Original Article

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Factors Affecting Metabolic Syndrome in Individuals With Chronic Spinal Cord Injury

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Objective To assess the validity of different anthropometric measures (waist circumference [WC], body mass index [BMI], and percentage body fat) in diagnosing metabolic syndrome (MetS) among individuals with SCI and provides preliminary data for future studies in setting obesity cutoff values for this population.

Methods This was a single-center retrospective cohort study. Sample information, anthropometric measures, and MetS variables of 157 individuals with chronic SCI were collected from an electronic medical records database.

Results Increasing age (odds ratio [OR]=1.040, p=0.016) and lower neurological level of injury (OR=1.059, p=0.046) were risk factors for MetS. Male BMI (r=0.380, p<0.001) and male WC (r=0.346, p<0.001) were positively correlated with the number of MetS subfactors. Individuals with non-obese WC, excluding central obesity, were associated with having no MetS subfactors (p=0.005), and individuals with obese WC were associated with one or more subfactors (p=0.005). BMI was associated with MetS diagnosis (area under the curve=0.765, p<0.001), with the calculated cutoff value for BMI being 22.8 kg/m^2.

Conclusion This study calls for a stricter BMI cutoff for individuals with SCI in diagnosing MetS and warrants a large population-based study to define central obesity according to sex and ethnicity.

Keywords Spinal cord injuries, Metabolic syndrome, Obesity

INTRODUCTION

Individuals with spinal cord injury (SCI), compared with the general population, have a higher risk of morbidity and mortality, with cardiovascular disease (CVD) being the most common cause [1]. In addition, metabolic syndrome (MetS), a component of central obesity, hypertension, hyperglycemia, and dyslipidemia, is associated with a higher CVD risk [2]. After SCI, individuals undergo drastic changes in terms of decreased physical activity, decreased muscle mass, and lower metabolism. These changes result in an increased prevalence of obesity, linked to an increased risk of MetS [3]. Thus, an accurate definition of obesity is vital in identifying individuals at risk of MetS for both weight assessment and management.

The emphasis on finding the optimal cutoff value to define obesity derives from the fact that central obesity is the most prevalent feature of MetS [4]. This statement is supported by a rapid parallel increase in the prevalence of overweight, obesity, type 2 diabetes, and MetS [5]. Furthermore, although there are cases of metabolically benign obesity, which is not accompanied by insulin resistance and atherosclerosis [6], the vast majority are insulin resistant. In particular, individuals with central accumulation of body fat are at a higher risk of insulin resistance and atherogenic abnormalities [7,8], whereas the risk is less for those with body fat distribution in the periphery [9]. Thus, due to the increasing recognition of central obesity as the most common feature of MetS, in this study, the diagnosis of MetS has been used as a surrogate for obesity.

After SCI, the percentage of visceral adipose tissue (VAT) quantified by computed tomography (CT) at the umbilical and L4–L5 levels was found to be 34% [10] and 45% [11], respectively, which is higher in individuals with SCI. Even after considering the decreased abdominal muscle tone, which results in measurement discrepancies in the supine versus seated position [12], Ravensbergen et al. [13] showed that individuals with SCI had 42% more VAT at the same WC than the general population. They evaluated the relationship between different anthropometric measures and the abdominal fat percentage, cardiovascular, metabolic risk factors, and the Framingham risk score among 27 individuals with SCI and suggested a waist circumference (WC) ≥94 cm as the optimal cutoff value. Sumrell et al. [12] conducted a study on 22 men with SCI to find the optimal WC cutoff value of 86.5 cm in the supine position. Inayama et al. [14] identified WC ≥81.3 cm to correspond with a visceral fat area of ≥100 cm^2 in 74 Japanese men with SCI in the supine position. These findings suggest that the cutoff point for WC should be lower in individuals with SCI.

The three commonly used anthropometric measures for identifying obesity are percentage body fat (PBF), body mass index (BMI), and WC. For these measures, the cutoff values for obesity were defined in the general population. However, when extrapolated to individuals with SCI, these cutoffs values for obesity run the risk of underdiagnosing MetS. The arbitrary nature of cutoffs for obesity was introduced by the International Diabetes Federation (IDF), proposing ethnically appropriate WC to be considered in diagnosing MetS [15]. However, the reevaluation of cutoff values in individuals with SCI, prone to body composition and metabolic changes, has been under-addressed.

Thus, the purpose of this study was (1) to identify the risk factors of MetS, (2) to determine the correlation and association between different anthropometric measures and the number of MetS subfactors, and (3) to provide preliminary data for future studies in setting obesity cutoff values for Korean patients with SCI.

MATERIALS AND METHODS

Approval of the Institutional Review Board at the National Rehabilitation Center was obtained before conducting the study (No. NRC-2020-02-021), and the study was performed following the Declaration of Helsinki of the World Medical Association.

Patients

A total of 166 Korean patients with chronic SCI (time since injury ≥1 year) were admitted to a single center in Seoul, Korea, from February to December 2019, for a 3-day comprehensive checkup program, which included a urodynamic study, blood and urine tests, serial vital sign check, and anthropometric measurements. Of the 166 patients, nine patients were excluded, as eight individuals had unknown SCI onset dates, and one patient had missing PBF data. Thus, 157 patients were enrolled in this study. In addition, retrospective sample information, anthropometric measures, and MetS variables were collected from electronic medical records.

We collected information regarding age, sex, time since injury, cause of injury, lesion severity (i.e., paraplegia, tetraplegia), the American Spinal Injury Association impairment scale (AIS) scores, and the level of injury severity. The motor complete injury was defined as AIS level A or B, and the motor incomplete injury was defined as AIS level C or D [16]. Detailed clinical and neurological examinations were based on the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI).

Anthropometric measurements

Anthropometric measurements of height (cm), weight (kg), WC, and PBF were performed. Height was mea-

sured from the vertex level to the foot to the nearest 1 cm. Weight was measured using a weighing scale to the nearest 0.1 kg, and for patients who were wheelchair-bound, the weight of the wheelchair was deducted from the sum of wheelchair and patient weight. The WC was measured at the narrowest level (i.e., umbilical level) at the end of normal expiration in the supine position. The PBF was measured through bioelectrical impedance analysis using InBodyS10 (Biospace Co. Ltd, Seoul, Korea). The BMI was calculated using the formula, BMI = kg/m^2, where kg is a person's weight in kilograms and m^2 is their height in meters squared.

Obesity classification

The World Health Organization (WHO) classification of BMI ≥30 kg/m^2 was used to define obesity. Although the National Institutes of Health classify individuals with WC >102 cm for men and >88 cm for women as obese, the ethnically appropriate cutoff levels for Korean adults, WC >90 cm for men and >85 cm for women, were adopted in this study [15]. We used the most recent 2009 guidelines from the American Society of Bariatric Physicians (ASBP), an American Medical Association (AMA) specialty board, PBF ≥25% for men and ≥30% for women, to define obesity.

MetS classification

The American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) [17] and the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [18] classifications were compared to diagnose MetS. The NCEP-ATP III criteria are easily applicable to clinical settings and large-scale epidemiological studies [19]. Recently, the AHA/NHLBI expanded the NCEP-ATP III criteria to include those who also received drug therapy for a more inclusive diagnosis [20]. The MetS classifications used are summarized in Supplementary Table S1. Diagnosis of MetS was set with three or more subfactors present. The WC cutoff value was substituted for Korean adults' ethnically appropriate cutoff value.

Triglyceride (TG), high-density lipoprotein (HDL) cholesterol, and fasting glucose levels were measured through blood tests on the second day of admission, after a 12-hour fasting period overnight. In addition, blood pressure was averaged from measurements taken in the morning on the second and third day of admission.

Statistical analysis

Descriptive statistics were used to summarize demographic and lesion characteristics. Binomial logistic regression was used to evaluate risk factors for MetS. The Pearson correlation test was used to determine the correlation between different anthropometric measures and the number of MetS subfactors in male and female patients. To further quantitatively analyze the relationship between obesity according to different anthropometric measures and the number of MetS subfactors, we performed cross-tabulation with linear-by-linear association chi-square test. The area under the ROC curve (AUC) was used to determine the cutoff value for different anthropometric measures and their validity, respectively, relative to the MetS diagnosis. We used the SPSS version 21.0 (IBM SPSS, Armonk, NY, USA) for statistical analysis, and a statistically significant difference was considered at $p < 0.05$.

RESULTS

Characteristics of the sample

The demographic and injury characteristics of the sample, summarized by descriptive statistics of the sample, are displayed in Table 1. The participants were predominantly men (n=110; 70.1%). The mean age at the time of the study was 49 years (standard deviation [SD]=12.3). The mean time since injury was 12 years (SD=7.9). Most injuries were due to trauma (n =133; 84.7%). More than half resulted in paraplegia (n=81; 51.6%), and AIS-A/complete injury (n=99; 63.1%) was the most common severity of the injury.

MetS prevalence

In NCEP-ATP III criteria, the prevalence of MetS was 23.6% (n=37), consisting of male (n=31, 28.2%) and female (n=6, 12.8%). In AHA/NHLIB criteria, the prevalence of MetS was 38.9% (n=61), consisting of men (n=42, 38.2%) and female (n=19, 40.4%). All individuals with NCEP-ATP III-classified MetS were included in the group with AHA/NHLBI-classified MetS.

MetS risk factors

Binomial logistic regression was used to evaluate risk factors for the diagnosis of MetS. Among the indepen-

dent variables, increasing age (odds ratio [OR]=1.040; 95% confidence interval [CI], 1.007–1.073; p=0.016) and lower neurological level of injury (NLI) (OR=1.059; 95% CI, 1.001–1.119; p=0.046) were significant risk factors for MetS (Table 2).

Correlation between the number of MetS subfactors and different anthropometric measures

Pearson correlation test was used to assess the correla-

tion between different anthropometric measures and the number of MetS subfactors, that is, elevated fasting glucose and TG, and reduced HDL-cholesterol levels, elevated values of the BP and WC, or whether on drug treatment for each subfactor, depending on the sex (Table 3). The BMI (r=0.380, p<0.001) and the WC (r=0.346, p<0.001) in men were significantly positively correlated with the number of MetS subfactors.

Association between the number of MetS subfactors and obesity

Further quantitative analysis of the linear relationship between the number of MetS subfactors and obesity according to different anthropometric measures was performed using cross-tabulation with a linear-by-linear association chi-square test (Table 4). As the WC is a dependent variable of the AHA/NHLBI criteria, the subfactor "elevated WC" was excluded from the analysis. Non-obese values for the WC were significantly associated with having no MetS subfactors (linear-by-linear association=7.872, p=0.005). Increased WC value was significantly associated with having one or more MetS subfactors (linear-by-linear association=7.872, p=0.005).

Cutoff values

The AUC were used to determine the cutoff value for anthropometric measures and their validity, respectively, relative to the diagnosis of MetS (Table 5). Assuming that AHA/NHLBI-classified MetS in individuals with SCI translated to a diagnosis of MetS, the WC was excluded from the anthropometric measures, as it was a dependent variable of the AHA/NHLBI classification. The BMI

Table 1. Demographic and lesion characteristics

Characteristic	Value
Age (yr)	49.3±12.3
Sex	
Male	110 (70.1)
Female	47 (29.9)
Time since injury (yr)	12.0±7.9
Cause of spinal cord injury	
Traumatic	133 (84.7)
Non-traumatic	24 (15.3)
Lesion severity	
Paraplegia	81 (51.6)
Tetraplegia	76 (48.4)
AIS grade	
A	99 (63.1)
B	20 (12.7)
C	18 (11.5)
D	20 (12.7)

Values are presented as mean±standard deviation or number (%).
AIS, American Spinal Injury Association impairment scale.

Table 2. Binomial logistic regression analysis of metabolic syndrome risk factors

	OR	95% CI	p-value
Sex (female)	0.854	0.395–1.847	0.689
Age (increasing)	1.040	1.007–1.073	0.016*
BMI (obese, BMI ≥30)	1.244	0.205–7.552	0.813
PBF (obese, male ≥25%, female ≥30%)	1.275	0.432–3.757	0.660
Time since injury (increasing)	0.980	0.936–1.025	0.378
Cause of injury (traumatic)	0.440	0.155–1.245	0.122
NLI (lower)	1.059	1.001–1.119	0.046*
Severity of injury (motor incomplete)	0.816	0.324–2.057	0.666

BMI, body mass index; PBF, percentage body fat; NLI, neurological level of injury; OR, odds ratio; CI, confidence interval.
*p<0.05.

Table 3. Pearson correlation coefficients between the number of metabolic syndrome subfactors and anthropometric measures

	Male		Female	
	r	**p-value**	**r**	**p-value**
WC	0.380	<0.001***	0.213	0.151
BMI	0.346	<0.001***	0.234	0.113
PBF	0.145	0.130	0.016	0.916

WC, waist circumference; BMI, body mass index; PBF, percentage body fat; r, Pearson correlation coefficient.
***p<0.001.

Table 4. Cross-tabulation between the number of metabolic syndrome (MetS) subfactors and obesity

Number of MetS subfactors	WC		BMI		PBF	
	Non-obese	**Obese**	**Non-obese**	**Obese**	**Non-obese**	**Obese**
0	24 (27.0)	2 (2.9)	26 (17.2)	0 (0)	7 (33.3)	19 (14.0)
1	21 (23.6)	22 (32.4)	40 (26.5)	3 (50.0)	5 (23.8)	38 (27.9)
2	27 (30.3)	25 (36.8)	52 (34.4)	0 (0)	2 (9.5)	50 (36.8)
3	12 (13.5)	13 (19.1)	23 (15.2)	2 (33.3)	5 (23.8)	20 (14.7)
4	5 (5.6)	6 (8.8)	10 (6.6)	1 (16.7)	2 (9.5)	9 (6.6)
p-value	7.872 (0.005)**		1.079 (0.299)		0.546 (0.460)	

WC, waist circumference; BMI, body mass index; PBF, percentage body fat.
Cutoff values: WC (male ≥90 cm, female ≥85 cm), BMI (male ≥30 kg/m^2, female ≥30 kg/m^2), PBF (male ≥25%, female ≥30%).
**p<0.01 by linear-by-linear association test.

Table 5. Cutoff values of different anthropometric measurements relative to the diagnosis of metabolic syndrome

	Cutoff value	Sensitivity	Specificity	AUC (95% CI)	p-value
BMI	22.835	0.721	0.729	0.765 (0.689–0.842)	<0.001***
PBF					
Male	37.650	0.595	0.588	0.603 (0.497–0.710)	0.690
Female	39.550	0.632	0.643	0.565 (0.386–0.744)	0.455

BMI, body mass index; PBF, percentage body fat; AUC, area under the curve; CI, confidence interval.
***p<0.001.

(AUC=0.765; 95% CI, 0.689–0.842, p<0.001) was significantly associated with diagnosis of MetS, with a cutoff value of 22.8 kg/m^2 (sensitivity=72.1%, specificity=72.9%).

DISCUSSION

The demographic data collected from our study showed a male-to-female ratio of 68.1% to 31.9%, in sync with the National Spinal Cord Injury Statistical Center (NSCISC) database of 33,406 people with SCI between 2015 and 2018. There, the male-to-female ratio was 78% to 22%. The mean age at the time of the study was 49.3±12.3 years, which is reflective of the aging population with SCI, with the average age at injury increasing from 29 to 43 years from the 1970s to 2018, according to the NSCISC database. Though the NSCISC database showed a greater prevalence of tetraplegia (59.9%) than paraplegia (39.5%), patients who visited our center for a 3-day checkup program were 51.6% paraplegic and 48.4% tetraplegic. This difference could be because most of the patients admitted to the 3-day checkup program were home-discharged, a more common practice among patients with paraplegia [21]. Our center had a higher proportion of complete SCI (n=99; 63.1%) to incomplete SCI (n=58;

36.9%) individuals, than 31.9% to 67.5% in the NSCISC database. The higher prevalence of individuals with complete SCI admitted to the 3-day checkup program could be because the program focuses on neurogenic bladder management and urodynamic study. Individuals with complete SCI have more difficulty managing the bladder drainage method [22].

Four definitions of MetS given by the IDF, AHA/NHLBI, NCEP-ATP III, and WHO criteria are commonly used in studies and clinical settings. Ma et al. [20] suggested that MetS defined by the IDF and AHA/NHLBI classifications presented with significantly higher carotid thickness. Skilton et al. [23] proposed that MetS diagnosed following the AHA/NHLBI classification was the strongest predictor of carotid atherosclerosis among males. At present, there are still ongoing debates regarding the optimal classification for MetS and the validity of extrapolating the same standards to individuals with SCI [24]. This study included all NCEP-ATP III-classified participants with MetS (n=37; 23.6%) in the group with AHA/NHLBI-classified MetS (n=61; 38.9%). Thus, the AHA/NHLBI criteria were deemed more inclusive in the diagnosis of MetS, which resulted in our decision to follow the AHA/NHLBI guidelines for this study.

Hirode and Wong [25] evaluated the trends in MetS prevalence among 17,048 adults (aged ≥20 years) from the general United States population using National Health and Nutrition Examination Survey data from 2011 to 2016. Among Asian adults, the MetS prevalence increased significantly from 19.9% to 26.2% over the study period (2011–2016), with a total mean prevalence of 23.2%. This study showed a similar prevalence of NCEP-ATPIII-classified MetS individuals (n=37; 23.6%). In addition, Gater et al. [26] conducted a cross-sectional study of 473 veterans with SCI. NCEP-ATP III-classified MetS was diagnosed in 22.9% of the veterans using BMI ≥30 kg/m^2 as the cutoff value for obesity. These studies show a similar prevalence of MetS between the general population and individuals with SCI. However, Maruyama et al. [10] found that 43% of 44 men with SCI were classified with MetS according to the NCEP-ATP III definition, using a WC cutoff value, which corresponded to the obesity cutoff point for visceral fat adiposity as 100 cm [27], defined by the Japanese Society for the Study of Obesity, as 85 cm for men and 90 cm for women. The higher prevalence of MetS in Japanese men with SCI than that in general Japanese workers (19.5% in

men and 7.9% in women) [28] differed from the prevalence of MetS in this study. Although the WC cutoff value for Japanese men is 5 cm lower than that of Korean men, the greater prevalence of MetS in the SCI population than the general population should be considered. It calls for a re-evaluation of the WC cutoff values.

Individuals with tetraplegia are known to have a higher risk of insulin resistance [29], lower metabolism, and lower daily activity, which increases the risk of MetS compared with those with paraplegia [30]. However, our finding points toward lower NLI as a risk factor, partly because individuals with paraplegia have increased independence in lifestyle and eating habits [31]. This phenomenon has also been reported in other studies, where individuals with paraplegia had higher average BMI, WC, biceps, and triceps skin fold thickness measures than those with tetraplegia [32]. Regarding the "elevated BP levels", a MetS subfactor, individuals with tetraplegia are predisposed to impaired control of the autonomic nervous system, which can lead to hypotension, bradycardia, and events of uncontrolled hypertension [33]. Since BP levels are generally taken from the resting state, individuals with tetraplegia are subject to being omitted from the "elevated BP levels" subfactor. However, it is known that autonomic dysregulation due to SCI is associated with a cardiovascular risk [34], which might be misrepresented by the current MetS classification defined for the general population.

While the BMI and WC values in men both showed a significant positive correlation with the number of MetS subfactors, the WC was the single anthropometric measure that was significantly associated with the number of the MetS subfactors, excluding "elevated WC values". Non-obese patients defined by their WC values (obese: men ≥90 cm, women ≥85 cm) had a significantly higher probability of having no subfactors by 27.0% compared with 2.9% of those classified as obese. Individuals classified as obese by their WC values had an increased chance of having one or more subfactors in every number of subfactors (Table 4). This suggests that obesity defined by the WC values is more closely associated with subfactors constituting MetS than the BMI. Inayama et al. [14] reported that although WC and BMI were both significantly associated with the visceral fat area, WC was more accurate than BMI. This result is in line with other studies favoring WC to define obesity in individuals with SCI,

as BMI fails to distinguish between fat and fat-free mass and is an insufficient biomarker of abdominal adiposity [5]. Other studies have underlined the reliability of the WC measurement as a simple method to determine abdominal adiposity and its clinically applicable nature, presenting strong associations with all-cause [35,36] and cardiovascular mortality [37,38].

Unfortunately, as the diagnosis of MetS was used in this study as a surrogate for obesity, the cutoff value for the WC could not be obtained due to its inclusion in the AHA/NHLBI criteria. However, the BMI, which is an independent variable of the AHA/NHLBI classification of MetS, was significantly associated with MetS diagnosis (AUC=0.765; 95% CI, 0.689–0.842; p<0.001) with 22.835 kg/m^2 (sensitivity=72.1%, specificity=72.9%) as a suggested cutoff value. Likewise, Laughton et al. [39] suggested that the BMI cutoff for obesity should be lowered to 22 kg/m^2 based on the percentage of fat mass and the C-reactive protein levels in a study of 77 individuals with chronic SCI. Inayama et al. [14] also identified 22.5 kg/m^2 as a BMI cutoff value corresponding to a visceral fat area of ≥100 cm^2. Although the BMI has limitations in reflecting body fat, it is more reliable than weight alone and constitutes readily available anthropometric measures, such as weight and height. The suggested cutoff value for BMI stresses the need to define obesity in the SCI population properly.

This study had several limitations. First, the sample size was relatively small. In addition, the sample was from a distinctive 3-day checkup program focusing on evaluating and managing neurogenic bladder in individuals with SCI, which led to a disproportionate deviation toward those with paraplegia and complete injury. Second, the patients were recommended for annual follow-ups, and since their overall well-being was being evaluated and managed regularly, the sample from the program might have had fewer MetS. Third, the PBF was measured using the bioelectrical impedance analysis, which is subject to validation in reading because individuals with SCI show a predisposition [40]. Fourth, the cutoff values used for defining obesity were based on the general population, which might have underestimated the prevalence of the MetS when applied to individuals with SCI. Finally, the use of the MetS as a surrogate for central obesity has its limitations; although central obesity is associated with atherogenic and insulin-related abnormalities, it is not a mandatory criterion of the AHA/NHLBI classification. Furthermore, it is unknown whether it causes or is correlated to MetS [4]. Although the WC was the single anthropometric measure with a significant positive correlation and association with the number of MetS subfactors, the cutoff value between the WC and MetS diagnosis could not be found due to their codependent nature. The cutoff value was investigated between different anthropometric measures and the MetS diagnosis using a classification made for the general population. Thus, the validity of the subfactors of the MetS itself is questionable when subjected to SCI, as they are prone to autonomic dysregulation. Lastly, since there is no consensus for SCI-specific WC cutoff values, we were predisposed to use the ethnically appropriate Korean adult WC cutoff values. However, in SCI conditions, using disease-specific cutoff values could be more accurate than ethnic-specific WC cutoff values, leading to potentially different observations in our study. Thus, further large-scale studies are required to determine the Korean SCI-specific cutoff values for the WC and BMI using dual-energy X-ray absorptiometry or other imaging methods that provide VAT quantification.

This study aimed to determine the optimal anthropometric measure and its cutoff value for individuals with SCI in diagnosing the MetS. Among the different anthropometric measures, the WC was the sole measure that had both a significant positive correlation and, based on the obesity cutoffs provided for the general population, a significant linear relationship between the number of the MetS subfactors and obesity. Although the cutoff value for WC could not be evaluated in this study, the results point to establishing stricter BMI cutoff values for individuals with SCI than for the general population in diagnosing the MetS. In addition, they warrant a large population-based study to redefine the cutoff value for central obesity in individuals with SCI according to sex and ethnicity.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTION

Conceptualization: Kim O, Kim T. Methodology: Shin

JW, Kim T, Lee BS, Kim O. Formal analysis: Kim T, Shin JW. Project administration: Kim T, Lee BS, Kim O. Visualization: Kim T, Lee BS, Kim O. Writing - original draft: Kim O, Shin JW. Writing - review and editing: Kim O, Shin JW. Approval of the final manuscript: all authors.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.5535/arm.21144.

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