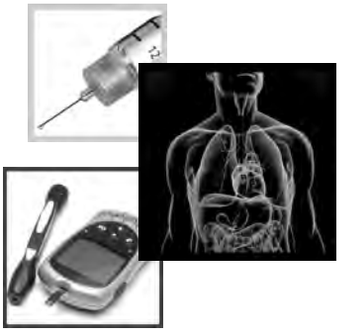
EDITORIAL

Diabetes Management



Can increased albumin excretion provide evidence of early renal and cardiovascular disease in adolescents with Type 1 diabetes?

M Loredana Marcovecchio[1] & David B Dunger*[,2]

"Several studies have shown that premature atherosclerosis represents the main cause of morbidity and mortality in patients with T1D."

Diabetic nephropathy (DN) and cardiovascular disease (CVD) are among the most common vascular complications of Type 1 diabetes (T1D) that negatively influence the long-term prognosis of young people with that condition [1]. Several studies have shown that premature atherosclerosis represents the main cause of morbidity and mortality in patients with T1D [2]. In longitudinal cohorts of adults with T1D from the USA and Europe, the incidence of coronary events has been found to be around 16% after 10 years of diabetes duration, significantly contributing to mortality [2]. This is confirmed by data from the Diabetes UK cohort of 23,751 patients with T1D, where by the age of 20–39 years, the standardized mortality rate for coronary artery disease was increased tenfold in men and 40-fold in women [3]. Recent data from the Scottish Registry Linkage Study have confirmed a high mortality associated with T1D, with an age-adjusted incidence risk rate for a first CVD event of 3.0 (95% CI: 2.4–3.8) in females and 2.3 (95% CI: 2.0–2.7) in males when compared to the non-diabetic population, and highlighted a higher rate of CVD events in subjects younger than 40 years [4]. Risk for CVD in patients with T1D seems to be strongly associated with the presence of DN, being tenfold greater for patients with DN compared with those without this complication [5]. This is also highlighted by recent studies reporting that, in the absence of renal complications, mortality in patients with T1D is similar to that in the general population, whereas it significantly increases in the presence of microalbuminuria or more advanced stages of DN [6,7].

DN is a common microvascular complication in patients with T1D, which manifests with progressive increases in urinary albumin excretion, along with changes in glomerular filtration rate, ultimately

KEYWORDS
• adolescents • albumin excretion • cardiovascular disease • stratified medicine • Type 1 diabetes

[1]Department of Paediatrics, University of Chieti, Chieti, Italy
[2]Department of Paediatrics, University of Cambridge, MRL Wellcome Trust-MRC Institute of Metabolic Science, NIHR Cambridge Comprehensive Biomedical Research Centre, Cambridge, UK
*Author for correspondence: Tel.: +44 1223 336886; Fax: +44 1223 336996; dbd25@cam.ac.uk

Future Medicine part of fsg

leading to the development of end-stage renal disease, for which DN is the main cause in developed countries [8]. More than 20 years ago, Borch-Johnsen *et al.* reported that urinary albumin excretion in the proteinuric range was a strong predictor of CVD mortality in patients with T1D [5]. Subsequent studies have not only confirmed this finding [9], but also shown that small increases in albumin excretion, in the normal and microalbuminuric range, predict CVD risk in adults with T1D as well as in non-diabetic populations [10,11]. High normal values of urinary albumin excretion have been directly associated with increased risk of stroke, hypertension and early development of atherosclerosis [12]. A potential factor linking increased albumin excretion and CVD is endothelial dysfunction, which is considered to be the initiating insult leading to organ/tissue damage in the context of diabetes [13]. Taken together, these data suggest that in adults with T1D albumin excretion should be considered a continuous risk factor for both renal and cardiovascular complications.

Is albumin excretion associated with CVD in adolescents with T1D?

Considering urinary albumin excretion as a continuous variable could be particularly pertinent to the study of young people with T1D, where abnormal albumin excretion may not become clinically evident as microalbuminuria until after puberty [8]. Based on data from longitudinal studies, microalbuminuria develops in 10–26% of adolescents with T1D after a 10–20-year disease duration, but this complication tends to be rare before puberty [14–16]. However, the same studies have shown that early increases in urinary albumin excretion, within the normal range, may occur during the first years after diagnosis [15]. In the Oxford Regional Prospective Study, a prospective study following around 500 young people with childhood-onset T1D, an albumin–creatinine ratio (ACR) in the upper tertile of the normal range at the age of 11–15 years predicted up to 85% of subjects who developed microalbuminuria in the following years, and all those who developed macroalbuminuria [14].

International guidelines recommend an annual assessment of albumin excretion in adolescents with T1D as the standard method for monitoring the development of DN [17], and based on the available data on adults with diabetes, it could also provide important information about CVD risk. However, so far data on the relationship between early increases in albumin excretion and CVD during adolescence are limited. Cohort studies of adolescents with T1D indicate that during adolescence increased urinary albumin excretion, even below the microalbuminuria range, can be associated with dyslipidemia, raised blood pressure, insulin resistance and presence of CVD risk factors in the parents, therefore suggesting a potential link between albumin excretion and risk for CVD [8].

> "Alarmingly, it has been reported that up to 86% of young people with T1D have at least one modifiable CVD risk factor, 45% at least two and 15% at least three…"

Alarmingly, it has been reported that up to 86% of young people with T1D have at least one modifiable CVD risk factor, 45% at least two and 15% at least three, and these CVD risk factors tend to track from childhood/adolescence to adulthood and negatively influence the long-term prognosis [18]. In addition, although hard end points such as stroke and ischemic heart disease are not evident during childhood and adolescents with T1D, early subclinical structural and functional vascular abnormalities have been repeatedly reported [8]. Carotid intima-media thickness (cIMT) has been shown to be increased in children with T1D when compared with age-matched controls [19]. Similarly, flow-mediated dilatation (FMD) and arterial stiffness are additional surrogate markers of CVD, which has been shown to be abnormal in T1D patients as young as 10 years of age [19,20]. These alterations appear to be even more marked in subjects with signs of involvement of the renal microvasculature, such as microalbuminuria [21], although data in this context are still limited and mainly based on small sample sizes. Clarifying these associations would be of clinical relevance, given that adult CVD has its roots during childhood and adolescence in at-risk populations, such as those with T1D [18].

Recent data from the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT), the first multicenter, multinational, randomized placebo-controlled trial assessing the efficacy of ACE inhibitors (quinapril) and statins (atorvastatin) in adolescents with T1D and increased albumin excretion has provided further insights into the link between urinary albumin excretion and early cardiovascular

risk [22]. During the screening phase of the trial, two sets of three early-morning urine samples have been collected from more the 3500 adolescents aged 10–16 years from the UK, Canada and Australia for the assessment of ACR. Tertiles of ACR have been generated, with the upper tertile (top 30%) defining adolescents at 'high risk' for vascular complications, whereas adolescents with ACR in the middle and lower tertiles are considered to be at 'low risk'. Around 740 of these adolescents underwent further investigations as part of the baseline assessment of AdDIT, including circulating markers of renal and CVD markers as well as direct measures of vascular function and structure, such as cIMT, FMD and pulse wave velocity. Interestingly, adolescents with urinary albumin excretion levels in the top 30% of the observed distribution showed increased glomerular filtration rates as well as increased cardiovascular risk, as indicated by higher lipid levels, mainly non-HDL-cholesterol and increased arterial stiffness, as reflected by higher values of pulse wave velocity, when compared with adolescents with T1D and lower ACR [22]. These 'high-risk' adolescents with raised albumin excretion have been entered into AdDIT to assess the efficacy of ACE inhibitors, statins or their combination in improving their renal and cardiovascular profiles. The vascular re-assessment at the end of the AdDIT trial will allow exploration of the hypothesis as to whether the early detected abnormalities in renal and cardiovascular parameters are reversible with early treatments. Overall, these data suggest that differentiating between low-normal and high-normal urinary albumin excretion may aid in renal and cardiovascular risk stratification, and promote prevention and early treatment strategies.

Conclusion

The recent results from AdDIT confirm previous data on the link between increases albumin excretion and CVD in adult populations with T1D, supporting the concept that early increases in albumin excretion during adolescence are markers not only of renal impairment but could reflect a more general vascular damage, and thus predict cardiovascular risk. Therefore, monitoring of albumin excretion rates as well as HbA1c during adolescence may be critical in identifying individuals where targeted interventions, such as improved glycemic control as well as renoprotective strategies using ACE inhibitors and statins, could reduce the long-term morbidity and mortality associated with the development of DN and CVD.

Financial & competing interests disclosure

AdDIT is funded by Diabetes UK, Juvenile Diabetes Research Foundation and British Heart Foundation. The authors also acknowledge support from the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Secrest AM, Becker DJ, Kelsey SF, Laporte RE, Orchard TJ. Cause-specific mortality trends in a large population-based cohort with long-standing childhood-onset Type 1 diabetes. *Diabetes* 59(12), 3216–3222 (2010).

2 Orchard TJ, Costacou T, Kretowski A, Nesto RW. Type 1 diabetes and coronary artery disease. *Diabetes Care* 29(11), 2528–2538 (2006).

3 Laing SP, Swerdlow AJ, Slater SD *et al.* Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia* 46(6), 760–765 (2003).

4 Livingstone SJ, Looker HC, Hothersall EJ *et al.* Risk of cardiovascular disease and total mortality in adults with Type 1 diabetes: Scottish registry linkage study. *PLoS Med.* 9(10), e1001321 (2012).

5 Borch-Johnsen K, Kreiner S. Proteinuria: value as predictor of cardiovascular mortality in insulin dependent diabetes mellitus. *Br. Med. J. (Clin. Res. Ed.)* 294(6588), 1651–1654 (1987).

6 Groop PH, Thomas MC, Moran JL *et al.* The presence and severity of chronic kidney disease predicts all-cause mortality in Type 1 diabetes. *Diabetes* 58(7), 1651–1658 (2009).

7 Schnell O, Cappuccio F, Genovese S, Standl E, Valensi P, Ceriello A. Type 1 diabetes and cardiovascular disease. *Cardiovasc. Diabetol.* 12(1), 156 (2013).

8 Marcovecchio ML, Tossavainen PH, Dunger DB. Status and rationale of renoprotection studies in adolescents with Type 1 diabetes. *Pediatr. Diabetes* 10(5), 347–355 (2009).

9 Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. *BMJ* 313(7060), 779–784 (1996).

10 Klausen K, Borch-Johnsen K, Feldt-Rasmussen B *et al.* Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 110(1), 32–35 (2004).

11 Gerstein HC, Mann JF, Yi Q *et al.* Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 286(4), 421–426 (2001).

12 Abdelhafiz AH, Ahmed S, El Nahas M. Microalbuminuria: marker or maker of cardiovascular disease. *Nephron. Exp. Nephr.* 119(Suppl. 1), e6–e10 (2011).

13 Schalkwijk CG, Stehouwer CD. Vascular complications in diabetes mellitus: the role of endothelial dysfunction. *Clin. Sci. (Lond.)* 109(2), 143–159 (2005).

14 Dunger D, Schwarze C, Cooper J *et al.* Can we identify adolescents at high risk for nephropathy before the development of microalbuminuria? *Diabet. Med.* 24, 131–136 (2007).

15 Schultz CJ, Neil HA, Dalton RN, Dunger DB. Risk of nephropathy can be detected before the onset of microalbuminuria during the early years after diagnosis of Type 1 diabetes. *Diabetes Care* 23(12), 1811–1815 (2000).

16 Stone ML, Craig ME, Chan AK, Lee JW, Verge CF, Donaghue KC. Natural history and risk factors for microalbuminuria in adolescents with Type 1 diabetes: a longitudinal study. *Diabetes Care* 29(9), 2072–2077 (2006).

17 Donaghue KC, Chiarelli F, Trotta D, Allgrove J, Dahl-Jorgensen K. ISPAD clinical practice consensus guidelines 2006–2007. Microvascular and macrovascular complications. *Pediatr. Diabetes* 8(3), 163–170 (2007).

18 Mcveigh GE, Gibson W, Hamilton PK. Cardiovascular risk in the young Type 1 diabetes population with a low 10-year, but high lifetime risk of cardiovascular disease. *Diabet. Obes. Metabol.* 15, 198–203 (2013).

19 Jarvisalo MJ, Raitakari M, Toikka JO *et al.* Endothelial dysfunction and increased arterial intima-media thickness in children with Type 1 diabetes. *Circulation* 109(14), 1750–1755 (2004).

20 Urbina EM, Wadwa RP, Davis C *et al.* Prevalence of increased arterial stiffness in children with Type 1 diabetes mellitus differs by measurement site and sex: the SEARCH for Diabetes in Youth Study. *J. Pediatr.* 156(5), 731–737 (2010).

21 Smith A, Karalliedde J, De Angelis L, Goldsmith D, Viberti G. Aortic pulse wave velocity and albuminuria in patients with Type 2 diabetes. *J. Am. Soc. Nephrol.* 16(4), 1069–1075 (2005).

22 Marcovecchio ML, Woodside J, Jones T *et al.* Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT): urinary screening and baseline biochemical and cardiovascular assessments. *Diabetes Care* 37(3), 805–813 (2014).