those with hypertension, and it is uncertain that all of those identified in this study will progress to renal impairment.

Nevertheless, these data show we are still falling well short of target glycaemic control in YP, and that those with T2D seem particularly vulnerable to potentially life-shortening complications. Some of the causative factors are non-modifiable, but glycaemia, blood pressure and obesity can be addressed and should be targeted at least as vigorously in YP with T2D as they are for T1D. After witnessing a steady decline in rates of end-stage renal disease in people with T1D (US Renal Data System, 2016), we may now be confronting a much greater increase in YP with T2D. ■

References on following page

JAMA

Higher prevalence of nephropathy in young people with T2D

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

1 The SEARCH observational study aimed to determine the prevalence of and risk factors for complications related to T1D and T2D in newly diagnosed young people (YP). YP with T1D (n=1748) and T2D (n=272), all diagnosed at <20 years of age, were followed from 2002 to 2015.

2 Outcomes measured included nephropathy (albumin:creatinine ratio ≥30 mg/g [~3 mg/mmol]), retinopathy (mild, moderate or proliferative), peripheral neuropathy (Michigan Screening Instrument score >2), cardiovascular autonomic neuropathy, arterial stiffness and hypertension.

3 There was a higher age-adjusted prevalence of all complications except cardiovascular autonomic neuropathy in T2D than in T1D. Notably, the prevalence of nephropathy in YP with T2D was four times higher than in those with T1D (19.9% vs 5.8%).

4 After adjustment for established risk factors measured over time, YP with T2D had significantly higher odds of nephropathy, retinopathy and peripheral neuropathy, but there was no significant difference in the odds of arterial stiffness or hypertension.

5 The prevalence of complications and comorbidities was high in both groups but was higher with T2D than T1D.

6 These findings support early monitoring of YP with diabetes for development of complications.

Dabelea D, Stafford JM, Mayer-Davis EJ et al; SEARCH for Diabetes in Youth Research Group (2017) Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. *JAMA* **317**: 825–35

Diabetes Obes Metab

Dapagliflozin response varies between patients

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

1 These authors sought to characterise the efficacy of dapagliflozin on albuminuria and determine whether the albuminuria-lowering effect varies among patients and whether this variability was reproducible.

2 In this crossover trial, people with T2D and albumin:creatinine ratio >11.3 mg/mmol on a stable dose of renin–angiotensin system (RAS) blockers were assigned to 6-week treatment periods with dapagliflozin 10 mg/day or placebo, separated by 6-week washout periods. The primary outcome was change in 24-hour urinary albumin excretion (UAE) rate. Responses to dapagliflozin were correlated to assess reproducibility in individual responses.

3 Thirty-three people completed the study. Compared with placebo, dapagliflozin reduced 24-hour UAE by 36.2% ($P<0.001$). Systolic blood pressure fell by 5.2 mmHg and estimated glomerular filtration rate by 5.3 mL/min. After treatment was discontinued, these changes were reversed.

4 Among the 15 people exposed to dapagliflozin twice, there were large variations in 24-hour UAE between individuals. There was a significant correlation in individuals' first and second responses.

5 The authors conclude that dapagliflozin plus a RAS blocker significantly reduces albuminuria. Albuminuria response to dapagliflozin varies among patients, and this variation is reproducible. The data support personalised therapy approaches.

Petrykiv SI, Laverman GD, de Zeeuw D et al (2017) The albuminuria-lowering response to dapagliflozin is variable and reproducible among individual patients. *Diabetes Obes Metab* 14 Mar [Epub ahead of print]

Diabetologia

Anti-ageing hormone deficiency in T1D

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

1 People with T1D and microalbuminuria are at high risk of cardiovascular disease and end-stage renal disease. The anti-ageing hormone Klotho has protective effects on the endothelium and has antioxidant actions.

2 Levels of circulating soluble Klotho were measured in 33 people with T1D and microalbuminuria and 45 with T1D and normoalbuminuria.

3 People with microalbuminuria had significantly lower levels of serum Klotho than those without microalbuminuria ($P=0.023$). This difference persisted after adjustment for variables such as age and estimated glomerular filtration rate.

4 The authors conclude that, in T1D, microalbuminuria is associated with soluble Klotho deficiency.

Maltese G, Fountoulakis N, Siow R et al (2017) Perturbations of the anti-ageing hormone Klotho in patients with type 1 diabetes and microalbuminuria. *Diabetologia* **60**: 911–4

J Diabetes Complications

CKD awareness in people with T2D

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

1 Chronic kidney disease (CKD) is often silent until the condition is advanced. Despite this, patient awareness of the condition and its related risk factors remains low.

2 This study of 345 adults with T2D examined the relationship(s) between CKD awareness and diagnosed CKD.

3 CKD awareness was defined as a positive response to "has a doctor, nurse or other health professional ever told you that you have a kidney disease?" and/or "have you ever had kidney failure that required dialysis or a kidney transplant?" CKD was diagnosed as estimated glomerular filtration rate (eGFR) ≤59 mL/min.

4 Based on eGFR, 31% of participants had CKD. However, only 63% of these were aware of it.

5 Non-Hispanic blacks, those with a college education, history of myocardial infarction or hypertension, and those with medical insurance were significantly more likely to be aware of CKD. Those with a history of stroke or depression, however, were significantly less likely to be aware of CKD.

6 CKD awareness was lower than diagnosed CKD rates. Strategies aiming to increase CKD awareness may lead to improved health outcomes.

Obadan NO, Walker RJ, Egede LE (2017) Independent correlates of chronic kidney disease awareness among adults with type 2 diabetes. *J Diabetes Complications* **31**: 988–91

Am J Kidney Dis

Diabetes control, ESRD and mortality

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

1 The association of HbA_{1c} with end-stage renal disease (ESRD) was studied in 6165 people with diabetes and chronic kidney disease over a median of 2.3 years. During this time, 957 died and 205 developed ESRD.

2 After multivariate adjustment, there was a higher risk of death with HbA_{1c} levels <42 and ≥75 mmol/mol (<6% and ≥9%). HbA_{1c} levels were not associated with ESRD.

3 Diabetes accounted for >12% of deaths overall and >19% of deaths among those with HbA_{1c} ≥75 mmol/mol (9%).

Navaneethan SD, Schold JD, Jolly SE et al (2017) Diabetes control and the risks of ESRD and mortality in patients with CKD. *Am J Kidney Dis* 10 Feb [Epub ahead of print]

"We are still falling well short of target glycaemic control in young people, and those with type 2 diabetes seem particularly vulnerable to complications."

References from commentary

Bilous R (2008) Microvascular disease: what does the UKPDS tell us about nephropathy? *Diabetic Med* **25**(Suppl 2): 25–9

DCCT/EDIC Research Group (2003) Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* **290**: 2159–67

Mayer-Davis EJ, Lawrence JM, Dabelea D et al (2017) Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. *N Engl J Med* **378**: 1419–29

US Renal Data System (2016) *Annual Data Report 2016: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, MD, USA