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Central adiposity associations to carbohydrate and lipid metabolism in individuals with complete motor spinal cord injury

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Abstract

Altered body composition has been suggested as a major factor for the high prevalence of impaired glucose tolerance, insulin resistance, and dyslipidemia in individuals with spinal cord injury (SCI). The contributions of visceral adipose tissue (VAT), trunk subcutaneous adipose tissue (SAT), and the VAT/SAT ratio to these metabolic derangements in SCI are poorly defined. Thirteen individuals with traumatic motor complete SCI underwent a metabolic study after overnight fasting to measure plasma glucose, insulin, and lipid concentrations. Fast spin echo magnetic resonance imaging was used to quantify the average cross-sectional area (CSA), volumes, and percentages of VAT and SAT across multiaxial slices. Dual-energy x-ray absorptiometry was performed to measure whole-body fat-free mass and fat mass. Visceral adipose tissue CSA was positively related to fasting plasma glucose ($r = 0.77$, $P = .002$) and to the ratio of cholesterol to high-density lipoproteins (HDL-C) ($r = 0.71$, $P = .006$). Visceral adipose tissue volume was related to total cholesterol ($r = 0.57$, $P = .043$) and to low-density lipoproteins ($r = 0.59$, $P = .032$). Trunk %SAT was negatively related to glucose concentration and area under the curve (both, $r = -0.61$, $P = .026$). Fasting plasma insulin was negatively related to the VAT CSA and VAT/SAT ratio (both, $r = -0.57$, $P = .043$). Partial correlations showed a negative association between trunk %SAT and glucose area under the curve ($r = -0.61$, $P = .02$) and a positive association with HDL-C ($r = 0.64$, $P = .033$). The findings suggest that an increase in VAT, SAT, and VAT/SAT is associated with the adverse metabolic profile commonly seen in individuals with SCI. Trunk %SAT is associated with a reduced risk of glucose intolerance and an increased HDL-C.

1. Introduction

Disorders of carbohydrate and lipid metabolism impose substantial health risks on individuals with spinal cord injury (SCI) [1-5]. Following SCI, an array of changes occurs that include skeletal muscle atrophy, decline in fat-free mass (FFM) and increase in percentage body fat mass (FM) [6,7]. These changes are associated with impaired glucose tolerance [1,2,5], insulin resistance [8], dyslipidemia [1-3], metabolic syndrome [9], and cardiovascular diseases [4]. Duckworth et al [5] showed that, in 45 individuals with chronic SCI, more than half were diagnosed with type 2 diabetes mellitus (DM). In veterans with SCI, the prevalence of type 2 DM was 22% compared with 6% in able-bodied controls [1]. Spinal cord injury is associated with dysfunction in lipid metabolism characterized by elevated serum total cholesterol, triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), and depressed high-density lipoprotein cholesterol (HDL-C) [1-3]. Depressed HDL-C has been estimated to affect more than 19% of individuals with SCI, which could increase the risk of coronary artery diseases up to 20% in this population [4]. Investigating factors that contribute to impairment in carbohydrate and lipid metabolism is of paramount importance to this population.

The Adult Treatment Panel III of the National Cholesterol Education Project guidelines focused on abdominal obesity as the primary criterion for evaluating the risks of metabolic syndrome in men and women [10]. *Abdominal obesity* is defined as a waist circumference (WC) greater than 102 cm in men and 88 cm in women [10]. This measurement reflects

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increases in both truncal visceral adipose tissue (VAT) and truncal subcutaneous adipose tissue (SAT). Nash and Mendez [11] reported that 76% of individuals with paraplegia had HDL-C less than 40 mg/dL and 34% had Adult Treatment Panel III–defined metabolic syndrome. In able-bodied and other clinical populations, an increase in VAT is associated with glucose intolerance and insulin resistance, supporting the notion that VAT may play an important role in the pathogenesis of impaired carbohydrate metabolism [12-16]. Abdominal obesity is also associated with altered lipid metabolism [14,16]. For example, a high waist to hip ratio is associated with high LDL-C and low HDL-C concentrations [16,17]; and obese men and women with high levels of VAT showed marked alterations in lipoproteins levels [16-18]. It has been suggested that increased VAT results in increased flux of free fatty acids (FFAs) to the liver through portal circulation. This may stimulate hepatic glucose and TG production as well as impair the clearance of insulin resulting in a state of hyperinsulinemia [12,18].

Several anthropometric measurements, such as WC and waist to hip ratio, have been used to reflect the increase in VAT and SAT and their associations to different metabolic disorders [19-23]. Although it is simple to apply clinically, WC cannot fully account for adipose tissue distribution; and hence, more powerful imaging tools have been used to more accurately quantify the fat distribution [13-16,19]. Magnetic resonance imaging (MRI) is now considered the criterion standard technique [15,24,25]. In individuals with SCI, a single-axial computerized tomography slice at L4 to L5 was recently used to measure VAT and SAT cross-sectional areas (CSAs) to determine their associations with other biochemical variables [26,27]. The findings included moderate associations between VAT and serum plasma insulin and negative relationships between VAT/SAT ratio and HDL-C. However, no significant relationships with plasma glucose, cholesterol, TG, or LDL-C were observed. Moreover, no relationships were observed between SAT and the studied variables. A simple explanation is that the use of a single-axial CSA is not sufficient to accurately determine the magnitude of VAT or SAT and their associations with other metabolic variables.

We have recently used multiaxial MRI to quantify the volumes of VAT and SAT in individuals with chronic SCI [28,29]. We showed that VAT and SAT represent about 6% and 10% of total body FM, respectively. These values were lower than what has been determined in able-bodied populations because of an increase in whole-body percentage FM in individuals with SCI. Moreover, FM and FFM were related to VAT and SAT volumes but not to a single-axial CSA. Therefore, the true relationships between central adiposity and metabolic profile may be affected by the adaptations in whole-body FM and FFM, reinforcing the need for more than a single slice measurement. The purpose of the current study is to evaluate the methodology used to reveal the relationships observed in other populations and to determine if the associations between VAT, SAT, VAT/SAT ratio, and several other metabolic variables are in fact different in the SCI population. We hypothesized that the use of MRI multiaxial slices would better identify the relationships between the studied variables compared with what has been previously reported.

2. Subjects and methods

2.1. Participants

Thirteen healthy men with chronic traumatic motor complete SCI ([mean ± SD] age, 35 ± 8 years; body weight, 74 ± 13 kg; height, 182 ± 7 cm; and body mass index [BMI], 23 ± 4 kg/m^2) participated in the study. Only men were chosen to ensure homogeneity of our sample and to reduce possible effects of sex on body composition. Furthermore, compared with women, men accumulate greater quantities of VAT [20,30]. The participants were at least 1 year postinjury with levels of injury ranging from C5 to T11 and American Spinal Injury Association classification A or B (motor complete SCI). Participants were recruited from the University of Michigan SCI model system (n = 5, C6-T11) and from Indiana University Hospitals (n = 8, C5-T11). Participants signed an informed consent statement that was approved by the local ethical committee at the University of Michigan and Indiana University, and they were compensated for participation.

Participants were included if they (1) were men between 18 and 45 years of age, with the maximum age chosen to avoid any confounding effects of the aging process on body composition; (2) were a minimum of 1 year postinjury, due to adaptations in body composition stabilizing by this time; and (3) had a level of injury C5 to T11 (those with injury above C5 have limited hand functions and are dependent on others to prepare their meals, which may indirectly influence their body composition, VAT, and SAT). Lower motor neuron injury is typically found in those with injury below T11 and leads to flaccid paralysis of the involved skeletal muscles that ultimately affects body composition [31].

Participants were excluded from the study if they had any of the following: cardiovascular disease, hypertension, DM, or dyslipidemia; were cigarette smokers or alcohol abuser; or had a grade II or greater pressure ulcers. Individuals with BMI greater than 30 were excluded because lower BMI cutoff points have been recommended that identify the risk of obesity in people with SCI [7,32]. Persons having MRI-incompatible materials, such as rods, screws, valves, and stents that were implanted for different medical purposes, were also excluded.

2.2. Anthropometrics and metabolic profile

Participants who met the study inclusion criteria were admitted to the General Clinical Research Center. All participants were instructed to abstain from exercise,

alcohol, and caffeine consumption 24 hours preceding the examination. After arrival, participants were asked to void their bladder and underwent a general physical examination that included measuring vital signs and a resting 12-lead electrocardiogram to rule out any preexisting cardiac problems. Body weight was then measured while wearing light clothing in a supine position using a hospital bed scale calibrated to 0.1 kg. Height was measured from the same position to the nearest 0.1 cm. Body mass index was calculated as weight in kilograms divided by height in square meters.

After an overnight fast for 10 to 12 hours, a Teflon catheter was inserted into an antecubital vein of one arm for blood sampling; and 4 mL per subject was sent for analysis of total cholesterol, TG, HDL-C, and LDL-C. After allowing the blood sample to clot for 30 minutes, the blood was centrifuged at 3000 rpm for 10 minutes; and the serum was transferred for analysis. A standard 75-g oral glucose tolerance test (OGTT) was then administered; and blood was drawn at 0 minute before and 30, 60, 90, and 120 minutes after administration. A 4-mL sample of blood was drawn at each time point to measure plasma glucose and insulin concentrations. All blood samples were sent to the Chemistry Pathology Laboratory for analysis. The plasma concentrations of TG, cholesterol, LDL-C, HDL-C, glucose, and FFA were determined using commercially available colorimetric assays (Sigma, Wako Chemicals US, Richmond, VA; and Thermo DMA, Roche, Minneapolis, MN, respectively). The ratio of cholesterol to HDL-C was then calculated. The plasma insulin concentration was measured using a commercially available radioimmunoassay kit (Linco Research, St. Charles, MO). Insulin sensitivity was determined using the Matsuda and Defronzo index and homeostasis model assessment of insulin resistance index (HOMA-IR) [33,34]. The values of plasma insulin and HOMA-IR were then log-transformed to normalize for parametric analyses. Plasma glucose and insulin concentrations were calculated as the average of concentrations at 0, 30, 60, 90, and 120 minutes throughout OGTT. The areas under the curve (AUCs) and the incremental AUC of plasma glucose and insulin were computed by integration with trapezoidal rule [35].

2.3. Dual-energy x-ray absorptiometry and MRI

Dual-energy x-ray absorptiometry (DXA) was used to study the whole-body FFM and FM (in kilograms). Body composition was measured using whole-body scans with a Lunar Prodigy Advance scanner (n = 5; Lunar DPX, DXA Scanner; Lunar, Madison, WI) and a Hologic QDR-2000 scanner (Hologic, Bedford, MA) (n = 8). Selection of 2 different densitometers was based on the availability of the DXA scanners at the 2 institutions at the time of the study. A whole-body standard phantom was used to correct for the source of error that may result from using 2 different densitometers; the results showed that the between-machine difference was 0.06% for FM and 7% for FFM. Whole-body %FM and FFM were calculated after excluding bone tissue, and the index of FM to FFM was used to determine relative distribution of FM. The coefficient of variability of repeated scans was less than 3%.

Magnetic resonance images were obtained with a 1.5- or 3-T whole-body scanner (General Electric Signa scanner, Milwaukee, WI). After arrival to the magnet, participants were taken to the scanner for a noncontrast abdominal MRI. T1-weighted imaging was performed using a fast spin echo sequence with the following parameters: axial in-phase/out-phase with a repetition time of 140 milliseconds and echo time of 4.2 and 1.8 milliseconds for the in-phase and the out-phase, respectively; a 46-cm field of view; matrix size of 256 × 256 or 320 × 320; 1 number of excitation; and acquisition time of 4-5 minutes). Transverse slices (0.8- or 1-cm thickness) were acquired every 0.4- or 1-cm gap from the xiphoid process to the femoral heads. Images were acquired in series of 2 stacks with L4 to L5 used as a separating point. After acquisition of a localizer sequence, the intervertebral space between the fourth and fifth lumbar vertebrae was identified by locating the umbilicus [24,25]. To ensure a short breath holding duration, 2 sets of 9 slices were captured. The first set extended superiorly from L4 to L5 to the xiphoid process, and the second set extended distally from L4 to L5 to the femoral heads. During scanning, participants were asked to take a deep breath in and hold their breath for 10 to 15 seconds. The breath holding technique was applied to reduce the respiratory motion artifact normally associated with acquisition of MRI in the abdominal region.

Images were analyzed on specifically designed software (Win Vessel 2, Ronald Meyer, PhD, Department of Physiology, Michigan State University, East Lansing, MI). The images were automatically segmented into fat (high-intensity), muscle (mid-intensity), and background/bone (low-intensity) regions [31,36]. The CSAs were computed automatically by summing the tissues' pixels and multiplying by pixel surface area. Pixel surface area was multiplied by (field of view/matrix size)^2. The volume (in cubic centimeters) was calculated by multiplying CSA by the slice thickness and interslice space. Selection of images was based on visual distinction of VAT and SAT regions within a single slice. To adjust for differences in torso length among our participants, consecutive slices were averaged in taller individuals (>10-14 slices); and truncal VAT and SAT volumes were calculated by summing the volumes of 10 slices in all participants. After anatomically matching for slices among our participants, we have chosen to average any 2 consecutive slices in taller individuals that cover the same anatomical region toward the femoral heads. This procedure was performed to standardize the number of slices among all participants. The VAT and SAT mass (in grams) was calculated by multiplying the corresponding volumes (in cubic centimeters) by fat density (0.92 g/cm^2). To test the effects of the anatomical site on the metabolic profile, VAT

and SAT CSAs across multiaxial slices were subdivided into 3 stacks including L1 to L3, L3 to L5, and L5 to S1. The coefficient of variability of a single examiner was less than 3% for VAT and 0.5% SAT.

2.4. Statistical analyses

Pearson correlation coefficients were used to examine for associations between body composition variables and metabolic profile. The VAT and SAT masses were adjusted to the whole-body FM to determine the relative impact on the metabolic profile. Exponential nonlinear regression equations were used to test for the associations between plasma insulin and the CSA and volumes of VAT and SAT as well as the VAT/SAT ratio because relationships between insulin and regional adipose tissue appeared to be better described with nonlinear than linear models [37]. A VAT/SAT ratio of 0.64 was the median of the studied population and was chosen as a cutoff point to study the effects on different metabolic variables. Because variation in body weight may have influenced the relationships between central adiposity and metabolic variables, partial correlations were used to these relationships independent of BMI, FM, and %FM. Independent *t* tests were used to test for differences in the metabolic variables after considering cutoff points of VAT CSA greater than 100 cm^2 and VAT/SAT ratio greater than 0.64. The CSAs of VAT and SAT at L3 to L4, L4 to L5, and L5 to S1 were chosen to determine the relationships of single-axial CSA slice on the metabolic profile in individuals with SCI. The 3 single-axial CSAs were the most common anatomical sites previously used to determine similar associations. All values are presented in mean ± SD, and statistical analyses were performed using SPSS version 15.0 (SPSS, Chicago, IL).

3. Results

The average CSA, volume, and percentage of VAT and SAT and the VAT/SAT ratios as well as the metabolic variables are presented in Table 1. It should be noted that no relationships were noted by any of the central adiposity measurements, insulin sensitivity, HOMA-IR, or plasma FFA concentrations. Plasma TG concentrations of 3 participants were identified as outliers, and the relationships with central adiposity were reported both with and without outliers.

3.1. Physical characteristics and metabolic profile

The age of the participants was positively associated with fasting plasma glucose ($r = 0.67$, $P = .01$), glucose concentration ($r = 0.58$, $P = .03$), and AUC ($r = 0.59$, $P = .03$). For lipid profile, age was associated with increase in plasma cholesterol ($r = 0.63$, $P = .02$) and TG ($r = 0.58$, $P = .036$) concentrations. Body mass index was related to plasma cholesterol ($r = 0.75$, $P = .003$), TG ($r = 0.62$, $P = .023$), and LDL-C ($r = 0.7$, $P = .007$) concentrations. Time since injury was related to increased fasting plasma glucose ($r = 0.57$, $P = .043$), glucose concentration ($r = 0.73$, $P = .004$), and AUC ($r = 0.74$, $P = .004$).

Table 1
Outcomes of central adiposity and metabolic profile in individuals with motor complete SCI

	SCI (n = 13)	VAT >100 cm^2 (n = 5)	VAT <100 cm^2 (n = 8)	VAT/SAT >0.64 (n = 5)	VAT/SAT <0.64 (n = 8)
Age (y)	35 ± 8	40 ± 9	32 ± 6*	39 ± 9	32 ± 6
BMI (kg/m^2)	23 ± 4	25 ± 3	21 ± 5	23 ± 5	23 ± 4
VAT CSA (cm^2)	99 ± 51	150 ± 43	66 ± 19‡	132 ± 66	77 ± 9*
VAT volume (cm^3)	1418 ± 674	1971 ± 621	1072 ± 452†	1758 ± 916	1205 ± 407
%VAT	5.7 ± 1.8	7 ± 1.5	5 ± 1.8*	7 ± 1.5	5 ± 1.8*
SAT CSA (cm^2)	164 ± 69	171 ± 42	161 ± 84	131 ± 55	185 ± 71
SAT volume (cm^3)	2420 ± 1030	2298 ± 896	2498 ± 1160	1829 ± 1133	2790 ± 825
%SAT	9.7 ± 3	7.7 ± 1.4	11 ± 3*	7 ± 1.8	11.5 ± 2.5‡
VAT/SAT ratio	0.68 ± 0.3	0.95 ± 0.3	0.5 ± 0.2†	1 ± 0.2	0.45 ± 0.1‡
Fasting glucose	89 ± 13	101 ± 9	82 ± 9‡	99 ± 10	83 ± 10†
Plasma glucose AUC (mg/dL min)	528 ± 135	612 ± 137	476 ± 110*	585 ± 112	493 ± 142
Fasting insulin	11 ± 4	8.5 ± 3.5	12.5 ± 4†	9 ± 4	12 ± 4
Plasma insulin AUC (μU/mL min)	320 ± 121	308 ± 74	327 ± 104	352 ± 119	299 ± 69
HOMA-IR	2.4 ± 0.9	2.1 ± 1	2.6 ± 1	2.2 ± 1	2.5 ± 1
Cholesterol (mg/dL)	163 ± 36	179 ± 29	153 ± 39	157 ± 39	167 ± 37
TG (mg/dL)	104 ± 42	101 ± 24	105 ± 51	87 ± 31	114 ± 46
LDL (mg/dL)	120 ± 38	132 ± 29	112 ± 42	114 ± 38	123 ± 40
HDL (mg/dL)	36 ± 7	33 ± 8	38 ± 5	34 ± 8	37 ± 6
Cholesterol to HDL ratio	4.7 ± 1.2	6 ± 1	4 ± 0.6‡	5 ± 1.4	4.5 ± 1

Values are presented as mean ± SD.
* *P* value between .05 and .08.
† *P* value < .05.
‡ *P* value < .005.

3.2. VAT and metabolic profile

Individuals with VAT CSA greater than 100 cm^2 had higher fasting plasma glucose, glucose AUC, and cholesterol to HDL-C ratio (Table 1). The average VAT CSA was positively related to VAT/SAT ratio (0.67, P = .012), fasting plasma glucose (r = 0.77, P = .002), TG (n = 10, r = 0.71, P = .02 and n = 13, r = 0.16, P = .5), and cholesterol to HDL-C ratio (0.71, P = .006), with a negative trend toward plasma HDL-C (r = −0.52, P = .08). The VAT volume was also related to fasting plasma glucose (Fig. 1A), plasma cholesterol (r = 0.57, P = .04), and LDL-C (r = 0.59, P = .03). Exponential nonlinear regression analyses showed a negative relationship between VAT CSA and fasting plasma insulin, suggesting a state of insulin resistance associated with pancreatic dysfunction (Fig. 1B). Partial correlations identified negative relationships between VAT CSA and fasting plasma insulin after controlling for FM (r = −0.61, P = .03) and %FM (r = −0.60, P = .04), but not with BMI. The relationship between fasting plasma glucose and single-axial CSA is presented (Fig. 2). The average CSAs of stacks of VAT at L1 to L3 (r = −0.55, P = .054), L3 to L5 (r = −0.55, P = .051), and L5 to S1 (r = −0.51, P = .075) were negatively related to fasting plasma insulin.

3.3. SAT and metabolic profile

Body mass index was positively related to SAT CSA (r = 0.61, P = .027) and volume (r = 0.77, P = .02), but not to trunk %SAT. The SAT volume was positively related to cholesterol (r = 0.59, P = .03), TG (n = 10, r = 0.61, P = .06 and n = 13, r = 0.57, P = .042), and LDL-C (r = 0.58, P = .03). Trunk %SAT was negatively related to VAT/SAT ratio (r = −0.71, P = .006), but not to VAT CSA or volume. It should be noted that those with VAT/SAT ratio greater than 0.64 had less trunk %SAT compared with those with a reduced ratio (Table 1), with no change in %VAT between both groups. This may suggest that those with a reduced trunk %SAT have higher VAT/SAT ratios. The relationship between trunk% SAT and plasma glucose at 30, 60, and 90 minutes following OGTT administration is presented (Fig. 3). Trunk %SAT was negatively related to glucose AUC (Fig. 4A) and glucose concentration (both, r = −0.61, P = .026). Moreover, trunk %SAT was negatively related to the incremental AUC of plasma glucose (r = −0.57, P = .04). Partial correlations showed that trunk %SAT was positively related to HDL-C (Fig. 4B), with a trend of negative associations between SAT volume and the cholesterol to HDL-C ratio (r = −0.55, P = .076). The SAT CSAs at L3 to

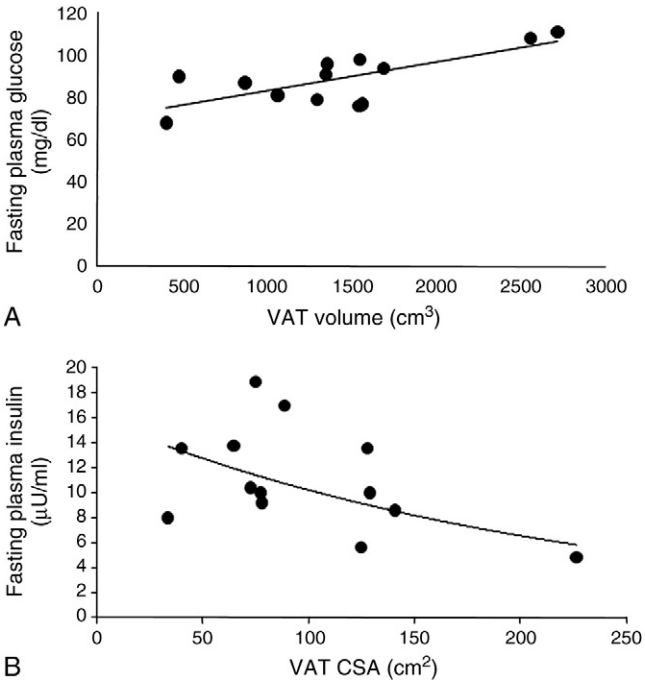

Fig. 1. Relationship between VAT and fasting plasma glucose and insulin concentrations. A, Linear relationship between VAT volume and fasting plasma glucose (r = 0.77, P< 0.05). B, Nonlinear negative relationship between VAT CSA and fasting plasma insulin (r = −0.57, P = .043).

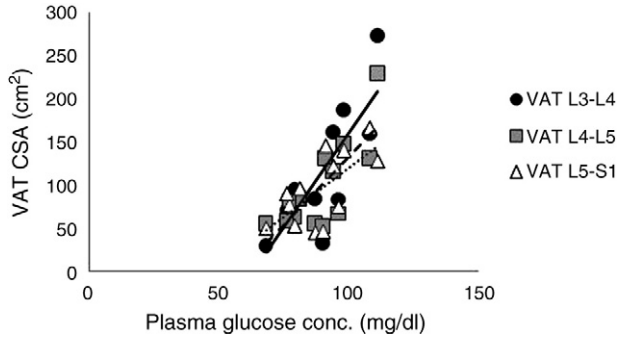

Fig. 2. Relationship between fasting plasma glucose concentration and single-axial CSA of VAT at L3 to L4 (r = 0.80, P = .001), L4 to L5 (r = 0.76, P = .002), and L5 to S1 (r = 0.67, P = .01). It should be noted that VAT L4 to L5 was positively related to glucose concentration at 30 minutes post-OGTT (r = 0.58, P = .038) and that no relationships were identified between plasma glucose or plasma insulin concentration and VAT at single-axial CSA.

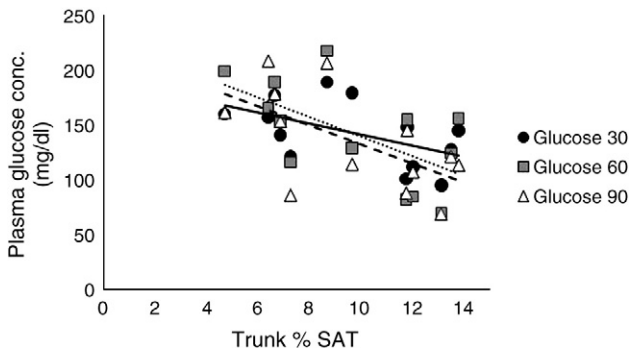

Fig. 3. Relationship between trunk %SAT and plasma glucose concentration at 30 (r = −0.52, P = .06), 60 (r = −0.60, P = .03), and 90 (r = −0.60, P = .03) minutes post-OGTT administration. The relationships with fasting plasma glucose (r = −0.34, P > .05) and 120 minutes post-OGTT (r = −0.50, P = .08) are not presented for purposes of clarity.

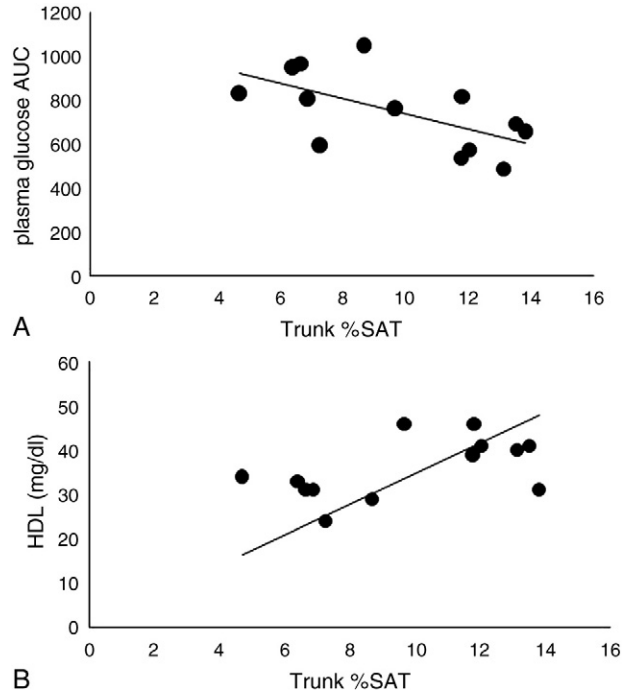

Fig. 4. Relationship between trunk %SAT and (A) plasma glucose AUC ($r = -0.61$, $P = .027$) and (B) HDL-C ($r = 0.64$, $P = .033$).

L4, L4 to L5, and L5 to S1 were not significantly related to any of the outcome variables of OGTT or lipid panel.

3.4. VAT/SAT ratio and metabolic profile

Individuals with SCI who had VAT/SAT ratio greater than 0.64 had impaired fasting glucose tolerance (Table 1), with no differences noted in lipid profile. The VAT/SAT ratio was positively related to fasting plasma glucose ($r = 0.62$, $P = .025$) and negatively related to fasting plasma insulin ($r = -0.57$, $P = .043$). Finally, the ratio showed a trend of negative association with HDL-C ($r = -0.53$, $P = .08$).

3.5. Body composition and metabolic profile

Table 2 presents the relationship between body composition variables, lipid profile, and fasting plasma glucose. Surprisingly, no significant relationships were noted between body composition variables, plasma insulin, and glucose concentrations or AUC. Both VAT and SAT were negatively related to fasting insulin per unit of FFM ($r = -0.52$, $P = .06$) and insulin concentration per unit of FFM ($r = -0.57$, $P = .047$). Finally, VAT CSA per unit of FFM was positively related to plasma TG (n = 10, $r = 0.77$, $P = .01$ and n = 13, $r = 0.12$, $P = .7$).

4. Discussion

Deterioration in body composition and its association with an unfavorable metabolic profile are well documented in individuals with SCI [1-6]. Compared with the existing knowledge in other clinical populations [12-19], the role of VAT and SAT on the metabolic profile after SCI is less well defined. We found that, compared with a single-axial CSA, the use of multiaxial slices more accurately predicts impairment in glucose tolerance, insulin resistance, and dyslipidemia in the SCI population. Moreover, trunk %SAT may have a protective effect on glucose and lipid profiles.

This is the first study that has investigated the associations of VAT and SAT with altered metabolic profile in individuals with SCI. Previous work clearly documented that carbohydrate dysfunction is up to 3-fold more prevalent in SCI than in the able-bodied population [1]. Moreover, this population is at high risk of developing dyslipidemia associated with a depressed HDL-C [1-3,10]. The role of VAT and SAT in the aforementioned metabolic disorders has just recently been investigated in individuals with SCI. Edwards et al [26] showed that individuals with SCI had greater VAT CSA (58%) and VAT/SAT (48%) compared with matched able-bodied controls. They also observed moderate relationships between VAT CSA and VAT/SAT ratio and with HOMA-IR and HDL-C, respectively. The study did not observe other relationships with VAT or VAT/SAT and plasma glucose or lipid profile. Maruyama et al [27] showed that, compared with BMI-matched able-bodied group, 43% of individuals with SCI are at risk of developing metabolic syndrome. The study showed small to moderate correlations between VAT and adiponectin or HOMA-IR, with no associations with TG or HDL-C.

Previous studies have grouped together both male and female participants with SCI in one group, and both have examined individuals with complete and incomplete SCI [26,27]. Men accumulate greater quantities of VAT compared with women [20,30], and body composition and metabolic profile adaptations may vary widely between both complete and incomplete injury [6,7,31,36]. These factors may have underestimated or skewed the relationships between VAT and other metabolic variables. Furthermore,

Table 2
Pearson correlation coefficients (*P* values) between body composition variables, lipid profile, and fasting plasma glucose

	Cholesterol	TG	Cholesterol to HDL ratio	HDL	LDL	Fasting glucose
%FFM	−0.81** (.001)	−0.370 (NS)	−0.41 (NS)	−0.40 (NS)	−0.76** (.003)	−0.51 (.07)
FM	0.76** (.002)	0.48 (.09)	0.51 (.07)	0.23 (NS)	0.67** (.01)	0.58* (.03)
FM/FFM	0.83** (.0001)	0.37 (NS)	0.35 (NS)	0.49 (NS)	0.82** (.001)	0.52 (.07)

NS indicates nonsignificant relationship.

considering the arrays of adaptations in body composition after SCI, a single-axial CSA slice may not be the best methodological approach to quantify VAT and SAT in this population. In the current study, we examined a homogenous sample of individuals with complete traumatic motor SCI. Moreover, we have applied multiaxial MRI technique to capture the adaptations in VAT and SAT across the whole trunk region.

Increase in VAT and SAT CSAs and VAT/SAT ratios across multiaxial slices are primary predictors of impaired glucose tolerance, insulin resistance, and lipid profile [12-18]. Because VAT only represents 6% of the whole-body FM in this population [28,29], the whole-body FM dominates determination of the metabolic profile (Table 2). However, VAT CSA and volume are predominantly related to fasting plasma glucose, with nonlinear relationship to fasting plasma insulin. The inverse relationship between VAT CSA and fasting plasma insulin we observed is the opposite of that seen in the general population, where increased VAT CSA is commonly associated with a state of hyperinsulinemia [12,13,15]. It is possible that skeletal muscle atrophy, or different patterns and/or timing of fat accumulation in SCI contributes to this observation, perhaps contributing to β-cell dysfunction earlier or at lower total fat loads than in an able-bodied population. In our data set, those with VAT CSA less than 100 cm^2 experienced a linear increase in plasma insulin; and those with VAT CSA greater than 100 cm^2 experienced a decline in their plasma insulin (Fig. 1). It is also possible that the level of injury may influence the relationship between VAT and fasting plasma insulin; 54% of the sample were individuals with tetraplegia with a BMI lower than 21 kg/m^2 and higher fasting plasma insulin. Partial correlation revealed negative relationships between VAT CSA and fasting plasma insulin after controlling for percentage and absolute whole-body FM. It was previously suggested that SCI could be used as a model of studying premature aging [1] because many of the metabolic and body composition adaptations accompanied with aging prematurely occur in individuals with SCI. We have observed strong relationships with age and metabolic profile, which could be a factor of age-associated increase in VAT and SAT. Impaired sympathetic nervous system (SNS) and incremental loss in FFM may be responsible for the age-related increase in VAT [8,29].

The atherogenic effects of altered lipid profile in individuals with SCI are well documented [1-4]. The increased risk of coronary heart disease is a function of increased LDL-C and depressed HDL-C in this population [3,4]. The degree of neurologic deficit, physical activity, smoking, and central adiposity are all factors that have been previously linked to dyslipidemia after SCI [4]. An inverse relationship was previously found between abdominal circumference and serum HDL-C, and a positive correlation was found with serum TG values [38]. In the current study, a negative relationship was noted between VAT/SAT ratio and HDL-C; and a positive correlation was found with VAT and SAT volumes and serum TG, LDL-C, and cholesterol. The findings suggest that both VAT and SAT contribute equally to alerted lipid profile; however, when VAT/SAT ratio increases, this becomes detrimental to HDL-C. It is feasible to mention that increase in VAT is an important predictor in the processes of obliteration of the cardioprotective role of HDL-C and elevation in both TG and LDL-C after SCI.

Similar to lipodystrophy syndrome, individuals with SCI are characterized by increased %VAT and reduction in % SAT, leading to an increased VAT/SAT ratio [39,40]. In those with type 2 DM, individuals with higher VAT and lower SAT CSAs are more likely to become insulin resistant [15]. We have observed improvement in plasma glucose concentrations and AUC as well as in HDL-C profile associated with increase in trunk %SAT. These relationships could possibly be mediated by increasing the levels of adiponectin and its effects on glucose and lipid metabolism [41]. Gavi et al [39] observed associated increase in the adiponectin level with increasing the ratio of leg to trunk SAT. Another study showed that, compared with trunk SAT, leg FM is associated with a favorable response toward glucose and lipid metabolism [40]. However, the ratio of trunk SAT to leg FM is altered in individuals with SCI because of increased leg %FM compared with trunk %FM [7,42]. This claim can be explained by the effect of SNS on adipose tissue metabolism. In a clinical trial, antihypertensive drugs were associated with increased adiponectin level via reducing SNS activity [43]. Therefore, impairment in SNS activity after SCI may explain the higher levels of adiponectin previously noted in individuals with SCI compared with able-bodied controls [44]. This view, however, is not always being supported [45].

A plethora of evidence supports the rationale that the primary mechanism responsible for insulin resistance in the able-bodied population is the abundance of FFA [41,46]. Visceral adipose tissue has a high rate of lipolytic activity that results in increasing the flux of FFA through portal circulation, resulting in production of TG and LDL-C, development of atherogenic dyslipidemia, and poor clearance of insulin [12,18]. We could not demonstrate any associations between plasma FFA, central adiposity measurements, and outcomes of OGTT and lipid profile. The findings may suggest that the mechanisms responsible for insulin resistance in this population vary from other clinical populations. Moreover, the studied population has a number of factors that could lead to insulin resistance such as skeletal muscle atrophy [36,47,48], accumulation of intramuscular fat [36,48], and impairment in the activity of SNS. Another possibility is that VAT could impair insulin resistance through the secretion of inflammatory biomarkers [49].

4.1. Limitations

The current study is cross-sectional in design, and cause-effect relationships cannot be determined. Because of availability, the DXA scanner that was located at each

study site was used in our investigation (eg, a machine from either Lunar or Hologic). The between-machine error was acceptably small, as shown by the use of a body standard phantom; and thus, the use of different scanners is unlikely to have significantly altered the relationships that we have observed. Although we had a relatively small sample size, our study population was more uniform than the ones reported in prior studies, in which individuals were included who had complete or incomplete SCI, were male or female, had diverse etiologies for SCI, and were persons with SCI who had significant medical conditions or healthy. We were also unable to determine the association between adiponectin or leptin and central adiposity. It is possible that adiponectin or leptin changes could mediate the metabolic effects of altered body fat distribution [50,51] and may help to identify the associations between central adiposity and metabolic profile in this population. Future studies need to account for the level of injury, age, and time since injury when studying central adiposity and metabolic profile in SCI.

5. Conclusions

The current study showed that, in individuals with SCI, increases in VAT, SAT, or VAT/SAT ratio are associated with an adverse metabolic profile, manifested by impaired glucose tolerance, insulin resistance, and dyslipidemia. The use of a single-axial CSA slice may not be sufficient to capture the true associations between central adiposity and metabolic profile in this population. Visceral adipose tissue CSA was negatively related to fasting plasma insulin, suggesting a state of insulin resistance associated with pancreatic dysfunction. Finally, trunk %SAT was positively associated with improved metabolic profile. This phenotype may warrant further investigation to identify the role of regional adiposity in influencing the metabolic profile after SCI.

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