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Insulin Secretion, Sensitivity, and Kidney Function in Young Individuals With Type 2 Diabetes

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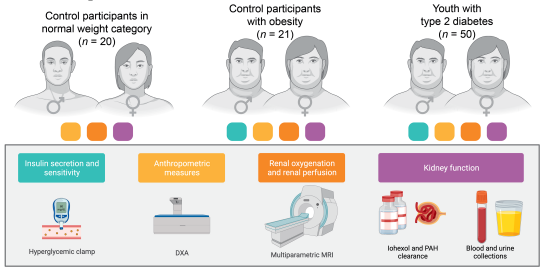
Aim

To explore the relationship between β-cell dysfunction, insulin resistance, and kidney function in youth with type 2 diabetes.

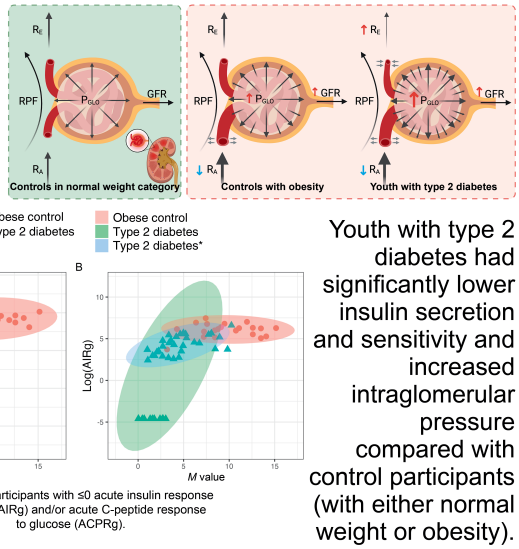
Participants & Methods



Conclusion

Our results suggest a strong association between β-cell dysfunction, insulin resistance, and adverse kidney parameters, indicating a need for early intervention strategies in this population.

Results



Youth with type 2 diabetes had significantly lower insulin secretion and sensitivity and increased intraglomerular pressure compared with control participants (with either normal weight or obesity).

GFR, glomerular filtration rate; PAH, p-aminohippurate; P_{GLO}, glomerular pressure; R_A, afferent arteriolar resistance; R_E, efferent arteriolar resistance; RPF, renal plasma flow.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  The study aimed to explore the relationship between β-cell dysfunction and kidney function in youth with type 2 diabetes.
- **What is the specific question(s) we wanted to answer?**
  Specifically, we examined how these factors influence intraglomerular hemodynamics and kidney oxygen availability.
- **What did we find?**
  Our findings show youth with type 2 diabetes had significantly lower insulin secretion and sensitivity and increased intraglomerular pressure compared with control participants with obesity.
- **What are the implications of our findings?**
  These results suggest a strong association between β-cell dysfunction and adverse kidney parameters, indicating a need for early intervention strategies in this population.

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OBJECTIVE

β-Cell dysfunction and insulin resistance magnify the risk of kidney injury in type 2 diabetes. The relationship between these factors and intraglomerular hemodynamics and kidney oxygen availability in youth with type 2 diabetes remains incompletely explored.

RESEARCH DESIGN AND METHODS

Fifty youth with type 2 diabetes (mean age ± SD 16 ± 2 years; diabetes duration 2.3 ± 1.8 years; 60% female; median HbA_{1c} 6.4% [25th, 75th percentiles 5.9, 7.6%]; BMI 36.4 ± 7.4 kg/m^2; urine albumin-to-creatinine ratio [UACR] 10.3 [5.9, 58.0] mg/g) 21 control participants with obesity (OCs; age 16 ± 2 years; 29% female; BMI 37.6 ± 7.4 kg/m^2), and 20 control participants in the normal weight category (NWCs; age 17 ± 3 years; 70% female; BMI 22.5 ± 3.6 kg/m^2) underwent iohexol and p-aminohippurate clearance to assess glomerular filtration rate (GFR) and renal plasma flow, kidney MRI for oxygenation, hyperglycemic clamp for insulin secretion (acute C-peptide response to glucose [ACPRg]) and disposition index (DI; ×10^3 mg/kg lean/min), and DXA for body composition.

RESULTS

Youth with type 2 diabetes exhibited lower DI (0.6 [0.0, 1.6] vs. 3.8 [2.4, 4.5] × 10^3 mg/kg lean/min; $P < 0.0001$) and ACPRg (0.6 [0.3, 1.4] vs. 5.3 [4.3, 6.9] nmol/L; $P < 0.001$) and higher UACR (10.3 [5.9, 58.0] vs. 5.3 [3.4, 14.3] mg/g; $P = 0.003$) and intraglomerular pressure (77.8 ± 11.5 vs. 64.8 ± 5.0 mmHg; $P < 0.001$) compared with OCs. Youth with type 2 diabetes and OCs had higher GFR and kidney oxygen availability (relative hyperoxia) than NWCs. DI was associated inversely with intraglomerular pressure and kidney hyperoxia.

CONCLUSIONS

Youth with type 2 diabetes demonstrated severe β-cell dysfunction that was associated with intraglomerular hypertension and kidney hyperoxia. Similar but attenuated findings were found in OCs.

The rapidly growing rate of youth-onset type 2 diabetes (T2D) in the United States poses a severe public health threat (1), with incidence projected to increase by 600% between 2017 and 2060 (2). Youth-onset T2D displays a more severe phenotype than adult-onset T2D, including more severe insulin resistance (IR), faster deterioration

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of β-cell function, and a higher rate of early diabetic kidney disease (DKD) when accounting for diabetes duration (3,4). Youth-onset T2D typically emerges during or shortly after puberty in adolescents with obesity. Preventing early β-cell and kidney injury is crucial, because this can be reversible if caught early, and the presence of such injury decreases life span (5). The Restoring Insulin Secretion (RISE) study showed that strategies effective in adults fail in youth. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study found that >50% of youth with T2D experienced glycemic failure within 5 years of diagnosis (6). Traditional risk factors like obesity, hyperglycemia, hypertension, or dyslipidemia do not fully explain youth-onset T2D severity or progression (5,6), highlighting the need to identify modifiable risk factors for targeted interventions to reduce the devastating impacts of this disease, such as intrarenal effects.

The kidneys are metabolically active and have high energy and oxygen requirements to sustain filtration, intraglomerular hemodynamic function, and tubular reabsorption (7). However, in T2D, emerging animal data suggest that the kidneys are not able to sufficiently compensate for the increased oxygen consumption ascribed to the effects of diabetes on substrate metabolism and oxygen use (8,9). Studies of intraglomerular hemodynamic function have focused largely on adults with type 1 diabetes (T1D) and adult-onset T2D (10,11). These studies have established that intraglomerular hemodynamic function is abnormal in early DKD (12) and provide compelling evidence that intraglomerular hemodynamic function can be only partially restored with therapeutic agents early in the course of DKD (13). However, no such data exist for youth-onset T2D, a disease that carries a significantly higher risk of progressive DKD than T1D or adult-onset T2D (14,15). Furthermore, no clinical data exist on the relationships among intraglomerular hemodynamic function, insulin secretion, insulin sensitivity, kidney perfusion, and oxygen availability in youth with T2D.

Accordingly, the aim of this study was to gain detailed knowledge of the factors underlying early DKD in youth-onset T2D. We enrolled 50 youth with T2D, 21 control participants with obesity (OCs), and 20 control participants in the normal weight category (NWCs) and performed assessments of glomerular filtration rate (GFR) by iohexol clearance, renal plasma flow (RPF) by p-aminohippurate (PAH) clearance, and kidney perfusion and oxygenation by multiparametric kidney MRI. Additionally, we measured insulin secretion and estimated whole-body and adipose insulin sensitivity in youth with T2D and OCs using a hyperglycemic clamp.

RESEARCH DESIGN AND METHODS

Study Design and Participants

Adolescents and young adults (N = 50) with T2D (age 12–21 years; diabetes onset at age <18 years; diabetes duration 1–10 years; HbA_{1c} <14%) from the Renal Hemodynamics, Energetics, and Insulin Resistance in Youth Onset Type 2 Diabetes (Renal-HEIR) study were recruited from the T2D clinics at the Children's Hospital Colorado, Anschutz Medical Campus, in Aurora, Colorado. T2D was defined according to the American Diabetes Association criteria plus the absence of glutamic acid decarboxylase, islet cell, zinc transporter 8, and/or insulin autoantibodies. Exclusion criteria are detailed in Supplementary Fig. 1. Medication use was recorded for all participants, and diabetes treatment was at the discretion of their medical provider. Individuals without T2D who were classified as having obesity (OCs, N = 21) were enrolled from our Lifestyle Medicine Tier 1 Clinic. Meanwhile, NWCs were identified from the Child Health Clinic at Children's Hospital Colorado (N = 20). Research visits were performed at the University of Colorado Clinical and Translational Research Center (CTRC), with fasting in the morning, and preceded by 3 days of restricted physical activity and a fixed-macronutrient and sodium- and protein-replete weight-maintenance diet. Participants remained fasted until after all study procedures were completed. The Renal-HEIR cohort was approved by the Colorado Multiple Institutional Review Board. Participants or parents provided written informed assent and/or consent as appropriate for age.

Clinical Measurements and Biochemistry

Blood pressure was measured in seated participants using an automated oscillometric sphygmomanometer on the brachial artery of the nondominant arm after 5 min of rest. Three readings were taken 1 min apart. Systolic and diastolic blood pressure were averaged from these measures.

CTRC Core Laboratories conducted all assays. Insulin was measured using a CLIA-certified chemiluminescent immunoassay (Beckman Coulter). Standard methods were used to assess fasting evaluations, such as free fatty acid (FFA), C-peptide, total cholesterol, LDL, HDL, triglyceride, glucose, and HbA_{1c} (Diabetes Control and Complications Trial calibrated) levels, in the CTRC laboratory.

GFR and RPF by Iohexol and PAH Clearance, eGFR, and UACR

Iohexol was administered through bolus i.v. injection (5 mL of 300 mg/mL; Omnipaque 300; GE Healthcare). Blood collections for iohexol plasma disappearance were drawn at +120, +150, +180, +210, and +240 min (16). The Jødal-Brøchner-Mortensen equation was used to calculate GFR (17). PAH (2 g/10 mL, with a dose of [weight in kg]/75 × 4.2 mL; Basic Pharma, Geleen, the Netherlands) was administered slowly over 5 min, followed by a continuous infusion of PAH (32 mg/mL) at a rate of 24 mL/h for 2 h. After an equilibration period, blood was drawn at 90 and 120 min, and RPF was calculated as PAH clearance divided by the estimated extraction ratio of PAH (18).

In adolescents with T2D and OCs, GFR and RPF were measured during mild hyperglycemia (goal blood glucose 190 mg/dL [10.6 mmol/L]) achieved by a modified

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**A complete list of Bjornstad Lab members can be found in the APPENDIX.*

hyperglycemic clamp with paired 20% dextrose, chosen to control for glycemic differences between the two groups and maintain steady-state glycemic concentrations during renal measures (13). In NWCs, GFR and RPF were measured during fasting without glucose control to represent normal physiology. Iohexol and PAH measurements were performed using high-performance liquid chromatography (Waters, Milford, MA) at the National Institute of Diabetes and Digestive and Kidney Diseases laboratory in Phoenix, Arizona, as described previously (19). By using measurements of GFR, RPF, hematocrit, and total protein, we calculated afferent and efferent arteriolar resistance and intraglomerular pressure by Gomez equations (10,20). We also calculated renal vascular resistance (mean arterial pressure/renal blood flow).

The full age spectrum serum creatinine and cystatin C equation was used to determine estimated GFR (eGFR) (21). Hyperfiltration by eGFR was defined as eGFR $\geq$135 mL/min/1.73 m^2, which represents 2 SDs above the mean for healthy youth in NHANES, and hyperfiltration by measured GFR (mGFR) was defined as mGFR $\geq$2 SDs above the mean of mGFR in NWCs in Renal-HEIR.

The urine albumin-to-creatinine ratio (UACR) was calculated as urine albumin (mg)/urine creatinine (g) measured during fasting from spot urine samples before and after renal clearance assessment and averaged. Participants with average UACR $\geq$30 mg/g were considered to have elevated albuminuria.

Insulin Secretion and Whole-Body and Adipose Insulin Sensitivity by Modified Hyperglycemic Clamp (youth with T2D and OCs only)

A hyperglycemic clamp was performed in participants with T2D and those with obesity without diabetes (i.e., OCs) to determine insulin secretion and insulin sensitivity. A 20% dextrose infusion was titrated to maintain hyperglycemia ($\sim$190–200 mg/dL) (22,23) for 240 min while participants rested in bed, based on bedside glucose readings every 10 min from a heated arterialized hand vein, similarly to our previous studies (24,25). Glucose was measured at bedside using a Stat Strip glucometer (Nova Biomedical) based on the glucose oxidase technique. Insulin, FFA, and C-peptide measurements were collected at baseline ($-$10 and $-$5 min), during the 10 min after an i.v. bolus of 20% dextrose with a target of achieving 190–200 mg/dL, and every 10 min during the steady state from 190 to 240 min. To assess first-phase insulin secretion in response to acute hyperglycemia, the acute insulin response to glucose (AIRg) was calculated as the incremental area under the curve for insulin levels during the first 10 min after glucose infusion using the trapezoidal rule. Similarly, the acute C-peptide response to glucose (ACPRg) was estimated by computing the incremental area under the curve for C-peptide levels during the same initial 10-min period. Both calculations subtracted the basal (preinfusion) insulin and C-peptide levels, respectively. The *M* value, an index of glucose disposal rate used to assess insulin sensitivity, was calculated from the mean glucose infusion rate during the steady state of the hyperglycemic clamp, adjusted for body weight (mg/kg/min) and lean body mass from DXA (mg/lean kg/min). A measure of insulin sensitivity normalized by steady-state insulin was then calculated by dividing the *M* value by the mean plasma insulin concentration during the steady-state period of the clamp (M/I). The disposition index (DI), a measure of the adequacy of insulin secretion relative to insulin sensitivity, was estimated as the product of the AIRg and the M/I index. Finally, adipose tissue insulin sensitivity was evaluated by assessing the suppression of FFAs during the hyperglycemic clamp. The extent of FFA suppression was calculated as the percentage decrease in FFA concentration from baseline to the steady-state period of the clamp, divided by the steady-state insulin concentration.

To allow a common measure of inulin sensitivity in all participants, we also estimated insulin sensitivity by an equation we previously validated against the hyperinsulinemic–euglycemic clamp: estimated insulin sensitivity = exp(4.64725 $-$ 0.02032 [waist (cm)] $-$ 0.09779 [HbA_{1c} (%)] $-$ 0.00235 [triglycerides (mg/dL)]).

Body Composition by DXA

Participants underwent DXA by standard methods on a Hologic device (Waltham, MA) to determine lean and fat mass.

Multiparametric and Functional Kidney MRI

All participants underwent a multiparametric kidney MRI scan on a Skyra Siemens 3T scanner at our Research Imaging Center. The scanning protocol included blood oxygen level–dependent (BOLD) MRI to estimate fractional oxygen availability (apparent relaxation rate R2* [s^{-1}]) (26). A multiple gradient-recalled echo sequence was used to acquire BOLD images in the coronal plane during breath hold at end expiration, before and after administration of the diuretic furosemide (20-mg i.v. injection). To account for variations in weight-based dosing, we adjusted for weight differences across the three groups. The higher the local deoxyhemoglobin level in the blood, the higher the R2* and the lower the local tissue oxygen content. The change in fractional renal oxygen availability (R2*) in response to furosemide provides an estimate of the oxygen-dependent tubular transport of sodium and renal oxygen consumption, called furosemide-suppressible oxygen consumption (FSOC). Participants also underwent pseudocontinuous arterial spin labeling MRI (pCASL) to measure renal perfusion (mL/min/100 g). The images were analyzed at the Prasad imaging laboratory at NorthShore, and the reader was blinded to the participants' clinical data.

Statistical Analysis

Participant characteristics were summarized as count and percentage, mean and SD, or median (25th, 75th percentiles) based on visual inspection of histograms for distribution. NWC, OC, and youth with T2D groups were compared using the χ^2 or Fisher exact test for categorical variables or the ANOVA or Kruskal-Wallis test for continuous variables. Pairwise comparisons were tested using the Tukey honestly significant differences test or Dunn test of multiple comparisons. Multiple linear regression was used to assess differences in kidney structure and function parameters between groups adjusting for sex, HbA_{1c}, and race/ethnicity. Pearson and Spearman correlations were computed based on distribution among clamp, MRI, and DXA parameters. Correlations were visually inspected with scatter plots, and interactions between groups were tested. Group differences were also evaluated after excluding participants who indicated

use of renin-angiotensin-aldosterone system (RAAS) and/or sodium–glucose cotransporter 2 (SGLT2) inhibitors as a sensitivity analysis. A P value of <0.05 was considered statistically significant. Analyses were performed using Python v.3.9.6 and R v.4.2.2.

RESULTS

Clinical Characteristics of Cohort

Participants were similar in age, but there were more girls and young women in the youth with T2D and NWC groups compared with in the OC group (Table 1). Both the youth with T2D and OC groups had greater representation of Latinos compared with the NWC group. The youth with T2D and OC groups exhibited greater BMI and systolic blood pressure compared with the NWC group. As expected, youth with T2D demonstrated the highest mean HbA_{1c} and also had the highest eGFR and median UACR among the three groups. Among youth with T2D, 90% had been prescribed metformin, 36% insulin, 26% SGLT2 inhibitors, 16% pioglitazone, 12% RAAS inhibitors, and 2% statins. Ten percent of OCs had also been prescribed RAAS inhibitors. NWCs had not been prescribed any of these medications.

Body Composition and Whole-Body and Adipose Insulin Sensitivity

Using DXA, we found that OCs had the highest lean, fat mass, trunk mass, and body fat percentages among the three groups (Table 2). Both OCs and youth with T2D had significantly higher values for these parameters than NWCs ($P < 0.0001$). The differences in DXA parameters between OCs and youth with T2D were not statistically significant.

Only OCs and youth with T2D underwent the hyperglycemic clamp procedure, and therefore, any comparison in clamp-derived parameters is limited to these two groups. Fasting FFA and insulin levels were similar between OCs and youth with T2D (Table 2). FFA suppression was lower in youth with T2D versus OCs (66.6% [36.1, 85.5%] vs. 93.5% [91.4, 94.9%]; $P < 0.0001$). Likewise, insulin sensitivity (M value 3.6 ± 2.7 vs. 9.6 ± 3.3 mg/kg lean/min; $P < 0.0001$), insulin secretion in the form of AIRg (31.8 [0.0, 113.0] vs. 471.0 [250.8, 591.0] pmol/L; $P < 0.0001$), steady-state insulin and C-peptide, and DI (0.6 [0.0, 1.6] vs. 3.8 [2.4, 4.5] $\times 10^3$ mg/kg lean/min; $P < 0.0001$) were lower in youth with T2D compared with OCs (Table 2). Supplementary Fig. 2 illustrates the relationships between insulin secretion and sensitivity measures in OCs and youth with T2D. OCs generally maintained consistent insulin secretion across a broad range of insulin sensitivities. In contrast, youth with T2D with lower insulin sensitivity also tended to demonstrate diminished insulin secretion. Notably, a subset of youth with T2D showed negligible insulin and/or C-peptide responses to hyperglycemia, indicating severe β-cell dysfunction. Insulin sensitivity normalized by steady-state insulin was similar between youth with T2D and OCs, which underscores the difference in insulin concentrations between these two groups during the hyperglycemic clamp (Table 2).

Measured GFR and RPF and Intraglomerular Hemodynamic Parameters

Both youth with T2D and OCs exhibited glomerular hyperfiltration, and absolute and BSA-indexed GFR and RPF were higher in these groups compared with in NWCs (Table 2). Intraglomerular pressure was highest in youth with T2D, followed by OCs and NWCs (78 ± 12 vs. 65 ± 5 vs. 56 ± 5 mmHg; $P < 0.0001$). This difference was statistically significant between youth with T2D and OCs and NWCs, but not between OCs and NWCs. Afferent arteriolar resistance was also lower in youth with T2D and OCs compared with NWCs, and efferent arteriolar resistance was higher in youth with T2D (Table 2 and Supplementary Fig. 3). All observations in group differences remained the same in the sensitivity analysis excluding participants using RAAS and/or SGLT2 inhibitors.

Kidney Structure and Function Parameters by Multiparametric MRI

Average kidney perfusions of the left and right kidneys were numerically higher in youth with T2D versus OCs and NWCs, although the differences were not statistically significant (Table 2). Right and left fractional cortical and medullary oxygen availability (R2*) were lower in youth with T2D and OCs compared with in NWCs (but not between youth with T2D and OCs), suggestive of higher oxygen availability (relative hyperoxia) in youth with T2D and OCs. Group differences remained statistically significant in the sensitivity analysis excluding participants using RAAS and/or SGLT2 inhibitors.

Participants with T2D exhibited the highest FSOC after adjusting for weight, but this did not reach statistical significance after adjustments for multiple comparisons.

Associations Among Insulin Secretion, Insulin Sensitivity, and Kidney Function and Energetics

In all participants, fat mass, trunk mass, and body fat percentage correlated positively with intraglomerular pressure (Fig. 1 and Supplementary Fig. 4). Across the three groups, fractional cortical and medullary oxygen availability (R2*) and FSOC were associated inversely with fat mass, trunk mass, and body fat percentage.

We did not identify a significant statistical interaction between diabetes status and kidney parameters in youth with T2D and OCs, which justified their combined analysis irrespective of diabetes status. In analyses limited to youth with T2D and OCs, higher fat and trunk mass correlated strongly with higher GFR, RPF, fractional cortical and medullary oxygen availability, and FSOC (Fig. 2 and Supplementary Fig. 5). Of the DXA parameters, higher trunk mass correlated significantly with higher intraglomerular pressure (Fig. 2 and Supplementary Fig. 5). Lower DI correlated inversely with higher intraglomerular pressure (R −0.34; $P = 0.01$). Lower AIRg and ACPRg correlated inversely with higher FSOC (Fig. 2 and Supplementary Fig. 5). A sensitivity analysis of youth with T2D excluding those who showed negligible insulin and/or C-peptide responses to hyperglycemia showed similar results in correlation between AIRg and ACPRg with FSOC (data not shown).

Insulin Secretion, Insulin Sensitivity, and Kidney Function and Energetics in Youth With T2D Stratified by Albuminuria and Glomerular Hyperfiltration

Participants with T2D and albuminuria exhibited higher fat mass and trunk mass and lower FFA suppression, M/I, and DI compared with their peers with T2D without albuminuria (Supplementary Table 1). Fractional cortical oxygen availability was

Table 1—Participant characteristics stratified by group

	NWCs (n = 20)	OCs (n = 21)	Youth with T2D (n = 50)	Pairwise difference*	P
Age, years	16.6 ± 3.0	16.1 ± 2.1	16.4 ± 2.1	—	0.791
Diabetes duration, years	NA	NA	2.3 ± 1.8	—	—
Sex				OT†, NO	0.016
Female	14 (70)	6 (29)	30 (60)		
Male	6 (30)	15 (71)	20 (40)		
Race/ethnicity				NT†, NO	<0.001
Hispanic or Latino	6 (30)	15 (71)	38 (76)		
Not Hispanic or Latino White	11 (55)	4 (19)	4 (8)		
Not Hispanic or Latino Black	1 (5)	1 (5)	7 (14)		
Not Hispanic or Latino other	2 (10)	1 (5)	1 (2)		
BMI, kg/m^2	22.5 ± 3.6	37.6 ± 7.4	36.4 ± 7.4	NT†, NO†	<0.001
Weight, kg	62.1 ± 14.2	112.3 ± 23.2	104.0 ± 24.6	NT†, NO†	<0.001
Height, cm	165.4 ± 10.8	172.6 ± 10.8	168.5 ± 8.0	—	0.052
Waist circumference, cm	81.5 ± 9.8	120.4 ± 15.9	114.4 ± 15.5	NT†, NO†	<0.001
Tanner stage‡				—	0.447
I	0 (0)	0 (0)	0 (0)		
II	1 (7)	0 (0)	0 (0)		
III	0 (0)	0 (0)	0 (0)		
IV	2 (13)	1 (8)	4 (9)		
V	12 (80)	12 (92)	40 (91)		
HbA_{1c}, %	5.2 (5.1, 5.4)	5.4 (5.3, 5.5)	6.4 (5.9, 7.6)	OT†, NT†	<0.001
SBP, mmHg	118 ± 10	127 ± 7	124 ± 8	NT, NO	0.002
DBP, mmHg	70 ± 7	70 ± 6	73 ± 8	—	0.138
Cholesterol, mmol/L	146 ± 28	158 ± 22	162 ± 29	—	0.091
LDL, mg/dL	92 ± 24	111 ± 22	109 ± 25	NT, NO	0.017
HDL, mg/dL	46 ± 9	37 ± 7	38 ± 8	NT†, NO†	<0.001
Baseline triglycerides, mg/dL	90 (65, 106)	127 (95, 160)	160 (109, 197)	NT†, NO	<0.001
Estimated insulin sensitivity§	9.35 (8.35, 11.63)	3.98 (3.16, 4.61)	3.70 (2.54, 4.55)	NT†, NO†	<0.001
eGFR, mL/min/1.73 m^2‖	107 (97, 117)	115 (103, 124)	120 (109, 141)	NT	0.005
UACR, mg/g	6.5 (4.3, 10.2)	5.3 (3.4, 14.3)	10.3 (5.9, 58.0)	OT, NT	0.003
Elevated UACR, ≥30 mg/g	3 (15)	4 (19)	15 (30)	—	0.365
Hyperfiltration by eGFR¶	2 (10)	2 (10)	16 (32)	—	0.045
Hyperfiltration by mGFR¶	1 (5)	13 (62)	26 (54)	NT, NO†	<0.001
Metformin use	0 (0)	0 (0)	45 (90)	OT†, NT†	<0.001
Insulin use	0 (0)	0 (0)	18 (36)	OT†, NT	<0.001
SGLT2 inhibitor use	0 (0)	0 (0)	13 (26)	OT†, NT	0.001
Thiazolidinedione use	0 (0)	0 (0)	8 (16)	OT†	0.041
RAAS inhibitor use	0 (0)	2 (10)	6 (12)	—	0.359
Statin use	0 (0)	0 (0)	1 (2)	—	1.000
GLP-1 use	0 (0)	0 (0)	1 (2)	—	1.000

Continuous variables are shown as mean ± SD or median (25th, 75th percentiles) and were tested using ANOVA or Kruskal-Wallis rank sum test. Categorical variables are shown as n (%) and were tested using χ^2 or Fisher exact test. DBP, diastolic blood pressure; GLP-1, glucagon-like peptide 1; NO, NWCs vs. OCs; NT, NWCs vs. youth with T2D; OT, OCs vs. youth with T2D; SBP, systolic blood pressure. *Pair abbreviations are shown if pairwise test was significant at $P < 0.05$. †$P < 0.001$. ‡Nineteen participants (21%) were missing Tanner stage. Breast Tanner stage was evaluated for female participants, and testicular volume Tanner stage was evaluated for male participants. §SEARCH for Diabetes in Youth study insulin sensitivity score: estimated insulin sensitivity = exp(4.64725 − 0.02032 [waist (cm)] − 0.09779 [HbA_{1c} (%)] − 0.00235 [triglycerides (mg/dL)]). ‖Full age spectrum. ¶Hyperfiltration by eGFR defined as eGFR by full age spectrum ≥135 mL/min/1.73 m^2, and hyperfiltration by mGFR defined as mGFR ≥2 SDs above mean body surface area–indexed mGFR of NWCs.

Table 2—DXA, intraglomerular hemodynamic function, MRI, and hyperglycemic clamp measures by group

	NWCs (n = 20)	OCs (n = 21)	Youth With T2D (n = 50)	Pairwise difference*	P
DXA					
Lean mass, kg	44 ± 11	62 ± 12	56 ± 11	NT†, NO†	<0.001
Fat mass, kg	19 ± 7	51 ± 15	44 ± 15	NT†, NO†	<0.001
Fat percentage, %	30 ± 7	45 ± 7	43 ± 7	NT†, NO†	<0.001
Trunk mass, kg	27 ± 8	53 ± 11	50 ± 13	NT†, NO†	<0.001
Intraglomerular hemodynamic function					
GFR, mL/min	136 ± 22	231 ± 60	209 ± 63	NT†, NO†	<0.001
GFR, mL/min/1.73 m^2	139 ± 8	168 ± 38	163 ± 42	NT, NO	0.021
RPF, mL/min	616 ± 60	913 ± 118	857 ± 169	NT†, NO†	<0.001
RPF, mL/min/1.73 m^2	624 ± 92	681 ± 103	663 ± 105	—	0.264
FF, %	23 ± 3	23 ± 5	24 ± 6	—	0.679
P_{GLO}, mmHg	56 ± 4	66 ± 6	79 ± 11	OT†, NT†	<0.001
R_A, dyne × s × cm^{-5}	2,298 ± 397	1,114 ± 481	865 ± 502	NT†, NO†	<0.001
R_E, dyne × s × cm^{-5}	1,153 (1,038, 1,252)	1,195 (989, 1,269)	2,166 (1,693, 2,415)	OT†, NT†	<0.001
RVR, mmHg/L/min × 1,000	0.08 ± 0.01	0.06 ± 0.01	0.07 ± 0.01	OT, NT†, NO†	<0.001
Multiparametric kidney MRI					
Average cortex 3D ASL, mL/min/100 g	196.9 ± 53.4	195.6 ± 45.7	217.7 ± 46.2	—	0.158
Average cortex R2*, s^{-1}	21.2 ± 2.3	18.9 ± 2.2	18.0 ± 1.8	NT†, NO	<0.001
Average medulla R2*, s^{-1}	27.8 ± 3.0	24.6 ± 2.8	24.5 ± 3.1	NT†, NO	<0.001
Average FSOC medulla, % (weight adjusted)‡	4.0 ± 0.6	4.2 ± 0.5	5.5 ± 0.3	—	0.014
Hyperglycemic clamp measures§					
Fasting FFAs, μmol/L	—	641.4 ± 147.6	714.3 ± 209.0	—	0.163
FFA suppression, %	—	93.5 (91.4, 94.9)	66.6 (36.1, 85.5)	—	<0.001
Fasting insulin, pmol/L	—	17.5 (12.0, 24.5)	17.0 (8.8, 25.8)	—	1.000
Steady-state insulin, pmol/L	—	1,233.0 (832.5, 1,488.0)	205.5 (81.8, 402.8)	—	<0.001
Steady-state C-peptide, nmol/L	—	16.8 ± 4.5	8.1 ± 4.6	—	<0.001
Insulin-to–C-peptide ratio	—	72.5 (60.5, 90.5)	27.1 (17.5, 43.8)	—	<0.001
M value, mg/kg lean/min	—	9.6 ± 3.3	3.6 ± 2.7	—	<0.001
M/I, (mg/kg lean/min)/pmol/L	—	0.008 (0.005, 0.010)	0.011 (0.006, 0.022)	—	0.062
DI, ×10^3 mg/kg lean/min	—	3.8 (2.4, 4.5)	0.6 (0.0, 1.6)	—	<0.001
AIRg, pmol/L	—	471.0 (250.8, 591.0)	31.8 (0.0, 113.0)	—	<0.001
ACPRg, nmol/L	—	5.3 (4.3, 6.9)	0.6 (0.3, 1.4)	—	<0.001

Continuous variables are shown as mean ± SD or median (25th, 75th percentiles) and were tested using ANOVA or Kruskal-Wallis rank sum test. Categorical variables are shown as n (%) and were tested using χ^2 or Fisher exact test. FF, filtration fraction; NO, NWCs vs. OCs; NT, NWCs vs. youth with T2D; OT, OCs vs. youth with T2D; P_{GLO}, glomerular pressure; R_A, afferent arteriolar resistance; R_E, efferent arteriolar resistance; RVR, renal vascular resistance. *Pair abbreviations are shown if pairwise test was significant at $P < 0.05$. †$P < 0.001$. ‡Weight-adjusted average FSOC mean shown as adjusted mean ± SE. §Hyperglycemic clamp measures not performed in NWCs.

numerically lower in participants with T2D and in participants with albuminuria compared with those without albuminuria, indicating relative hyperoxia in albuminuria, although these relationships were not statistically significant.

After stratifying youth with T2D by glomerular hyperfiltration status, we found lower medullary fractional oxygen availability in those with hyperfiltration compared with in those without, although this only achieved statistical significance in the left kidney (Supplementary Table 2).

CONCLUSIONS

The current study highlights a substantial prevalence of glomerular hyperfiltration, intraglomerular hypertension, and elevated albuminuria among young individuals with T2D, conditions associated with central adiposity and parameters of impaired insulin sensitivity and insulin secretion. Uniquely, to our knowledge, this is the first study integrating iohexol, PAH, and hyperglycemic clamps in youth with T2D and the first to compare these individuals with OCs and NWCs. Additionally, using mutliparametric MRI, we observed the novel finding of cortical and medullary hyperoxia in both young individuals with T2D and OCs. Moreover, higher FSOC was associated with lower insulin secretion in young individuals with T2D and obesity.

The current study used functional methods to achieve a deeper understanding of the relationship between early kidney injury, obesity, IR, and β-cell dysfunction in youth with T2D. Glomerular hyperfiltration is prevalent in youth with T2D, serving as an early marker of DKD. The kidneys' high metabolic activity, essential for filtration, intrarenal hemodynamic function, and tubular reabsorption, makes them susceptible to oxidative stress and ultimately hypoxia (typically later in the disease stage) (19,20,27). Hypoxia can arise from an imbalance between kidney oxygen delivery and demand and is increasingly proposed as a common pathway in the development of DKD (28,29). Animal studies of T2D suggest that the kidneys are unable to compensate adequately for increased oxygen consumption early in the disease (30–32). In this study, we found the highest medullary oxygen consumption in youth with T2D. This aligns with experimental models and published kidney biopsy data from a small subset of participants in Renal-HEIR.

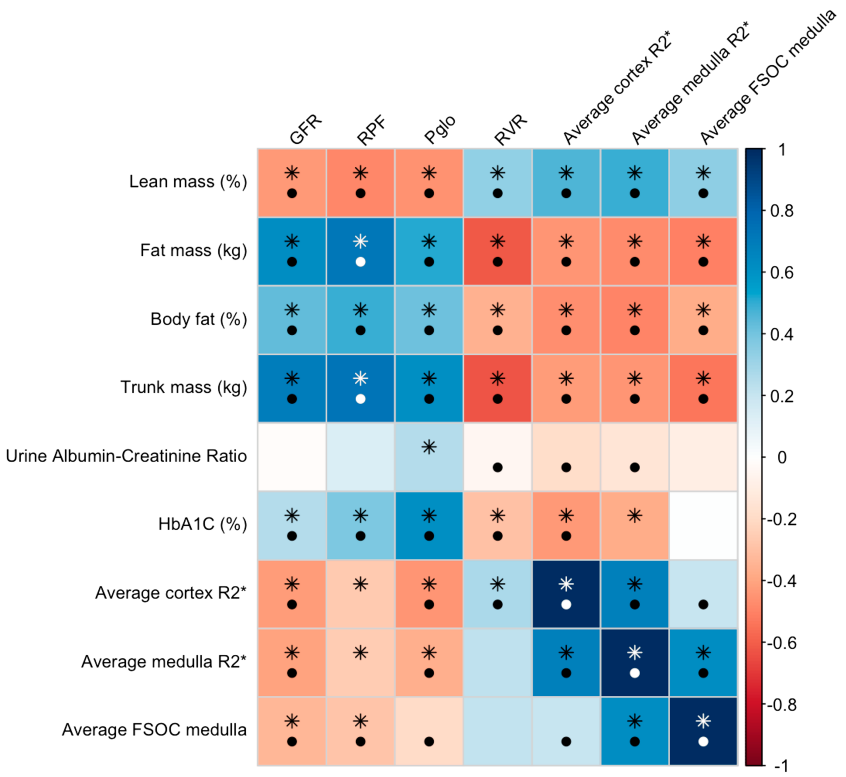

Figure 1—Correlation heatmap of all participants combined and multivariable linear regression. Color gradient represents the direction of correlation, with negative correlations depicted in red and positive correlations in blue. Spearman correlation analysis was performed to assess the relationship for UACR and HbA_{1c}. Significant correlation coefficients ($P < 0.05$) are denoted by stars. Significant associations in multivariable linear regression models, adjusted for sex and HbA_{1c} (or sex alone in models with HbA_{1c}), are indicated by dots ($P < 0.05$). Pglo, glomerular pressure; RVR, renal vascular resistance.

Biopsy data from this subset revealed transcriptional changes across most kidney segments, indicative of hypermetabolism (33). Indeed, the transcriptional changes observed in youth with T2D showed increased glycolysis, β-oxidation, and TCA cycle activity in the kidney (33).

However, in the current study, we also documented higher cortical and medullary oxygen availability (lower R2* values) in youth with T2D and/or obesity, suggesting relative hyperoxia. Given glomerular hyperfiltration, hypermetabolism, and increased oxygen consumption, we expected lower instead of higher oxygen availability. The exact etiology of this apparent hyperoxia remains unclear, but it could potentially be ascribed to impaired oxygen use and might also represent a higher set point of cortical and medullary oxygenation in early DKD in youth with T2D (34). In a prior study, we found that adults with T1D and early DKD also demonstrated medullary hyperoxia compared with NWCs (35). Additionally, a study in 24 patients with T1D or T2D showed that medullary hyperoxia at baseline was associated with a greater annual loss in eGFR, indicating that medullary hyperoxia might be important for the progression of early DKD (34). Experimental models have implicated hyperoxia in generating reactive oxygen species, disturbance of antioxidant balance, and induction of mitochondrial stress, all of which can lead to hyperoxia-induced cellular compromise, although this has yet to be examined in clinical studies of DKD (36).

Higher intraglomerular pressure was observed in both youth with T2D and OCs, although it was significantly higher in those with diabetes. The higher intraglomerular pressure in youth with T2D compared with in OCs seemed to result from greater efferent arteriolar tone. The higher efferent arteriolar tone in youth with T2D may have been influenced by the compounded effects of β-cell dysfunction and IR (37), potentially altering the RAAS, although delineating these specific mechanisms will require additional distinct research projects for conclusive evidence. It is also worth noting that SGLT2 inhibitors are thought to attenuate intraglomerular hypertension in T2D by postglomerular vasodilation (i.e., modulation of efferent arteriolar tone) (38). Our findings underscore the role of obesity in contributing to kidney disease in youth, even in individuals without diabetes (39). Although obesity does not fully account for the severity and progression disparities of T2D in youth versus adults, weight loss can bring about significant positive changes (40). These observations offer promise for gut hormone–based therapies, such as glucagon-like peptide 1 and glucagon-like peptide 1/glucose-dependent insulinotropic polypeptide receptor agonists, in protecting against early kidney disease in youth with obesity both with and without T2D.

There are strengths of this study worth highlighting. To limit physiological variability, our study procedures were performed under standardized conditions. The direct assessments of GFR and RPF provided an accurate ascertainment of intraglomerular hemodynamic function, and the hyperglycemic clamp permitted assessment of insulin secretion and sensitivity. The multiparametric MRI analyses provided estimates of perfusion and oxygen availability. Despite these strengths, our study has certain limitations. The cross-sectional design precludes the ability to ascertain causal relationships. However, we are actively observing many of these participants through a longitudinal observational study. Moreover, our sample size, particularly for the OCs and NWCs, was relatively small, which may limit the generalizability of our findings as well as the statistical power. Furthermore, our findings might not be applicable to youth with T2D exhibiting poorer glycemic control, even though our participants had control levels similar to those reported in the TODAY study for youth with comparable disease duration (5). Significant discrepancies in hyperfiltration rates were evident in OCs between GFR estimates from creatinine, cystatin C, and iohexol clearance, especially pronounced in OCs, suggesting potential eGFR inaccuracies in participants with high BMI. Additionally, BOLD MRI generates an indirect measure of oxygen availability based on the relaxation rate of deoxygenated

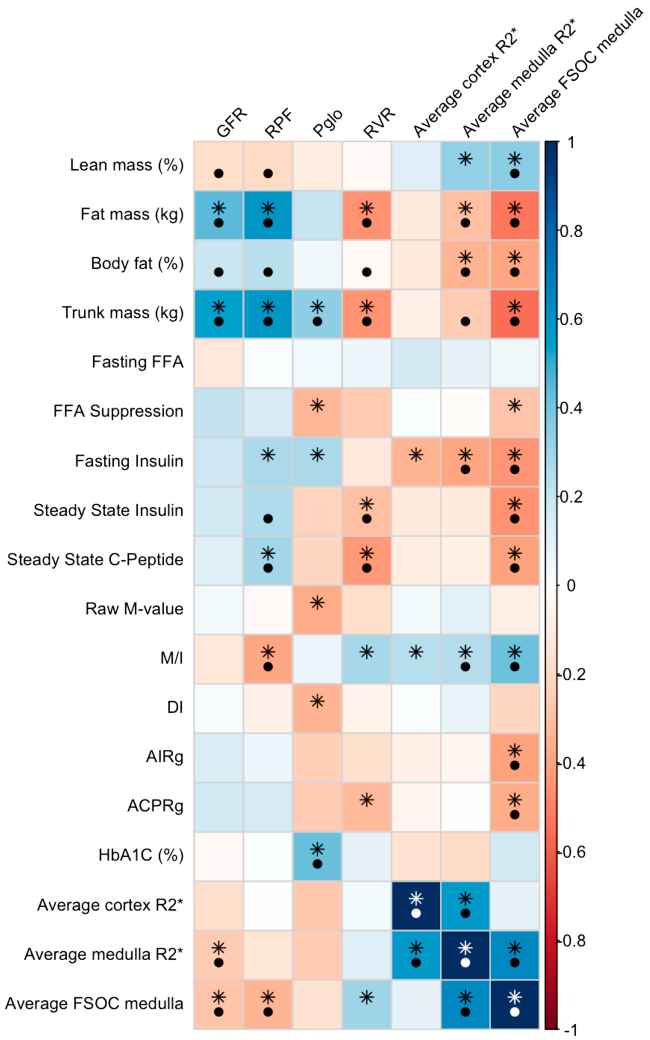

Figure 2—Correlation heatmap limited to youth with T2D and OCs and multivariable linear regression. Color gradient represents the direction of correlation, with negative correlations depicted in red and positive correlations in blue. Spearman correlation analysis was performed to assess the relationships for FFA suppression, fasting insulin, steady-state insulin, M/I, DI, AIRg, ACPRg, and HbA_{1c}. Significant correlation coefficients ($P < 0.05$) are denoted by stars. Significant associations in multivariable linear regression models, adjusted for sex and HbA_{1c} (or sex alone in models with HbA_{1c}), are indicated by dots ($P < 0.05$). Pglo, glomerular pressure; RVR, renal vascular resistance.

hemoglobin. It is confounded by factors such as tissue fluid and acid levels. Another limitation is the use of a hyperglycemic clamp rather than a hyperinsulinemic–euglycemic clamp to assess insulin sensitivity, but hyperglycemic clamps are also validated for this purpose and have the advantage of simultaneously assessing insulin secretion and allowing the controlled hyperglycemia needed for the kidney measures. Despite the limitations, this study represents the most comprehensive assessment of kidney function in youth with T2D to date.

In conclusion, intraglomerular hypertension and perturbed energetics are common in youth with T2D and associated strongly with obesity and parameters of insulin secretion and sensitivity. Further work is required to understand the relationship between these early pathophysiological factors and future clinical risk in order to design targeted early therapeutic interventions that are critical to prevent adult-onset kidney complications. In future studies, we will delve deeper into the multifactorial pathogenesis of DKD in youth-onset T2D.

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Duality of Interest. P.B. reports serving or having served as a consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, LG Chemistry, Sanofi, Novo Nordisk, and Horizon Pharma and on the advisory boards and/or steering committees of AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, and XORTX Therapeutics. D.C. has received honoraria from Boehringer Ingelheim, Eli Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi Tanabe Pharma, AbbVie, Janssen, Bayer, Prometic, Bristol-Myers Squibb, Maze Therapeutics, CSL-Behring, Otsuka Pharmaceutical, Novartis, Yeungene, and Novo Nordisk and has received operational funding for clinical trials from Boehringer Ingelheim, Eli Lilly, Merck, Janssen, Sanofi, AstraZeneca, and Novo Nordisk. A.S. reports personal fees from Horizon Therapeutics, CVS Caremark, AstraZeneca, Bayer, and Tate and Latham (medicolegal consulting). R.J.J. reports stock with XORTX Therapeutics, equity with Colorado Research Partners, and honoraria from Horizon Therapeutics. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. P.B. designed the study. P.B. and Y.J.C. wrote the manuscript. P.B., Y.J.C., C.P., S.G., I.M., L.R., M.B., G.S., T.D., L.D., K.T., L.L., P.P., R.G.N., R.J.J., and K.J.N. performed the research procedures, researched data, contributed to discussion, and reviewed/edited the manuscript. Y.J.C., T.V., and L.P. assisted in analyses, contributed to discussion, and reviewed/edited the manuscript. A.D., P.N., J.K., H.C.L., D.C., D.H.v.R., A.S., P.S., and R.G.N. contributed to discussion and reviewed/edited the manuscript. P.B. and Y.J.C. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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APPENDIX

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