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# Metabolic Syndrome in Adolescents With Spinal Cord Dysfunction

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## Abstract

**Objective:** The purpose of this study was to determine the prevalence of components of the metabolic syndrome in adolescents with spinal cord injury (SCI) and spina bifida (SB), and their associations with obesity in subjects with and without SCI and SB.

**Methods:** Fifty-four subjects (20 SCI and 34 SB) age 11 to 20 years with mobility impairments from lower extremity paraparesis were recruited from a hospital-based clinic. Sixty able-bodied subjects who were oversampled for obesity served as controls (CTRL). Subjects were categorized as obese if their percent trunk fat measured by dual x-ray absorptiometry (DXA) was >30.0% for males and >35.0% for females. Ten SCI, 24 SB, and 19 CTRL subjects were classified as obese. Fasting serum samples were collected to determine serum glucose, insulin, and lipid concentrations. Metabolic syndrome was defined as having  $\geq 3$  of the following components: (a) obesity; (b) high-density lipoprotein (HDL) <45 mg/dL for males; <50 mg/dL for females; (c) triglycerides  $\geq 100$  mg/dL; (d) systolic or diastolic blood pressure  $\geq 95$ th percentile for age/height/gender, and (e) insulin resistance determined by either fasting serum glucose 100–125 mg/dL; fasting insulin  $\geq 20\mu\text{U}/\text{mL}$ ; or homeostasis model assessment of insulin resistance  $\geq 4.0$ .

**Results:** Metabolic syndrome was identified in 32.4% of the SB group and 55% of the SCI group. Metabolic syndrome occurred at a significantly higher frequency in obese subjects (SB = 45.8%, SCI = 100%, CTRL = 63.2%) than nonobese subjects (SB = 0%, SCI = 10%, CTRL = 2.4%).

**Conclusions:** The prevalence of metabolic syndrome in adolescents with SB/SCI is quite high, particularly in obese individuals. These findings have important implications due to the known risks of cardiovascular diseases and diabetes mellitus associated with metabolic syndrome in adults, particularly those with spinal cord dysfunction.

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**Key Words:** Spinal cord injuries; Insulin resistance; Metabolic syndrome; Adolescence; Obesity; Cardiovascular disease

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## INTRODUCTION

The prevalence of obesity has reached epidemic proportions worldwide (1–3). Obesity is caused by chronic positive energy balance due to increased energy intake and/or decreased energy expenditure/physical activity when combined with a genetic propensity for weight gain (4,5). Obesity in North American children and adolescents has tripled within the last twenty years (6), with a 45% increase in the United States since National Health and Nutrition Examination Survey (NHANES) III data were collected in 1994 (7). Based on NHANES 2003–2004, 17.1% of children and adolescents are  $\geq 95$ th percentile Body Mass Index for age (6).

An important consequence of obesity is an increased prevalence of parameters associated with metabolic syndrome, a constellation of known risk factors for the development of type 2 diabetes (8–10), cardiovascular disease (10–13), and stroke (11,14,15). Metabolic syndrome has been shown to predict cardiovascular and coronary heart disease mortality (12,16,17). Obesity has been implicated as the primary inciting factor of the metabolic syndrome (18–20). Vanhala et al tracked 439 subjects from childhood to adulthood, and of the 30 adults who were identified with metabolic syndrome, 100% were obese as adults and 75% had been obese as children (21). Adolescent-onset obesity that persisted into adulthood increased the potential for lifelong problems, including increased severity of diseases associated with increased weight/adiposity (21).

The central features of metabolic syndrome are abdominal adiposity, hypertension, increased fasting glucose concentrations/abnormal glucose tolerance, and dyslipidemia characterized by increased serum triglycerides (TG), low serum high-density lipoprotein (HDL), and/or small dense low-density lipoprotein (LDL) particles (22). Insulin resistance as evidenced by hyperinsulinemia appears to be a key feature and may be an underlying/predisposing factor in the syndrome.

Adolescents with spina bifida (SB) or spinal cord injury (SCI) have limited mobility and physical activity, reduced total lean body mass, and reduced resting energy expenditure, leading to an increased risk for obesity. These patients typically have reduced lean body mass in the lower extremities, with increased abdominal and lower extremity fat tissue accumulation (23–31). More than 50% of children with SB have body mass index (BMI) values greater than the 95th percentile (32). Adults with SCI have been shown to have an increased prevalence of obesity (33,34); however, minimal research has been conducted to examine the relationship between obesity and increased risk factors for adverse health outcomes among adolescents with spinal cord dysfunction. Furthermore, paralysis was an exclusionary criterion for performing blood pressure measurements and collecting blood and urine samples in NHANES 2001–2002 (35).

Since obese adolescents have a greater prevalence of metabolic syndrome compared to nonobese adolescents and a greater risk of ultimately developing early onset of type 2 diabetes and cardiovascular disease, we hypothesized that adolescents with spinal cord dysfunction due to SB or SCI would exhibit a higher prevalence and severity of metabolic syndrome than able-bodied adolescents and that the prevalence of metabolic syndrome in these adolescents would be associated with their obesity status. We also sought to determine whether spinal cord dysfunction that occurs congenitally (SB) increased the incidence and severity of markers associated with metabolic syndrome compared to spinal cord dysfunction acquired as a consequence of a SCI years after birth.

## **METHODS**

### **Study Population**

Fifty-four adolescents who have spinal cord dysfunction with thoracic and upper lumbar paraplegia (34 due to SB and 20 due to SCI, all of whom were more than 1 y post injury) were recruited from specialty SB and SCI clinics at our institution. All SB and SCI patients at our clinic were asked to participate in this study. Although we used a convenience sample of adolescents with spinal cord dysfunction, the rate of obesity in our study is similar to the rates of obesity in the general population of adolescents with SCI and SB (36–39). Sixty able-bodied adolescents were recruited from the community through written advertisements and in person at the orientation session of the Fit Teen Program at the University of California Davis Medical Center prior to participating in their weight loss program. We oversampled obese controls (31.7% controls were obese compared to 17.1% in NHANES 2003–2004) to ensure groups of adequate size to detect an effect due to obesity compared to spinal cord dysfunction. Subjects were aged 11 to 20 years of age. Everyone who agreed to participate from the clinic, community, or Fit Teen program was included in the study unless excluded due to surgery within the past 4 months, cognitive impairment that would interfere with testing procedures, inability to understand instructions in English, known diabetes, medications for blood pressure or cholesterol management, or pregnancy. The Institutional Review Board for University of California at Davis and at Shriners Hospitals of Northern California for Children approved this study. Minors signed assent forms that explained the procedures and their rights before, during, and after the study. Written consent was also obtained from a parent or guardian. Testing was conducted in accordance with the approved protocol.

### **Procedures**

The subjects visited the laboratory once after 12 hours of fasting. They were instructed to avoid unusual physical activity for the 24 hours prior to testing. Testing began between 7 AM and 9 AM. Height or length was measured to determine stature. Weight, waist circumference, and percentage of trunk fat by DXA (Hologic QDR4500A, version 11.2.1 Whole Body, Hologic, Bedford, MA) (40) were measured as indices of obesity. The spine itself was excluded from all scans so that subjects with and without hardware would be compared equally. Waist circumference was measured with a tape measure, snug without binding, parallel to the ground, at the umbilicus. Blood pressure was measured twice, with the appropriate pediatric or adult size cuff fitted on the right arm, while the subject was seated, after 30 minutes of rest. Height, BMI, and blood pressure values were standardized to z-scores to enable comparisons among different age groups. BMI z-scores were calculated based on the LMS formula proposed by Cole et al (41,42). To avoid overstating hypertension in SB, we used 50th percentile

for age in lieu of actual height percentile for subjects with SB to determine z-scores for systolic blood pressure (43). Fasting serum samples were analyzed for glucose, insulin, TG, total cholesterol, HDL, and LDL concentrations.

### Definitions of Metabolic Syndrome

Although several major studies have been conducted to assess the prevalence of metabolic syndrome in pediatric populations (44–46), there is no consensus for the cutoff values used to classify metabolic syndrome. Nevertheless, most studies appear to agree with classifying adolescents as having metabolic syndrome if they have  $\geq 3$  of the following criteria: obesity, insulin resistance/impaired glucose tolerance, high blood pressure, high TG, and low HDL. The values for obesity include a BMI z-score of  $\geq 2.0$  (97th percentile) adjusted for age and sex (45), 90th percentile BMI for age and sex, (46), total body fat mass as determined by DXA  $\geq 30\%$  in males and  $\geq 35\%$  in females (47), or a waist circumference of  $>90$ th percentile (13). Previously proposed criteria for obesity in adolescents with SB are 20% total body fat in males and 25% total body fat in females (48) and  $+2$  root mean square of the residual from the regression of skinfold thickness and hydrostatic weighing (30). Insulin resistance has been defined 3 ways; impaired glucose tolerance based on a 2-hour postprandial blood glucose between 140 and 200 mg/dL (45), fasting blood glucose  $\geq 110$  mg/dL (13,44,46), and fasting insulin  $\geq 75$ th percentile (49). Blood pressure has been indicated as high with either systolic or diastolic blood pressure  $>90$ th percentile for age, sex, and height (13,44,46), or with  $>95$ th percentile for age and sex (45). Triglycerides were considered high with 75th, (49) 90th (13,46), and 95th percentiles (44,45). Low HDL has been indicated with  $<5$ th (45), 10th (13,44), and 25th percentiles (49).

Therefore, given the lack of consensus, which makes comparison between studies somewhat difficult, we established the following criteria to determine risk factors in this study, as shown in Table 1, that while unique to our study, were based on Adult Treatment Panel III Guidelines to metabolic syndrome adjusted for gender, age, and puberty (44): abdominal adiposity for obesity categories were represented as percent trunk fat  $\geq 30.0\%$  for males and  $\geq 35.0\%$  for females (47); blood pressure  $\geq 95$ th percentile for height, age, and gender; dyslipidemia with HDL concentrations  $<45$  mg/dL for males and  $<50$  mg/dL for females and/or triglyceride levels  $\geq 100$  mg/dL; insulin resistance or impaired glucose tolerance represented as  $\geq 1$  of the following: fasting serum glucose 100 to 125 mg/dL, fasting serum insulin concentration  $\geq 20$   $\mu$ U/mL, or the homeostasis model assessment of insulin resistance (HOMA-IR)  $\geq 4.0$  (8,50–52).

We recognize that percent trunk fat is not the typical criterion that is used to measure obesity in the pediatric population; however, we believe that percent fat as measured by DXA has advantages compared with other indices of adiposity such as BMI and waist circumference

in the SCI and SB populations because their body habitus has been shown to be significantly different from the normative population (29,36,37,39,53–56). One limitation with using DXA measured percent trunk fat is that it does not differentiate between visceral and subcutaneous adiposity; however, Svendsen et al found a correlation between DXA trunk fat percent and CT abdominal fat ( $r = 0.9$ ) (57). Therefore, we studied the association between percent trunk fat determined by DXA with both waist circumference and BMI.

### Biochemical Analysis

Serum glucose was measured using the Dade Behring Glucose Oxidase method, and serum insulin was measured by chemiluminescence with a Bayer reagent (Tarrytown, NY). HOMA-IR was calculated using the formula of Matthews et al (58)  $HOMA-IR = [(fasting\ plasma\ insulin\ concentration\ (mU/mL) \times fasting\ plasma\ glucose\ (mmol/L)] / 22.5$ . Serum HDL, total cholesterol, and TG were measured on a Beckman Coulter Synchron LX. LDL was calculated according to the Friedewald Formula.

### Statistical Analysis of Data

A 3-factor ANOVA was used to assess whether diagnosis (CTRL, SCI, SB), obesity (nonobese  $<30.0\%$  trunk fat in males and  $<35.0\%$  in females, obese  $\geq 30.0\%$  trunk fat in males and  $\geq 35.0\%$  in females), or gender significantly affected each of the components that comprise metabolic syndrome. Nonsignificant interactions were removed in a stepwise hierarchical fashion. HOMA-IR and insulin were log transformed to conform to the normal distribution. Comparisons of differences between groups were made with post hoc tests using Tukey corrections. ANOVA and regression analysis were done with SPSS version 11.5 (SPSS, Chicago, IL). Chi-square analysis was used to determine frequency of all nonparametric measures including gender and age using Systat version 10 (SPSS, Chicago, IL).

## RESULTS

### Anthropometrics

The demographic and metabolic characteristics of the obese and nonobese CTRL, SB, and SCI groups are shown in Tables 2 and 3. The 3 groups were not significantly different with respect to age ( $P = 0.548$ ) and gender ( $P = 0.643$ ). There was a significant difference in body weight between SB and CTRL, with SB weighing 14.6% less than CTRL ( $P < 0.001$ ), but no significant difference between SCI and CTRL or between SB and SCI was observed. As shown in Figure 1A and B, there was a high degree of correlation between percent of trunk fat as determined by DXA with both waist circumference ( $r^2 = 0.57$  for males;  $r^2 = 0.88$  for females) and BMI ( $r^2 = 0.62$  for males;  $r^2 = 0.73$  for females). Percent total body fat and percent trunk fat as determined by DXA was significantly different between each group, with SB averaging 6.3% more trunk fat than SCI and 11.5% more trunk fat than

**Table 1.** Cutoff Criteria Used to Classify Metabolic Syndrome Risk Factors\*

	Abdominal Adiposity†	Blood Pressure	HDL‡	TG§	Impaired Glucose Tolerance or Insulin Resistance
Value	% Trunk fat $\geq 30.0/35.0$ males/females	$\geq 95$ th percentile for height, age, and gender	$< 45/50$ mg/dL for males/females	$\geq 100$ mg/dL	Fasting serum glucose (FBG) 100–125 mg/dL or fasting blood insulin (FBI) $\geq 20$ $\mu$ U/mL or HOMA-IR $\geq 4.0$

\*HDL, high-density lipoprotein; TG, triglyceride; HOMA-IR, homeostasis model of insulin resistance.

†Based on 85th percentile of percent fat mass.

‡Based on 10th to 25th percentile in males and 10th to 15th percentile in females.

§Based on 85th to 95th percentile.

||Based on American Diabetes Association recommendation for FBG, the level of FBI that suppressed lipolysis in adipose tissue by 50% (Gerald Reaven Sept 2000 Canadian Association of Cardiac Rehabilitation Interview).

CTRL (among all 3 groups,  $P < 0.001$ ; and between SB and SCI and between SB and CTRL,  $P = 0.004$ ). Obese SCI had been injured almost twice as long as nonobese SCI subjects ( $P < 0.001$ ). There was a gender effect, with 10.4% higher total fat in female than in male subjects ( $P < 0.001$ ), and an interaction between diagnosis and obesity ( $P = 0.018$ ). Females had 10.1% more trunk fat percentage than male subjects ( $P < 0.001$ ). Height z-scores for SB were 3.3 lower than those of control subjects ( $2.9 \pm 0.3$  vs  $0.4 \pm 0.1$ ;  $P < 0.001$ ) and 2.6 lower than for SCI ( $2.9 \pm 0.3$  vs  $0.3 \pm 0.4$ ;  $P < 0.001$ ). Consequently, BMI z-scores were 0.7 higher in SB than CTRL and 1.36 higher in SB than SCI ( $1.4 \pm 0.2$  vs  $0.7 \pm 0.1$ ;  $P < 0.001$  and  $1.4 \pm 0.2$  vs  $0.1 \pm 0.5$ ;  $P < 0.001$ , respectively).

### Blood Pressure

As shown in Table 3, there was no diagnosis effect for systolic blood pressure z-scores; however, there was a significant obesity effect and no diagnosis–obesity interaction effect. The systolic blood pressure z-scores

were significantly higher in obese groups as compared to nonobese groups (overall  $1.1 \pm 0.2$  vs  $0.0 \pm 0.2$ ;  $P < 0.001$ ) and between SCI and SB when comparing nonobese subjects only ( $0.7 \pm 0.6$  vs  $0.6 \pm 0.4$ ;  $P = 0.0275$ ).

### Lipids

There were no significant differences in serum LDL concentrations between groups; however, LDL was 13.3 mg/dL higher in obese subjects than in nonobese subjects ( $113.0 \pm 3.8$  mg/dL vs  $99.7 \pm 2.9$  mg/dL;  $P = 0.006$ ). Similarly, while there were no differences in serum triglyceride concentrations between SB, SCI, and control groups ( $P = 0.231$ ), triglyceride levels averaged 26.2 mg/dL higher in obese than in nonobese subjects ( $101.7 \pm 5.9$  mg/dL vs  $75.5 \pm 5.2$  mg/dL;  $P = 0.001$ ). Fasting TG was elevated in 26.5% of SB, 45.0% of SCI, and 29.3% of control subjects. Serum HDL concentrations were 8.5 mg/dL lower in SCI than in control subjects ( $P = 0.003$ ), 6.2 mg/dL lower in obese groups

**Table 2.** Demographics by Mobility Groups\*

Characteristic (mean $\pm$ SD)	Control (n = 60)	SB (n = 34)	SCI (n = 20)
Age, y	16.2 $\pm$ 2.5	16.3 $\pm$ 2.5	16.9 $\pm$ 3.0
Gender, %			
Female	55.0	47.1	45.0
Male	45.0	52.9	55.0
Ethnicity, %			
Hispanic	10.0	21.0	15.0
African American	10.0	2.9	5.0
White	65.0	76.5	75.0
Asian American	15.0	0	5.0
Duration of injury, y	...	16.3 $\pm$ 2.5	4.8 $\pm$ 4.0

\*SB, spina bifida; SCI, spinal cord injury.

**Table 3.** Metabolic Components by Mobility Groups\*

Characteristic (mean ± SD)	Control (n = 60)	SB (n = 34)	SCI (n = 20)
BMI z-score (median)	0.73 ± 1.11 (0.72)	1.43 ± 1.07† (1.67)	0.07 ± 2.29‡ (0.59)
Height, in	65.8 ± 4.3	57.0 ± 4.5†	64.2 ± 5.8‡
Height z-score	0.35 ± 1.11	-2.91 ± 1.68	-0.32 ± 1.76
Weight, lb	156.2 ± 50.5	133.4 ± 30.8†	142.4 ± 48.5
DXA % trunk fat	25.7 ± 12.8	37.2 ± 9.6†	30.9 ± 13.4†‡
DXA % total body fat	28.0 ± 11.2	40.0 ± 8.5†	33.9 ± 12.5†‡
Systolic blood pressure z-score	0.53 ± 1.27	1.00 ± 1.03	0.15 ± 1.88
Fasting serum glucose, mg/dL	88.9 ± 6.5	84.9 ± 6.3†	86.2 ± 5.9
Fasting serum insulin, μU/mL	10.8 ± 7.9	10.6 ± 5.4	12.9 ± 9.4
HOMA-IR	2.4 ± 1.8	2.2 ± 1.2	2.8 ± 2.1
HDL, mg/dL (median)	44.2 ± 10.8 (41.0)	40.8 ± 11.0 (38.0)	35.7 ± 7.4† (36.5)
TG, mg/dL (median)	87.7 ± 46.0 (78.0)	84.3 ± 39.6 (78.5)	94.4 ± 42.4 (86.5)
LDL, mg/dL	105.4 ± 22.1	112.4 ± 30.3	97.1 ± 26.2
Total chol, mg/dL	167.2 ± 29.7	170.3 ± 32.9	151.6 ± 28.2

\*SB, spina bifida; SCI, spinal cord injury; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; HOMA-IR, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; TG, triglyceride; LDL, low-density lipoprotein; chol, cholesterol.

†Significantly different from control value ( $P \leq 0.05$ ).

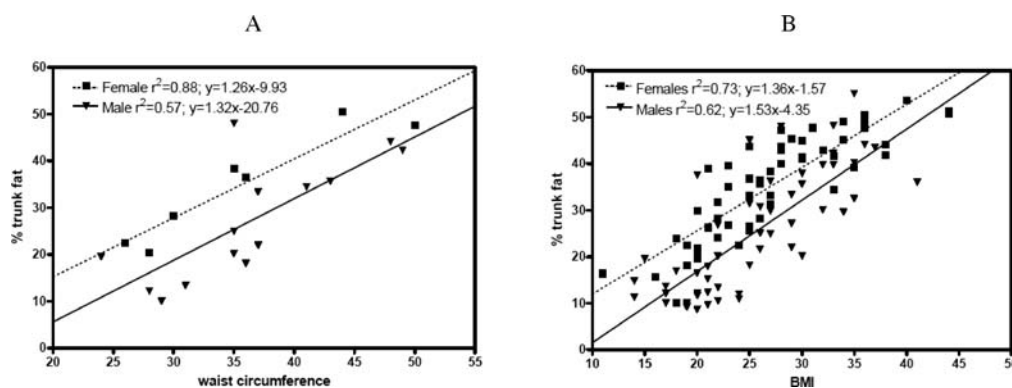
‡Significantly different from SB value ( $P \leq 0.05$ ).

(38.4 ± 1.3 mg/dL vs 44.6 ± 1.4 mg/dL;  $P = 0.001$ ), and 5.1 mg/dL lower in males than in females (39.0 ± 1.2 mg/dL vs 44.1 ± 1.6 mg/dL;  $P = 0.002$ ). Although mean fasting serum HDL was lower in SB than in controls, as shown in Table 3, the difference was not statistically significant ( $P = 0.239$ ); and the median values for HDL in SB and SCI were similar. Fasting HDL concentrations were lower than the cutoff in 73.5% of SB, 90.0% of SCI, and 67.2% of control subjects. There were no differences in total serum cholesterol between diagnosis groups or based on obesity; however, fasting serum total cholesterol concentrations in male subjects averaged 17.9 mg/

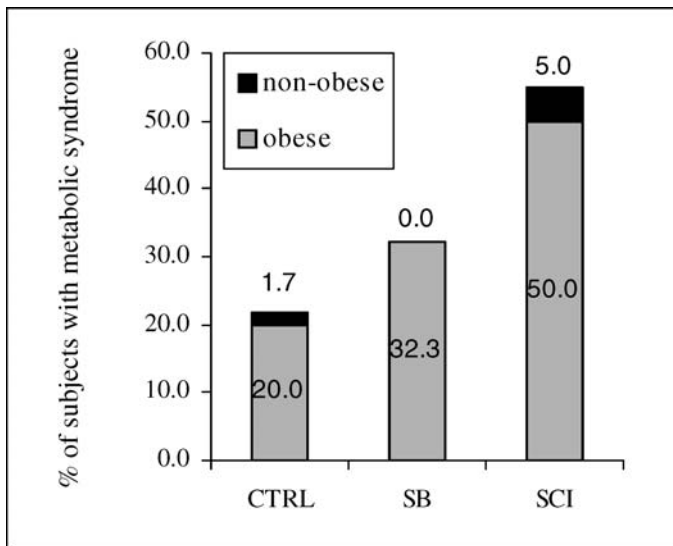
dL lower than in female subjects (156.0 ± 3.3 mg/dL vs 174.0 ± 4.5 mg/dL;  $P = 0.002$ ).

### Serum Glucose and Insulin Resistance

Overall, differences in fasting serum glucose concentrations between SB and control groups were statistically significant ( $P = 0.012$ ), although only 1 subject (obese control) had glucose intolerance. Fasting serum glucose was significantly lower in SB vs controls ( $P = 0.011$ ), but fasting serum glucose was not significantly lower in SCI subjects versus controls ( $P = 0.222$ ). Values for fasting serum insulin concentrations and HOMA-IR were more



**Figure 1.** Relationship of waist circumference to DXA % trunk fat (A). Male  $r^2 = 0.57$  ( $P = 0.0018$ );  $y = 1.32x - 20.76$ . Female  $r^2 = 0.88$  ( $P = 0.0017$ );  $y = 1.26x - 9.93$ . Relationship of BMI to DXA % trunk fat (B). Male  $r^2 = 0.57$  ( $P < 0.0001$ );  $y = 1.32x - 20.76$ . Female  $r^2 = 0.88$  ( $P < 0.0001$ );  $y = 1.26x - 9.93$ .



**Figure 2.** Prevalence of metabolic syndrome by group.

than doubled in obese subjects compared to nonobese subjects ( $15.8 \pm 1.1 \mu\text{U/mL}$  vs  $6.9 \pm 0.5 \mu\text{U/mL}$  for insulin,  $P < 0.001$ ; and  $3.4 \pm 0.3$  vs  $1.5 \pm 0.1$  for HOMA-IR,  $P < 0.001$ ). There was an interaction of diagnosis and obesity for insulin ( $P = 0.003$ ) and for HOMA-IR ( $P = 0.004$ ). Fasting insulin was elevated in 5.9% of SB, 30.0% of SCI, and 10.3% of control subjects; and 8.8% of SB, 30.0% of SCI, and 17.2% of control subjects had high HOMA-IR. Insulin and HOMA-IR correlated with systolic blood pressure ( $r = 0.227$ ;  $P = 0.006$  and  $r = 0.274$ ;  $P = 0.006$ , respectively). HOMA-IR had a high correlation with trunk fat percentage ( $r = 0.614$ ;  $P < 0.001$ ).

### Metabolic Syndrome

In our clinic population, 32% of SB subjects and 55.0% of SCI subjects met the criteria established for metabolic syndrome ( $\geq 3$  risk factors/components) as shown in Figure 2. Only 5.9% of SB and 5.0% of SCI subjects had no components of metabolic syndrome, whereas 32.4% of SB and 35.0% of SCI subjects had 1 risk factor and 61.8% of SB and 60.0% of SCI subjects had  $\geq 2$  risk factors of metabolic syndrome. With the exception of only 2 subjects, those who had only 1 risk factor were not obese. All 5 indicators of metabolic syndrome were significantly affected by obesity, regardless of diagnostic group. As shown in Table 6, 100% of the obese SCI subjects, 45.8% of the obese SB subjects, and 63.2% of the obese CTRL subjects met the criteria for metabolic syndrome. A  $3 \times 2$  contingency table revealed that there was a strong association between diagnostic group (SCI, SB, and CTRL) and presence of metabolic syndrome ( $\chi^2 = 0.012$ ). The Fisher exact test demonstrated that the obese SCI group had a significantly higher percentage of subjects with metabolic syndrome than did the obese SB group ( $P < 0.005$ ) and approached significance when compared to the CTRL group ( $P = 0.063$ ). In contrast,

there was no significant association between the presence of metabolic syndrome and diagnostic group in the nonobese subjects ( $P = 0.396$ ). Only 10% of the nonobese SCI subjects, 0% of the nonobese SB subjects, and 2.4% of the nonobese control subjects met the criteria for metabolic syndrome. The most common 3 risk factors observed in this study were increased trunk fat, decreased fasting serum HDL concentration, and increased fasting serum triglyceride concentration, as shown in Table 5.

### DISCUSSION

Our results represent the first known evidence that adolescents with SCI or SB and obesity have an increased prevalence of components of the metabolic syndrome, similar to what has been reported in adults with spinal cord injury (59,60) and able-bodied children with obesity (10,45,47,61–65). This finding is significant given that the occurrence of  $\geq 3$  components of the metabolic syndrome, documented in our study in many obese adolescents with spinal cord dysfunction, is associated with a threefold increased risk of developing cardiovascular disease and fivefold higher risk of developing diabetes, in addition to other comorbidities of obesity/diabetes such as diabetic neuropathy and nephropathy, polycystic ovary syndrome, sleep apnea, hepatic steatosis, gallstones, and certain types of cancer at an earlier age (11,66). Even though the sample sizes are small, the data from this study suggest that obese individuals with SCI have a significantly higher risk of metabolic syndrome than either obese SB subjects or obese able-bodied subjects do. The increased association of metabolic syndrome in obese SCI subjects as compared to obese SB subjects may be due to metabolic adaptation in utero and/or during development for subjects with SB. Although obese SCI subjects had a greater prevalence of metabolic syndrome than obese SB subjects, the importance of obesity in SB should not be overlooked since there is an increased prevalence of obesity among children with thoracic and upper lumbar spinal cord dysfunction due to SB and SCI associated with lower limb paralysis and loss of lean tissue in the lower extremities (28,29,31,33,36,37,39,53–56,67), reduced resting energy expenditure (28,67), increased sedentary existence (68), and reduced fitness levels (69).

Obesity is the primary contributing factor for both able-bodied adolescents and mobility-impaired adolescents with SCI and SB to develop additional risk factors in the constellation referred to as the metabolic syndrome; however, determining the most appropriate assessment of obesity is problematic in subjects with SCI and SB. The loss of lower limb muscle mass and segmental growth retardation of limbs due to paralysis, increase in total body and trunk fat, increasing regional and total body adiposity, and decreasing lean tissue with age, as well as the occurrence of progressive skeletal deformities in the lower limb and trunk, skew BMI calculations, resulting in overestimation of BMI in

**Table 4.** Metabolic Components by Mobility Groups and Obesity\*

Characteristic (Mean ± SD)	Nonobese Control (n = 41)	Obese Control (n = 19)	Nonobese SB (n = 10)	Obese SB (n = 24)	Nonobese SCI (n = 10)	Obese SCI (n = 10)
BMI z-score† (median)	0.16 ± 0.82 (0.01)	1.95 ± 0.50‡ (2.06)	0.60 ± 1.53 (1.10)	1.78 ± 0.55‡ (1.92)	-1.40 ± 2.32§ (-0.50)	1.54 ± 0.92‡ (1.69)
Height, in	65.9 ± 4.4	65.6 ± 4.2	56.6 ± 5.0	57.2 ± 4.4	64.8 ± 7.4	63.6 ± 4.0
Height z-score	0.27 ± 1.06	0.52 ± 1.20	-3.06 ± 1.99+	-2.85 ± 1.58	-0.33 ± 1.93§	-0.31 ± 1.68
Weight, lb	135.3 ± 38.1	201.3 ± 44.5	109.4 ± 22.9	143.3 ± 28.4	114.4 ± 34.4	170.3 ± 45.1
DXA % trunk fat	18.4 ± 6.9	41.4 ± 6.9‡	26.0 ± 7.7	41.9 ± 5.7‡	18.9 ± 5.8§	42.8 ± 5.4‡
DXA % total body fat	21.9 ± 7.0	40.9 ± 6.4‡	31.6 ± 8.3	43.5 ± 5.7‡	23.0 ± 6.2§	44.9 ± 4.8‡
Systolic BP z-score	0.21 ± 1.31	1.15 ± 0.92‡	0.63 ± 1.03	1.16 ± 1.02	-0.71 ± 2.01§	1.02 ± 1.31‡
Fasting serum glucose, mg/dL	88.7 ± 6.9	89.3 ± 5.5	86.2 ± 6.1	84.3 ± 6.4	84.4 ± 6.4	87.9 ± 5.1
Fasting serum insulin, µU/mL	7.3 ± 3.9	17.8 ± 9.1‡	7.2 ± 3.2	12.1 ± 5.6‡	4.9 ± 2.4	21.0 ± 6.1‡
HOMA-IR	1.6 ± 0.9	4.0 ± 2.2‡	1.5 ± 0.7	2.5 ± 1.2‡	1.0 ± 0.5	4.6 ± 1.5‡
HDL, mg/dL† (median)	46.7 ± 11.3 (44.0)	39.1 ± 7.8‡ (39.0)	43.1 ± 10.6 (41.0)	39.9 ± 11.3 (37.0)	37.7 ± 7.9+	33.6 ± 6.5 (35.5)
TG, mg/dL† (median)	79.3 ± 44.5 (69.0)	105.0 ± 45.2‡ (88.0)	68.5 ± 31.2 (60.5)	90.9 ± 41.4 (81.5)	67.6 ± 29.7 (59.5)	121.2 ± 36.2‡ (126.0)
LDL, mg/dL	100.7 ± 21.1	114.9 ± 21.5‡	105.1 ± 33.3	115.4 ± 29.2	90.3 ± 10.9	103.8 ± 35.1
Total chol, mg/dL	163.4 ± 30.0	175.0 ± 28.2	162.2 ± 40.8	173.6 ± 29.4	141.5 ± 11.8	161.6 ± 36.3

\*SB, spina bifida; SCI, spinal cord injury; DXA, dual-energy x-ray absorptiometry; BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; TG, triglyceride; LDL, low-density lipoprotein; chol, cholesterol.

†Medians are included where means appear to be skewed by individual extreme values.

‡Indicates a significant difference from nonobese subjects in the same mobility group (SB, SCI, or control) ( $P \leq 0.05$ ).

§Indicates that SCI value is significantly different from SB value ( $P \leq 0.05$ ).

||Indicates a significant difference from control value ( $P \leq 0.05$ ).



**Table 5.** Percent of Individuals With Metabolic Syndrome Risk Factors by Group\*

	Nonobese Control	Obese Control	Nonobese SB	Obese SB	Nonobese SCI	Obese SCI
% Trunk fat	0.0	100.0	0.0	100.0	0.0	100.0
Blood pressure	12.2	26.3	10.0	29.2	20.0	30.0
HDL	56.1	84.2	70.0	75.0	80.0	100.0
TG	24.4	36.8	10.0	33.3	20.0	70.0
HOMA-IR	4.9	42.1	0.0	12.5	0.0	60.0
Fasting serum glucose	2.5	0.0	0.0	0.0	0.0	0.0

\*SB, spina bifida; SCI, spinal cord injury; HDL, high-density lipoprotein; TG, triglyceride; HOMA-IR, homeostasis model assessment of insulin resistance.

nonobese SB and underestimation in SCI subjects (29,70). Since percent trunk fat by DXA correlated well against waist circumference as shown in Figure 1A, we used the percent trunk fat as an indicator of central adiposity for all subjects regardless of mobility status. As a result, 74% of SB subjects and 50% of SCI subjects were classified as overweight based on the percentage of trunk fat when determining whether they met the criteria for obesity, as opposed to only 52.9% and 25.0%, respectively, based on BMI z-score. Seventy-five percent of SB females were obese compared to 66.7% of SB males. These results concur with those by Shurtleff and others that in adolescence, female subjects with SB have increased fat mass compared to male subjects with SB (36,37,71). Total body fat is approximately 18% in ambulatory SB in compared to  $\geq 31\%$  in nonambulatory SB (29,31,56), and 58% of SB are obese (30). The finding that paraplegic SCI subjects with greater amounts of total body fat had longer duration of injury agrees with those of Manns et al (59). The NHANES III disability survey reported 30% increased prevalence of obesity in participants with a disability (30% vs 23%) (72,73).

One hundred percent of obese SCI subjects and 45.8% of obese SB subjects in our study met the criteria for metabolic syndrome ( $\geq 3$  risk factors/components), as compared to the reported 30% occurrence of metabolic syndrome in overweight and obese adolescents from the NHANES III data (13,44,45,72,73). Very low proportions of nonobese subjects studied had all 5 components of the

metabolic syndrome (approximately 5% of SCI, 0% of SB, and 3% of control subjects), comparable to 0% of able-bodied children reported in NHANES III (13). SCI, SB, or able-bodied adolescents who do not become obese have a low likelihood of exhibiting components of the metabolic syndrome. Regardless of the presence or absence of spinal cord impairment,  $\leq 10\%$  of nonobese subjects studied had  $\geq 3$  components of the metabolic syndrome. It would be worth exploring in the future whether complete vs incomplete injury to the spinal cord as opposed to location of the injury itself accounts for the different rates of metabolic syndrome in patients with spinal cord dysfunction.

Risks associated with increased systolic blood pressure in obese adolescent subjects have been previously documented (74–77). Therefore, increased systolic blood pressure observed in our obese subjects is of concern because there is both increased incidence of hypertension and an increase in intimal–medial thickness in the carotid arteries (77). Furthermore, the Muscatine Study data, which tracked 754 children and adolescents (mean age 15 y; range 8–18 y) into adulthood (mean age 44 y; range 40–49 y) revealed increased systolic blood pressure in adolescence persisted into adulthood, especially when they remained obese as adults (76).

Studies of lipid profiles in disabled populations have primarily been conducted in adults. Obesity with dyslipidemia in 45% of adult SCI subjects has been previously identified (78). Although SB adolescents in this

**Table 6.** Percent With Increased Risk Factors by Group\*

	Nonobese Control	Obese Control	Nonobese SB	Obese SB	Nonobese SCI	Obese SCI
0 Factors	29.3	0	20.0	0.0	10.0	0.0
1 Factor	48.8	5.3	70.0	16.7	70.0	0.0
2 Factors	19.5	31.6	10.0	37.5	10.0	0.0
$\geq 3$ Factors	2.4	63.2	0.0	45.8	10.0	100.0

\*SB, spina bifida; SCI, spinal cord injury.

study had decreased levels of HDL and increased levels of LDL and total cholesterol compared to controls, the differences were not statistically significant. Rendeli et al also reported no significant differences in lipid profiles between SB children and adolescents (ages 1–16 y) and able-bodied controls (79). The trend towards decreased HDL and increased TG observed in our spinal cord dysfunction groups agrees with the results found in adult neuromuscular disease patients by Aitkens and colleagues (80). A higher proportion of their disabled group had decreased HDL and increased systolic blood pressure (80). They identified decreased HDL, increased BMI, and increased TG as the top 3 risk factors in both their disabled population and able-bodied control group. This corresponds with the top 3 risk factors observed in our study—increased percent trunk fat, decreased HDL, and elevated TG—and is also consistent with the study of overweight adolescents by de Ferranti et al (44). We observed 74.0% SB, 90.0% SCI, and 65.0% of CTRL to have decreased HDL and increased systolic blood pressure. Values for fasting serum HDL concentrations were lower in SCI than controls. Bauman et al observed decreased HDL concentrations in SCI compared with control subjects, with significant differences reported in males, whites, and Hispanics, but not in females or African Americans (81–84). SCI subjects in our study had HDL values <35 mg/dL at a rate of 35%, which corresponded to 24 to 40% of SCI in studies by Bauman et al. Forty-five percent of subjects with SCI in our study had HDL ≤45 mg/dL. These results are similar to those of Dopler-Nelson et al, who found that 49% of adults with SCI had significantly increased TG and 30% had decreased HDL (85). Since decreased HDL is an independent risk factor for increased myocardial infarction in adulthood and appears to be due to immobilization (82,86,87), these results further suggest that adolescents with spinal cord dysfunction who develop components of the metabolic syndrome will be at increased risk for cardiovascular disease in adulthood.

Although normal fasting blood glucose was observed in 99% of subjects in this study, they may still be at risk for developing diabetes (10). SB, SCI, and able-bodied subjects with documented type 1 or type 2 diabetes were excluded from our study. It was perhaps surprising that SB subjects had lower rates of insulin resistance than SCI subjects based on HOMA-IR, given that SB are disabled from birth and the percent trunk fat and percent total body fat are similar in obese SB and obese SCI. It is possible that the differences observed between SB and SCI may be due to a higher proportion of visceral fat in SCI subjects (88).

HOMA-IR level was not significantly different among SB, SCI, and control subjects. These interpretations are based on insulin values from 1 fasting time point and may indicate a different outcome had they been based on a 2-hour postprandial glucose load; however, HOMA-IR has been indicated as a valid measure of impaired glucose

tolerance in lieu of a glucose challenge (8,89). Insulin resistance in spinal cord dysfunction appears to be directly related to denervation of skeletal muscle (90). There were no SB or SCI subjects with glucose intolerance; however, 8.8% of SB, 30.0% of SCI, and 16.7% of controls had hyperinsulinemia and/or insulin resistance based on fasting insulin concentrations and/or HOMA-IR values, even though known diabetes was an exclusion criterion. This is approximately half the rate reported by Jones et al in their study of 20 SCI male adults (78). The relationship of HOMA-IR to BMI is inconsistent with that observed by Bacha et al ( $r^2 = 0.308$  in our study, compared to  $r^2 = 0.73$ ) (91). Associations between HOMA-IR and BMI z-score and between HOMA-IR and systolic blood pressure z-score were also reported by Arnlov et al (92). They found that insulin resistance in younger adults with normal BMI and blood pressure was predictive of future hypertension. All of the SCI subjects in this study with insulin resistance were obese with dyslipidemia. Obesity in adolescence tracks into adulthood and consequently increases the risk of developing metabolic syndrome. Vanhala et al showed that of 30 adults with metabolic syndrome, 93% were obese adults and 70% had been obese as children (21). Fifty percent to 80% of overweight children will remain overweight as adults (93,94). Children with BMI ≥75th percentile followed for approximately 12 years in the Bogalusa Heart Study had 11.7 times the rate of having metabolic syndrome as adults (87). The number of risk factors in youth is predictive of decreased carotid artery elasticity in adulthood, with systolic blood pressure as an independent predictor (17). This may account for the increased incidence of cardiovascular disease as a leading cause of mortality in SCI at a younger age than in the general population (95–98). Most alarming is the overall pattern of the increased risk in adolescence for developing complications due to a more sedentary lifestyle and increased prevalence of obesity at a younger age than in previous generations.

## CONCLUSIONS

The results of this study document that subjects with SCI or SB have a very high risk of having components of the metabolic syndrome, and this increased risk is primarily due to their increased prevalence of obesity. Obese able-bodied subjects, obese SB subjects, and obese subjects with SCI had high rates of abdominal adiposity as assessed by percent trunk fat and body fat percentage, and an increased number of components of the metabolic syndrome, mainly low serum HDL concentrations, high TG levels, and insulin resistance compared with nonobese control, SB, and SCI subjects. In our sample, the obese SCI subjects had a higher prevalence of metabolic syndrome than the obese SB and obese able-bodied subjects did. Prevention of obesity in children with spinal cord dysfunction will likely be critical to the avoidance of metabolic syndrome components and the promotion of optimal health. Ideally, this should

begin in infancy in SB and very soon after the occurrence of a traumatic SCI. This early emphasis on health promotion for children and adolescents with spinal cord dysfunction will require nutrition education, modified caloric intake to achieve a more optimal balance of energy intake and energy expenditure, and exercise including strengthening, aerobic exercise, and community physical activity and recreation participation (69). Prevention of obesity and management of metabolic syndrome components among obese patients should be a high priority in any rehabilitation program for children and adolescents with spinal cord dysfunction.

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