Nephropathy

Will young people with type 2 diabetes have renal complications by the time they reach the age of 40?

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A striking and challenging feature of the increased incidence of type 2 diabetes is the number of children and young adults who are developing the condition. In adolescents from a Pacific Islander background in New York, incidence rates are comparable to those for type 1 diabetes seen in white Europid children in the UK (Imperatore et al, 2012). Although in the UK we are not experiencing such high incidence rates of type 2 diabetes in young people at the moment, the increasing number of obese children in the UK (Ells et al, 2008) suggests that it is only a matter of time.

As if the diabetes itself was not enough of a problem, it transpires that these youngsters are developing complications at an alarming rate. The TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) clinical trialists have reported the baseline prevalence and subsequent incidence during a median follow-up of 3.9 years of hypertension and microalbuminuria in 699 young people with recent-onset type 2 diabetes taking part in a randomised controlled trial of three different metformin-based therapeutic interventions (summarised alongside). The baseline prevalence of hypertension was found to be around one third of that seen in the newly diagnosed adults recruited to the UKPDS (The UK Prospective Diabetes Study), but microalbuminuria rates were similar at 6.3% (Bilous, 2008). Rates of hypertension and microalbuminuria approximately tripled during follow-up, with transition rates from normo to microalbuminuria similar to those seen in the UKPDS. Fortunately, creatinine clearances (an estimate of glomerular filtration rate [GFR]) remained >70 mL/min/1.73 m^2 in the vast majority, but, if they continue to behave as the adult UKPDS patients, then many will develop renal impairment and end-stage renal disease before the age of 40, with all of the catastrophic personal and public health consequences that accompany renal replacement therapy.

Does this study provide guidance as to what can be done to avert this scenario? Of the modifiable risk factors explored by the investigators, BMI was a major determinant of hypertension and hyperglycaemia of microalbuminuria. Weight-reducing strategies were notably unsuccessful and may, in any case, be too late once diabetes has developed. Concerted action by government and public health bodies is clearly needed to stem the rising tide of obesity in young people. Glycaemic control offers the best option to prevent microalbuminuria, but based upon the experience of the TODAY investigators they are likely to require multiple therapies including insulin, which may result in further weight gain and potentially exacerbate hypertension.

This paper does not describe the effectiveness of lisinopril in reducing blood pressure and albuminuria, but 205 participants were on the therapy by study end and 79 required the maximal dose of 80 mg/day. This represents a potential problem for the girls in the study as angiotensin-converting enzyme (ACE) inhibitors are contraindicated in pregnancy, and this underlines the limited safe therapeutic options in younger people with type 2 diabetes.

This paper is one of several in the same issue of *Diabetes Care* that deal with the TODAY trial, and each covers separate complications. Because of this approach, several outcomes of interest, such as concomitant retinopathy, are missing from this paper. Moreover, we are not told whether those with both hypertension and albuminuria fared worse, nor are we given any information about changes in estimated creatinine clearance and its relationship to increases in blood pressure and albuminuria.

The overall message is clear and stark, however. Unless we address type 2 diabetes in young people with an active combination of primary prevention of both the disease and its complications, the long-term societal health consequences could be dire.

Bilous R (2008) Microvascular disease: what does the UKPDS tell us about diabetic nephropathy? *Diabet Med* **25**(Suppl 2): S25–9

Ells LJ, Shield JP, Lidstone JS et al (2008) Teesside Schools Health Study: body mass index surveillance in special needs and mainstream school children. *Public Health* **122**: 251–4

Imperatore G, Boyle JP, Thompson TJ et al (2012) Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. *Diabetes Care* **35**: 2515–20

DIABETES CARE

TODAY Study: Investigating microalbuminuria in young people

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

1 Few studies have examined the incidence and progression of microalbuminuria and hypertension in young people with T2D.

2 The TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) study group analysed the effects of diabetes treatment, glycaemic control, sex and ethnicity on microalbuminuria and hypertension in a population of young people with T2D.

3 In total, 699 young people aged 10–17 years were included in the analysis. Participants were randomised to receive metformin, metformin together with rosiglitazone, or metformin with an intensive lifestyle intervention. The trial's primary study outcome was loss of glycaemic control lasting for a minimum of 6 months.

4 Average follow-up was 3.9 years. Of 699 participants, 319 (45.1%) achieved the primary outcome. At the end of the study, 33.8% of the cohort were hypertensive, compared to 11.6% at baseline.

5 Both male sex and high BMI were associated with a significantly increased risk for hypertension.

6 The incidence of microalbuminuria increased from 6.3% at baseline to 16.6% at study end. Elevated HbA_{1c} and loss of glycaemic control were positively associated with microalbuminuria risk.

7 The authors concluded that the prevalence of microalbuminuria and hypertension increased throughout the study period and emphasised the need for obesity prevention to begin at a young age.

TODAY Study Group (2013) Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. *Diabetes Care* **36**: 1735–41

DIABETES CARE

Renal risk stratification: 5-year risk models for ESRD

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

1 Diabetes is the leading cause of end-stage renal disease (ESRD) in many countries around the world. Accurate risk prediction could increase early detection and aid prevention efforts.

2 The authors aimed to develop and validate a risk model that could measure the 5-year risk of ESRD (such as renal transplantation, death from renal failure and dialysis) in a primary care cohort with T2D and no existing ESRD.

3 Participants with T2D (n=25 736) were identified from the New Zealand Diabetes Cohort Study. Cox proportional hazards models were applied to develop risk models, which were subsequently validated in a separate cohort.

4 Individuals were followed up for a total of 11 years. During this time, there were 637 (2.5%) ESRD events.

5 Models that considered age, sex, ethnicity, diabetes duration, HbA_{1c}, previous history of cardiovascular disease, smoking, systolic blood pressure, albuminuria and serum creatinine displayed a good predictive performance with high levels of discrimination and calibration in both the derivation cohort and the validation cohort (n=5877; C-statistics 0.89–0.92).

6 The authors concluded that 5-year renal risk models considering the above factors displayed a sound predictive performance in two large primary care populations of people with T2D.

Elley CR, Robinson T, Moyes SA et al (2013) Derivation and validation of a renal risk score for people with type 2 diabetes. *Diabetes Care* 25 Jun [Epub ahead of print]

DIABETES CARE

Microvascular complications: Effects of glucose control

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

1 The authors sought to compare the effects of different glucose-control strategies on the incidence of myocardial infarction (MI) and nephropathy in a population of people with T2D.

2 In total, 58 000 adults with T2D were followed-up. Logistic marginal structural models were applied to assess the time-hazards associated with each method of glucose control.

3 After adjustment for variables such as age, sex and BMI, more aggressive glucose-control strategies were significantly associated with a decreased incidence and progression of albuminuria. Aggressive glucose control was not associated with a reduced incidence of MI or nephropathy.

4 The authors concluded that aggressive glucose control strategies have varied effects on the incidence of microvascular complications.

Neugebauer R, Fireman B, Roy JA et al (2013) Impact of specific glucose-control strategies on microvascular and macrovascular outcomes in 58,000 adults with type 2 diabetes. *Diabetes Care* [Epub ahead of print]

BMJ OPEN

Does dietary protein restriction slow nephropathy progression?

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

1 The authors performed a systematic review and meta-analysis to determine the effect of a low-protein diet on kidney function in people with diabetes-related nephropathy.

2 MEDLINE, EMBASE, Cochrane Library and ClinicalTrials.gov were searched to identify 13 randomised controlled trials comprising 779 participants for inclusion.

3 A low-protein diet was significantly associated with an improvement in glomerular filtration rate (GFR) regardless of diabetes type, length of intervention period and stage of nephropathy (5.82 mL/min/1.73 m^2, 95% CI, 2.30–9.33, I^2=92%; n=624), but only when participants had considerable compliance to their diet.

4 The authors concluded that a low-protein diet was beneficial for diabetic nephropathy, with no adverse effects observed within the cohort.

Nezu U, Kamiyama H, Kondo Y et al (2013) Effect of low-protein diet on kidney function in diabetic nephropathy: meta-analysis of randomised controlled trials. *BMJ Open* **3**: e002934

DIABETOLOGIA

Does RAAS blockade affect renal inflammatory pathways?

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

1 The aim of this study was to investigate the effects of renin–angiotensin–aldosterone system (RAAS) blockade on hyperglycaemia-induced urinary cytokine/chemokine excretions.

2 Renal haemodynamic function and urinary cytokine/chemokine levels were measured in people with T1D (n=27) before and after treatment with aliskiren.

3 Hyperglycaemia-induced increases in filtration fraction, urinary fibroblast growth factor-2 (FGF2), IFN-a2 and macrophage-derived chemokine (MDC) were observed prior to aliskiren therapy. After aliskiren therapy, there was no change in filtration fraction or biomarker production in response to hyperglycaemia.

Cherney DZ, Reich HN, Scholey JW et al (2013) The effect of aliskiren on urinary cytokine/chemokine responses to clamped hyperglycaemia in type 1 diabetes. *Diabetologia* **56**: 2308–17

"Aggressive glucose control was not associated with a reduced incidence of myocardial infarction or nephropathy."