Different alterations of glomerular filtration rate and their association with uric acid in children and adolescents with type 1 diabetes or with overweight/obesity

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Abstract

Background: Hyperfiltration (HF) occurs early in diabetes or obesity (OB)-associated renal disease. Alterations of glomerular filtration rate (GFR) in childhood OB remain unclear.

Objectives: To compare the prevalence of GFR alterations and its association with uric acid in children and adolescents with type 1 diabetes (T1D) vs overweight (OW)/OB.

Methods: Cross-sectional study of 29 youths (aged: 13 ± 2 years) with T1D (disease duration: 7 ± 3 years) and 165 with OW/OB (aged: 11 ± 3 years). Patients with an albumin-creatinine ratio >3.39 mg/mmol were excluded. GFR was estimated with creatinine-cystatin C Zappitelli equation. HF and low GFR were defined by a GFR > 135 and <90 mL/min.1.73 m2, respectively.

Results: HF was higher in children with T1D vs OW/OB (28% vs 10%, $P < .005$). Children with OW/OB also showed a 10% of low GFR. In patients with T1D, HbA1c ($\beta = .8$, $P < .001$), and systolic blood pressure ($\beta = 11.4$, $P < .005$) were independent predictors of GFR ($R2 = .65$). In OW/OB, HF cases were almost limited to prepubertal children and low GFR to pubertal ones. GFR in OW/OB was associated with age ($\beta = -2.2$, $P < .001$), male sex ($\beta = -11.6$, $P < .001$), and uric acid ($\beta = -.05$, $P < .001$) in adjusted models ($R2 = .33$).

Conclusions: GFR alterations were different between youths with T1D and with OW/OB. Higher uric acid, older age, and puberty were related to lower GFR values in OW/OB children. Longitudinal studies will determine if low GFR is consequence of a rapid GFR decline in pediatric patients with OW/OB.

KEYWORDS

children, diabetes, hyperfiltration, obesity, renal disease, uric acid

1 Introduction

Obesity (OB) and diabetes are the leading risk factors for chronic kidney disease (CKD) that have been pushing upward its prevalence in the last years.1 CKD is an important contributor to disability, morbidity, and mortality and constitutes one of the non-communicable causes of death that increased

the most in the past 20 years.2 Thus, the need for markers of early renal dysfunction is at the spotlight.3 In the development of CKD in children and adolescents with type 1 diabetes (T1D) and those without diabetes but with overweight (OW)/OB, an early stage of renal hyperfiltration (HF) is proposed. In children and adolescents with T1D, HF has been associated with increased risk of microalbuminuria and of a rapid decline in glomerular filtration rate (GFR),4,5 a predominant clinical feature of diabetic nephropathy.6 Nonetheless, a recent report from the DCCT/EDIC has underestimated the role of HF as a risk factor for CKD or macroalbuminuria in 446 adults with T1D followed during a median of 28 years.7 Therefore, if HF has clinical relevance in children and adolescents with T1D remains yet to be determined. Unlike HF, increasing uric acid levels were associated with worse renal outcomes, cardiovascular events and mortality in adults with T1D.8,9 However, adolescents with T1D showed reduced uric acid levels, underscoring its use as a risk factor in these patients.10,11 Even though, increasing uric acid levels in pediatric T1D may still be associated with a rapid GFR decline, as an inverse correlation with GFR was shown.10,11 On the other hand, a study showed that children and adolescents with OW/OB without diabetes featured HF at a similar proportion than those with T1D.12 However, no other studies compared both pediatric populations. The comparison of GFR values between children with OW/OB vs normal-weight peers showed inconsistent results; thus, the impact of childhood OW/OB on renal function remains unclear.12-16 While some authors reported associations between decreased GFR and increasing body mass index (BMI) and presence of cardiometabolic risk factors, others did the same with elevated GFR.12-16 In an Italian retrospective study including 2957 children (aged: 3-18 years) with OB, z-BMI positively correlated with GFR. However, pubertal development, HOMA-IR, and duration of OB were all inversely correlated with GFR and the study concluded that longer duration of OB in children could impact negatively the GFR.14 If similar alterations of the GFR are present or not in children and adolescents with T1D and with OW/OB without diabetes is relevant for establishing prevention strategies. In regard to uric acid levels, an association with cardiometabolic risk factors in children and adolescents with OW/OB was clearly established.15,17,18 However, its association with GFR alterations has not been analyzed in this age group. The TODAY study showed that higher uric acid levels were associated with increased risk of hypertension and microalbuminuria in youth with

type 2 diabetes (T2D).19 Thus, uric acid constitutes a candidate biomarker for screening youths with OB showing elevated risk of renal impairment. The importance of identifying such patients arises from the prolonged exposure to other comorbid CKD risk factors, apart from OB, like insulin resistance and dyslipidemia. This fact might contribute to explain why at similar ages children and adolescents with T2D presented a 2.5x higher risk of diabetic kidney disease and a 4x higher risk of renal failure than those with T1D.20,21 Our hypothesis was that GFR alterations and its associations with uric acid levels in children with OW/OB would be similar to those observed in children with T1D. The aim of this study was to evaluate and to compare the prevalence of GFR alterations, and to analyze its association with uric acid in children and adolescents with T1D vs OW/OB. Secondary analysis included the effects of cardiometabolic risk factors over serum uric acid in OW/OB.

2 | METHODS

2.1 | Study design and sample size

This was a prospective, single-center, cross-sectional study. The expected prevalence of renal HF in the group of patients with OW/OB was 15% according to the literature.12 The sample size to detect such prevalence with a 5% of accuracy and a 95% confidence was 196. In order to calculate the number of patients with T1D in the study, an expected HF prevalence of 30% was set.4,12 Next, we used a non-inferiority approach for the comparison of two proportions with a critical value (α) = .05, an 80% power and a non-inferiority margin (δ) of −0.10. The resulting number of patients with T1D to be included was 24. OpenEpi (Emory University, Atlanta, Georgia) and R (R Foundation, Vienna, Austria) were used for sample size calculations.

2.2 | Study population

Children and adolescents (aged: 5-17 years) with OW/OB and without diabetes who were referred for nutritional counseling to the Servicio de Diabetes y Nutrición Infanto-Juvenil, Complejo Médico Churruca-Visca, Buenos Aires, Argentina during April 2017 to April 2019 were invited to participate (n = 196). Exclusion criteria were: (a) any congenital, concomitant, or incident endocrine disease (n = 5); (b) congenital hepatic or renal diseases (n = 1); (c) asthma or autoimmune diseases (n = 6); (d)

clinical signs of any infectious disease or a high sensitivity C-reactive protein (hsCRP) > 10 mg/L (n = 14); (e) urinary albumin-creatinine ratio (ACR) > 3.39 mg/mmol in a first-morning void (n = 3); and (f) use of psychiatric medication (n = 2). The final number of children and adolescents with OW/OB studied was 165. Although this number was lower than estimated through sample size calculations, the observed power for the comparison of GFR alterations was 70%. T1D was diagnosed according to ISPAD guidelines.22 Every child and adolescent with T1D (aged: 5-17 years) followed up in our center was invited to participate in the study. Out of 40 patients with T1D, 36 agreed to participate. Exclusion criteria were ACR >3.39 mg/mmol (n = 2), fasting c-peptide levels >0.2 mmol/L (n = 1), concomitant liver disease and use of any other medication different from insulin. One patient was excluded as it was born prematurely with an extremely low birth weight (900 g), as well as, three other patients who missed the protocol examinations. The final number of children and adolescents with T1D was 29. All the patients studied in the protocol and their legal tutors or parents gave their written consent and assent to participate in the study. The Bioethics Committee of the Complejo Médico Churruca- Visca reviewed and approved the study protocol. All the procedures within the study followed the Ethical Principles stated in the Declaration of Helsinki.

2.3 | Clinical and biochemical assessment

Every patient did a clinical examination including weight, height, waist circumference, and blood pressure (BP). BMI was calculated and OW/OB classified according to the definitions of the World Health Organization (WHO).23 WC was measured at the midpoint between the iliac crest and the last rib and elevated WC classified as >90th percentile according to the Bogalusa Heart Study.24 BP was recorded as the average of two measurements made after the patient was rested in the sitting position for 5 minutes. Guidelines of the American Association of Pediatrics were used to define elevated BP.25 Pubertal development was assessed by Tanner criteria. Puberty was defined by a Tanner stage >I in children aged >10 years or less if signs of pubertal development were present. All the patients collected a first-morning void and blood samples were drawn after 12 hours overnight fast. To avoid the interference of physical exercise in ACR values, subjects were asked not to perform any physical activity 2 days before the urine sample collection. Creatinine (IDMS-traceable Jaffé,

Beckman Coulter) and cystatin C (immunoturbidimetry, Diazyme, Poway, California) were measured in a DxC 800 autoanalyzer (Beckman Coulter). The GFR was calculated by the combined creatinine and cystatin C Zappitelli equation.26 Nonesterified fatty acids (NEFA) levels were measured by a spectrophotometric method (Randox, Kearneysville West Virginia). Glucose, uric acid, insulin, lipids, hsCRP, and ACR were measured by standardized methods (Beckman Coulter). HF was defined as GFR > 135 mL/ min.1.73 m2 and low GFR as <90 mL/min.1.73 m2. The reference interval of GFR used (90-135 mL/min.1.73 m2) was accepted by a verification process in 26 samples from normal weight children and adolescents according to the EP28-A3c CLSI protocol.

2.4 | Statistical analysis

The Shapiro–Wilk test was used to evaluate the normal distribution of continuous variables. Comparisons were made by the Student t test or Mann-Whitney U test, according to data distribution. For the comparison of categorical variables, chi-square test was used. When comparing more than three categories, Benjamini-Hochberg correction for multiple comparisons was applied. Two-way analysis of variance (ANOVA) was used to evaluate differences between male and female patients with or without GFR alterations across the children with OW/OB. Variables with a skewed distribution were log-transformed before entering the analysis. Univariate correlations were assessed by Spearman Correlation test. Stepwise multiple linear regression was used to look for independent predictors of GFR and uric acid levels. Standardized residuals from linear regression tests were checked for normality to be confident of the model adequacy. SPSS 25.0 (IBM) was used for statistical analyses. Statistically significant tests showed a significance value (P) < .05.

3 | RESULTS

3.1 | General characteristics of the studied population

The 29 patients with T1D were exclusively under treatment with insulin. Continuous subcutaneous insulin infusion was the treatment modality in seven patients, while the rest were using multiple daily injections. Regarding the metabolic control, 3 patients had an HbA1c <53 mmol/mol and 12 of them <69 mmol/mol. The median disease duration was 7 years, (Q1-Q3) (5-10) years. Out of the 29

patients, eight showed positive autoantibodies for other diseases (one celiac disease and seven thyroid antibodies). None of them presented any microvascular or macrovascular complication. Table 1 shows the general characteristics of the children and adolescents with T1D and with OW/OB. The group of patients with T1D was older and predominantly pubertal in comparison with the patients with OW/OB. As expected, both groups differed in the z-BMI, waist circumference, glucose metabolism markers, and NEFA levels. Regarding lipid levels, T1D patients showed higher HDL-C levels (Table 1). In addition, patients with T1D exhibited lower cystatin C and uric acid, as well as higher GFR and ACR than OW/OB. Creatinine concentration was similar between patients with T1D and OW/OB. A significant interaction on GFR values was observed between the groups and pubertal stage (F = 6.610; P = .011). The difference in GFR was larger among pubertal patients of the different groups (125 ± 23 vs 104 ± 17 mL/min.1.73 m2, for T1D and OW/OB groups, respectively). The prevalence of elevated BP and the concentration of hsCRP was similar between the groups.

3.2 | Alterations of the GFR in the studied population The prevalence of HF in children and adolescents with T1D was significantly higher than in those with OW/OB (Figure 1). In the OW/OB group, a 10% of the subjects showed low GFR (Figure 1). Pooled together, the alterations of the GFR were similarly prevalent among T1D and OW/OB patients (28% vs 20%, P = .220, respectively).

3.3 | Correlation of GFR with uric acid levels and cardiometabolic risk factors in T1D

In patients with T1D, GFR correlated with HbA1c (r = .58, P = .001); z-SBP (r = .59, P = .001); and triglycerides (r = .38, P = .041). Uric acid levels and other cardiometabolic risk factors were not significantly correlated with GFR (P > .05). In a sex- and age-adjusted model HbA1c (β(95% CI) = 0.8 (0.4-1.1), P < .001) and z-SBP (β = 11.4 (4.0-18.8), P = .005) were independent predictors of GFR describing more than half of its variability (R2 = .65).

3.4 | Correlation of GFR with uric acid levels and cardiometabolic risk factors in OW/OB

In children and adolescents with OW/OB, the GFR alterations differed according to pubertal stage. Almost every patient, except one with HF, was prepubertal and almost all the patients with low GFR, except one, were pubertal (see Supplementary Material for description of these two cases). For further

analyses, these two patients were excluded and comparisons were made on prepubertal children (n = 94) by separate from pubertal ones (n = 69). Clinical and biochemical characteristics of these patients divided by pubertal development according to sex and the presence of GFR alterations are in Tables S1 and S2. Prepubertal children with HF showed an improved cardiometabolic risk profile characterized by lower WC, uric acid and NEFA levels than those with GFR values between 90 and 135 mL/ min.1.73 m2 (Table S1). Differences between female and male prepubertal children were evident in cystatin C and ACR but not in creatinine or uric acid levels (Table S1). Among the pubertal patients, those with low GFR were preferentially male and showed higher LDL-C, non-HDL-C and uric acid than those with GFR between 90 and 135 mL/min.1.73 m2. Sex differences were observed in HDL-C, cystatin C, and GFR (Table S2). Table S3 shows the univariate correlations of GFR with metabolic variables in prepubertal and pubertal children by separate. The only variables that differently correlated with GFR according to the pubertal stage were ACR, NEFA, and plasma lipids. In prepubertal children, GFR directly correlated with ACR and inversely with NEFA levels (Table S3). In pubertal subjects, HDL-C positively correlated with GFR, while LDL-C did it inversely (Table S3). A trend toward a lower GFR was evident as age, pubertal development, WC, LDL-C, uric acid, NEFA, and other cardiometabolic risk factors increased. Therefore, correlations were assessed in the whole group despite known physiological differences due to pubertal development (ie, higher HOMA-IR, lower LDL-C, etc.). As expected age, male sex and pubertal stage were negatively correlated with GFR (all $P < .001$). Furthermore, in age- and sex-adjusted correlations, uric acid and NEFA levels were significantly correlated with GFR ($r = -.24$, $P = .003$ and $r = -.20$, $P = .014$, respectively). To evaluate if these factors were independent predictors of GFR, a stepwise multivariate linear regression was done. This analysis showed that age, sex, and uric acid levels explained a 33% of GFR variability in the studied population of children and adolescents with OW/OB (Table 2). When age was not included in the model, pubertal stage took its place in the regression model without major deviations (data not shown). As several cardiometabolic risk factors correlated with uric acid, we performed a regression analysis to evaluate the independent contributors to uric acid levels in OW/OB (Table 3). Elevated BP, age, z- BMI, and NEFA levels were independent

predictors of almost half of uric acid variability in a model adjusted by pubertal stage, insulin resistance, GFR, and plasma lipids.

4 | DISCUSSION

The present study shows that GFR values were lower in children and adolescents with OW/OB as they present higher age, uric acid levels and go through pubertal development. On the other hand, HF in children and adolescents with T1D was related to worse metabolic and BP control, as also pointed out by others.4,5 Thus, refuting our hypothesis, the alterations of GFR were different between children and adolescents with T1D and with OW/OB without diabetes. Although contrary to a previous study,12 our results show that HF prevalence is lower in children and adolescents with OW/OB vs T1D. HF was an early event related to lower WC, NEFA, and uric acid in prepubertal children with OW/OB. The decreased presence of metabolic alterations in these patients could be explained by shorter exposure time to unhealthy weight gain. In further support to this notion, a trend toward higher prevalence of severe OB, consequence of sustained weight gain along the lifetime, was observed among prepubertal children without HF. In addition, low GFR was evident in pubertal youths with OW/OB. Our results are in line with the ones of Marzuillo et al who showed that duration of OB and puberty negatively affected GFR in OW/OB children.14 The observed differences in the GFR alterations between the studied groups could be relevant to explain the different kidney outcomes between children and adolescents with T1D vs T2D.20,21 However, whether these represent different physiopathological mechanisms or are the consequence of a more rapid development associated with longer exposure to OB or other renal disease risk factors remains unknown. In support to the latter, a recent study showed an association of GFR < 90 mL/ min.1.73 m2, with male sex and elevated uric acid levels in children and adolescents (aged: 7-18 years) with T1D but without albuminuria, resembling our results in male pubertal subjects with OW/OB showing low GFR.27 Uric acid was the only biomarker that independently contributed to explain the variance of GFR in children and adolescents with OW/OB. In addition, uric acid levels summarized data from many cardiometabolic risk factors in the present series. In agreement with other studies,17,18,28 elevated BP, older age, and increasing z-BMI and NEFA levels contributed to explain almost 50% of

uric acid variations. In this aspect, uric acid levels as a renal disease marker in children with OW/OB merit further studies. The role of uric acid as a risk biomarker for diabetic kidney disease has already been established in children and adolescents with T2D and adults with T1D.8,19 However, in agreement with other study,10 uric acid was not correlated with renal function or cardiometabolic risk factors in our group of children and adolescents with T1D. A recent study showed that T1D duration may condition the association of uric acid with renal disease risk, limiting its use in pediatric diabetes care.29 Our study highlights several limitations to the use of HF in clinical practice in childhood OB. First, the time in which HF occurs could vary between individuals according to OB duration and pubertal development; thus, many children with higher risk of early renal impairment may go unnoticed. Second, the use of any of the proposed GFR cut-off to define HF in the clinical practice could lead to a large number of misclassified cases among children with OW/OB. If longitudinal studies confirm our results of a declining GFR during childhood OB, then percentual or absolute change values of GFR decline per time unit would be suitable for identifying youths at risk for early renal impairment. For this purpose, in the present study, the creatinine and cystatin C-combined Zappitelli equation was considered adequate. While creatinine levels correlated with age and pubertal development, cystatin C concentration did not (data not shown). Thus, the use of cystatin C, having sex into consideration, would be relevant for an adequate assessment of renal function in children and adolescents with OW/OB. The correlation observed by others between GFR estimations and z-BMI could have been related to the lack of cystatin C measurement, the use of GFR equations that include weight in its formula, like the Bouvet equation, or the inclusion of normal weight individuals in the analyses.12,14,26 The present was a cross-sectional study and it was not possible to confirm if the patients with OW/OB will show or not a rapid decline in GFR. The lack of data on OB duration limited the interpretation of our results, in particular among pubertal children. In addition, non-alcoholic fatty liver disease (NAFLD), which is prevalent in childhood OB (up to 34%;30), was not part of the protocol examinations. A recent report showed that NAFLD was a significant predictor of low GFR among a series of 230 children and adolescents with OW/OB (46% showing NAFLD).31 Longitudinal studies will clarify the relationship between NAFLD and impaired renal function in childhood OB. The strengths of our study rely on the exclusion of patients with

microalbuminuria and with any other inflammatory condition (based on clinical and biochemical parameters) that could have affected the biochemical variables studied. In addition, the use of a creatinine and cystatin C equation for the calculation of GFR is a clear strength in comparison to other studies only using creatinine concentration. However, our classification was based only in one evaluation of the GFR and the reported frequencies of GFR alterations may be biased. Nonetheless, the observed prevalence of HF in youths with T1D and of GFR alterations in OW/OB was similar to previous reports.10,12 In the present study, the GFR reference range was previously verified in a group of 26 children and adolescents with normal weight. This point combined with the fact that subjects with HF and low GFR were found in the same study supports our evaluation of the GFR. However, the lack of metabolic data in normal weight subjects could suppose a limitation to our conclusions beyond those regarding GFR alterations. Finally, although some patients showed 2 years of diabetes duration, insulin deficiency was ascertained by a fasting C-peptide >0.2 nmol/L as an exclusion criterion. In conclusion, GFR alterations were different between children and adolescents with T1D and with OW/OB. Higher uric acid, older age, and puberty were related to lower GFR values in OW/OB children. Whether these represent different physiopathological mechanisms or are the consequence of a more rapid impairment of renal function associated with longer exposure to cardiometabolic risk factors remains to be determined.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

María Soledad Peredo, Lucrecia Brovarone, Cecilia Diez, María Laura Kabakian, and María Pía Santucci performed the general clinical evaluation and recruited the patients. María Pía Santucci, Cecilia Diez, and María Laura Kabakian were coordinators for the patient recruitment. María Luz Muzzio, Romina Scricciolo, and Tomás Meroño performed the biochemical assessments. María Pía Santucci, María Laura Kabakian, and Tomás Meroño conceived the study and managed the Ethical Review Board approval. María Pía Santucci, Cristina Andrés- Lacueva, and Tomás Meroño done the statistical analyses and wrote the first draft of the manuscript. María Pía Santucci, María Luz Muzzio, Romina Scricciolo, Cristina Andrés-Lacueva, María Laura Kabakian, and Tomás Meroño performed a literature search, provided clinical insights for the theoretical framework of the study, and contributed to data interpretation. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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401 **FIGURES**

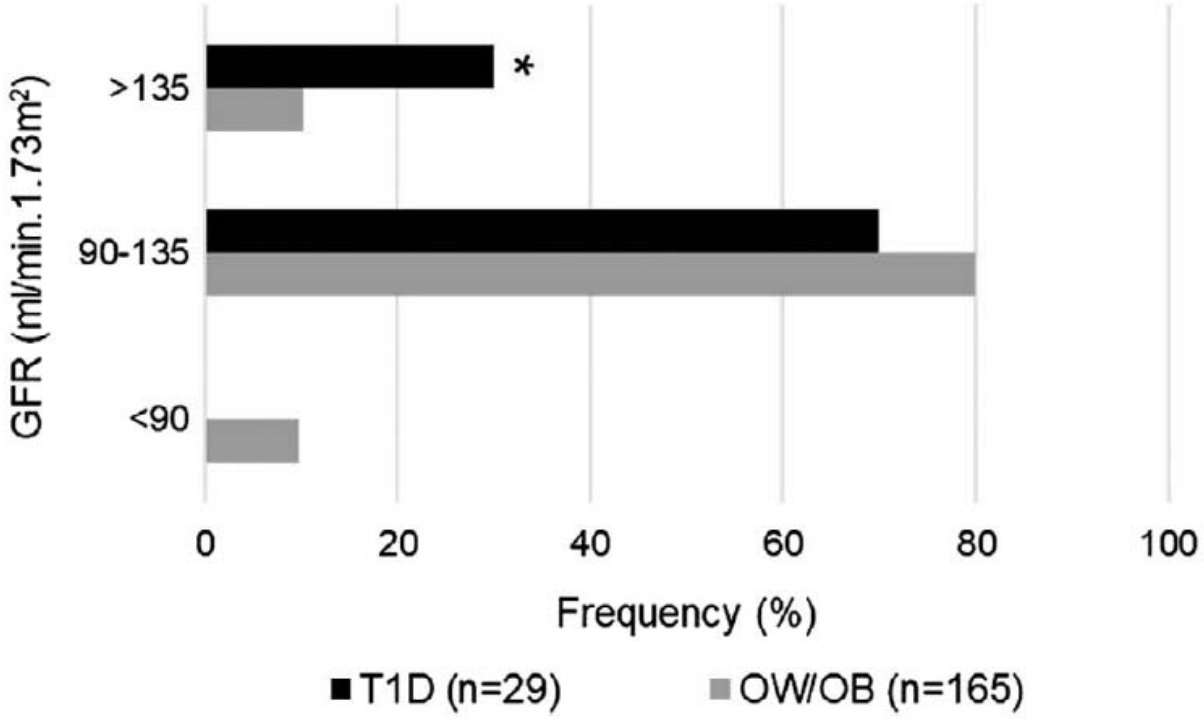

FIGURE 1 Alterations of the GFR in children and adolescents with type 1 diabetes or with OW/OB. GFR calculated by creatinine and cystatin C-Zappitelli equation. $^{*}\chi^2 = 10.619$, $P < .005$ with Benjamini-Hochberg correction for multiple comparisons. GFR, glomerular filtration rate; OW/OB, overweight/obesity; T1D, type 1 diabetes

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TABLES

TABLE 1 Characteristics of the children and adolescents with T1D or with OW/OB

	T1D (n = 29)	OW/OB (n = 165)	*P*
Age (y)	13 (11-15)	11 (8-13)	<.001
Male sex (n, %)	11 (37)	88 (53)	.093
Pubertal (n, %)	21 (70)	70 (42)	.005
z-BMI	1.0 (0.2-1.4)	2.7 (2.3-3.4)	<.001
BMI categories (n, %)			<.001
OW	13 (45)	23 (14)	
OB	1 (3)	88 (53)	
Severe OB	0 (0)	54 (33)	
Elevated BP (n, %)	5 (17)	30 (18)	.612
WC (cm)	74 (68-79)	89 (79-100)	<.001
Glucose (mmol/L)	11.7 (8.3-14.6)	5.1 (4.8-5.3)	<.001
HbA1c (mmol/mol)	78 ± 18	33 ± 4	<.001
ALT (U/L)	14 (11-17)	18 (15-29)	<.001
AST (U/L)	21 (18-23)	24 (21-28)	<.001
TG (mmol/L)	0.7 (0.5-1.0)	1.0 (0.8-1.5)	<.001
TC (mmol/L)	4.6 ± 1.0	4.1 ± 0.7	.003
HDL-C (mmol/L)	1.58 (1.27-1.89)	0.98 (0.88-1.19)	<.001
LDL-C (mmol/L)	2.6 ± 0.8	2.5 ± 0.6	.495
Non-HDL-C (mmol/L)	3.1 ± 1.0	3.0 ± 0.7	.572
NEFA (mmol/L)	0.47 (0.36-0.66)	0.79 (0.60-1.00)	<.001
Uric acid (μmol/L)	196 ± 54	286 ± 77	<.001
Creatinine (μmol/L)	48 (39-59)	45 (40-55)	.598
Cystatin C (mg/L)	0.73 (0.66-0.81)	0.81 (0.73-0.91)	<.001
GFR (mL/min.1.73 m^2)	125 ± 25	112 ± 19	.021
ACR (mg/mmol)	0.68 (0.57-1.58)	0.57 (0.45-0.79)	.019
hsCRP (mg/L)	1.9 (0.6-2.9)	2.1 (0.8-4.5)	.373

Note: Data are expressed as mean ± SD or median (Q1-Q3).
Abbreviations: ACR, urinary albumin to creatinine ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate (calculated with combined Zappitelli equation); HbA1c, hemoglobin A1c; HDL, high density lipoprotein; hsCRP, high sensitivity C-reactive protein; LDL, low density lipoprotein; NEFA, nonesterified fatty acids; OB, obesity; OW, overweight; TC, total cholesterol; T1D, type 1 diabetes; TG, triglycerides; WC, waist circumference.

TABLE 2 Multivariate linear regression using GFR (mL/min.1.73 m^2) as dependent variable (n = 163)

	β (95% CI)	*T*	*P*	R^2
Step 1				.20
Age (y)	−3.86 (−3.82-−1.89)	−5.862	<.001	
Step 2				.29
Age (y)	−2.74 (−3.64-−1.84)	−6.032	<.001	
Male sex	−12.06 (−17.05-−7.06)	−4.771	<.001	
Step 3				.33
Age (y)	−2.19 (−3.10-−1.12)	−4.207	<.001	
Male sex	−11.61 (−16.51-−6.72)	−4.689	<.001	
Uric acid (μmol/L)	−0.05 (−0.09-−0.02)	−2.744	<.001	

Note: Variables excluded from the model: pubertal stage, z-BMI, and NEFA levels.
Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; NEFA, non-esterified fatty acids.

TABLE 3 Multivariate linear regression using uric acid (μmol/L) as dependent variable (n = 163)

	β (95 CI%)	T	P	R^2
Step 1				.20
Elevated BP	80.66 (45.50-115.83)	4.566	<.001	
Step 2				.35
Elevated BP	77.92 (46.13-109.71)	4.880	<.001	
Age (y)	11.59 (6.28-16.91)	4.345	<.001	
Step 3				.42
Elevated BP	62.94 (31.68-94.19)	4.010	<.001	
Age (y)	15.13 (9.70-20.56)	5.545	<.001	
z-BMI	26.92 (10.76-43.07)	3.318	<.001	
Step 4				.47
Elevated BP	48.97 (17.67-80.27)	3.116	<.001	
Age (y)	16.59 (11.31-21.87)	6.259	<.001	
z-BMI	27.68 (12.26-43.11)	3.575	<.001	
NEFA (mmol/L)	77.56 (24.83-130.28)	2.930	<.001	

Note: Variables excluded from the model: sex, pubertal stage, GFR, HOMA-IR, TG, LDL-C, and hsCRP.

Abbreviations: BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; HOMA, homeostasis model assessment; hsCRP, high sensitivity C-reactive protein; LDL, low density lipoprotein; NEFA, nonesterified fatty acids; TG, triglycerides.