

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

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23 **Abstract**

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

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

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

32 **Results:** HF was higher in children with T1D vs OW/OB (28% vs 10%, $P < .005$). Children with
33 OW/OB also showed a 10% of low GFR. In patients with T1D, HbA1c ($\beta = .8$, $P < .001$), and systolic
34 blood pressure ($\beta = 11.4$, $P < .005$) were independent predictors of GFR ($R^2 = .65$). In OW/OB, HF
35 cases were almost limited to prepubertal children and low GFR to pubertal ones. GFR in OW/OB
36 was associated with age ($\beta = -2.2$, $P < .001$), male sex ($\beta = -11.6$, $P < .001$), and uric acid ($\beta = -.05$,
37 $P < .001$) in adjusted models ($R^2 = .33$).

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

42 **KEYWORDS**

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

44 **1 Introduction**

45 Obesity (OB) and diabetes are the leading risk factors for chronic kidney disease (CKD) that have
46 been pushing upward its prevalence in the last years.¹ CKD is an important contributor to disability,
47 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

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

86 **2 | METHODS**

87 **2.1 | Study design and sample size**

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

96 **2.2 | Study population**

97 Children and adolescents (aged: 5-17 years) with OW/OB and without diabetes who were referred
98 for nutritional counseling to the Servicio de Diabetes y Nutrición Infanto-Juvenil, Complejo Médico
99 Churruca-Visca, Buenos Aires, Argentina during April 2017 to April 2019 were invited to participate
100 (n = 196). Exclusion criteria were: (a) any congenital, concomitant, or incident endocrine disease (n
101 = 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,

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

137 **2.4 | Statistical analysis**

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

149 **3 | RESULTS**

150 **3.1 | General characteristics of the studied population**

151 The 29 patients with T1D were exclusively under treatment with insulin. Continuous subcutaneous
152 insulin infusion was the treatment modality in seven patients, while the rest were using multiple daily
153 injections. Regarding the metabolic control, 3 patients had an HbA1c <53 mmol/mol and 12 of them
154 <69 mmol/mol. The median disease duration was 7 years, (Q1-Q3) (5-10) years. Out of the 29

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

167 **3.2 | Alterations of the GFR in the studied population** The prevalence of HF in children and
168 adolescents with T1D was significantly higher than in those with OW/OB (Figure 1). In the OW/OB
169 group, a 10% of the subjects showed low GFR (Figure 1). Pooled together, the alterations of the GFR
170 were similarly prevalent among T1D and OW/OB patients (28% vs 20%, $P = .220$, respectively).

171 **3.3 | Correlation of GFR with uric acid levels and cardiometabolic risk factors in T1D**

172 In patients with T1D, GFR correlated with HbA1c ($r = .58$, $P = .001$); z-SBP ($r = .59$, $P = .001$); and
173 triglycerides ($r = .38$, $P = .041$). Uric acid levels and other cardiometabolic risk factors were not
174 significantly correlated with GFR ($P > .05$). In a sex- and age-adjusted model HbA1c ($\beta(95\% \text{ CI}) =$
175 $0.8 (0.4-1.1)$, $P < .001$) and z-SBP ($\beta = 11.4 (4.0-18.8)$, $P = .005$) were independent predictors of
176 GFR describing more than half of its variability ($R^2 = .65$).

177 **3.4 | Correlation of GFR with uric acid levels and cardiometabolic risk factors in OW/OB**

178 In children and adolescents with OW/OB, the GFR alterations differed according to pubertal stage.
179 Almost every patient, except one with HF, was prepubertal and almost all the patients with low GFR,
180 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

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

210 **4 | DISCUSSION**

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

235 uric acid variations. In this aspect, uric acid levels as a renal disease marker in children with OW/OB
236 merit further studies. The role of uric acid as a risk biomarker for diabetic kidney disease has already
237 been established in children and adolescents with T2D and adults with T1D.^{8,19} However, in
238 agreement with other study,¹⁰ uric acid was not correlated with renal function or cardiometabolic
239 risk factors in our group of children and adolescents with T1D. A recent study showed that T1D
240 duration may condition the association of uric acid with renal disease risk, limiting its use in pediatric
241 diabetes care.²⁹ Our study highlights several limitations to the use of HF in clinical practice in
242 childhood OB. First, the time in which HF occurs could vary between individuals according to OB
243 duration and pubertal development; thus, many children with higher risk of early renal impairment
244 may go unnoticed. Second, the use of any of the proposed GFR cut-off to define HF in the clinical
245 practice could lead to a large number of misclassified cases among children with OW/OB. If
246 longitudinal studies confirm our results of a declining GFR during childhood OB, then percentual or
247 absolute change values of GFR decline per time unit would be suitable for identifying youths at risk
248 for early renal impairment. For this purpose, in the present study, the creatinine and cystatin C-
249 combined Zappitelli equation was considered adequate. While creatinine levels correlated with age
250 and pubertal development, cystatin C concentration did not (data not shown). Thus, the use of cystatin
251 C, having sex into consideration, would be relevant for an adequate assessment of renal function in
252 children and adolescents with OW/OB. The correlation observed by others between GFR estimations
253 and z-BMI could have been related to the lack of cystatin C measurement, the use of GFR equations
254 that include weight in its formula, like the Bouvet equation, or the inclusion of normal weight
255 individuals in the analyses.^{12,14,26} The present was a cross-sectional study and it was not possible
256 to confirm if the patients with OW/OB will show or not a rapid decline in GFR. The lack of data on
257 OB duration limited the interpretation of our results, in particular among pubertal children. In
258 addition, non-alcoholic fatty liver disease (NAFLD), which is prevalent in childhood OB (up to
259 34%;³⁰), was not part of the protocol examinations. A recent report showed that NAFLD was a
260 significant predictor of low GFR among a series of 230 children and adolescents with OW/OB (46%
261 showing NAFLD).³¹ Longitudinal studies will clarify the relationship between NAFLD and impaired
262 renal function in childhood OB. The strengths of our study rely on the exclusion of patients with

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

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287 **CONFLICT OF INTEREST**

288 The authors declare no potential conflict of interest.

289 **AUTHOR CONTRIBUTIONS**

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

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302 **REFERENCES**

303 1. Whaley-Connell A, Sowers JR. Obesity and kidney disease: from population to basic science and
304 the search for new therapeutic targets. *Kidney Int.* 2017;92(2):313-323.
305 <https://doi.org/10.1016/j.kint.2016.12.034>.

306 2. Carney EF. Epidemiology: Global Burden of Disease Study 2013 reports that disability caused by
307 CKD is increasing worldwide. *Nat Rev Nephrol.* 2015;11(8):446. [https://doi.org/10.1038/nrneph.](https://doi.org/10.1038/nrneph.2015.98)
308 2015.98.

309 3. Bittner V. Time to rethink prevention of chronic kidney disease? *J Am Coll Cardiol.*
310 2019;74(11):1477-1479. <https://doi.org/10.1016/j.jacc.2019.07.036>.

311 4. Lovshin JA, Škrti c M, Bjornstad P, et al. Hyperfiltration, urinary albumin excretion, and
312 ambulatory blood pressure in adolescents with type 1 diabetes mellitus. *Am J Physiol.*
313 2018;314(4):F667-F674. <https://doi.org/10.1152/ajprenal.00400.2017>.

- 314 5. Amin R, Turner C, van Aken S, et al. The relationship between microalbuminuria and glomerular
315 filtration rate in young type 1 diabetic subjects: The Oxford Regional Prospective Study. *Kidney Int.*
316 2005;68(4):1740-1749. <https://doi.org/10.1111/j.1523-1755.2005.00590.x>.
- 317 6. Krolewski AS, Skupien J, Rossing P, Warram JH. Fast renal decline to end-stage renal disease: an
318 unrecognized feature of nephropathy in diabetes. *Kidney Int.* 2017;91(6):1300-1311.
319 <https://doi.org/10.1016/j.kint.2016.10.046>.
- 320 7. Molitch ME, Gao X, Bebu I, et al. Early glomerular hyperfiltration and long-term kidney outcomes
321 in type 1 diabetes: the DCCT/EDIC experience. *Clin J Am Soc Nephrol.* 2019;14(6):854-861.
322 <https://doi.org/10.2215/CJN.14831218>.
- 323 8. Ficociello LH, Rosolowsky ET, Niewczas MA, et al. High-normal serum uric acid increases risk
324 of early progressive renal function loss in type 1 diabetes: results of a 6-year follow-up. *Diabetes*
325 *Care.* 2010;33(6): 1337-1343. <https://doi.org/10.2337/dc10-0227>.
- 326 9. Pilemann-Lyberg S, Hansen TW, Tofte N, et al. Uric acid is an independent risk factor for decline
327 in kidney function, cardiovascular events, and mortality in patients with type 1 diabetes. *Diabetes*
328 *Care.* 2019;42(6):1088-1094. <https://doi.org/10.2337/dc18-2173>.
- 329 10. Lytvyn Y, Mahmud FH, Daneman D, et al. Association between plasma uric acid levels and
330 cardiorenal function in adolescents with type 1 diabetes. *Diabetes Care.* 2016;39(4):611-616.
331 <https://doi.org/10.2337/dc15-2345>.
- 332 11. Bjornstad P, Roncal C, Milagres T, et al. Hyperfiltration and uricosuria in adolescents with type
333 1 diabetes. *Pediatr Nephrol.* 2016;31(5):787- 793. <https://doi.org/10.1007/s00467-015-3299-8>.
- 334 12. Franchini S, Savino A, Marcovecchio ML, Tumini S, Chiarelli F, Mohn A. The effect of obesity
335 and type 1 diabetes on renal function in children and adolescents. *Pediatr Diabetes.* 2015;16(6):427-
336 433. <https://doi.org/10.1111/pedi.12196>.
- 337 13. Correia-Costa L, Afonso AC, Schaefer F, et al. Decreased renal function in overweight and obese
338 prepubertal children. *Pediatr Res.* 2015; 78(4):436-444. <https://doi.org/10.1038/pr.2015.130>.

339 14. Marzuillo P, Grandone A, Di Sessa A, et al. Anthropometric and biochemical determinants of
340 estimated glomerular filtration rate in a large cohort of obese children. *J Ren Nutr.* 2018;28(5):359-
341 362. <https://doi.org/10.1053/j.jrn.2018.01.001>.

342 15. Ricotti R, Genoni G, Giglione E, et al. High-normal estimated glomerular filtration rate and
343 hyperuricemia positively correlate with metabolic impairment in pediatric obese patients. *PLoS One.*
344 2018;13(3): e0193755. <https://doi.org/10.1371/journal.pone.0193755>.

345 16. Di Bonito P, Sanguigno E, Forziato C, et al. Glomerular filtration rate and cardiometabolic risk
346 in an outpatient pediatric population with high prevalence of obesity. *Obesity.* 2014;22(2):585-589.
347 <https://doi.org/10.1002/oby.20497>.

348 17. Lurbe E, Torro MI, Alvarez-Pitti J, Redon J, Borghi C, Redon P. Uric acid is linked to
349 cardiometabolic risk factors in overweight and obese youths. *J Hypertens.* 2018;36(9):1840-1846.
350 <https://doi.org/10.1097/HJH.0000000000001814>.

351 18. Viazzi F, Antolini L, Giussani M, et al. Serum uric acid and blood pressure in children at
352 cardiovascular risk. *Pediatrics.* 2013;132(1):e93- e99. <https://doi.org/10.1542/peds.2013-0047>. 19.
353 Bjornstad P, Laffel L, Lynch J, et al. Elevated serum uric acid is associated with greater risk for
354 hypertension and diabetic kidney diseases in obese adolescents with type 2 diabetes: an observational
355 analysis from the treatment options for type 2 diabetes in adolescents and youth (TODAY) study.
356 *Diabetes Care.* 2019;42(6):1120-1128. <https://doi.org/10.2337/dc18-2147>.

357 20. Dart AB, Sellers EA, Martens PJ, Rigatto C, Brownell MD, Dean HJ. High burden of kidney
358 disease in youth-onset type 2 diabetes. *Diabetes Care.* 2012;35(6):1265-1271.
359 <https://doi.org/10.2337/dc11-2312>.

360 21. Dabelea D, Stafford JM, Mayer-Davis EJ, et al. Association of type 1 diabetes vs type 2 diabetes
361 diagnosed during childhood and adolescence with complications during teenage years and young
362 adulthood. *JAMA.* 2017;317(8):825-835. <https://doi.org/10.1001/jama.2017.0686>.

- 363 22. Mayer-Davis EJ, Kahkoska AR, Jefferies C, et al. ISPAD Clinical Practice Consensus Guidelines
364 2018: definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr*
365 *Diabetes*. 2018;19:7-19. <https://doi.org/10.1111/pedi.12773>.
- 366 23. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO
367 growth reference for school-aged children and adolescents. *Bull World Health Organ*.
368 2007;85(9):660-667. <https://doi.org/10.2471/blt.07.043497>.
- 369 24. Freedman DS, Serdula MK, Srinivasan SR, Berenson GS. Relation of circumferences and
370 skinfold thicknesses to lipid and insulin concentrations in children and adolescents: the Bogalusa
371 Heart Study. *Am J Clin Nutr*. 1999;69(2):308-317. <https://doi.org/10.1093/ajcn/69.2.308>.
- 372 25. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and
373 management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904.
374 <https://doi.org/10.1542/peds.2017-1904>.
- 375 26. Bacchetta J, Cochat P, Rognant N, Ranchin B, Hadj-Aissa A, Dubourg L. Which creatinine and
376 cystatin C equations can be reliably used in children? *Clin J Am Soc Nephrol*. 2011;6(3):552-560.
377 <https://doi.org/10.2215/CJN.04180510>.
- 378 27. Di Bonito P, Mozzillo E, Esposito M, et al. Non-albuminuric reduced eGFR phenotype in children
379 and adolescents with type 1 diabetes. *Diabetes Res Clin Pract*. 2019;155:107781.
380 <https://doi.org/10.1016/j.diabres.2019.07.005>.
- 381 28. Valle M, Martos R, Cañete MD, et al. Association of serum uric acid levels to inflammation
382 biomarkers and endothelial dysfunction in obese prepubertal children. *Pediatr Diabetes*.
383 2015;16(6):441-447. <https://doi.org/10.1111/pedi.12199>.
- 384 29. Lytvyn Y, Bjornstad P, Lovshin JA, et al. Association between uric acid, renal haemodynamics
385 and arterial stiffness over the natural history of type 1 diabetes. *Diabetes Obes Metab*.
386 2019;21(6):1388-1398. <https://doi.org/10.1111/dom.13665>.

387 30. Anderson EL, Howe LD, Jones HE, Higgins JPT, Lawlor DA, Fraser A. The prevalence of non-
388 alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis. PLoS
389 One. 2015; 10(10):e0140908. <https://doi.org/10.1371/journal.pone.0140908>.
390 31. Di Costanzo A, Pacifico L, D'Erasmus L, et al. Nonalcoholic fatty liver disease (NAFLD), but not
391 its susceptibility gene variants, influences the decrease of kidney function in overweight/obese
392 children. Int J Mol Sci. 2019;20(18):4444. <https://doi.org/10.3390/ijms20184444>.

393 **SUPPORTING INFORMATION**

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

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399 <https://doi.org/10.1111/pedi.13008>

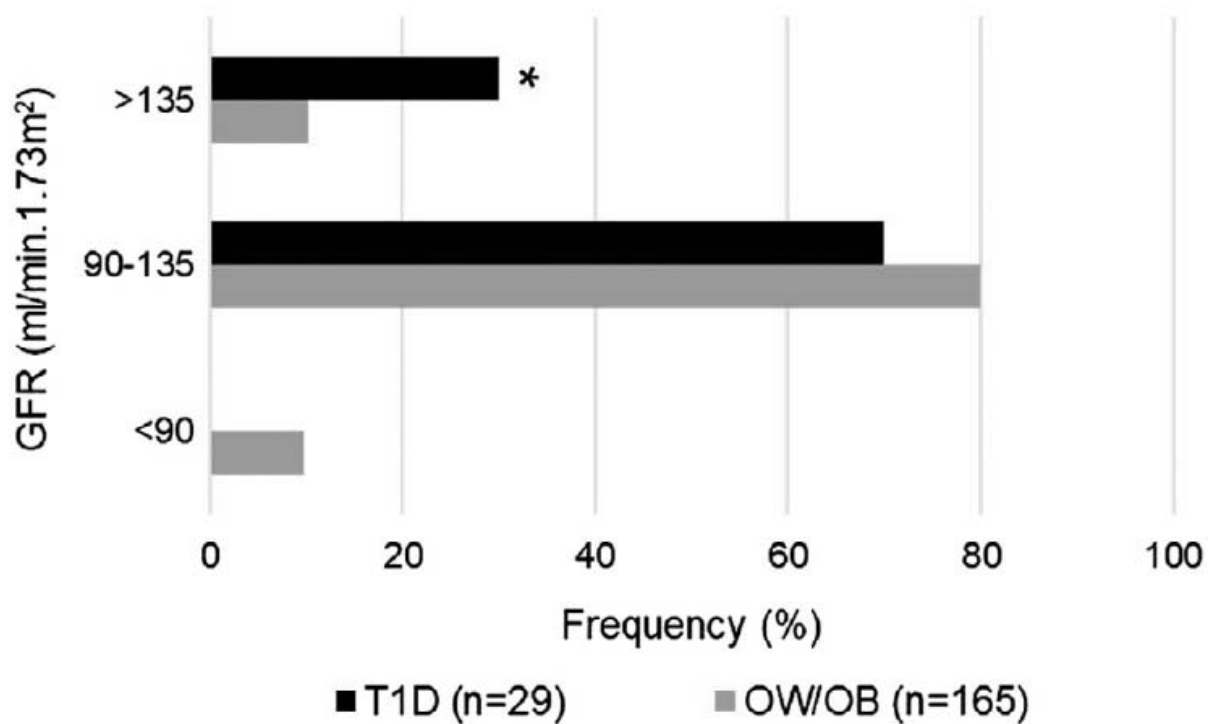


FIGURE 1 Alterations of the GFR in children and adolescents with type 1 diabetes or with OW/OB. GFR calculated by creatinine and cystatin C-Zappitelli equation. $\chi^2 = 10.619$, $P < .005$ with Benjamini-Hochberg correction for multiple comparisons. GFR, glomerular filtration rate; OW/OB, overweight/obesity; 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 m²) 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 (μ mol/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 ($\mu\text{mol/L}$) 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.

