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The ratio of pericardial to subcutaneous adipose tissues is associated with insulin resistance

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Abstract

Objective—To examine the association between pericardial adipose tissue (PAT) and the ratio of PAT to subcutaneous adipose tissue (SAT) with insulin resistance in adults with and without type 1 diabetes (T1D).

Methods—Data for this report came from a substudy of the Coronary Artery Calcification in Type 1 Diabetes cohort (n=83; 38 with T1D, 45 without T1D). Insulin resistance was measured by hyperinsulinemic-euglycemic clamp. Abdominal computed tomography (CT) was used to measure visceral adipose tissue (VAT) and SAT. PAT was measured from CT scans of the heart.

Results—PAT and the ratio of PAT to SAT was higher in males compared to females. After adjustment for demographics, diabetes, blood pressure and lipid factors, BMI, VAT and log PAT/SAT ratio, log PAT was positively associated with the glucose infusion rate (GIR) in females

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only (β=3.36 ±1.96, p=0.097, p for sex interaction=0.055). Conversely, the log PAT/SAT ratio was significantly associated with decreased GIR in both males and females (β=−2.08 ±1.03, p=0.047, p for sex interaction=0.768).

Conclusions—In conclusion, we found a significant association between the PAT/SAT ratio and insulin resistance, independent of BMI, VAT and PAT. These results highlight the importance of considering fat distribution independent of volume.

Keywords

adipose tissue; insulin resistance; diabetes; epidemiology

Introduction

While the loss of insulin production due to the antibody-mediated destruction of pancreatic beta cells is the primary pathology underlying type 1 diabetes (T1D), the presence of increased insulin resistance (IR) in both adults and children with T1D has also been demonstrated and is associated with accelerated atherosclerosis(1, 2, 3, 4, 5).

Increasing evidence suggests that the distribution of adipose tissue throughout the body may be more important in the development of IR than overall obesity(6). Visceral adipose tissue (VAT) has been associated with IR due to the high production of inflammatory cytokines, high lipolytic rate, and increased free fatty acid (FFA) mobilization(6, 7, 8, 9, 10). In contrast, subcutaneous adipose tissue (SAT) is more insulin sensitive (IS) and may act as a buffer against the lipolytic activity of VAT. Likewise, functional SAT insufficiency results in increased lipid deposition in visceral and ectopic fat depots(8, 9, 11, 12, 13). Indeed, some studies have examined the VAT/SAT ratio and identified a correlation with IR, and other cardiometabolic risk factors(14, 15, 16, 17).

PAT is an ectopic fat depot made up of paracardial adipose tissue external to the pericardium and epicardial adipose tissue (EAT) directly surrounding the coronary arteries, that has been shown to be associated with coronary heart disease, diabetes, and inflammation (18, 19, 20, 21, 22). Presence of inflamed and hypertrophic adipocytes could result in increased FFA, cytokine release, and ultimately prove detrimental to the myocardium and coronary arteries, as well as increasing systemic IR (22, 23). PAT has been shown to be associated with HOMA-IR and the oral glucose IS index (24, 25, 26), yet, previous studies have not determined the association between PAT and IR in those with T1D. In addition, studies investigating the relationship between PAT and IR utilizing more accurate measures of IS obtained from hyperinsulinemic-euglycemic clamps are lacking, and it is unclear whether the association is independent of VAT. The pathogenic effects of PAT may be balanced by the relative protective effects of SAT, however, no studies to date have reported on whether the ratio of PAT to SAT is related to IR.

The objective of this report is to examine the cross-sectional association between PAT volume and the PAT/SAT ratio with the glucose infusion rate (GIR), a measure of IS obtained during hyperinsulinemic-euglycemic clamp, with adjustment for VAT and BMI.

Methods

Subjects

Data for this report came from a substudy of the Coronary Artery Calcification in Type 1 Diabetes (CACTI) cohort in which hyperinsulinemic-euglycemic clamps were performed on 87 subjects (40 with T1D, 47 non-DM) selected from participants from the 6-year follow-up exam. The CACTI study design has been described previously(27). Briefly, the full cohort consisted of a total of 1416 participants (652 with T1D, 764 controls). All of the T1D subjects carried a diagnosis of T1D and were treated with insulin within one year of the T1D diagnosis. The hyperinsulinemic-euglycemic clamp substudy has been described in detail elsewhere(4). Inclusion criteria for the substudy included HbA1c ≤9.5%, albumin excretion rate <200 μg/min, triglycerides <400 mg/dl, and blood pressure (BP) <160/100 mmHg. Informed consent was provided by all study participants. The protocol was reviewed and approved by the Colorado Multiple Institutional Review Board (IRB#s: 97-661, 05-0443). PAT measurement was performed under an ancillary study that was reviewed by the University of South Florida Institutional Review Board (IRB#: Pro00013500).

PAT Volume Measurement

Electron beam computed tomography (EBCT) scans were performed for scoring of coronary artery calcium using an ultrafast Imatron C-150XLP scanner (Imatron, San Francisco, CA). PAT volume was measured by a single trained reader from the EBCT scans taken at the 6-year exam using Analyze Direct 11.0 volume analysis software (Mayo Clinic, Minneapolis, MN). PAT volume assessment began with the slice 3 mm above the left main coronary artery. The heart was manually traced using a spline edge detection feature of the software. Anatomical boundaries included the chest wall, descending aorta and bronchus. The process was repeated for each 3 mm slice until 30 mm below the left main coronary artery. PAT volume was quantified using the software's automated functions using threshold values of −190 to −30 Hounsfield units to distinguish fat from other tissues. As the pericardium was not distinguished, PAT volume included adipose tissue internal and external to the pericardium. Four subjects were excluded from PAT volume measurement due to inconsistencies in the available scans. Ten subjects were randomly selected for quality control assessment and were randomly interspersed in the reading queue. PAT measurement was highly reliable with an intra-reader reliability assessed by the intraclass correlation coefficient of 0.993.

Exam Measurements

Physical exam measurements taken at the 6-year CACTI exam included height, weight, waist (WC) and hip circumference, and systolic and diastolic BP. BMI was calculated as kilograms of body weight per meters^2 of height. A fasting blood sample was collected and stored at −80° C until assayed for measurement of cholesterol (total and HDL), triglyceride levels, and adiponectin. LDL cholesterol was calculated using the Friedewald equation. All subjects were given standardized questionnaires to obtain demographics, medical history, medication use, current and past smoking status, insulin dose, and family medical history. Female subjects were asked about their reproductive history, menopausal status, and history of hormone replacement therapy. Percentage of energy intake from fats (%fat) and

carbohydrates (%carb) were estimated based on average food consumption from a validated self-administered food-frequency questionnaire. Minutes of moderate or vigorous intensity activity over the previous week was obtained from the Modifiable Activity Questionnaire(28) and combined into a single variable of moderate intensity-equivalent activity (moderate + (vigorous*2); MIEA). A square-root transformation was applied for inclusion in the regression models. A single 6-mm thick image at the L4–L5 levels was obtained using abdominal computed tomography during suspended respiration in order to measure VAT and SAT, as previously described(27). Since the main independent variables of interest were measured at the 6-year follow-up visit, exam measurements taken at the 6-year follow-up exam were used as covariates in the models.

Hyperinsulinemic-Euglycemic Clamps

Hyperinsulinemic-euglycemic clamps were performed using the three stage method of DeFronzo et al(29) and were performed within a median of 207 days (range: 10 to 967 days) after the 6-year exam. Each stage lasted 1.5 hours and included administration of a primed continuous infusion of insulin at 4, 8, and then 40 $mU/m^2/min$, respectively. The mean GIR was obtained during the hyperinsulinemic-euglycemic steady state in the last 30 minutes of the high insulin infusion stage. FFA were measured using spectrophotometric assay (Olympus AU400e Chemistry Analyzer) from blood samples obtained prior to performing the clamp and during the last 10 minutes of each stage. The RQ was measured prior to the beginning of the clamp and then during each stage of the clamp by indirect calorimetry using a metabolic cart (Parvo Medics, Sandy, UT). High molecular weight (HMW) adiponectin was measured by ELISA (Millipore, Billerica, MA) from the fasting plasma samples obtained at the clamp visit.

Statistical Analysis

Statistical comparisons of characteristics by diabetes and sex were performed using the t-test, the Wilcoxon rank sum test, and the chi-square or Fisher's exact test, as appropriate. For regression analyses, continuous data that were not normally distributed were log transformed, including PAT, VAT, SAT, PAT/SAT ratio, triglycerides, and HMW adiponectin. Multivariable linear regression was used to model the association between log PAT or the log PAT/SAT ratio and GIR adjusted for covariates. β estimates are presented per 1 standard deviation of log PAT or log PAT/SAT ratio. Additionally, we examined whether these relationships were mediated by fasting FFA, FFA suppression calculated as the percentage change from fasting to stage 2 of the clamp, the change in the respiratory quotient (ΔRQ), a measure of substrate oxidation(30), from the fasting to the final stage of the clamp, and HMW adiponectin. Mediation was examined by including the potential mediating terms in the final models to examine alteration of effects. Formal tests for mediation were performed using the product of coefficients method to estimate the size of the mediated effect and the R package RMediation to build 95% confidence intervals using the distribution-of-the-product method(31). To account for the potential post-menopausal hormonal changes that may affect lipid distribution in women(6), we examined the effect of menopause and hormone replacement therapy upon the relationship between PAT/SAT ratio and GIR. As sexual dimorphism in fat distribution and function have been reported(6, 9), we performed stratified analyses by sex. Interaction terms for diabetes status were also examined. Statistical

significance was considered as $p<0.05$ for most analyses and $p<0.1$ for interactions. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Participant characteristics stratified by sex and diabetes are shown in Table 1. Among males, participants with and without T1D were similar for age, race, BMI, WC, waist to hip ratio (WHR), BP, and smoking status. For females, age, BMI, WC, BP, and smoking status were similar, but the percentage of white participants was lower in those without T1D, and the WHR was higher in females with T1D. For both males and females, total cholesterol, triglycerides, and LDL were lower in participants with T1D. HDL was higher in males with T1D compared to males without, but did not differ in females. More participants with T1D were on BP and lipid-lowering medications, although the difference was not statistically significant for BP-lowering medication among females. In males, %fat and %carb was similar between those with and without T1D, but %fat was significantly higher and %carb was significantly lower in females with T1D. Minutes of MIEA per week was not significantly different between those with and without T1D for either sex. As expected, HbA1c and fasting glucose values were higher in those with T1D. As demonstrated in our earlier study(4), GIR was lower in those with T1D for both sexes. PAT and VAT volumes were higher in males compared to females, with no statistically significant differences by diabetes status. SAT volume was higher in males with T1D compared to those without, although not significantly. Among males, the PAT/SAT ratio was significantly lower in those with T1D compared to those without, but was significantly higher in females with T1D.

Correlations between PAT, the PAT/SAT ratio, or VAT and measures of adiposity by sex are presented in Table 2. BMI, WC, WHR, and log VAT were significantly positively correlated with log PAT in both males and females. The log PAT/SAT ratio was marginally inversely correlated with BMI, but was not correlated with WC, WHR, or log VAT in males and females. VAT was significantly positively correlated with BMI, WC, and WHR in both males and females.

Age-, sex-, and diabetes-adjusted adiposity and metabolic factors by GIR tertiles are presented in Table 3. PAT, VAT, BMI, WC, and WHR significantly decreased across the tertiles of GIR. The PAT/SAT ratio and SAT were lower in tertile 3 compared to tertile 1, but was not statistically significant. The RQ and FFA suppression significantly increased across tertiles of GIR. Fasting FFA was higher in tertiles 2 and 3 compared to tertile 1 but was not significant. Total and HMW adiponectin increased across the tertiles of GIR, with borderline significance.

Table 4 shows the results of linear regression models of log PAT or log PAT/SAT ratio on GIR as the dependent variable. A significant interaction (p for interaction < 0.1) between log PAT and sex was observed in model 4 and was of borderline significance in models 2 and 3. In model 1, adjusted for diabetes, race, age, systolic BP, LDL, log triglycerides, BP and lipid lowering medication, %fat and %carb, and square-root transformed minutes of MIEA, PAT was borderline significantly inversely associated with GIR in males, but not females. After adjusting for BMI, the associations were attenuated for both males and females (model 2).

Additional adjustment for VAT did not alter the association for males, but reversed the association for females (model 3). After adding the log PAT/SAT ratio to the model, a borderline significant positive association between log PAT and GIR was found in females only (p=0.097) with a significant p for interaction (p=0.055; Figure 1A). The relationship between the log PAT/SAT ratio and GIR did not differ significantly by sex (Figure 1B). Across all models, log PAT/SAT ratio was inversely associated with GIR. After full adjustment for all of the variables in model 1, BMI, VAT, and PAT, the log PAT/SAT ratio was significantly associated with decreased GIR (IS), and hence, increased IR.

Addition of the RQ resulted in a not significant increase in the association between log PAT and GIR in males and attenuated the association in females (Table 5, model 2). In addition, there was no longer a significant difference by sex (p for interaction 0.326; data not shown). Addition of the RQ to the log PAT/SAT ratio model attenuated the relationship (p=0.130). Separate adjustment for fasting FFA, FFA suppression, and log HMW adiponectin had little effect upon the results (Table 5, models 3, 4, and 5). In formal mediation testing, the RQ was a partial mediator of the relationship between log PAT and GIR in females with a significant mediation effect (4.00 95% CI 0.13, 9.33).

There were no differences by diabetes status (p for interaction in log PAT and log PAT/SAT ratio models = 0.627 and 0.355, respectively). In sensitivity analyses among females only, inclusion of menopausal status and hormone replacement therapy in the models did not alter these results (data not shown).

Discussion

This study is the first to show a significant association between the PAT/SAT ratio and IR measured using the hyperinsulinemic/euglycemic clamp in a population of adults with and without T1D. Sex-stratified models showed a borderline positive association between log PAT volume and GIR in females only (figure 1A). However, when accounting for PAT volume relative to SAT volume, the association was in the expected direction with increased PAT relative to SAT associated with decreased IS, and increased IR in both males and females, independent of absolute volume of PAT or VAT (figure 1B). Taken together, these results suggest that the relative ectopic to subcutaneous fat distribution may be an important factor in IR, independent of the absolute volume, and that fat distribution should be considered in addition to volume.

Our results suggest that women with T1D have a more android deposition of fat (higher WHR, larger WC, higher volume of VAT and PAT, and lower volume of SAT) relative to women without T1D, although in this small sample, only the difference in WHR was significant. This more android deposition is reflected in the significantly higher PAT/SAT ratio. In contrast, men with T1D had lower PAT, VAT, and WHR, and higher SAT than men without T1D. These observations are supported by previous findings at baseline from the full CACTI cohort for VAT, WHR, and WC(27). As shown previously, correlates of IR, such as triglycerides and BMI, are similar between those with and without T1D, but relationships are left-shifted in those with T1D(4). Similarly, we have shown that increasing PAT to SAT volume was associated with decreased GIR, regardless of sex or diabetes status. Using the

PAT/SAT ratio may help to account for the sex-specific differences in fat deposition. However, at any given value of the PAT/SAT ratio, those with T1D would still be more insulin resistant than those without T1D.

An association between PAT and IR has been reported from other studies. In the Multi-Ethnic Study of Atherosclerosis (MESA), PAT was found to be significantly associated with HOMA-IR independent of BMI and WC(24). Similarly, Pucci, et al. found a significant correlation between PAT thickness measured by echocardiography and HOMA-IR in subjects with obesity, even after adjustment for BMI(26). Studies have also found an association between EAT and HOMA-IR(32). While these studies support our findings of an association between PAT and IR, HOMA-IR is a surrogate measure of IR. There are no studies that have looked at PAT and IR measured from hyperinsulinemic-euglycemic clamp, although one study did find a significant association between echocardiographically determined EAT and glucose uptake during hyperinsulinemic-euglycemic clamp in subjects with obesity(33). Additionally, our study extends these findings to a population of adults with and without T1D and with a low prevalence of obesity.

No previous studies have examined the PAT/SAT ratio and IR. However, Kaess, et al. found that the VAT/SAT ratio was significantly associated with log HOMA-IR in both men and women after adjustment for BMI(14). Additional adjustment for VAT in the models attenuated the results in both groups, although more so for men than women ($p=0.79$ v $p=0.05$, p for interaction 0.001). Gastaldelli, et al. found that the VAT/SAT ratio was inversely associated with IS estimated from a 3-h OGTT independent of BMI(15). In a study of 36 men with type 2 diabetes, Miyazaki, et al. found that the VAT/SAT ratio was significantly associated with endogenous glucose production (a measure of hepatic and renal IR) during hyperinsulinemic-euglycemic clamp but not total glucose disposal (a measure of peripheral IR)(17). Differences in findings may be related to small sample size, differences in the populations studied (healthy versus type 2 diabetes), and the method used for determining IR. These studies all support our conclusion that the ratio of ectopic fat to subcutaneous fat is an important determinant of cardiometabolic health and should be considered in addition to volume.

Obesity has long been associated with IR, although the exact mechanisms have been debated(7, 12). Dysfunctional hypertrophic adipocytes result in impaired fatty acid metabolism and increased release of free fatty acids (FFA) (7, 8, 12). In addition, increases in pro-inflammatory cytokines, such as interleukin 6, TNF-α, and CRP, and decreases in the anti-inflammatory adiponectin associated with increasing visceral adipose tissue contribute to reductions in IS(11, 12, 34, 35).

Metabolic inflexibility, the inability to switch substrate utilization from fat oxidation during fasting to carbohydrate oxidation during the fed state, has been associated with obesity, diabetes, and male gender(36, 37, 38). In the current study, whole body metabolic flexibility, as measured by the RQ from the fasting to insulin-stimulated state during hyperinsulinemic-euglycemic clamp, attenuated the relationship between both PAT and the PAT/SAT ratio and GIR (Table 5). The effect of adding the ΔRQ to the model was particularly strong for women, and the sex difference in the relationship between PAT and GIR was no longer

significant. These results suggest that the ability to switch from lipid to carbohydrate oxidation may be an important factor in the relationship between ectopic fat and IR, although with a cross-sectional study, it is not possible to draw conclusions whether increased ectopic fat leads to impaired metabolic flexibility, or vice versa. Alternatively, in the setting of a hyperinsulinemic euglycemic clamp where insulin levels are fixed, the RG may simply reflect IS, thus explaining its apparent mediation of the relationship between PAT measures and GIR. Studies show that increased ectopic fat deposition leads to dysfunctional hypertrophic adipocytes and SAT insufficiency resulting in increased free fatty acids (FFA), decreased insulin-stimulated glucose uptake in muscle and suppression of endogenous glucose production(7, 8, 12, 35). Results of mediation testing suggested that FFA suppression was not an important mediator of the relationship between PAT and the PAT/SAT ratio and GIR. The addition of fasting FFA and HMW adiponectin did not further attenuate any of the results.

The hyperinsulinemic-euglycemic clamps were performed at a median of only 207 days after the CACTI 6-year visit, which is insufficient to characterize the temporal relationship between PAT measures and IR. Due to the inability to reliably identify the pericardium from EBCT scans taken with a 3-mm slice thickness, especially in lean individuals, we chose to measure PAT, which included both the pericardial fat external to the pericardium, and EAT. This reduced the potential for bias in attempting to measure one depot exclusively over the other, however, these fat depots may have different associations with IR. However, there is a high correlation between EAT and PAT (r=0.92)(19), suggesting that EAT can be linearly predicted by PAT and that statistical associations would be similar between the two measures. The GIR during the hyperinsulinemic-euglycemic clamp technique provides a measure of peripheral IS. In the absence of tracer data, we are unable to determine the relative contributions of PAT compared to VAT on the effect of insulin on tissues located in closer proximity to VAT. While IR could be reliably characterized by the use of data from hyperinsulinemic-euglycemic clamps, the small sample size may lead to spurious associations, especially in stratified models. While this is the first study to look specifically at the PAT/SAT ratio and IR, our results are supported by other studies that have looked at the VAT/SAT ratio and IR, and in general by studies that have found an association between PAT and IR.

Conclusion

In conclusion, we found a significant association between the PAT/SAT ratio and IR measured from hyperinsulinemic-euglycemic clamp, independent of BMI, and VAT and PAT volume, with similar associations in both men and women. These results highlight the importance of considering fat distribution in addition to volume. They also suggest that excess deposition of metabolically active ectopic fat around the heart may have implications beyond local effects to the coronary vasculature.

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STUDY IMPORTANCE QUESTIONS

1. What is already known about this subject?

- Pericardial adipose tissue volume (PAT) has been associated with HOMA-IR and the oral glucose insulin sensitivity index in type 2 diabetes.
- Subcutaneous adipose tissue (SAT) is considered to be more insulin sensitive than visceral adipose tissue (VAT), and acts as a buffer against VAT lipolytic activity.
- A higher VAT/SAT ratio has been correlated with insulin resistance and cardiometabolic risk factors.

2. What does your study add?

- The PAT/SAT ratio is inversely associated with insulin sensitivity in adults with and without type 1 diabetes.
- Consideration of PAT relative to SAT may provide a better measure of metabolic imbalance than the PAT volume alone.

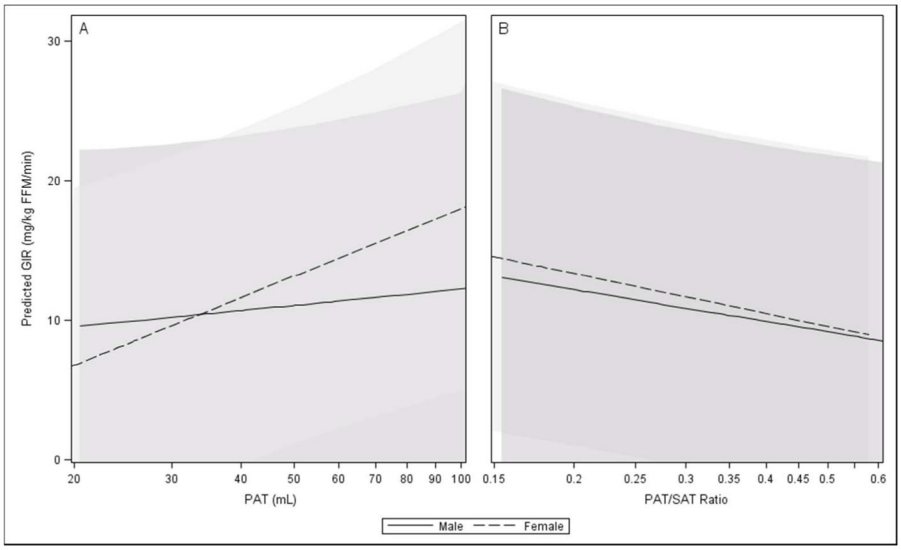

Figure 1.

Predicted GIR for PAT (panel A) and PAT/SAT ratio (panel B) by sex. Models were adjusted for diabetes, race, age, systolic blood pressure, LDL, log triglycerides, blood pressure and hypertension lowering medication, percentage of energy from fats and carbohydrates, square-root transformed minutes of moderate intensity-equivalent activity per week, BMI, log VAT, and log PAT/SAT ratio or log PAT, respectively. Solid lines represent males; dashed lines represent females. Abbreviations: GIR, glucose infusion rate; PAT, pericardial adipose tissue; SAT, subcutaneous adipose tissue.

Table 1

Participant characteristics by sex and diabetes status

Variable	Male (n=36)			Female (n=47)		
	T1D (n=18)	Non-DM (n=18)	p-value*	T1D (n=20)	Non-DM (n=27)	p-value*
Age (years)†	45.9 ±9.4	46.8 ±6.1	0.738	43.8 ±8.1	44.2 ±7.4	0.849
Race (% White)‡	16 (88.9)	18 (100.0)	0.486	20 (100.0)	19 (70.4)	0.014
Duration of diabetes (years)†,§	29.2 ±7.9	N/A	N/A	28.4 ±8.3	N/A	N/A
BMI (kg/m^2)†	27.9 ±3.9	26.8 ±3.6	0.402	26.1 ±4.3	25.2 ±4.3	0.459
BMI category‡			0.900			0.910
Normal (18.5–<25 kg/m^2)	4 (22.2)	4 (22.2)		8 (40.0)	13 (48.5)	
Overweight (25–<30 kg/m^2)	9 (50.0)	11 (61.1)		10 (50.0)	12 (44.4)	
Obese (≥30 kg/m^2)	5 (27.8)	3 (16.7)		2 (10.0)	2 (7.4)	
Waist circumference (cm)†	95.9 ±8.2	96.4 ±10.9	0.897	83.8 ±12.3	79.0 ±9.4	0.136
Waist to hip†	0.90 ±0.05	0.93 ±0.05	0.144	0.80 ±0.08	0.75 ±0.06	0.024
PAT (cm^3)//	43.4 (33.4–58.2)	55.7 (47.0–76.1)	0.150	28.0 (23.3–41.1)	25.4 (20.0–30.3)	0.119
VAT (cm^3)//	56.5 (45.5–73.0)	68.3 (47.1–90.7)	0.169	37.5 (25.0–60.1)	35.0 (25.0–44.7)	0.739
SAT (cm^3)//	165.5 (124.3–196.4)	129.3 (89.5–150.4)	0.091	146.5 (103.4–197.0)	160.8 (116.8–191.3)	0.782
PAT/SAT ratio//	0.30 (0.21–0.39)	0.47 (0.36–0.56)	0.012	0.20 (0.15–0.37)	0.15 (0.14–0.20)	0.047
HbA1c (%)†	7.7 ±1.1	5.4 ±0.32	<0.001	7.7 ±1.1	5.5 ±0.35	<0.001
Fasting glucose (mg/dl)†	154.9 ±61.4	89.7 ±7.2	<0.001	165.4 ±73.2	84.7 ±9.3	<0.001
Cholesterol (mg/dl)†	161.6 ±28.9	197.4 ±33.2	0.002	152.9 ±30.5	182.5 ±29.8	0.002
Triglycerides (mg/dl)//	67.5 (54.0–74.0)	111.5 (67.0–164.0)	0.005	58.5 (48.0–77.5)	77.0 (60.0–109.0)	0.020
HDL (mg/dl)†	59.7 ±16.5	48.8 ±14.3	0.041	62.7 ±15.3	65.5 ±18.1	0.570
LDL (mg/dl)†	88.5 ±21.9	123.3 ±26.5	<0.001	77.0 ±26.6	100.3 ±29.3	0.008
On cholesterol-lowering meds‡	12 (66.7)	2 (11.1)	0.001	11 (55.0)	2 (7.4)	<0.001
Systolic blood pressure (mmHg)†	117.3 ±9.3	120.9 ±8.2	0.225	110.4 ±10.0	109.4 ±11.1	0.748
Diastolic blood pressure (mmHg)†	79.0 ±5.5	81.4 ±7.0	0.270	72.4 ±8.1	73.0 ±7.0	0.783

Variable	Male (n=36)			Female (n=47)		
	T1D (n=18)	Non-DM (n=18)	p-value*	T1D (n=20)	Non-DM (n=27)	p-value*
On blood pressure-lowering meds‡	11 (61.1)	2 (11.1)	0.002	6 (30.0)	3 (11.1)	0.104
Ever smoker‡	3 (16.7)	6 (33.3)	0.443	8 (40.0)	7 (25.9)	0.355
Current smoker‡	1 (5.6)	1 (5.6)	1.000	3 (15.0)	0 (0.0)	0.070
Percent of energy from fat†	36.4 ±5.8	37.5 ±5.9	0.565	38.1 ±6.8	34.6 ±5.1	0.047
Percent of energy from carbohydrates†	42.6 ±7.8	39.5 ±7.2	0.230	39.1 ±4.7	44.9 ±7.2	0.003
Minutes of moderate intensity-equivalent activity per week//,¶	0 (0–540)	170 (0–360)	0.725	0 (0–180)	120 (0–170)	0.162
GIR (mg/kg FFM/min)†	5.3 ±3.8	10.0 ±5.4	0.005	6.2 ±3.5	15.6 ±5.0	<0.001

Abbreviations: T1D, type 1 diabetes; non-DM, without diabetes mellitus; BMI, body mass index; PAT, pericardial adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; HbA1c, hemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GIR, glucose infusion rate;

*p-value comparing T1D vs Non-DM among males and females, respectively

†Data presented as mean ±SD, p-value from t-test

‡Data presented as number (%), p-value from chi-square or Fisher's exact

§Among subjects with diabetes

//Data presented as median (25^{th} percentile–75^{th} percentile), p-value from Wilcoxon rank sum test

¶Minutes of moderate intensity + 2 × vigorous intensity activity per week

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Table 2

Spearman correlation coefficients between log PAT or log PAT/SAT ratio and measures of adiposity by sex

	Log PAT		Log PAT/SAT ratio		Log VAT	
Variable	**Males r (p-value)**	**Females r (p-value)**	**Males r (p-value)**	**Females r (p-value)**	**Males r (p-value)**	**Females r (p-value)**
BMI	0.60 (<0.001)	0.57 (<0.001)	−0.29 (0.081)	−0.28 (0.062)	0.60 (<0.001)	0.80 (<0.001)
Waist circumference	0.67 (<0.001)	0.60 (<0.001)	−0.26 (0.125)	−0.22 (0.134)	0.67 (<0.001)	0.80 (<0.001)
Waist to hip ratio	0.39 (0.017)	0.49 (0.001)	0.01 (0.947)	0.13 (0.392)	0.53 (0.001)	0.44 (0.002)
Log VAT	0.68 (<0.001)	0.67 (<0.001)	0.08 (0.624)	−0.08 (0.576)	N/A	N/A

Abbreviations: PAT, pericardial adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index; VAT, visceral adipose tissue

Table 3

Age-, sex-, and diabetes-adjusted adiposity and metabolic factors by GIR tertiles

	GIR			
Variable	**Tertile 1**	**Tertile 2**	**Tertile 3**	**p-value**
PAT/SAT †	0.27 (0.22–0.33)	0.27 (0.23–0.32)	0.23 (0.19–0.28)	0.264
PAT (mL) †	43.6 (36.6–52.0)	35.8 (30.8–41.8)	28.5 (23.7–34.1)	0.003
SAT (mL) †	161.4 (131.5–198.1)	133.7 (111.8–160.0)	124.9 (100.8–154.8)	0.127
VAT (mL) †	59.1 (49.1–71.1)	43.3 (36.8–51.0)	33.0 (27.3–40.0)	<0.001
BMI (kg/m^2) *	28.5 (26.8–30.3)	25.7 (24.2–27.2)	24.9 (23.1–26.6)	0.011
Waist circumference (cm) *	94.6 (90.2–98.9)	86.2 (82.5–89.8)	82.3 (78.0–86.5)	0.001
Waist to hip *	0.87 (0.85–0.90)	0.84 (0.82–0.86)	0.80 (0.77–0.82)	<0.001
RQ *	0.01 (−0.01–0.03)	0.07 (0.05–0.09)	0.13 (0.11–0.16)	<0.001
Fasting FFA *	505.6 (432.8–578.5)	551.2 (489.3–613.1)	541.1 (469.5–612.7)	0.540
FFA suppression (%) *	7.1 (−9.1–23.2)	50.2 (36.4–63.9)	69.4 (53.5–85.3)	<0.001
Total adiponectin (μg/mL) †	7.8 (6.1–10.1)	9.5 (7.7–11.7)	11.3 (8.7–14.7)	0.081
HMW adiponectin (μg/mL) †	3.2 (2.2–4.5)	4.2 (3.1–5.7)	5.1 (3.6–7.3)	0.097

Abbreviations: GIR, glucose infusion rate; PAT, pericardial adipose tissue; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; BMI, body mass index; RQ, respiratory quotient; FFA, free fatty acids; HMW, high molecular weight

* Data presented as least squares adjusted means (95% CI), p-value from linear regression with GIR tertiles as an ordinal predictor, adjusted for age, sex, and diabetes

† Data presented as least squares adjusted geometric mean (95% CI), p-value from linear regression with log transformed dependent variable and GIR tertiles as an ordinal predictor, adjusted for age, sex, and diabetes

Table 4

Linear regression of log PAT or log PAT/SAT ratio on GIR

	Log PAT			Log PAT/SAT	
	Males (N=36)	**Females (N=47)**	**p for log**	**(N=83)**	**p for log**
Model	**β (±SE)*, p-value**	**β (±SE)*, p-value**	**PAT* sex**	**β (±SE)*, p-value**	**PAT/SAT* sex**
Model 1†	−2.62 (±1.27), 0.051	0.05 (±1.05), 0.962	0.218	−1.03 (±0.68), 0.136	0.782
Model 2‡	−1.03 (±1.46), 0.485	−0.49 (±1.30), 0.707	0.201	−1.35 (±0.70), 0.057	0.835
Model 3§	−1.33 (±1.78), 0.462	1.48 (±1.46), 0.320	0.111	−0.96 (±0.74), 0.200	0.807
Model 4//	−0.18 (±2.38), 0.940	3.36 (±1.96), 0.097	0.055	−2.08 (±1.03), 0.047	0.768

Abbreviations: PAT, pericardial adipose tissue; SAT, subcutaneous adipose tissue; GIR, glucose infusion rate; BMI, body mass index; VAT, visceral adipose tissue; LDL, low-density lipoprotein

*Per 1 SD

†Adjusted for diabetes, race, age, systolic blood pressure, LDL, log triglycerides, on blood pressure and lipid lowering medication, percent of energy from fats and carbohydrates, and square-root transformed minutes of moderate intensity-equivalent activity weekly; additionally adjusted for sex in log PAT/SAT ratio models

‡Adjusted for variables in Model 1 + BMI

§Adjusted for variables in Model 2 + VAT

//Adjusted for variables in Model 3 + log PAT/SAT ratio or log PAT, respectively

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Table 5

Mediation of the relationship between log PAT or log PAT/SAT ratio on GIR by RQ, fasting FFA, and log HMW adiponectin

	Log PAT				Log PAT/SAT	
	Males (N=36)		Females (N=47)		(N=83)	
Model	**β (±SE)*, p-value**	**Mediation effect size†**	**β (±SE)*, p-value**	**Mediation effect size†**	**β (±SE)*, p-value**	**Mediation effect size†**
Model 1‡	−0.18 (±2.38), 0.940		3.36 (±1.96), 0.097		−2.08 (±1.03), 0.047	
Model 2§	1.30 (±2.06), 0.536	−1.59 (−8.23, 4.29)	0.55 (±1.65), 0.740	4.00 (0.13, 9.33)	−1.33 (±0.86), 0.130	−0.75 (−3.03, 1.39)
Model 3//	−0.69 (±2.53), 0.788	1.03 (−2.22, 5.69)	3.34 (±2.00), 0.105	0.04 (−1.56, 1.75)	−2.12 (±1.05), 0.047	0.08 (−0.54, 0.83)
Model 4#	−0.40 (±2.00), 0.844	0.43 (−5.26, 6.33)	3.38 (±1.78), 0.067	−0.03 (−3.92, 3.85)	−2.36 (±0.94), 0.014	0.51 (−1.14, 2.32)
Model 5¶	−0.31 (±2.39), 0.897	0.26 (−2.65, 3.72)	3.32 (±2.02), 0.110	0.08 (−1.80, 2.14)	−2.17 (±1.04), 0.042	0.15 (−0.52, 1.08)

Abbreviations: PAT, pericardial adipose tissue; SAT, subcutaneous adipose tissue; GIR, glucose infusion rate; RQ, respiratory quotient; FFA, free fatty acids; HMW, high molecular weight; BMI, body mass index; VAT, visceral adipose tissue; LDL, low-density lipoprotein

* per 1 SD

† Mediation effect size estimated using product of coefficients method with unstandardized coefficients; 95% CI's estimated using the distribution of the product method

‡ Adjusted for diabetes, race, age, systolic blood pressure, LDL, log triglycerides, on blood pressure and hypertension lowering medication, percent of energy from fats and carbohydrates, square-root transformed minutes of moderate intensity-equivalent activity weekly, BMI, log VAT, and log PAT/SAT ratio or log PAT, respectively; additionally adjusted for sex in log PAT/SAT ratio models

§ Adjusted for variables in Model 1 + RQ

// Adjusted for variables in Model 1 + fasting FFA

Adjusted for variables in Model 1 + FFA suppression

¶ Adjusted for variables in Model 1 + log HMW adiponectin