Impact of Obesity on Measures of Cardiovascular and Kidney Health in Youth With Type 1 Diabetes as Compared With Youth With Type 2 Diabetes

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OBJECTIVE

Insulin resistance and obesity are independently associated with type 1 diabetes (T1D) and are known risk factors for cardiovascular and kidney diseases, the leading causes of death in T1D. We evaluated the effect of BMI on cardiovascular and kidney outcomes in youth with T1D versus control youth with normal weight or obesity and youth with type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

Pubertal youth ($n = 284$) aged 12–21 years underwent assessments of resting heart rate (RHR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), leptin, hs-CRP, adiponectin, ratio of urine albumin to creatinine, and estimated glomerular filtration rate. Participants with T1D underwent bicycle ergometry for VO_2peak, monitoring for peripheral brachial artery distensibility (BAD), endothelial function testing for reactive hyperemic index, and aortic MRI for central arterial stiffness or shear.

RESULTS

In adolescents with T1D, RHR, SBP, DBP, mean arterial pressure, leptin, hs-CRP, and hypertension prevalence were significantly higher, and BAD, descending aorta pulse wave velocity, and VO_2peak lower with an obese versus normal BMI. Although hypertension prevalence and RHR were highest in obese adolescents with T1D and adiponectin lowest in youth with T2D, other measures were similar between obese adolescents with T1D and those with T2D.

CONCLUSIONS

Obesity, now increasingly prevalent in people with T1D, correlates with a less favorable cardiovascular and kidney risk profile, nearly approximating the phenotype of youth with T2D. Focused lifestyle management in youth-onset T1D is critically needed to reduce cardiovascular risk.

The prevalence of pediatric overweight and obesity is increasing globally. In 2016, an estimated 340 million youth (18%) aged 5–19 years were affected worldwide—an increase from 4% in 1975 (1). A similar trend has been observed in youth with type 1 diabetes (T1D) (2–4) and is likely secondary to factors such as decreased physical activity and sleep and increased high-calorie food consumption, as well as an

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overemphasis on carbohydrate counting and/or aggressive insulin management strategies to target euglycemia. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive insulin management improved glycemia and complications in T1D; however, it also resulted in weight gain, central adiposity, hypertension, dyslipidemia, and generalized inflammation, all factors associated with cardiovascular disease (CVD) (5). Whereas CVD risk in type 2 diabetes (T2D) has been independently associated with obesity, insulin resistance (IR), and features of metabolic syndrome (6–9), these associations have been less clearly elucidated in T1D. Our group and others have shown that lean youth and adults with T1D demonstrate IR independent of elevations in BMI; however, IR is not typically associated with features of the metabolic syndrome or low adiponectin (10,11). A better understanding of factors contributing to the risk for T1D-associated CVD and diabetic kidney disease, the leading causes of morbidity and mortality, is critical (12,13).

Despite the ever-increasing prevalence of obesity in today's youth, only a few studies have evaluated the additive effect of childhood obesity on early measures of cardiovascular and kidney health in T1D. Limited studies have demonstrated higher rates of hypertension, dyslipidemia, and microalbuminuria in obese versus healthy weight youth with T1D (14,15). Thus, further evaluation of the impact of BMI on cardiovascular and kidney outcomes in T1D, and how those outcomes compare with those in similarly obese individuals with T2D, is critical because evidence of a similar progression toward complications would support not only closer attention to weight management but also additional exploration of treatment regimens that move beyond insulin therapy in obese youth with T1D.

We hypothesized that high BMI would negatively affect the cardiovascular and kidney profiles in T1D and that obese youth with T1D would demonstrate profiles similar to youth with T2D. To test this hypothesis, we comprehensively evaluated cardiovascular and kidney outcomes including resting heart rate (RHR), blood pressure (BP), peripheral arterial stiffness, central arterial stiffness, distensibility and wall shear stress (WSS), endothelial function, cardiopulmonary fitness, inflammatory markers, adipokine levels, urinary albumin excretion, and estimated glomerular filtration rate (eGFR) in lean and obese adolescents without diabetes; lean, overweight, and obese adolescents with T1D; and obese adolescents with T2D.

RESEARCH DESIGN AND METHODS

The studies included in this analysis were approved and monitored by the Colorado Multiple Institutional Review Board and an independent safety officer. All participants and their guardians provided written, informed assent and/or consent, as appropriate.

Participants

We included in this study 284 adolescents aged 12–21 years from the following three of our studies at the Children's Hospital Colorado using identical methods: Effects of Metformin on Cardiovascular Function in Adolescents With Type 1 Diabetes (EMERALD; ClinicalTrials.gov Identifier: NCT01808690), Resistance to Insulin in Type 1 and Type 2 Diabetes (RESISTANT), and Androgens and Insulin Resistance (AIRS). The latter two studies were completed before National Clinical Trial requirements for observational studies were established. Details of these study cohorts were previously described (16–18). Participants were recruited from 2013 to 2017 from the Barbara Davis Center for Diabetes and the Endocrinology and Lifestyle Medicine clinics at the Children's Hospital Colorado, and private endocrinology practice clinics. Baseline evaluations of 135 adolescents with T1D, 59 adolescents with T2D, and 90 adolescents without diabetes were available. Participant groups were recruited to be similar for BMI between the lean control and lean T1D groups and between the obese control, obese T1D, and obese T2D groups, and similar for HbA_{1c} between the T1D and T2D groups.

Screening included a history, physical examination, Tanner staging, and fasting laboratory testing. Inclusion criteria included Tanner stage >1 and sedentary status (i.e., <3 h of self-reported physical activity per week). T1D was defined as diabetes according to American Diabetes Association criteria plus the presence of ≥ 1 diabetes-associated autoantibody, a persistent insulin requirement since diabetes diagnosis, and a diabetes duration of ≥ 1 year. T2D was defined as diabetes according to American Diabetes Association criteria and an absence of diabetes-associated autoantibodies. Exclusion criteria included a resting BP $>$140/90 mmHg (no participants met this exclusion criterion), HbA_{1c} $>$12%, hemoglobin level $<$9 mg/dL, serum creatinine level $>$1.5 mg/dL, smoking, pregnancy, breast feeding, implanted metal, medications with antihypertensive effects or effects on insulin sensitivity (i.e., oral or inhaled glucocorticoids, noninsulin antihyperglycemic agents, immunosuppressants, and atypical antipsychotics), weight $>$136 kg (because of MRI table requirements), BMI below the fifth percentile, severe illness or diabetic ketoacidosis in the preceding 60 days; and, for control groups, diabetes by HbA_{1c}.

Pubertal staging was completed by a board-certified pediatric endocrinologist using the standards of Tanner and Marshall for breast development (girls) and pubic hair (girls and boys) (19,20). Testicular size was also documented (boys).

All assessments were performed in the morning after fasting for at least 10 h. Visits were preceded by 3 days without strenuous physical activity or caffeine intake and a Clinical and Translational Research Center–prepared fixed macronutrient and weight-maintenance diet (i.e., 55% of calories from carbohydrates, 30% from fat, and 15% from protein). Study visits for menstruating girls were scheduled in the follicular phase, whenever possible.

For participants with diabetes, visits were rescheduled for significant hypoglycemia in the preceding 24 h, or hyperglycemia with high ketone levels. An insulin-correction bolus was administered at home the morning before presentation if indicated for glucose targets.

Anthropometrics

BMI *z*-scores were calculated using the Centers for Disease Control and Prevention 2000 growth-chart standards (21). BMI groups were defined as lean ($<$85th percentile), overweight (85th to $<$95th percentile), or obese ($\geq$95th percentile).

Vascular Measures

BP was measured using a manual cuff–pressure oscillometer technique. Systolic BP (SBP) and diastolic BP (DBP) percentiles were calculated from the Pediatric Task Force database (22). Mean arterial pressure (MAP) and pulse pressure (PP) were calculated as [2(DBP) + SBP]/3 and

(SBP − DBP), respectively. RHR was measured with the participant seated after ≥5 min of rest. Subsequently, in the EMERALD cohort, the DynaPulse 5200A Pathway system (PulseMetric, Inc., San Diego, CA) was used to noninvasively measure peripheral arterial stiffness via brachial artery distensibility (BAD) using sphygmomanometer pulse waveform analysis of arterial pressure signals (16), and endothelial function was estimated by the reactive hyperemia index (RHI) via the EndoPAT 2000 device (Itamar Medical, Caesarea, Israel), a noninvasive technique combining traditional flow-mediated dilation with pneumatic fingertip probes to measure arterial pulse wave amplitude.

In addition, in the EMERALD participants, central vascular stiffness and blood flow were assessed with aortic MRI, as previously described (16), in a 3T scanner (Skyra; Siemens, Erlangen, Germany) using a 32-channel coil. A free-breathing phase contrast sequence was applied with Cartesian encoding and retrospective sorting (repetition time: 14–28 ms, 30–50 phases; echo time: 2.2–3.5 ms; matrix: 160 × 256; flip angle: 25°) with 100% k-space sampling and no additional temporal interpolation. Depending on participant size and field of view (128–225 × 210–360 mm), the cross-sectional pixel resolution was 0.82 × 0.82–1.56 × 1.56 mm^2 with a slice thickness of 5 mm. Phase-contrast acquisition time for each plane varied by heart rate, between 2 and 3 min. Velocity-encoding values were adjusted according to the maximum velocities encountered during scout sequences to avoid aliasing artifact (typically 100–250 cm/s).

This phase-contrast sequence was applied orthogonally to the ascending aorta at ~1 cm above the sinotubular junction, a plane that also corresponded to an orthogonal plane across the descending aorta, ~3–5 cm below the origin of the left subclavian artery. Both magnitude (tissue intensity) and phase-velocity maps were obtained, and raw data were transferred to an offline processing system (MatLab; Mathworks, Inc., Natick, MA) to determine the pulse wave velocity (PWV), relative area change (RAC), and WSS. Using the flow-area method (change in volume flow through the vessel [dQ] divided by change in cross-sectional surface area of the vessel [dA]: dQ/dA), flow and area waveforms were generated from time-frame–segmented respective phase and magnitude images (23,24). Flow-area diagrams assessed regional PWV by computing dQ/dA slope from early systolic data points. Central aortic distensibility was measured using the RAC, calculated as ([maximum area − minimum area]/minimum area) × 100%. WSS was calculated from segmented phase and magnitude images, as described previously, using an eight-point model to calculate through-plane WSS from the shear curve, yielding maximum systolic WSS and time-averaged WSS.

Exercise Testing

EMERALD participants performed bicycle ergometry via a graded cycle ergometer protocol (Lode, Groningen, the Netherlands) for VO_2peak by standard methods as previously described (6,10). Oxygen consumption (VO_2 [mL/kg/min]), carbon dioxide production (VCO_2 [mL/kg/min]), and minute ventilation were measured breath-by-breath at rest and during exercise using a metabolic cart (Ultima CPX; Medical Graphics, St. Paul, MN). VCO_2/VO_2 equals the respiratory exchange ratio (RER). Work rate was increased in 10, 15, or 20 W/min increments, depending on sex and age, while participants maintained a 65 rotations/min speed. VO_2peak (mL/kg/min and mL/lean kg/min) was defined as the peak VO_2 and HR averaged over 10 s at an RER ≥1.1. Data were excluded if RER was <1.1. Lean mass was assessed by DXA as previously described (6,10).

Laboratory Studies

Samples for the following serum and urine studies were collected in the morning after fasting, and, for participants with diabetes, samples were collected after an overnight insulin drip to normalize glycemia: HbA_{1c}, adiponectin, leptin, hs-CRP, brain natriuretic peptide (BNP), cystatin C, serum and urine creatinine, and urine microalbumin. HbA_{1c} was measured via DCCT-calibrated, ion-exchange high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA). All other laboratory evaluations were performed by standard methods in the Clinical and Translational Research Center laboratory (16–18).

Kidney Measures

We determined eGFR (mL/min/1.73 m^2) using the combined serum creatinine–cystatin C full-age spectrum equation validated in pediatrics and adults: eGFR (full-age spectrum combined) = 107.3/([α × ($S_{cr}Q_{crea}$)] + [(1 − α) × (S_{cysC}/Q_{cysC})]), where Q_{crea} is the median serum creatinine (S_{cr}) level in a healthy population, in order to account for both age and sex, as previously described (25). Q_{cysC} is 0.82 mg/L for all individuals <70 years old. The coefficient α is a weighting factor for the normalized kidney biomarkers and α = 0.5 was used here (i.e., the denominator is the average of both normalized biomarkers) (26). Hyperfiltration was defined conservatively a priori as an eGFR ≥141 mL/min/1.73 m^2, which includes the 95th percentile for adolescents without diabetes in our previous cohort and the 99th percentile for healthy adolescents in the National Health and Nutrition Examination Survey (27,28).

Statistical Analysis

Analyses were performed in SPSS, version 24 (IBM, Armonk, New York) or SigmaStat, version 4.0 (Systat Software, Inc., San Jose, CA). Variables were evaluated for the distributional assumption of normality using normal plots and Shapiro-Wilk tests. Demographic and clinical characteristics in nondiabetic control participants, participants with T1D, and participants with T2D were compared using *t* tests for normally distributed continuous variables and χ^2 test for categorical variables. Differences between groups were evaluated by *t* test or one-way ANOVA if variables were continuous and χ^2 test if variables were categorical. Multivariable linear regression models adjusted for sex were performed for group comparisons. Within-T1D group comparisons were adjusted for sex and diabetes duration. Comparisons between obese T1D and T2D groups were adjusted for sex, diabetes duration, and BMI. Post hoc analysis with Holms-Sidak correction when variances were equal or Dunnett analysis when variances were unequal were used to correct for multiple comparisons. Correlations were also performed between BMI as a continuous variable and all reported outcomes for the participants with T1D. Data are reported as either mean ± SD, if normally distributed, or median (25th, 75th percentile), if positively skewed. Significance was based on α = 0.05.

RESULTS

Demographic data are summarized in Table 1. The groups were similar in age.

Table 1—Baseline characteristics of adolescents without diabetes vs. those with T1D stratified by BMI classification vs. those with T2D

	Control		T1D			
	Lean control	Obese control	Lean T1D (BMI <85th percentile)	Overweight T1D (BMI 85– <95th percentile)	Obese T1D (BMI ≥95th percentile)	T2D
Participants, *n*	43	47	82	28	25	59
Age (years)	15.0 ± 2.1	14.5 ± 2.0	15.7 ± 2.5	16.2 ± 2.3	15.6 ± 2.1[c]	15.4 ± 2.3
Female sex (%)	63	68	50	79[e]	32[c,h]	71
Race/ethnicity, *n* (% of total)						
White	25 (58)	17 (36)[a]	71 (87)[b]	26 (93)	20 (80)[d]	11 (19)[j]
Hispanic	8 (19)	20 (43)[a]	6 (7)[a]	0 (0)	3 (12)[c]	34 (57)[j]
Other	10 (23)	10 (21)	5 (6)[a]	2 (7)	2 (8)	14 (24)
Tanner stage*	5 (4, 5)	5 (4, 5)	5 (4, 5)	5 (5, 5)[e]	5 (4, 5)[g]	5 (5, 5)
BMI (kg/m^2)	20.9 ± 2.6	32.4 ± 5.9[b]	20.8 ± 2.2	26.3 ± 2.7[f]	31.1 ± 3.1[fh]	33.6 ± 5.9[i]
Diabetes duration (years)	NA	NA	7.2 ± 4.2	7.3 ± 4.0	5.5 ± 3.6	2.1 ± 1.9[j]
HbA_{1c} (%)	5.2 ± 0.3	5.3 ± 0.3	8.5 ± 1.4[b]	8.6 ± 1.6	8.7 ± 1.5[d]	8.1 ± 2.4

Data are expressed as mean ± SD unless otherwise specified. NA, not applicable. *Median (interquartile range). [a]$P < 0.05$ vs. lean control group. [b]$P < 0.001$ vs. lean control group. [c]$P < 0.05$ vs. obese control group. [d]$P < 0.001$ vs. obese control group. [e]$P < 0.05$ vs. lean T1D. [f]$P < 0.001$ vs. lean T1D. [g]$P < 0.05$ vs. overweight T1D. [h]$P < 0.001$ vs. overweight T1D. [i]$P < 0.05$ vs. obese T1D. [j]$P < 0.001$ vs. obese T1D.

Tanner stage was higher in the overweight T1D group versus both the lean and obese T1D groups. HbA_{1c} was similar across diabetes groups per study design. The nondiabetic control and T2D groups had a higher percentage of female participants, whereas the obese T1D group had a higher percentage of male participants. A higher percentage of lean control participants and individuals with T1D were White, whereas the obese control group and T2D group had a higher percentage of Hispanic participants. Diabetes duration was significantly longer in the T1D group versus the T2D group and was adjusted for in the analysis.

Anthropomorphic and laboratory data are listed in Table 2. BNP, BAD, RHI, and aortic MRI data for individuals with T1D stratified by BMI are reported in Table 3. Correlations between BMI and all cardiovascular and kidney health outcome measures in youth with T1D are reported in Table 4.

Hemodynamic Measures

RHR was significantly higher in the obese T1D group versus the obese control, lean T1D, and T2D groups. Similarly, SBP and DBP were significantly higher in both the lean and obese T1D groups versus their respective BMI-stratified control groups. SBP and DBP, as well as their corresponding

Table 2—Cardiovascular vital signs and laboratory measures in adolescents without diabetes vs. those with T1D stratified by BMI classification vs. those with T2D

	Control		T1D			
	Lean control	Obese control	Lean T1D	Overweight T1D	Obese T1D	T2D
Participants, *n*	43	47	82	28	25	59
Vital sign						
HR (bpm)	65 ± 11	63 ± 9	68 ± 13	77 ± 13	78 ± 10[de]	72 ± 13[i]
SBP (mmHg)	110 ± 9	116 ± 9	114 ± 11[a]	123 ± 9[f]	124 ± 9[d]	121 ± 12
DBP (mmHg)	64 ± 8	69 ± 8	68 ± 8[a]	73 ± 8[f]	73 ± 7[cf]	70 ± 10
SBP percentile	48 ± 24	70 ± 20	57 ± 29	82 ± 17[f]	81 ± 19[cf]	76 ± 22
DBP percentile	47 ± 24	63 ± 22	54 ± 25	70 ± 21[e]	72 ± 19[cf]	64 ± 27
Prevalence of hypertension* (%)	5	11	10	26	44[cfg]	12[i]
PP (mmHg)	46 ± 6	47 ± 8	47 ± 10	51 ± 11[f]	52 ± 12	51 ± 10
MAP (mmHg)	80 ± 8	85 ± 7	83 ± 8[a]	89 ± 7[f]	90 ± 5[df]	87 ± 10
Kidney function measure						
Serum creatinine (mg/dL)	0.7 ± 0.13	0.7 ± 0.18	0.7 ± 0.16	0.7 ± 0.13	0.7 ± 0.14[g]	0.6 ± 0.15
ACR**	6.5 (5.3, 7.9)	5.6 (4.4, 7.1)	11.3 (8.6, 14.8)[a]	10.9 (7.1, 17.0)	8.1 (5.2, 12.7)[c]	14.8 (9.3, 23.5)
Prevalence of microalbuminuria* (%)	0	3	18[a]	13	12	31
eGFR (FAS) (mL/min/1.73 m^2)	105 ± 18	104 ± 22	113 ± 39	105 ± 22	113 ± 22	128 ± 36
Prevalence of hyperfiltration* (%)	9	8	14	9	13	33
Laboratory measure						
Adiponectin (μg/mL)**	8.5 (7.5, 9.8)	7.7 (6.7, 8.9)	10.7 (9.6, 11.8)[a]	9.7 (7.7, 12.3)	8.6 (7.2, 10.4)	5.1 (4.4, 5.9)[i]
Leptin (ng/mL)**	7.0 (4.9, 10.0)	31.9 (27.3, 37.1)	7.7 (6.3, 9.5)	21.5 (16.3, 28.3)[f]	25.9 (21.1, 31.9)[fh]	28.0 (23.3, 33.5)
hs-CRP (mg/L)**	0.4 (0.3, 0.6)	1.0 (0.7, 1.3)	0.4 (0.3, 0.5)	1.0 (0.6, 1.6)	1.8 (1.2, 2.8)[cf]	2.7 (1.9, 3.7)

Data are expressed as mean ± SD unless otherwise specified. Comparisons made include the following: lean T1D vs. overweight T1D vs. obese T1D; obese T1D vs. T2D; obese control vs. T1D. FAS, full age spectrum. *Percent of total. **Geometric mean (95% CI). [a]$P < 0.05$ vs. lean control group. [b]$P < 0.001$ vs. lean control group. [c]$P < 0.05$ vs. obese control group. [d]$P < 0.001$ vs. obese control group. [e]$P < 0.05$ vs. lean T1D. [f]$P < 0.001$ vs. lean T1D. [g]$P < 0.05$ vs. overweight T1D. [h]$P < 0.001$ vs. overweight T1D. [i]$P < 0.05$ vs. obese T1D. [j]$P < 0.001$ vs. obese T1D.

Table 3—Cardiovascular measures in lean, overweight, and obese youth with T1D

	T1D		
	Lean T1D	Overweight T1D	Obese T1D
Participants, *n*	26	9	13
Laboratory measure			
BNP (pg/mL)	44 ± 21	40 ± 23	42 ± 24
Peripheral vascular function measure			
RHI	2.04 ± 1.09	1.89 ± 0.67	1.73 ± 0.61
BA distensibility ($mmHg^{-1}$)	6.26 ± 1.19	5.94 ± 0.90	5.36 ± 0.61[a]
Central vascular function measure			
AA WSS_{MAX} ($dyne/cm^2$)	11.2 ± 2.7	11.0 ± 1.5	10.7 ± 2.6
AA WSS_{TA} ($dyne/cm^2$)	2.7 ± 0.7	2.6 ± 0.6	2.7 ± 0.8
AA PWV (m/s)*	3.4 (2.6, 4.4)	3.8 (2.4, 5.8)	2.7 (1.9, 3.8)
AA RAC (%)	25.7 ± 4.4	25.0 ± 7.3	29.3 ± 2.9
AA OSI	0.04 ± 0.04	0.03 ± 0.03	0.02 ± 0.03
AA distensibility (10^{-3} $mmHg^{-1}$)	5.5 ± 1.1	5.0 ± 1.6	5.4 ± 0.6
DA WSS_{MAX} ($dyne/cm^2$)	15.9 ± 4.5	17.9 ± 4.1	13.6 ± 3.2
DA WSS_{TA} ($dyne/cm^2$)	4.1 ± 1.3	4.5 ± 1.2	4.0 ± 1.0
DA PWV (m/s)	3.9 ± 1.2	4.9 ± 1.6[a]	3.6 ± 1.1[c]
DA RAC (%)	22.1 ± 4.6	22.5 ± 5.3	22.5 ± 4.1
DA OSI	0.04 ± 0.05	0.02 ± 0.01	0.01 ± 0.02
DA distensibility (10^{-3} $mmHg^{-1}$)	4.8 ± 1.1	4.6 ± 1.2	4.2 ± 0.6
Cardiopulmonary fitness measure			
VO_2 peak (mL/min/kg)	31 ± 7	24 ± 5[a]	23 ± 4[bc]
VO_2 peak (mL/min/lean kg)	43 ± 8	39 ± 7	36 ± 11[a]

Data are expressed as mean ± SD unless otherwise specified. AA, ascending aorta; BA, brachial artery; BNP, brain natriuretic peptide; DA, descending aorta; OSI, oscillatory shear index; WSS_{MAX}, maximum WSS; WSS_{TA}, time average WSS. *Geometric mean (95% CI). [a]$P < 0.05$ vs. lean T1D. [b]$P < 0.001$ vs. lean T1D. [c]$P < 0.05$ vs. overweight T1D. [d]$P < 0.001$ vs. overweight T1D.

percentiles, increased with increasing BMI across the T1D groups, with the obese T1D group not differing significantly from the T2D group. Prevalence of hypertension was highest in obese youth with T1D and was significantly higher than in the obese control, lean T1D, overweight T1D, and T2D groups. In addition, PP was significantly higher in the overweight T1D group versus the lean T1D group. MAP increased across T1D BMI groups, with a significant difference in the overweight T1D and obese T1D groups versus the lean T1D group. The MAP of the obese T1D group did not differ significantly from that of the T2D group.

RHI-assessed endothelial function did not differ significantly among the three BMI-stratified T1D groups. BAD-assessed peripheral arterial stiffness was significantly greater in the obese T1D group versus the lean T1D group. MRI-assessed central aortic stiffness, the descending artery PWV, was significantly greatest in the overweight T1D group.

Less favorable values of RHR, SBP, DBP, SBP percentile, DBP percentile, prevalence of hypertension, PP, MAP, BAD, ascending aorta oscillating shear index, and descending artery PWV all correlated significantly with higher BMI within participants with T1D (Table 4).

Cardiopulmonary Fitness

VO_2peak was significantly lower with increasing BMI in the T1D group, and this effect persisted whether evaluated per kilogram of body mass or lean mass. Lower VO_2peak per kilogram of body mass and per kilogram of lean mass correlated significantly with higher BMI within the participants with T1D (Table 4). VO_2peak in the obese T1D group was similar to that of our previously published VO_2peak data in obese adolescents with T2D of similar BMI (21.9 ± 4.2 mL/kg/min; 42.8 ± 7.6 mL/lean kg/min), and it was lower than that of both a lean adolescent control group (40.4 ± 9.9 mL/kg/min; 53.1 ± 8.5 mL/lean kg/min) and an obese adolescent control group (27.2 ± 5.3 mL/kg/min; 49.5 ± 5.6 mL/lean kg/min) (6).

Laboratory Studies

The median adiponectin concentration was paradoxically higher in the lean T1D group than in the lean control group, and higher in the obese T1D group than in the T2D group. Nevertheless, adiponectin did tend to decrease with increasing BMI in the T1D groups. The leptin and hs-CRP concentrations increased significantly across T1D BMI groups, in which both the leptin and hs-CRP median concentrations in the obese T1D group were significantly higher than in the lean T1D group and were similar to the that of the T2D group. BNP did not differ significantly between the T1D BMI-stratified groups. Lower adiponectin and higher leptin and hs-CRP levels correlated significantly with higher BMI within participants with T1D, whereas BNP did not (Table 4).

Kidney Measures

The median albumin-to-creatinine ratio (ACR) was significantly higher in lean and obese youth with T1D versus their respective lean and obese control groups. Similarly, microalbuminuria prevalence was significantly higher in lean youth with T1D versus lean control participants. No kidney measures correlated significantly with BMI within participants with T1D (Table 4). Obese youth with T1D did not differ significantly from youth with T2D in any kidney measure.

CONCLUSIONS

Obesity is increasingly prevalent in youth (1), including youth with T1D (2,4). We demonstrate that a higher BMI portends a more abnormal cardiovascular profile among adolescents with T1D, which is similar to, or less favorable than, youth with T2D on numerous metrics. We show that vital signs including RHR, SBP, DBP, MAP, and prevalence of hypertension, as well as serologic studies including leptin and hs-CRP concentrations were more unfavorable in adolescents with T1D as BMI increased. In addition, comprehensive functional measurements including cardiopulmonary fitness, peripheral arterial stiffness, and central aortic stiffness supported the relationship between high BMI and negatively affected cardiovascular profiles in adolescents with T1D. To our knowledge, ours is the first study to concurrently compare three unique adolescent populations: lean and obese control participants; lean, overweight, and obese individuals with T1D; and individuals with T2D, and to comprehensively evaluate the effect of obesity on early cardiovascular dysfunction and cardiovascular and kidney risk profiles within T1D.

RHR as well as SBP and DBP have long served as readily accessible methods for

Table 4—Correlations between BMI and all cardiovascular and kidney health outcome measures in youth with T1D

	BMI	
	R^2	*P* value
Vital sign		
HR (bpm)	0.30	0.02
SBP (mmHg)	0.36	<0.01
DBP (mmHg)	0.34	<0.01
SBP percentile	0.32	<0.01
DBP percentile	0.29	<0.01
Prevalence of hypertension	0.25	<0.01
PP (mmHg)	0.18	0.04
MAP (mmHg)	0.40	<0.01
Kidney function measure		
Serum creatinine (mg/dL)	0.16	0.08
ACR	−0.13	0.15
Prevalence of microalbuminuria	−0.13	0.15
eGFR (FAS) (mL/min/1.73 m^2)	−0.07	0.42
Prevalence of hyperfiltration	−0.12	0.17
Laboratory measure		
Adiponectin (μg/mL)	−0.20	0.02
Leptin (ng/mL)	0.61	<0.01
hs-CRP (mg/L)	0.60	<0.01
BNP (pg/mL)	0.13	0.44
Peripheral vascular function measure		
RHI	−0.08	0.61
BA distensibility ($mmHg^{-1}$)	−0.29	0.04
Central vascular function measure		
AA WSS_{MAX} ($dyne/cm^2$)	0.13	0.44
AA WSS_{TA} ($dyne/cm^2$)	−0.09	0.62
AA PWV (m/s)	−0.04	0.84
AA RAC (%)	−0.15	0.43
AA OSI	0.40	0.02
AA distensibility (10^{-3} $mmHg^{-1}$)	−0.27	0.11
DA WSS_{MAX} ($dyne/cm^2$)	−0.23	0.18
DA WSS_{TA} ($dyne/cm^2$)	0.02	0.89
DA PWV (m/s)	0.33	0.04
DA RAC (%)	−0.03	0.87
DA OSI	0.18	0.32
DA distensibility (10^{-3} $mmHg^{-1}$)	0.21	0.25
Cardiopulmonary fitness measure		
VO_2 peak (mL/min/kg)	−0.51	<0.01
VO_2 peak (mL/min/lean kg)	−0.25	0.02

AA, ascending aorta; BA, brachial artery; DA, descending aorta; FAS, full age spectrum; WSS_{MAX}, maximum WSS; WSS_{TA}, time average WSS.

monitoring cardiovascular health. Higher RHR independently predicts all-cause mortality in adults with T2D and correlates with major cardiovascular outcomes and death (29,30). Case-control and discordant T1D twin studies also have demonstrated a higher average RHR in those with versus those without T1D (31,32). The DCCT established that intensive insulin treatment was associated with a lower mean RHR in adolescents and adults with T1D (33), and the SEARCH for Diabetes in Youth Study subsequently related increased adiposity, higher BP, and hyperlipidemia with arterial stiffness, a direct indicator of cardiovascular dysfunction, in youth with T1D (34). We demonstrated that not only did RHR, SBP, and DBP increase with BMI in youth with T1D, the obese T1D group also had a significantly higher RHR, SBP, DBP, and MAP than that of the obese control participants, with values similar to the T2D group. Of note, the prevalence of hypertension was actually higher in the obese T1D group than in the T2D group. These results support the conclusion that T1D uniquely places individuals at risk for complications including cardiovascular dysfunction, independent of HbA_{1c} and BMI, which were similar in the two groups.

Similar to BP, adiposity has been associated with kidney dysfunction in T1D. We previously demonstrated that intraglomerular pressure and renal vascular resistance increase with greater adiposity in adults with T1D, a finding not seen in healthy adults without diabetes (35). In our analyses, adolescents with T1D had a higher ACR than did BMI-matched control participants without diabetes, but ACR and eGFR were not different by BMI within the T1D group. However, adolescents with T1D had similar ACR and eGFR elevations as those with T2D when controlling for BMI. This finding is worth additional study and longitudinal follow-up, because elevations in eGFR, even before the cutoff for hyperfiltration, occur prior to microalbuminuria and are a better predictor of future impairments in kidney function than is microalbuminuria in both T1D and T2D (7,28,36,37).

Findings from serologic studies have also demonstrated utility in the detection of CVD risk. The hs-CRP, a marker of generalized inflammation, is associated with increased abdominal obesity in adults with T1D (38), whereas concentrations of leptin, an adipokine with anorexigenic effects, increase in the setting of obesity in other populations (39). We found a significant increase in both hs-CRP and leptin concentrations with obesity in our T1D group, with elevations similar to the T2D group. These changes parallel lower cardiopulmonary fitness with increasing BMI in T1D, similar to our previous finding of an independent inverse association between leptin levels and both VO_2peak and insulin sensitivity in T1D (40). We and others have reported reduced cardiopulmonary fitness in normal-weight youth and adults with T1D (41,42), and we now demonstrate further decline in cardiopulmonary fitness in adolescents with T1D with elevated BMI. Finally, although we confirm our previous reports and those of others of paradoxically normal or high adiponectin levels in T1D despite concurrent IR and elevated leptin (10), adiponectin levels tended to decrease with increasing BMI in youth with T1D in the present study. More work is required to understand the dissociation of adiponectin from IR and leptin within T1D.

Peripheral arterial stiffness and endothelial dysfunction have been reported in youth with T1D versus control groups (43,44). Endothelial function tended to

be lower with increased BMI in T1D in our study but the difference, which was not significant, was potentially due to the use of EndoPAT rather than gold-standard flow-mediated dilation with brachial artery ultrasound. The SEARCH for Diabetes in Youth Study compared BAD-assessed peripheral arterial stiffness in youth with T1D versus those with T2D and demonstrated that peripheral arterial stiffness was largely a function of central adiposity and BP, independent of diabetes type (45,46). Our data similarly indicate that peripheral arterial stiffness was significantly higher in heavier adolescents with T1D in this study. A larger sample size and longitudinal data are needed to understand the significance and implications of our finding that descending aorta PWV was highest in the overweight T1D group versus the obese T1D group. Our study is novel in that we also include aortic MRI measures for gold-standard evaluation of central aortic stiffness. Data from previous study demonstrated that adolescents with T1D had impaired aortic health, as seen in an elevated ascending aorta and descending aorta PWV and WSS, and reduced distensibility (16). We now show that the descending aorta is most affected in the T1D group, but more research is needed to understand why increased BMI appears to preferentially associate with this segment of the thoracic aorta. Of note, we also recently showed that metformin reduced BMI, fat mass, and insulin dose in adolescents with T1D, which was associated with improvements in insulin sensitivity, MRI-assessed aortic PWV, and carotid intima-media thickness (16), supporting the use of interventions targeting BMI in T1D to improve cardiovascular function and reduce CVD risk.

There are several notable strengths and limitations of this study. First, we combined data from carefully designed studies that used identical methods, thus allowing for a large sample size. Second, our study allowed for a variety of comparisons between normal-weight and obese individuals with and without T1D and T2D. Third, we used comprehensive gold-standard methods to assess cardiovascular health, including aortic phase-contrast MRI to assess central aortic stiffness, WSS, oscillatory shear index, and RAC, and graded bicycle ergometry, as well as peripheral measures of vascular stiffness and endothelial function. Fourth, we controlled for the acute effects of recent physical activity and diet by limiting strenuous activity and completing a prestudy visit admission with study diet and an overnight fast. We also recruited only sedentary participants to control for the effects of chronic physical activity. Fifth, we controlled for the effects of chronic glycemia in T1D and T2D with a similar average HbA_{1c} between groups and for the impact of puberty on cardiometabolic outcomes by excluding prepubertal participants. Last, we were careful to ensure a similar BMI between the lean groups and between the obese groups, and we controlled for differences in sex, diabetes duration, and, where appropriate, BMI between groups in our analysis.

Limitations of this study include the cross-sectional study design, the relatively small sample size in the overweight and obese T1D groups, and the differences in race/ethnicity between groups. Of note, our participants with T1D were primarily White, which could have biased our findings toward the null hypothesis, yet derangements in cardiometabolic and kidney health were still demonstrated. Despite these limitations, our study highlights the significant negative impact of obesity on cardiovascular health in youth with T1D. Our study also demonstrates that obese adolescents with T1D, despite lacking classical features of metabolic syndrome, share a similar cardiovascular and kidney profile as youth with T2D, raising concern for poor long-term outcomes.

In conclusion, we demonstrate that a higher BMI is associated with a less favorable cardiovascular and kidney risk profile in youth with T1D, as evidenced by derangements in many measures of cardiovascular, kidney, and metabolic health in the setting of an elevated BMI in T1D. In addition, the profile of cardiovascular and kidney derangements seen in obese youth with T1D nearly approximated that of youth with T2D. Thus, although data previously indicated that long-term outcomes of youth-onset T2D appeared to portend higher cardiovascular and kidney risk than in youth-onset T1D, this gap may narrow if obesity continues to rise in T1D. Consequently, closer attention to weight-loss strategies and lifestyle management is critical in youth with T1D to help mitigate the risk for future CVD. Potential future directions include longitudinal studies evaluating the effect of maintaining a normal BMI or achieving weight loss with an elevated BMI in youth with T1D in an approach to comprehensively reduce cardiovascular and kidney risk factors.

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Author Contributions. K.L.T. interpreted data and wrote the manuscript. K.B. interpreted data, contributed to writing sections of the manuscript, and reviewed and edited the manuscript. M.S., I.M., S.H., L.P., U.T., and L.B. analyzed and interpreted data and reviewed and edited the manuscript. P.B. interpreted data

and reviewed and edited the manuscript. A.D.B. collected data and reviewed and edited the manuscript. M.C.-G. reviewed and edited the manuscript. J.G.R. and J.E.B.R. contributed to study design and reviewed and edited the manuscript. K.J.N. designed the study, collected data, interpreted data, and reviewed and edited the manuscript. K.J.N. is the guarantor of this work and, as such, has full access to the data set and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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