Adiposity Impacts Intrarenal Hemodynamic Function in Adults With Long-standing Type 1 Diabetes With and Without Diabetic Nephropathy: Results From the Canadian Study of Longevity in Type 1 Diabetes

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OBJECTIVE

Central adiposity is considered to be an important cardiorenal risk factor in the general population and in type 1 diabetes. We sought to determine the relationship between central adiposity and intrarenal hemodynamic function in adults with long-standing type 1 diabetes with and without diabetic nephropathy (DN).

RESEARCH DESIGN AND METHODS

Patients with type 1 diabetes (n = 66, duration ≥50 years) and age-/sex-matched control subjects (n = 73) were studied. The cohort was stratified into 44 DN Resistors (estimated glomerular filtration rate [eGFR] >60 mL/min/1.73 m^2 and <30 mg/day urine albumin) and 22 patients with DN (eGFR ≤60 mL/min/1.73 m^2 or ≥30 mg/day urine albumin). Intrarenal hemodynamic function (glomerular filtration rate for inulin [GFR_{INULIN}], effective renal plasma flow for p-aminohippuric acid [$ERPF_{PAH}$]) was measured. Afferent arteriolar resistance, efferent arteriolar resistance, renal blood flow, renal vascular resistance [RVR], filtration fraction, and glomerular pressure were derived from the Gomez equations. Fat and lean mass were quantified by DXA.

RESULTS

Whereas measures of adiposity did not associate with GFR_{INULIN} or $ERPF_{PAH}$ in healthy control subjects, trunk fat mass inversely correlated with GFR_{INULIN} (r = −0.46, P < 0.0001) and $ERPF_{PAH}$ (r = −0.31, P = 0.01) and positively correlated with RVR (r = 0.53, P = 0.0003) in type 1 diabetes. In analyses stratified by DN status, greater central adiposity related to lower GFR_{INULIN} values in DN and DN Resistors, but the relationships between central adiposity and $ERPF_{PAH}$ and RVR were attenuated and/or reversed in patients with DN compared with DN Resistors.

CONCLUSIONS

The adiposity-intrarenal hemodynamic function relationship may be modified by the presence of type 1 diabetes and DN, requiring further study of the mechanisms by which adiposity influences renal hemodynamic function.

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Diabetic nephropathy (DN) remains a major cause of end-stage renal disease (ESRD) and cardiovascular disease (1). Central adiposity is considered to be an important cardiorenal risk factor that is augmented by intensive insulin therapy and is increasingly recognized in people with type 1 diabetes (2,3). In fact, the obesity epidemic is affecting youth and adults with type 1 diabetes (4–7), increasing their lifetime risk for early death due to cardiorenal disease (8).

Epidemiologic data also indicate that greater centrally distributed fat may paradoxically offer cardiac and renal protection (9) in people with chronic kidney disease (CKD) and ESRD, especially in the elderly (10). This paradoxical relationship is termed the "central obesity paradox," although it is a misnomer because the phenomenon is not limited to obese individuals (11). The mechanisms whereby increased adiposity mediates nephroprotection remains unclear, but proposed explanations include better hemodynamic stability, altered cytokine profiles, and more effective sequestration of uremic toxins (12). It is unknown whether central adiposity confers nephroprotection in people with long-standing type 1 diabetes and DN.

Epidemiologic studies are limited to estimating glomerular filtration rate (GFR), which may correlate poorly with measured GFR, and have not provided data on effective renal plasma flow (ERPF) or other parameters of intrarenal hemodynamic function, including renal blood flow (RBF), renal vascular resistance (RVR), and filtration fraction (FF), glomerular pressure (P_{GLO}), afferent arteriolar resistance (R_A), and efferent arteriolar resistance (R_E). There are a few human studies examining the interactions between intrarenal hemodynamic function and central adiposity (13,14), but, to our knowledge, no such studies in adults with long-standing type 1 diabetes with and without DN have been performed.

Accordingly, the aim of this study was to define the relationships between central adiposity by DXA and intrarenal hemodynamic function measured by *p*-aminohippuric acid (PAH) and inulin clearance. We hypothesized that central adiposity would negatively correlate with GFR and ERPF, and positively correlate with RVR in adults with type 1 diabetes. Finally, we hypothesized that these associations would differ among adults with type 1 diabetes with and without DN, which would be consistent with the central obesity paradox.

RESEARCH DESIGN AND METHODS

Study Design

This was a cross-sectional cohort evaluation of 75 participants with type 1 diabetes with a duration of ≥50 years with DN and without DN (DN Resistors) and 75 age- and sex-matched control subjects to determine mechanisms of nephropathy resistance and to clinically phenotype nephropathy, retinopathy, neuropathy, and macrovascular disease for future biomarker studies. This represents an exploratory analysis within the second phase of the Canadian Study of Longevity in Type 1 Diabetes.

Study Population

Participants with type 1 diabetes were recruited from among those who took part in the mail-based survey of the first phase of the Canadian Study of Longevity in Type 1 Diabetes, whereas control subjects without diabetes were friends or family members of the participants with type 1 diabetes or were recruited through community advertisement. Inclusion criteria for the participants with type 1 diabetes included a duration of ≥50 years of type 1 diabetes, inclusion criteria for control subjects without diabetes included any race and sex-matched 1:1 within 5 years of age of a participant with type 1 diabetes, and an inclusion criterion common to both control subjects without diabetes and participants with type 1 diabetes was the ability to understand and cooperate with study procedures. Exclusion criteria for control subjects without diabetes included the presence of the following: *1*) diabetes or a fasting plasma glucose concentration >7.0 mmol/L or *2*) preexisting kidney disease, microalbuminuria, or estimated GFR (eGFR) <45 mL/min/1.73 m^2. Exclusion criteria common to both control subjects without diabetes and participants with type 1 diabetes were any current eye infection, corneal damage, severe movement disorder, or proparacaine allergy that would preclude safe in vivo corneal confocal microscopy examination. The study participants were recruited consecutively. All participants provided written informed consent, and the study and its procedures were approved by the institutional ethics board of the University Health Network and Mount Sinai Hospital in Toronto, ON, Canada. Sixty-six participants with type 1 diabetes and 73 control subjects without diabetes had data available for intrarenal hemodynamic function and lean and fat mass, and were included in the analyses.

Measurement of Intrarenal Hemodynamic Function

All participants underwent renin-angiotensin-aldosterone system (RAAS) inhibitor washout 30 days prior to renal measurements, which occurred on Study Day 2 after a screening visit (Study Day 1). Treatment with RAAS inhibitor agents (including ACE inhibitors, angiotensin receptor blockers, direct renin inhibitors, and aldosterone antagonists) was discontinued; study staff reviewed daily blood pressure measurements through home monitoring (ambulatory blood pressure meters were provided to participants); and treatment with non-RAAS antihypertensive agents was initiated if required, with evaluation of urinary albumin and serum creatinine and potassium (15,16). For 7 days prior to the infusion, participants were instructed to maintain a minimum sodium intake of 150 mmol/day and a protein diet of 1.5 g/kg/day. Compliance was evaluated by measurement of 24-h urine sodium and urea excretion on the 7th day (15,16). Participants with type 1 diabetes and control subjects without diabetes underwent the same procedures, except that participants with type 1 diabetes underwent a euglycemic clamp during the morning of Study Day 2 prior to and during measurements of renal hemodynamic function. During the euglycemic clamp, blood glucose level was measured every 10–15 min, and the insulin infusion was titrated to achieve a blood glucose concentration between 4 and 6 mmol/L for ~4 h prior to and during the renal measurements.

Patients arrived at the Renal Physiology Laboratory (University Health Network, University of Toronto, Toronto, ON, Canada) at ~0800 h. After a brief physical examination and body weight measurements were performed, a venous catheter was placed in the antecubital vein (or dorsal metacarpal vein) of the nondominant arm for blood sampling (with patients in a semirecombinant position). A second venous catheter was placed in the opposite arm (antecubital or dorsal metacarpal) of participants with diabetes for the infusion of dextrose (5% dilution) or

insulin (0.2 units/mL dilution) as part of the euglycemic clamp. After a rest period of ~15 min, blood work (HbA_{1c}, blood glucose, electrolytes, lipids, creatinine, urea, uric acid, aldosterone, and plasma renin concentration) and urine parameters (albumin, protein, electrolytes) were collected, and vital signs were measured at the bedside. Blood work and urine analysis were performed using conventional assay methods by the Department of Clinical Biochemistry at the University Health Network. Ad libitum water consumption was allowed during the experimental period, up to a maximum of 500 mL. Patients remained supine throughout the study and during measurements, but could ambulate for voiding. Blood pressure was measured with an automated sphygmomanometer (53000 Vital Signs Monitor; Welch-Allyn Inc.) at the same time that blood was drawn for analysis of renal hemodynamic parameters. The average of two values was used to assess systolic, diastolic, and mean arterial blood pressure at each time point (GFR for inulin [GFR_{INULIN}] and ERPF for PAH [$ERPF_{PAH}$] at 60 min and again at 90 min).

Renal hemodynamic function was measured using inulin and PAH clearance techniques standardized per 1.73 m^2 of body surface area, which represent GFR_{INULIN} and $ERPF_{PAH}$, respectively (17,18). FF was determined by dividing the GFR_{INULIN} by the $ERPF_{PAH}$. RBF was calculated by dividing the $ERPF_{PAH}$ by (1 − hematocrit). RVR was derived by dividing the mean arterial pressure (MAP) by the RBF. Intrarenal hemodynamics (R_A, R_E, and P_{GLO}) were estimated using Gomez equations, as described previously (19).

Determination of DN Resistor Status

For analysis, participants with type 1 diabetes were categorized as DN Resistors if they had an eGFR for MDRD ($eGFR_{MDRD}$) ≥60 mL/min/1.73 m^2 or 24-h urine albumin excretion <30 mg/day; otherwise, they were assigned to the DN group. The control subjects without diabetes were assigned to the control group irrespective of their $eGFR_{MDRD}$ and 24-h urine results.

Quantification of Lean and Fat Mass

Body composition was determined by DXA using a Hologic Discovery A Bone Densitometer on Study Day 1. We evaluated whole-body lean and fat mass, in addition to measures of central adiposity (trunk fat mass, trunk/limb fat ratio, and trunk fat percentage).

Statistical Analysis

Statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute, Cary, NC). Continuous variables were assessed for normality (Shapiro-Wilk test and inspection of histograms). Comparisons of clinical characteristics among control subject, DN Resistor, and DN subgroups were made using ANOVA, the Kruskal-Wallis test, or the χ^2 test, depending on variable distribution. Pearson correlation and generalized linear regression models (unadjusted and adjusted for age, sex, HbA_{1c}, and systolic blood pressure [SBP]) were used to examine the relationships between measures of central adiposity and intrarenal hemodynamic function. We examined the sex-adjusted means of GFR, ERPF, and RVR across tertiles of trunk fat percentage. Analyses were considered to be exploratory and hypothesis generating, and adjustments for multiple comparisons were not used. An α-level of 0.05 was used for tests of statistical significance.

RESULTS

Baseline Characteristics

There were no differences in mean age (66 ± 8 vs. 65 ± 8 years, $P = 0.41$) or sex distribution (41% vs. 43% women, $P = 0.74$) between adults with and without type 1 diabetes. RAAS inhibitor use was present in 82% of patients with type 1 diabetes and 14% of control subjects. Based on nephropathy stratification criteria, DN subgroups had low $eGFR_{MDRD}$ and high 24-h urine albumin excretion levels. $eGFR_{MDRD}$ was similar between control subjects and DN Resistors (Table 1).

Differences in Fat and Lean Mass Parameters in Adults With and Without Type 1 Diabetes

Compared with adults with type 1 diabetes, control subjects had greater total body fat mass (27.1 ± 9.8 vs. 23.4 ± 7.5 kg, $P = 0.01$), whole-body fat percentage (35.2 ± 8.2% vs. 32.0 ± 8.1%, $P = 0.02$), trunk fat mass (12.9 ± 5.5 vs. 10.9 ± 4.2 kg, $P = 0.01$), and trunk fat percentage (34.0 ± 8.3% vs. 30.0 ± 8.2%, $P = 0.004$). Similar differences were observed with whole-body and trunk fat z scores between adults with and without type 1 diabetes. No differences were observed for lean fat mass between adults with and without type 1 diabetes.

Differences in Fat and Lean Mass Parameters in Patients With DN and DN Resistors

DN and DN Resistors were of similar age, diabetes duration, and sex distribution (Table 1). Although there was a trend toward greater whole-body and central adiposity in patients with DN compared with DN Resistors, the numerical differences in BMI, trunk fat percentage or whole-body fat percentage, and fat mass did not reach statistical significance.

Intrarenal and Systemic Hemodynamic Function

Parameters of intrarenal hemodynamic function across the three groups are shown in Table 1. Compared with patients with DN, DN Resistors had higher baseline GFR_{INULIN} and $ERPF_{PAH}$ levels. Compared with control subjects, DN Resistors had similar baseline GFR_{INULIN}, $ERPF_{PAH}$, and MAP levels. Among the calculated variables, compared with patients with DN, DN Resistors had higher RBF levels, similar FF and P_{GLO} levels, and lower R_A and R_E levels (Table 1). Compared with control subjects, DN Resistors had higher P_{GLO}, lower R_A, and higher R_E levels. Baseline RVR was similar between control subjects and DN Resistors, but was markedly higher in patients with DN ($P < 0.001$).

Relationships Between Fat and Lean Mass With Intrarenal Hemodynamic Function in Adults With and Without Type 1 Diabetes

In adults with type 1 diabetes, BMI ($r = -0.32$, $P = 0.009$), trunk fat mass ($r = -0.46$, $P < 0.0001$), trunk fat percentage ($r = -0.42$, $P = 0.0005$), whole-body fat mass ($r = -0.42$, $P = 0.0004$), and whole-body fat percentage ($r = -0.35$, $P = 0.004$) were inversely correlated with the GFR_{INULIN}, and these associations remained significant after adjusting for age, sex, HbA_{1c} level, and SBP (Table 2). Measures of whole-body and fat mass also inversely correlated with $ERPF_{PAH}$ and RBF and positively with R_A and RVR in univariable and multivariable models (Table 2 and Supplementary Table 1). Whole-body lean mass was not associated with intrarenal hemodynamic function in adults with type 1 diabetes.

In adults without type 1 diabetes, BMI, trunk fat mass, trunk fat percentage,

whole-body fat mass, and whole-body fat percentage were not associated with GFR_{INULIN}, $ERPF_{PAH}$, RVR, or calculated measures of intrarenal hemodynamic function (Table 2 and Supplementary Table 1). Conversely, whole-body lean mass was associated with lower R_E ($r = -0.40$, $P = 0.0005$), lower FF ($r = -0.26$, $P = 0.01$), and RVR ($r = -0.25$, $P = 0.04$), and these associations remained significant after adjusting for age, sex, HbA_{1c}, and SBP (Table 2 and Supplementary Table 1). Differences in sex-adjusted GFR_{INULIN}, $ERPF_{PAH}$, and RVR across tertiles of trunk fat percentage for adults without type 1 diabetes are shown in Fig. 1 and Supplementary Figs. 2 and 3, respectively.

Relationships Between Fat and Lean Mass With Intrarenal Hemodynamic Function in DN and DN Resistors

In DN, BMI, whole-body fat mass, and whole-body fat percentage were not associated with GFR_{INULIN} values; however, trunk fat mass ($r = -0.43$, $P = 0.047$), trunk fat percentage ($r = -0.50$, $P = 0.02$), trunk fat *z* score ($r = -0.62$, $P = 0.003$), and trunk/limb fat ratio ($r = -0.56$, $P = 0.007$) inversely correlated with GFR_{INULIN} values. The associations between central adiposity and GFR_{INULIN} remained significant after multivariable adjustments (Table 3). Although the measures of neither central nor whole-body adiposity were associated with $ERPF_{PAH}$, whole-body fat, trunk fat mass, trunk fat percentage, and trunk/limb fat ratio related inversely to FF and R_E values (Supplementary Table 2).

In DN Resistors, trunk fat mass ($r = -0.44$, $P = 0.004$), trunk percentage fat ($r = -0.32$, $P = 0.03$), and whole-body fat mass ($r = -0.41$, $P = 0.007$) inversely correlated with GFR_{INULIN} values. All measures of whole-body and central adiposity inversely correlated with $ERPF_{PAH}$ and RBF (Table 3). Trunk fat mass, trunk fat percentage, and whole-body fat were negatively associated with P_{GLO} values. Similar relationships were observed among trunk fat *z* scores, trunk/limb fat ratio, and P_{GLO} values. Trunk fat and trunk fat percentage were positively associated with R_A, R_E, and RVR (Supplementary Table 2), and these

Table 1—Clinical and biochemical characteristics of the study participants

	Control subjects ($n = 73$)	DN Resistors ($n = 44$)	DN ($n = 22$)	*P* for trend	*P* for control subjects vs. DN Resistors	*P* for DN Resistors vs. DN
Clinical characteristics						
Sex (M/F)	32/41	22/22	8/14	0.57	0.52	0.29
Age (years)	65 ± 8	65 ± 7	68 ± 8	0.18	0.73	0.08
Duration of type 1 diabetes (years)		55 ± 6	55 ± 5			0.92
Weight (kg)	75.7 ± 16.2	73.3 ± 12.5	73.1 ± 12.1	0.60	0.39	0.95
BMI (kg/m^2)	27.2 ± 5.5	26.4 ± 3.5	27.0 ± 4.8	0.65	0.36	0.61
RAAS inhibition	10 (14)	34 (78)	20 (91)	<0.001	<0.001	0.18
SBP (mmHg)	129 ± 19	133 ± 16	134 ± 14	0.31	0.24	0.73
DBP (mmHg)	79 ± 10	71 ± 10	69 ± 9	<0.001	<0.001	0.37
Heart rate (bpm)	67 ± 9	71 ± 13	69 ± 10	0.20	0.07	0.51
Total daily insulin (units/kg)		0.48 ± 0.16	0.49 ± 0.24			0.79
Adiposity						
Whole-body fat mass (kg)	27.1 ± 9.9	22.6 ± 7.4	25.7 ± 8.2	0.04	0.01	0.18
Whole-body fat percentage (%)	35.1 ± 8.2	30.8 ± 8.5	34.6 ± 7.5	0.02	0.008	0.08
Trunk fat mass (kg)	13.0 ± 5.5	10.4 ± 3.9	12.2 ± 5.1	0.03	0.009	0.17
Trunk fat percentage (%)	33.8 ± 8.3	28.9 ± 8.6	32.5 ± 8.4	0.01	0.003	0.11
Lean mass (kg)	49.2 ± 11.0	50.6 ± 10.6	47.9 ± 8.1	0.61	0.57	0.32
Measured parameters of intrarenal hemodynamic function						
GFR_{INULIN} (mL/min/1.73 m^2)	105 ± 19	108 ± 16	93 ± 15	0.005	0.51	0.002
$ERPF_{PAH}$ (mL/min/1.73 m^2)	497 ± 131	478 ± 101	385 ± 70	<0.001	0.39	0.002
MAP (mmHg)	85 ± 11	88 ± 7	89 ± 8	0.18	0.19	0.55
Hematocrit (L/L)	0.38 ± 0.04	0.35 ± 0.03	0.34 ± 0.03	<0.001	<0.001	0.16
Plasma protein (g/L)	61 ± 5	56 ± 6	59 ± 4	<0.001	<0.001	0.02
RVR (mmHg/L/min · 1,000)	115 ± 38	125 ± 32	157 ± 30	<0.001	0.15	<0.001
Derived parameters of intrarenal hemodynamic function						
RBF (mL/min/1.73 m^2)	803 ± 216	742 ± 163	584 ± 112	<0.001	0.09	0.002
FF (%)	0.22 ± 0.04	0.23 ± 0.04	0.25 ± 0.05	0.01	0.13	0.10
P_{GLO} (mmHg)	44.6 ± 2.8	49.3 ± 4.1	49.1 ± 3.7	<0.001	<0.001	0.74
R_A (dyne · s · cm^{-5})	4,448 ± 2,055	4,400 ± 1,614	5,652 ± 1,622	<0.001	0.89	0.01
R_E (dyne · s · cm^{-5})	1,215 ± 267	2,310 ± 451	2,592 ± 656	<0.001	<0.001	0.01
Biochemical characteristics						
HbA_{1c} (%)	5.7 ± 0.4	7.3 ± 0.8	7.6 ± 1.0	<0.001	<0.001	0.03
HbA_{1c} (mmol/mol)	39 ± 4	56 ± 9	60 ± 11	<0.001	<0.001	0.03
Glucose (mmol/L)	5.4 ± 1.6	8.1 ± 3.4	9.4 ± 4.1	<0.001	<0.001	0.09
$eGFR_{MDRD}$ (mL/min/1.73 m^2)	84 ± 14	81 ± 12	57 ± 14	<0.001	0.19	<0.001
Urine ACR (mg/mmol)	1.0 [0.7, 2.2]	1.0 [0.7, 1.6]	9.5 [5.1, 16.3]	<0.001	0.69	<0.001

Data are expressed as the mean ± SD, median [interquartile range], or *n* (%), unless otherwise indicated. ACR, albumin-to-creatinine ratio; DBP, diastolic blood pressure; F, female; M, male.

Table 2—Relationships between adiposity and measured parameters of intrarenal hemodynamic function in adults with and without type 1 diabetes

	Control subjects without diabetes			Patients with type 1 diabetes		
Variables	GFR_{INULIN}	$ERPF_{PAH}$	RVR	GFR_{INULIN}	$ERPF_{PAH}$	RVR
WB adiposity						
WB fat mass (per kg)						
r	−0.12, *P* = 0.33	−0.09, *P* = 0.45	0.12, *P* = 0.33	**−0.42, *P* = 0.0004**	**−0.31, *P* = 0.01**	**0.28, *P* = 0.02**
β ± SE*	−0.17 ± 0.24, *P* = 0.49	1.01 ± 1.52, *P* = 0.52	0.42 ± 0.45, *P* = 0.35	**−1.07 ± 0.25, *P* < 0.0001**	**−3.18 ± 1.46, *P* = 0.03**	**0.97 ± 0.48, *P* = 0.046**
β ± SE†	−0.17 ± 0.25, *P* = 0.49	1.00 ± 1.61, *P* = 0.54	0.34 ± 0.46, *P* = 0.46	**−1.08 ± 0.25, *P* < 0.0001**	**−3.28 ± 1.46, *P* = 0.03**	0.94 ± 0.48, *P* = 0.054
WB fat percentage (per %)						
r	−0.18, *P* = 0.13	−0.06, *P* = 0.60	**0.26, *P* = 0.03**	**−0.35, *P* = 0.004**	**−0.34, *P* = 0.006**	**0.29, *P* = 0.02**
β ± SE*	−0.46 ± 0.39, *P* = 0.26	0.05 ± 2.58, *P* = 0.99	0.93 ± 0.73, *P* = 0.19	**−1.43 ± 0.31, *P* < 0.0001**	**−4.32 ± 1.81, *P* = 0.02**	1.13 ± 0.60, *P* = 0.06
β ± SE†	−0.49 ± 0.42, *P* = 0.25	−0.10 ± 2.72, *P* = 0.97	0.86 ± 0.77, *P* = 0.27	**−1.43 ± 0.31, *P* < 0.0001**	**−4.33 ± 1.45, *P* = 0.02**	1.12 ± 0.60, *P* = 0.06
BMI (per kg/m^2)						
r	−0.06, *P* = 0.64	**0.23, *P* = 0.046**	−0.02, *P* = 0.88	**−0.32, *P* = 0.009**	−0.18, *P* = 0.16	0.13, *P* = 0.29
β ± SE*	0.25 ± 0.42, *P* = 0.56	4.58 ± 2.64, *P* = 0.07	0.10 ± 0.78, *P* = 0.90	**−1.44 ± 0.48, *P* = 0.004**	−4.49 ± 2.61, *P* = 0.09	1.20 ± 0.86, *P* = 0.17
β ± SE†	0.28 ± 0.44, *P* = 0.53	5.12 ± 2.77, *P* = 0.07	−0.13 ± 0.81, *P* = 0.87	**−1.46 ± 0.49, *P* = 0.004**	−4.96 ± 2.64, *P* = 0.07	1.08 ± 0.88, *P* = 0.22
Central body adiposity						
Trunk fat mass (per kg)						
r	−0.13, *P* = 0.27	−0.08, *P* = 0.51	0.11, *P* = 0.35	**−0.46, *P* < 0.0001**	**−0.31, *P* = 0.01**	**0.28, *P* = 0.02**
β ± SE*	−0.40 ± 0.42, *P* = 0.35	1.10 ± 2.66, *P* = 0.69	0.90 ± 0.78, *P* = 0.25	**−1.88 ± 0.42, *P* < 0.0001**	**−5.56 ± 2.48, *P* = 0.03**	**1.68 ± 0.81, *P* = 0.04**
β ± SE†	−0.42 ± 0.44, *P* = 0.35	1.04 ± 2.87, *P* = 0.72	0.78 ± 0.82, *P* = 0.34	**−1.89 ± 0.43, *P* < 0.0001**	**−5.77 ± 2.48, *P* = 0.02**	1.62 ± 0.82, *P* = 0.052
Trunk fat percentage (per %)						
r	−0.20, *P* = 0.10	−0.07, *P* = 0.58	**0.25, *P* = 0.03**	**−0.42, *P* = 0.0005**	**−0.36, *P* = 0.003**	**0.31, *P* = 0.01**
β ± SE*	−0.44 ± 0.33, *P* = 0.18	−0.82 ± 2.12, *P* = 0.70	1.00 ± 0.60, *P* = 0.10	**−1.18 ± 0.25, *P* < 0.0001**	**−3.78 ± 1.46, *P* = 0.01**	**1.02 ± 0.49, *P* = 0.04**
β ± SE†	−0.48 ± 0.35, *P* = 0.17	−1.07 ± 2.26, *P* = 0.64	0.93 ± 0.64, *P* = 0.15	**−1.18 ± 0.25, *P* < 0.0001**	**−3.85 ± 1.46, *P* = 0.01**	**1.00 ± 0.49, *P* = 0.04**
WB lean mass (per kg)						
r	0.11, *P* = 0.36	0.22, *P* = 0.059	**−0.25, *P* = 0.04**	−0.07, *P* = 0.55	0.06, *P* = 0.65	−0.05, *P* = 0.69
β ± SE*	0.05 ± 0.04, *P* = 0.90	3.04 ± 2.63, *P* = 0.25	0.22 ± 0.76, *P* = 0.77	−0.31 ± 0.33, *P* = 0.36	−1.81 ± 1.77, *P* = 0.31	0.56 ± 0.58, *P* = 0.33
β ± SE†	0.06 ± 0.04, *P* = 0.90	3.02 ± 2.66, *P* = 0.26	0.16 ± 0.77, *P* = 0.83	−0.31 ± 0.34, *P* = 0.37	−1.88 ± 0.77, *P* = 0.29	0.53 ± 0.58, *P* = 0.36

Data are expressed as the mean ± SD, unless otherwise indicated. Boldface type indicates statistical significance ($P < 0.05$). WB, whole body. *β ± SE adjusted for age, sex, and HbA_{1c}. †β ± SE adjusted for age, sex, HbA_{1c}, and SBP.

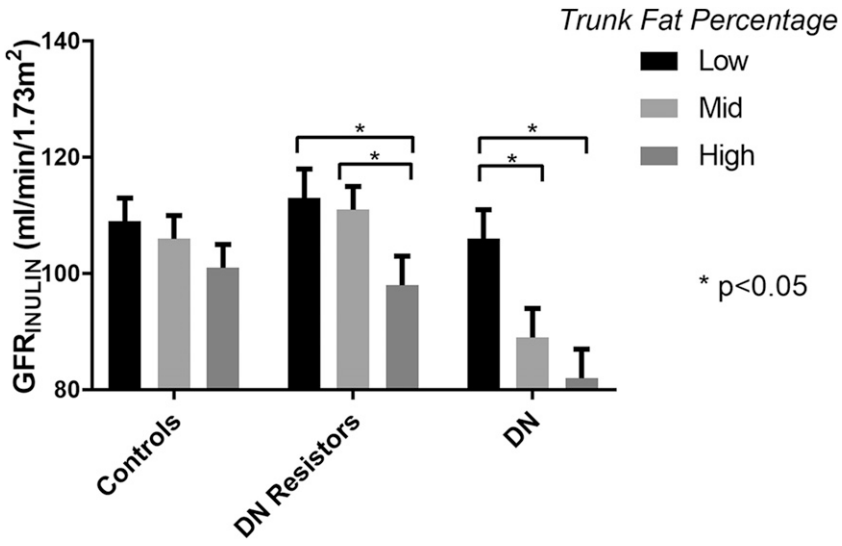

Figure 1—Sex-adjusted means of GFR across tertiles of trunk fat percentage.

associations remained significant in multivariable models.

Differences in sex-adjusted GFR_{INULIN}, $ERPF_{PAH}$, and RVR values across tertiles of trunk fat percentage for control subjects, DN Resistors, and patients with DN are shown in Fig. 1 and Supplementary Figs. 1 and 2, respectively. In control subjects, there were no significant differences in GFR, ERPF, or RVR values across tertiles of trunk fat percentage. In DN Resistors, participants in the high tertile for trunk fat percentage had lower GFR and ERPF values and higher RVR values compared with those in the low tertile. In patients with DN, participants in the high tertile for trunk fat percentage had lower GFR values compared with those in the middle and low tertiles. Although the differences in $ERPF_{PAH}$ values across the tertiles of trunk fat percentage did not significantly differ in participants with DN, participants in the middle fat percentage tertile had higher RVR values than those in the low and high tertiles.

CONCLUSIONS

Although adults with long-standing type 1 diabetes had lower levels of whole-body fat compared with control subjects, the measures of central and whole-body adiposity were not associated with intrarenal hemodynamic dysfunction in control subjects. Conversely, strong associations with adiposity were observed specifically in those with type 1 diabetes with measures of intrarenal hemodynamic function. In adults with type 1 diabetes, greater central adiposity strongly correlated with lower GFR_{INULIN} and $ERPF_{PAH}$ values and with higher R_A and RVR values. When stratified by DN status, there were similarities and differences in the relationships between adiposity and intrarenal hemodynamic function in both groups. Whereas central adiposity negatively correlated with GFR_{INULIN} in both adults with DN and DN Resistors, central adiposity was associated with lower R_E and FF values in adults with DN compared with greater R_A, R_E, FF, and RVR values in DN Resistors. How intrarenal hemodynamic function (e.g., R_A, R_E, FF, and RVR) relates differently to central adiposity in adults with long-standing type 1 diabetes with and without DN is unclear, but may be explained by the central obesity paradox. In other words, the attenuated associations among central obesity, $ERPF_{PAH}$, and RVR and the inverse relationship with FF and R_E may represent adaptive changes of adipocytes in response to DN in adults with long-standing type 1 diabetes.

Obesity has reached epidemic proportions worldwide. In North America, obesity affects more than one-third of the adult population, and in the U.S. alone obesity accounts for >$140 billion in annual medical costs (20,21). The prevalence of overweight and obesity has also increased among individuals with type 1 diabetes (4–7). The incidence of obesity was recently reported to be 37% in one cohort of adults with newly diagnosed type 1 diabetes (22), and 78% of men in the urological assessment component of the Epidemiology of Diabetes Interventions and Complications (EDIC) study were overweight or obese (23). These data are unfortunately not unique to North America, with similar prevalence and incidence observed in adults with type 1 diabetes in Australia (24) and Israel (25). Large epidemiologic studies show that central adiposity confers a higher risk of incident CKD (26–28). Similar findings have also been observed in translational studies that demonstrated that central obesity is associated with unfavorable renal hemodynamic function, including lower GFR and ERPF (13), but also abnormally elevated GFR and ERPF early in the course of the disease (29). Although controversial, epidemiologic data suggest that once CKD is established, obesity may paradoxically be associated with improved survival, especially in those with advanced CKD and ESRD (the central obesity paradox) (11). It is also important to note that the association between central fat distribution and impaired renal function is not limited to obese people. Pinto-Sietsma et al. (30) demonstrated relative renal impairment in lean participants with a central pattern of fat distribution, which suggests that the central distribution of fat may be more important than whole-body fat in determining renal risk.

Despite compelling evidence linking central obesity and kidney disease, the mechanisms underlying this relationship remain unclear. Studies suggest that central adiposity may contribute to kidney disease by indirect and direct mechanisms. The indirect mechanisms are often ascribed to the associated comorbidities, including insulin resistance, hypertension, dyslipidemia, and diabetes (30–33). Adiposity may also directly affect renal function via alterations in intrarenal hemodynamics, oxidative stress, and the numbers of proinflammatory adipokines and cytokines (34,35). For example, adipocytes may directly synthesize proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6 that have been implicated in the development of CKD (36,37). Greater concentrations of leptin in obesity has also been associated with increased oxidative stress, sympathetic nervous system activity, glomerulosclerosis, and proteinuria (38).

Notwithstanding the obesity epidemic and DN continuing to be the leading cause of ESRD and dialysis in the Western world, human physiology studies characterizing the relationships between central

Table 3—Relationships between adiposity and measured parameters of intrarenal hemodynamic function in adults with type 1 diabetes with and without DN

	DN Resistors			Adults with DN		
Variables	GFR_{INULIN}	$ERPF_{PAH}$	RVR	GFR_{INULIN}	$ERPF_{PAH}$	RVR
WB adiposity						
WB fat mass (per kg)						
r	**−0.41, *P* = 0.007**	**−0.46, *P* = 0.002**	**0.45, *P* = 0.003**	−0.35, *P* = 0.11	0.28, *P* = 0.20	−0.22, *P* = 0.33
β ± SE*	**−0.98 ± 0.34, *P* = 0.007**	**−4.46 ± 2.03, *P* = 0.03**	**1.53 ± 0.64, *P* = 0.02**	**−1.04 ± 0.44, *P* = 0.03**	1.31 ± 2.10, *P* = 0.54	−0.03 ± 0.80, *P* = 0.97
β ± SE†	**−0.99 ± 0.35, *P* = 0.007**	**−4.50 ± 2.04, *P* = 0.03**	**1.51 ± 0.64, *P* = 0.02**	**−0.98 ± 0.45, *P* = 0.046**	1.12 ± 2.18, *P* = 0.61	−0.01 ± 0.83, *P* = 0.89
WB fat percentage (per %)						
r	−0.28, *P* = 0.07	**−0.39, *P* = 0.009**	**0.33, *P* = 0.03**	−0.33, *P* = 0.13	0.12, *P* = 0.60	−0.06, *P* = 0.81
β ± SE*	**−1.28 ± 0.40, *P* = 0.003**	**−5.40 ± 2.37, *P* = 0.03**	**1.65 ± 0.77, *P* = 0.04**	**−1.42 ± 0.52, *P* = 0.02**	0.40 ± 2.64, *P* = 0.88	−0.11 ± 1.00, *P* = 0.91
β ± SE†	**−1.28 ± 0.40, *P* = 0.003**	**−5.44 ± 2.39, *P* = 0.03**	**1.63 ± 0.77, *P* = 0.04**	**−1.40 ± 0.52, *P* = 0.02**	0.34 ± 2.70, *P* = 0.90	−0.13 ± 1.02. *P* = 0.90
BMI (per kg/m^2)						
r	−0.29, *P* = 0.053	**−0.35, *P* = 0.02**	**0.35, *P* = 0.02**	−0.36, *P* = 0.10	0.24, *P* = 0.29	−0.28, *P* = 0.20
β ± SE*	−0.97 ± 0.68, *P* = 0.16	−5.61 ± 3.80, *P* = 0.15	1.84 ± 1.22, *P* = 0.14	**−1.96 ± 0.77, *P* = 0.02**	0.57 ± 3.82, *P* = 0.88	−0.38 ± 1.44, *P* = 0.79
β ± SE†	−1.02 ± 0.69, *P* = 0.15	−5.92 ± 3.85, *P* = 0.13	1.70 ± 1.23, *P* = 0.17	**−1.85 ± 0.82, *P* = 0.04**	−0.00 ± 4.04, *P* = 0.99	0.17 ± 1.53, *P* = 0.91
Central body adiposity						
Trunk fat mass (per kg)						
r	**−0.44, *P* = 0.004**	**−0.53, *P* = 0.0002**	**0.53, *P* = 0.0003**	**−0.43, *P* = 0.047**	0.33, *P* = 0.14	−0.27, *P* = 0.22
β ± SE*	**−1.84 ± 0.64, *P* = 0.006**	**−10.34 ± 3.62, *P* = 0.007**	**3.54 ± 1.14, *P* = 0.004**	**−1.69 ± 0.66, *P* = 0.02**	3.28 ± 3.19, *P* = 0.32	−0.54 ± 1.23, *P* = 0.66
β ± SE†	**−1.86 ± 0.64, *P* = 0.006**	**−10.47 ± 3.65, *P* = 0.007**	**3.48 ± 1.14, *P* = 0.004**	**−1.60 ± 0.69, *P* = 0.03**	3.04 ± 3.32, *P* = 0.37	−0.70 ± 1.28, *P* = 0.59
Trunk fat percentage (per %)						
r	**−0.32, *P* = 0.03**	**−0.47, *P* = 0.001**	**0.41, *P* = 0.006**	**−0.50, *P* = 0.02**	0.16, *P* = 0.48	−0.11, *P* = 0.63
β ± SE*	**−1.05 ± 0.33, *P* = 0.004**	**−5.85 ± 1.93, *P* = 0.004**	**1.83 ± 0.62, *P* = 0.006**	**−1.22 ± 0.38, *P* = 0.005**	0.98 ± 2.01, *P* = 0.63	−0.27 ± 0.76, *P* = 0.72
β ± SE†	**−1.06 ± 0.34, *P* = 0.004**	**−5.94 ± 1.95, *P* = 0.004**	**1.79 ± 0.62, *P* = 0.007**	**−1.19 ± 0.38, *P* = 0.007**	0.89 ± 2.06, *P* = 0.67	−0.32 ± 0.78, *P* = 0.69
WB lean mass (per kg)						
r	−0.17, *P* = 0.29	−0.04, *P* = 0.82	0.08, *P* = 0.63	−0.07, *P* = 0.75	0.13, *P* = 0.57	−0.18, *P* = 0.43
β ± SE*	−0.22 ± 0.38, *P* = 0.57	−2.06 ± 2.13, *P* = 0.34	0.52 ± 0.69, *P* = 0.46	−0.11 ± 0.88, *P* = 0.90	2.53 ± 3.66, *P* = 0.50	0.84 ± 1.39, *P* = 0.55
β ± SE†	−0.21 ± 0.39, *P* = 0.59	−1.98 ± 2.17, *P* = 0.37	0.60 ± 0.69, *P* = 0.39	−0.39 ± 1.00, *P* = 0.70	1.96 ± 4.29, *P* = 0.65	0.58 ± 1.62, *P* = 0.73

Boldface type indicates statistical significance ($P < 0.05$). WB, whole body. *β ± SE adjusted for age, sex, and HbA_{1c}. †β ± SE adjusted for age, sex, HbA_{1c}, and SBP.

adiposity and intrarenal hemodynamics in type 1 diabetes are lacking. The current set of studies allowed us to define the relationships between adiposity and gold standard measures of intrarenal hemodynamic function in control subjects without diabetes and adults with long-standing type 1 diabetes of extreme phenotypes (DN vs. DN Resistors). Whereas, adults with type 1 diabetes had lower whole-body and central adiposity compared with their peers without diabetes, we demonstrated type 1 diabetes–specific interactions between adiposity and intrarenal hemodynamic function. Furthermore, some of these relationships differed between adults with DN and DN Resistors. In adults with type 1 diabetes without DN, central adiposity is related to increased afferent and efferent arteriolar tone, higher RVR, higher FF, and lower RBF. Conversely, in adults with type 1 diabetes with DN, greater central adiposity was associated with lower efferent arteriolar tone and consequently lower FF. Interestingly, there were no associations among central adiposity, RBF, or RVR in adults with type 1 diabetes with DN. Notably, greater central obesity related to lower GFR_{INULIN} values in both adults with DN and DN Resistors. Why certain intrarenal hemodynamic parameters relate differently to central adiposity in adults with long-standing type 1 diabetes with and without DN remains unclear. Several mechanisms may explain the paradoxical relationship observed between central obesity and certain intrarenal hemodynamic parameters in adults with long-standing type 1 diabetes and DN, such as adaptive changes of adipocytes. Adipocytes may directly play a role by altering their production of adipokines, including adiponectin, which improves podocyte function and reduces albuminuria (39). Alternatively, the impairment of intrarenal hemodynamic function in patients with DN might lead to attenuated responsiveness to adipocyte signaling.

There are limitations to the current study worth mentioning, including the small sample size and cross-sectional design, that do not allow us to determine causality. To ensure meaningful analyses, we performed careful a priori power calculations and deep phenotyping of intrarenal hemodynamic function and adiposity. To gain additional information about the human intrarenal circulation in vivo, we used Gomez equations to calculate R_A, R_E, P_{GLO}, and filtration pressure (19). Although the control, DN Resistor, and DN groups were similar demographically by design, we cannot rule out the presence of differences in unmeasured variables or residual confounding. Furthermore, findings from this study may not be generalizable to youth with type 1 diabetes or individuals with type 1 diabetes of short duration. The longevity cohort is also subject to survivorship bias since participants had to survive 50 years with type 1 diabetes to be eligible for the study, and those with progressive or advanced nephropathy may not have been captured because of related mortality, which limits the overall generalizability of the findings. Finally, our analyses were considered to be exploratory and hypothesis generating, and adjustments for multiple comparisons were not used. The strengths of this study include direct measures of GFR and ERPF by inulin and PAH, along with central adiposity by DXA in a cohort of control subjects and adults with type 1 diabetes at extreme phenotypes (DN vs. DN Resistors).

In conclusion, we demonstrated strong relationships among whole-body, central adiposity, and intrarenal hemodynamic function in adults with long-standing type 1 diabetes, but not in control subjects. There were also important differences between DN and DN Resistors among the adults with type 1 diabetes. When taken together, our observations suggest that the adiposity-intrarenal hemodynamic function relationships may vary according to DN status. The mechanisms discriminating the relationships between adiposity and intrarenal hemodynamic function in DN and DN Resistors in adults with long-standing type 1 diabetes are not known but could be explained by the central obesity paradox observed in CKD cohorts without diabetes.

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Duality of Interest. P.B. has a consultancy agreement with Boehringer Ingelheim but has not yet received any consulting fees from them. J.A.L. has received consulting fees, speaker honoraria, or both from Novo Nordisk, Eli Lilly & Co., Merck Sharp & Dohme, and AstraZeneca. G.B. has received speaker honoraria from Johnson & Johnson. H.A.K. has received support from Sanofi. B.A.P. has received speaker honoraria from Medtronic, Johnson & Johnson, Roche, GlaxoSmithKline Canada, Novo Nordisk, and Sanofi; has received research grant support from Medtronic and Boehringer Ingelheim; and serves as a consultant for NeuroMetrix. D.Z.I.C. has received consulting fees, speaker honoraria, or both from Janssen, Boehringer Ingelheim, Eli Lilly & Co., AstraZeneca, Merck, and Sanofi and has received operating funds from Janssen, Boehringer Ingelheim, Eli Lilly & Co., AstraZeneca, and Merck. No other potential conflicts of interest relevant to this article were reported.

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