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SHORT COMMUNICATION

Urinary podocyte-derived microparticles in youth with type 1 and type 2 diabetes

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Abstract

Aims/hypothesis The release of podocyte-derived microparticles into the urine may reflect early kidney injury in diabetes. We measured the urinary excretion of podocyte-derived microparticles in youth with type 1 and type 2 diabetes, and related the values to blood pressure, renal function and blood glucose levels.

Methods Cross-sectional, exploratory analysis of urine samples and clinical data from youth with type 1 ($n = 53$) and type 2 ($n = 50$) diabetes was carried out. Urinary podocyte-derived microparticle numbers, measured by flow cytometry, were assessed in relation to measures of blood glucose levels and renal function.

Results Podocyte-derived microparticle excretion (MPE) normalised to urinary creatinine (MP/UCr) was higher in type 1 vs type 2 diabetes (median [IQR] MP/UCr: 7.88 [8.97] vs 1.84 [8.62]; $p < 0.0001$), despite the type 2 diabetes group having higher blood pressure (systolic blood pressure, median [range]: 124 [110–154] vs 114 [94–143] mmHg) and higher proportions of microalbuminuria (44.0% vs 13.2%), but shorter time since diabetes diagnosis (median [range]: 1.2 [0.0–7.0] vs 6.4 [2.0–13.9] years), than the type 1 diabetes cohort. MPE in youth with type 1 diabetes was associated with blood glucose ($p = 0.01$) and eGFR ($p = 0.03$) but not HbA_{1c}, systolic or diastolic blood pressure or urine albumin/creatinine ratio. After adjustment for age at baseline, duration of diabetes, sex and BMI, the association with eGFR remained significant ($p = 0.04$). No associations were found between MPE and these clinical variables in youth with type 2 diabetes.

Conclusions/interpretation Significant associations between podocyte MPE, blood glucose levels and eGFR were observed in youth with type 1 diabetes but not in those with type 2 diabetes, notwithstanding increased renal pathology in the type 2 diabetes cohort. These findings suggest that podocyte injury differs in the two diabetes cohorts.

Dylan Burger, Farid H. Mahmud and Alison B. Dart contributed equally to this study.

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Research in context

What is already known about this subject?

- Podocyte-derived microparticles are released under conditions of hyperglycaemia and mechanical strain and may be an early marker of diabetic kidney disease (DKD)
- DKD onset and progression in youth is associated with risk of cardiovascular disease and other diabetes-related complications

What is the key question?

- What is the pattern of podocyte microparticle excretion (MPE) and how does this relate to clinical variables in adolescents with type 1 and type 2 diabetes?

What are the new findings?

- Podocyte-derived MPE was found to be higher in individuals with type 1 diabetes as compared with those with type 2 diabetes, despite type 2 diabetic participants having more evidence of renal disease
- In individuals with type 1 diabetes, podocyte-derived MPE correlated with blood glucose and eGFR, while these associations were not observed in individuals with type 2 diabetes

How might this impact on clinical practice in the foreseeable future?

- The mechanism(s) responsible for podocyte injury may differ between adolescents with type 1 and type 2 diabetes. Podocyte-derived microparticles may be more useful markers of early diabetic kidney disease in adolescents with type 1 diabetes, although longitudinal follow-up studies are needed to support this

Keywords Albuminuria · Blood pressure · eGFR · Hyperglycaemia · Microparticles · Podocytes · Type 1 diabetes · Type 2 diabetes · Urine · Youth

Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACR	Albumin/creatinine ratio
AdDIT	Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial
MPE	Microparticle excretion
MP/UCr	Microparticle excretion normalised to urinary creatinine

Introduction

Early diabetic kidney disease (DKD) is characterised by ultrastructural changes, including mesangial matrix expansion and loss of podocytes, which may precede increases in albumin excretion rate [1]. Many studies of diabetic nephropathy have confirmed that the podocyte is an early cellular target of injury [2].

Microparticles are cell-membrane-derived vesicles released by cells in response to various stimuli [3]. In vitro, podocytes release higher concentrations of microparticles under high glucose concentrations and mechanical strain [4]. In murine models of diabetes, the urinary excretion rate of podocyte-derived microparticles increases before there is an increase in albumin excretion rate [4]. Recently, we reported an increase in podocyte-derived microparticles in the urine of adults with type 1 diabetes, in the absence of microalbuminuria [5]. These data suggest that podocyte-derived microparticles may be early markers of kidney injury.

Our aim was to evaluate podocyte-derived microparticle excretion (MPE) in youth with type 1 and type 2 diabetes and relate MPE values to clinical and laboratory variables. We hypothesised that MPE would be higher in youth with type 2 diabetes, as compared with those with type 1 diabetes, given that type 2 diabetes is associated with a more severe nephropathy phenotype [6]. We further hypothesised that podocyte MPE would increase with higher blood glucose levels, GFR and blood pressure.

Methods

Individuals with type 1 diabetes were recruited from the Canadian arm of the observational Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) [7]. These participants were eligible for the AdDIT RCT, but declined to participate in the drug trial. Type 2 diabetes participants were recruited from the Improving Renal Complications in Adolescents With Type 2 Diabetes Through REsearch (iCARE) study [8]. A current diagnosis of cancer was an

exclusion criteria. Study participants gave informed consent. Studies were approved by the appropriate institutional review board at the Hospital for Sick Children and University of Manitoba.

In the type 1 diabetes cohort, first morning urine was used for microparticle analysis. For the type 2 diabetes cohort, random urine was obtained and used. Urine samples (200 μl) were processed by sequential centrifugation at 4°C, first at 2500 *g* for 10 min, followed by 20,000 *g* for 20 min. A single venous blood sample was also taken at the time of urine collection for the analysis of blood glucose levels and HbA_{1c}. HbA_{1c} was measured by enzymatic assay (Architect Analyzer; Abbott Diagnostics, USA).

Quantification of podocyte microparticles was performed using our nanoscale flow cytometry approach, as previously described [4, 5]. Podocyte origin was confirmed by co-staining with an anti-podoplanin phycoerythrin (PE)-conjugated antibody (1:25, Biolegend, CA, USA). Samples were analysed by nanoscale flow cytometry (CytoFLEX S, Beckman Coulter, USA) and ApogeeMix beads were used for size calibration (Catalogue no. 1493; Apogee Flow Systems, UK). Microparticles were defined as particles between ~100 and 1000 nm in diameter. Levels of urinary microparticles were normalised to urinary creatinine levels and podocyte microparticle levels were expressed as number/μmol creatinine, with an inter-assay variability of 19%.

Albumin/creatinine ratio (ACR) was measured in fresh first morning urine samples in both groups. Normal albumin excretion was defined as ACR <2.0 mg/mmol, whilst microalbuminuria was defined as ACR of 2.0–20 mg/mmol. eGFR was calculated using the cystatin-c based Larsson equation [7] for individuals with type 1 diabetes, and the validated iCARE equation was used for type 2 diabetic participants [9]. Hyperfiltration was defined as an eGFR >135 ml min^{-1} [1.73 m]$^{-2}$ [7]. Hypertension was defined as per the American Academy of Pediatrics (AAP) paediatric guidelines [10]. Systolic and diastolic blood pressure percentiles were calculated using the Pediatric Canadian Endocrine Shiny apps calculator, which uses the American Academy of Pediatrics 2017 guidelines (https://apps.cpeg-gcep.net/BPz_cpeg/, accessed July 2019).

As per institutional guidelines, individuals with type 2 diabetes who presented with clinical features not consistent with diabetic nephropathy underwent a renal biopsy.

Statistical analysis For group comparisons, normality of distribution was assessed by the Shapiro–Wilk test. Normally distributed variables were assessed by two-sample *t* tests, whilst non-normally distributed variables were assessed by the Wilcoxon test. Proportions were assessed using Fisher's exact test. MPE values were compared using the Mann–Whitney test. The χ^2 test was used to assess the independence of proportions of hyperfiltration and microalbuminuria. Spearman's rank correlation coefficient was used to assess relationships between MPE values, blood glucose levels, eGFR, systolic and diastolic blood pressure, urine ACR and, in the type 2 diabetes participants, 24 h ambulatory blood pressure monitoring (ABPM) loads (per cent of time >95th percentile). Single and multiple linear regression analysis was used to assess the associations between podocyte microparticle number and either blood glucose or eGFR with covariates. Multiple linear regression covariates included age at baseline (years), diabetes duration (years), sex and BMI (kg/m^2). The regression coefficient parameters, β ± SEM, represent the change in MPE rate associated with a 1-unit increase in the indicated independent variable. A p value <0.05 was considered statistically significant.

Results

Youth with type 2 diabetes had shorter diabetes duration, higher blood pressure, higher frequency of microalbuminuria and higher BMI compared with type 1 diabetes participants, with no differences seen in HbA_{1c} levels (Table 1).

We observed that MPE normalised to urinary creatinine (MP/UCr) was significantly higher in the type 1 diabetes compared with type 2 diabetes group (median [IQR] MP/UCr: 7.88 [8.97] vs 1.84 [8.62]; $p < 0.0001$; Fig. 1a). We did not observe any differences in MPE values between male and female participants in either diabetes group (electronic supplementary material [ESM] Fig. 1). There was a positive correlation between fasting blood glucose levels and MPE in type 1 diabetes ($r = 0.28$, $p = 0.04$; Fig. 1b and ESM Table 1), while no relationship was observed with HbA_{1c} ($r = 0.21$, $p = 0.12$; ESM Table 1). On multivariate regression analysis, prior to adjustment, an association was seen with blood glucose (β = 0.49 [95% CI 0.10, 0.88]; $p = 0.01$), which weakened after adjustment for age, duration, sex and BMI (0.38 [95% CI −0.05, 0.81]; $p = 0.08$; ESM Table 2). In individuals with type 2 diabetes, there was no relationship between MPE and blood glucose levels (ESM Tables 1 and 2).

There was a modest correlation between MPE and eGFR values in the participants with type 1 diabetes ($r = 0.25$, $p = 0.07$; Fig. 1c and ESM Table 1). In multivariate regression analysis, eGFR was significantly associated with MPE in individuals with type 1 diabetes before (β = 0.06 [95% CI 0.008, 0.12]; $p = 0.03$) and after adjustment for age, duration, sex and BMI (β = 0.07 [95% CI 0.005, 0.13]; $p = 0.04$; ESM Table 2). In contrast, there was no relationship between the MPE and eGFR values in type 2 diabetes (ESM Table 1 and ESM Table 2).

There was no relationship between podocyte MPE and the ACR in participants with type 1 diabetes ($r = 0.21$, $p = 0.12$; ESM Table 1). However, there was a relationship between podocyte MPE and ACR in type 1 diabetes when the analysis was restricted to individuals with normal ACR values ($r = 0.48$,

Table 1 Baseline characteristics of study cohort

Clinical characteristic	Youth with type 1 diabetes ($n = 53$)	Youth with type 2 diabetes ($n = 50$)	p value
Age, years	14.7 ± 1.6	14.6 ± 2.2	0.850
Sex, male, *n* (%)	26 (49)	17 (34)	0.140
Ethnicity, *n* (%)			
White	32 (60.4)	0 (0.0)	
First Nations	0 (0.0)	46 (92.0)	
Metis	0 (0.0)	2 (4.0)	
Black	6 (11.3)	0 (0.0)	
South Asian	3 (5.7)	0 (0.0)	
South-East Asian	4 (7.5)	0 (0.0)	
Mexican	0 (0.0)	1 (2.0)	
Other	8 (15.1)	1 (2.0)	
Maternal diabetes status, *n* (%)	ND		
Normoglycaemic		22 (44)	
Pregestational diabetes		22 (44.0)	
Gestational diabetes		6 (12)	
HbA_{1c}			0.800
mmol/mol	68.3 (43.2–123.0)	66.2 (33.3–133.9)	
%	8.4 (6.1–13.4)	8.2 (5.2–14.4)	
Time since diabetes diagnosis, years	6.4 (2.0–13.9)	1.2 (0.0–7.0)	<0.001
BMI, kg/m^2	21.5 (14.7–30.5)	30.9 (21.4–45.5)	<0.001
BMI *z* score	0.6 ± 1.0	2.8 ± 1.0	<0.001
SBP, mmHg	114.0 (94.0–143.0)	124.0 (110.0–154.0)	<0.001
SBP percentile	0.65 ± 0.23	0.86 ± 0.13	<0.001
DBP, mmHg	68.0 (51.0–83.0)	71.5 (60.0–98.0)	0.020
DBP percentile	0.58 ± 0.20	0.70 ± 0.24	0.020
Blood pressure classification, *n* (%)			0.003[a]
Normal	35 (63.0)	8 (32.0)	0.007
Elevated	14 (26.4)	7 (28.0)	1.000
Stage 1 hypertension	3 (5.7)	6 (24.0)	0.030
Stage 2 hypertension	1 (1.9)	4 (16.0)	0.030
ACR, mg/mmol	0.8 (0.1–7.0)	2.1 (0.0–66.7)	0.170
Microalbuminuria, *n* (%)[b]	7 (13.2)	22 (44.0)	0.001[c]
eGFR, ml min^{-1} [1.73 m]$^{-2}$	140.3 ± 32.6	147.1 ± 22.2	0.150
Hyperfiltration, *n* (%)[d]	25 (47)	30 (60)	0.090[c]
Microscopic haematuria (>5 RBCs on microscopy), *n* (%)	ND	3 (6)	
Renal biopsy performed, *n* (%)	ND	4 (8)[e]	

Values are expressed as mean ± SD for normally distributed variables or as median (minimum–maximum) for non-normally distributed, as determined by the Shapiro–Wilk test, unless stated otherwise

For analysis, normally distributed variables (age, eGFR, BMI *z* scores and blood pressure percentiles) were compared using two-sample *t* tests, while non-normally distributed variables (HbA_{1c}, ACR, BMI, time since diabetes diagnosis and blood pressure values) were compared using the two-sample Wilcoxon test

[a] Blood pressure classification was analysed using Fisher's exact test

[b] Microalbuminuria was defined as ACR >2 mg/mmol

[c] Microalbuminuria and filtration status were analysed by χ^2 test

[d] Hyperfiltration was defined as eGFR >135 ml min^{-1} [1.73 m]$^{-2}$. Data are presented as the number of individuals with hyperfiltration divided by the number of individuals with normal filtration, shown as a percentage

[e] Of these four participants, $n = 3$ had IgA nephropathy and $n = 1$ had diabetic nephropathy

DBP, diastolic blood pressure; ND, no data; RBC, red blood cell; SBP, systolic blood pressure

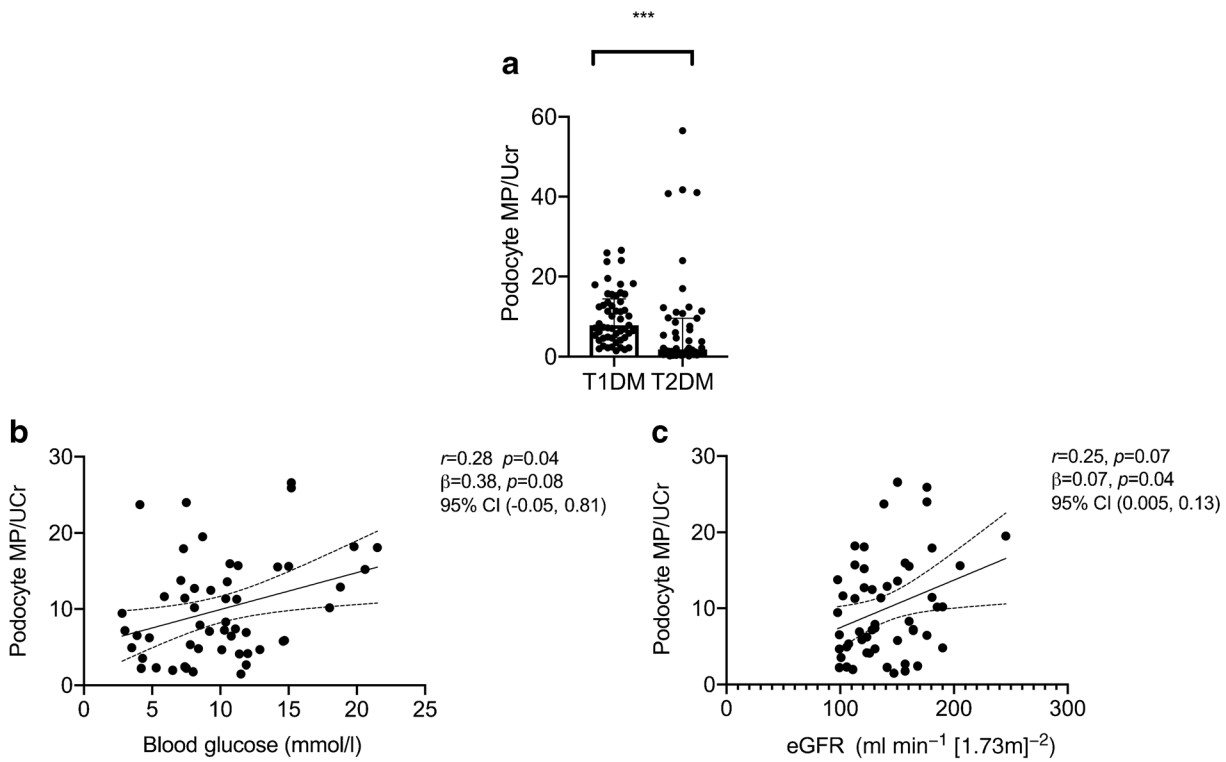

Fig. 1 Podocyte microparticles (MPs) and their relationship to clinical variables. (**a**) Podocyte MP numbers in adolescents with type 1 diabetes (T1DM) vs type 2 diabetes (T2DM). (**b**, **c**) The relationship between podocyte MPE and blood glucose levels (**b**) and eGFR (**c**) in adolescents with T1DM. ***$p < 0.001$

$p = 0.0029$; data not shown). In type 2 diabetes, there was no relationship between the MPE and ACR (ESM Tables 1 and 2).

We saw no relationship between MPE and spot blood pressure measurements in the type 1 or type 2 diabetes cohort (ESM Tables 1 and 2). However, in individuals with type 2 diabetes with hyperfiltration ($r = 0.41$, $p = 0.04$) or with microalbuminuria ($r = 0.41$, $p = 0.05$), a relationship with sleep systolic load and sleep diastolic load upon ABPM was observed, respectively (ESM Fig. 2).

Discussion

This exploratory study evaluated a novel targeted biomarker of podocyte injury in youth with diabetes. We focused on measures of podocyte injury because both experimental and clinical observations implicate the podocyte in the pathogenesis of early and progressive diabetic nephropathy [11, 12]. Interestingly, we observed higher podocyte MPE in participants with type 1 diabetes as compared with individuals with type 2 diabetes, which is contrary to our initial hypothesis. We observed no effect of sex on podocyte MPE, although male sex has been shown to be a risk factor for diabetic nephropathy [13]. This disparity in findings could be explained by the fact that our study examined individuals prior to the development of significant diabetic nephropathy. However, previous studies have also not shown a sex-related difference in podocyte MPE [5].

Potential explanations for the decreased podocyte MPE in our type 2 diabetes cohort may include decreased nephron endowment secondary to adverse intrauterine environment stressors, as 12% of our participants with type 2 diabetes were born to mothers with diabetes in pregnancy, which has been shown to affect nephron number [14]. Non-diabetic glomerular disease was also observed in this cohort and in youth with type 2 diabetes in previous studies, which may have an impact on podocyte function [15]. Additionally, nephropathy in type 2 diabetes is known to be associated with significant pathological structural heterogeneity, with more advanced tubulo-interstitial and vascular lesions, as compared with type 1 diabetes [16].

The risk of diabetic nephropathy is related to hyperglycaemia, and in vitro and in vivo studies of podocytes show that exposure to high glucose concentrations increases microparticle release [4, 17]. We observed a positive correlation between glucose levels and MPE in individuals with type 1 diabetes, although there was no relationship with HbA_{1c}, suggesting that acute excursions in blood glucose may be an important determinant of microparticle release. This is consistent with our previous observations of increased podocyte MPE values with acute hyperglycaemia in type 1 diabetes [5].

We also observed a positive relationship between eGFR and podocyte microparticle values in type 1 diabetic participants,

but not in individuals with type 2 diabetes, suggesting that podocyte microparticle values are more dependent on eGFR in type 1 diabetes. In vitro studies of podocytes have shown that cyclical mechanical strain promotes release of microparticles [4]. Although hyperfiltration rates between the groups were not different, it is possible that mechanical strain on podocytes differed due to variable renin-angiotensin-aldosterone system (RAAS) activation, intrarenal haemodynamic function differences and, possibly, advanced glycosylation end-product formation [18]. Blood pressure can also contribute to mechanical strain; however, we did not observe a relationship between MPE and blood pressure in our type 1 diabetic cohort. This may have been due to the relatively low number of participants with hypertension in our study. In the type 2 diabetes group, using ABPM data, we did observe relationships between MPE values and sleep systolic and diastolic loads, which are important blood pressure parameters.

Overall, we did not observe a relationship between urinary albumin excretion and podocyte MPE in either of the two cohorts; however, there was a correlation when the analysis was restricted to participants with type 1 diabetes and ACR values in the normal range. This suggests that podocyte MPE may be an early marker of injury that occurs prior to albuminuria, as reported in animal models [4].

Strengths of this report include evaluation of well-characterised adolescent cohorts. The main limitation of our study is that participants did not undergo a kidney biopsy and, therefore, we could not relate MPE to kidney morphology. Another potential confounder was the different urine collection times between the two groups.

In conclusion, urinary podocyte MPE was increased in youth with type 1 diabetes as compared with youth with type 2 diabetes. The relationships of podocyte MPE rate with blood glucose levels and eGFR were stronger in the type 1 diabetes cohort vs the type 2 diabetes cohort. Further longitudinal follow-up studies will be necessary to determine if early podocyte MPE values are predictive of the progression of chronic kidney disease.

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Data availability Data used for the analysis is available on request, by contacting the corresponding author.

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Contribution statement All authors made substantial contributions to the conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and were involved in the final approval prior to publication. KMS is the guarantor of this work.

References

1. Fioretto P, Mauer M (2007) Histopathology of diabetic nephropathy. Semin Nephrol 27(2):195–207. https://doi.org/10.1016/j.semnephrol.2007.01.012
2. Susztak K, Raff AC, Schiffer M, Bottinger EP (2006) Glucose-induced reactive oxygen species cause apoptosis of podocytes and podocyte depletion at the onset of diabetic nephropathy. Diabetes 55(1):225–233
3. Shah R, Patel T, Freedman JE (2018) Circulating extracellular vesicles in human disease. N Engl J Med 379(10):958–966. https://doi.org/10.1056/NEJMra1704286
4. Burger D, Thibodeau JF, Holterman CE, Burns KD, Touyz RM, Kennedy CR (2014) Urinary podocyte microparticles identify prealbuminuric diabetic glomerular injury. J Am Soc Nephrol 25(7):1401–1407. https://doi.org/10.1681/ASN.2013070763
5. Lytvyn Y, Xiao F, Kennedy CR et al (2017) Assessment of urinary microparticles in normotensive patients with type 1 diabetes. Diabetologia 60(3):581–584. https://doi.org/10.1007/s00125-016-4190-2
6. Dart AB, Martens PJ, Rigatto C, Brownell MD, Dean HJ, Sellers EA (2014) Earlier onset of complications in youth with type 2 diabetes. Diabetes Care 37(2):436–443. https://doi.org/10.2337/dc13-0954
7. Har RL, Reich HN, Scholey JW et al (2014) The urinary cytokine/chemokine signature of renal hyperfiltration in adolescents with type 1 diabetes. PLoS One 9(11):e111131. https://doi.org/10.1371/journal.pone.0111131
8. Dart AB, Wicklow BA, Sellers EA et al (2014) The Improving Renal Complications in Adolescents With Type 2 Diabetes Through the REsearch (iCARE) Cohort Study: rationale and protocol. Can J Diabetes 38(5):349–355. https://doi.org/10.1016/j.jcjd.2014.07.224
9. Dart AB, McGavock J, Sharma A, Chateau D, Schwartz GJ, Blydt-Hansen T (2019) Estimating glomerular filtration rate in youth with obesity and type 2 diabetes: the iCARE study equation. Pediatr Nephrol. https://doi.org/10.3390/genes10110921
10. Flynn JT, Kaelber DC, Baker-Smith CM et al (2017) Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics 140(3). https://doi.org/10.1542/peds.2017-1904
11. Pagtalunan ME, Miller PL, Jumping-Eagle S et al (1997) Podocyte loss and progressive glomerular injury in type II diabetes. J Clin Invest 99(2):342–348. https://doi.org/10.1172/JCI119163
12. Toyoda M, Najafian B, Kim Y, Caramori ML, Mauer M (2007) Podocyte detachment and reduced glomerular capillary endothelial fenestration in human type 1 diabetic nephropathy. Diabetes 56(8):2155–2160. https://doi.org/10.2337/db07-0019
13. Raile K, Galler A, Hofer S et al (2007) Diabetic nephropathy in 27,805 children, adolescents, and adults with type 1 diabetes: effect of diabetes duration, A1C, hypertension, dyslipidemia, diabetes onset, and sex. Diabetes Care 30(10):2523–2528. https://doi.org/10.2337/dc07-0282
14. Hokke S, Arias N, Armitage JA et al (2016) Maternal glucose intolerance reduces offspring nephron endowment and increases glomerular volume in adult offspring. Diabetes Metab Res Rev 32(8):816–826. https://doi.org/10.1002/dmrr.2805
15. Sellers EA, Blydt-Hansen TD, Dean HJ, Gibson IW, Birk PE, Ogborn M (2009) Macroalbuminuria and renal pathology in First

Nation youth with type 2 diabetes. Diabetes Care 32(5):786–790. https://doi.org/10.2337/dc08-1828
16. Dalla Vestra M, Saller A, Bortoloso E, Mauer M, Fioretto P (2000) Structural involvement in type 1 and type 2 diabetic nephropathy. Diabetes Metab 26(Suppl 4):8–14
17. Perkins BA, Bebu I, de Boer IH et al (2019) Risk factors for kidney disease in type 1 diabetes. Diabetes Care 42(5):883–890. https://doi.org/10.2337/dc18-2062
18. Vallon V, Komers R (2011) Pathophysiology of the diabetic kidney. Compr Physiol 1(3):1175–1232. https://doi.org/10.1002/cphy.c100049