

## Influence of neurological level of injury in bones, muscles, and fat in paraplegia

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**Abstract**—To investigate the influence of the neurological level of injury in bone mineral content (BMC) and mechanical properties, lean mass (LM), and fat mass (FM) among paraplegics with a similar duration of paralysis (DOP), we separated 30 paraplegics into group A (15 men, high-level paraplegia) and group B (15 men, low-level paraplegia) and compared them with group C (33 men, nondisabled). In all subjects, we measured stress-strain index (SSI) at 14% (SSI<sub>2</sub>) and 38% (SSI<sub>3</sub>) of the tibia length and the difference between them using peripheral quantitative computed tomography (XCT 3000 [Stratec Medizintechnik, Pforzheim, Germany]) and lower-limb BMC, LM, and FM (g) using whole-body dual-energy X-ray absorptiometry (Norland XR-36 [Norland Medical Systems, Inc; Fort Atkinson, Wisconsin]). Bone strength parameters, BMC, and LM were statistically decreased, but we found no difference in paraplegic FM compared with group C. We found a correlation between the DOP and the difference between SSI<sub>3</sub> and SSI<sub>2</sub> in group B ( $r = 0.53$ ,  $p = 0.03$  and  $r = 0.5$ ,  $p = 0.04$ , respectively). We correlated DOP with FM in group A's lower limbs ( $r = 0.5$ ,  $p = 0.05$ ). Because of the nonsignificant DOP, the groups with paraplegia act differently in tibia mechanical properties and lower-limb body composition.

**Key words:** bone, bone mineral content, bone strength, dual-energy X-ray absorptiometry, fat mass, lean mass, lower limb, men, paraplegia, peripheral quantitative computed tomography.

### INTRODUCTION

The effects of spinal cord injury (SCI) on bone in paralyzed body areas are well documented [1–3]. Additional studies have shown that bone loss and deterioration of body

composition are more severe in the sublesional regions of subjects with SCI and tetraplegics than in those of paraplegics [2–4]. The duration of paralysis (DOP) was inversely related to bone and muscle loss as well as fat gain in paraplegics [5–9]. Clinical studies also indicated that neurological injuries are associated with the development of rapid and severe osteoporosis that is not only due to compromised biomechanical function but could also originate in the central nervous system [10–13]. However, the importance of neurological level of injury (NLOI) and the influence of the DOP among patients with paraplegia grouped by high and low NLOI are inadequately investigated concerning bone mineral content (BMC), lean mass (LM), fat mass (FM), and the mechanical properties of bone. Peripheral

**Abbreviations:** ANOVA = analysis of variance, ASIA = American Spinal Injury Association, BMC = bone mineral content, BMI = body mass index, DEXA = dual-energy X-ray absorptiometry, DOP = duration of paralysis, FM = fat mass, LM = lean mass, NLOI = neurological level of injury, pQCT = peripheral quantitative computed tomography, SCI = spinal cord injury, SD = standard deviation, SNS = sympathetic nervous system, SSI = stress-strain index, SSI<sub>2</sub> = SSI at 14% of tibia length, SSI<sub>3</sub> = SSI at 38% of tibia length, T = thoracic, SSI<sub>3-2</sub> = difference between SSI<sub>3</sub> and SSI<sub>2</sub>.

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quantitative computed tomography (pQCT) allows the noninvasive evaluation of bone strength parameters of long bones [14]. Dual-energy X-ray absorptiometry (DEXA [XR-36; Norland Medical Systems, Inc; Fort Atkinson, Wisconsin]) measures body composition precisely and accurately; gives a regional distribution of BMC, FM, and LM; and offers an alternative way of measuring body composition [15].

The aim of our present study was (1) to compare possible changes in the tibia's mechanical strength to the non-disabled tibia and (2) to investigate lower-limb BMC, LM, and FM in relation to NLOI and DOP in patients with paraplegia above thoracic (T) 7 NLOI versus patients with paraplegia with NLOI between T7 and T12.

## MATERIALS AND METHODS

### Demographics

We included 30 subjects with complete chronic paraplegia (an absence of sensory or motor function below the NLOI, including the lowest sacral segment) in comparison with 33 nondisabled subjects. We considered neurological stabilization and the absence of spinal shock to be chronic paraplegia (range: 1.5–22.0 yr). We separated the subjects as follows (values expressed as mean  $\pm$  standard deviation [SD]): group A (15 males with high-level paraplegia [T4–T7 NLOI] (range: 1.5–22.0 yr), aged  $32.88 \pm 15.60$  yr, DOP  $5.97 \pm 5.90$  yr) and group B (15 males with low-level paraplegia [T8–T12 NLOI] (range: 1.5–20.0 yr), aged  $39.47 \pm 13.81$  yr, DOP  $5.65 \pm 5.80$  yr). We recruited the control group (group C) from volunteers of similar age, height, and weight to the subjects with paraplegia. We considered group C to be nondisabled after a physical examination and comprehensive medical history review if they were free of any previous fracture, endocrine or metabolic bone disease, malignancy, drug abuse, alcoholism, and hepatic or renal disorders.

### Methods

We recruited volunteers with paraplegia from the Greek Paraplegic Society using an announcement for participation in clinical research at Athens University. We designed the protocol according to the Declaration of Helsinki and all subjects gave written informed consent. We certify that we followed all applicable institutional and governmental regulations concerning the ethical use of human volunteers during the course of this research.

Subjects with paraplegia underwent a physical examination by a rehabilitation specialist (Dr. Dionyssiotis), who defined the NLOI according to the international standards of the American Spinal Injury Association (ASIA) protocol and the ASIA Impairment Scale [16]. We recorded anthropometric factors for all subjects, including age, height, weight, and body mass index (BMI) (**Table 1**), and clinical parameters for subjects with paraplegia, including age at injury, DOP, and NLOI, according to a questionnaire designed for this protocol [5]. None of the subjects with SCI was younger than 25 years at the time of examination or experienced heterotopic ossifications. We also excluded subjects with chronic use of drugs that promote bone loss and with coexisting diseases that impair bone tissue.

We assessed spasticity using the Ashworth Scale [17]. In the present study, all subjects with paraplegia were above T12 NLOI with various degrees of spasticity according to the Ashworth Scale. We examined all subjects using pQCT. We performed measurements with an XCT-3000 (Stratec Medizintechnik; Pforzheim, Germany) at the left tibia (one leg study) [14]. We used the distal end of the tibia as an anatomical marker. We derived the stress-strain index (SSI) parameter, a bone strength estimator, from the section modulus and the volumetric density of the cortical area at 14 (SSI<sub>2</sub>) and 38 percent (SSI<sub>3</sub>) of the tibia length proximal to the distal end of the tibia [18]. In subjects with paraplegia, we measured height of participants while in supine position before the examination and weight while they were in seated position in the wheelchair

**Table 1.**

Anthropometric data of subjects.

Parameter	Groups (Mean $\pm$ SD)			ANOVA <i>p</i> -Value
	Control ( <i>n</i> = 33)	High-Level Paraplegia ( <i>n</i> = 15)	Low-Level Paraplegia ( <i>n</i> = 15)	
Age (yr)	37 $\pm$ 19	35 $\pm$ 14	43 $\pm$ 16	0.37
Weight (kg)	81.36 $\pm$ 13.00	76.67 $\pm$ 17.12	76.67 $\pm$ 17.12	0.08
Height (m)	1.76 $\pm$ 0.05	1.77 $\pm$ 0.06	1.75 $\pm$ 0.10	0.68
BMI (kg/m <sup>2</sup> )	26.12 $\pm$ 5.00	22.94 $\pm$ 2.21	24.86 $\pm$ 3.50	0.02

ANOVA = analysis of variance, BMI = body mass index, SD = standard deviation.

(after subtracting the wheelchair's weight). We also calculated the BMI (weight [kg]/height<sup>2</sup> [m]) of each subject. We also examined all subjects using DEXA to estimate regional lower-limb BMC, LM, and FM (g). The coefficient of variation was  $2.3 \pm 0.9$  percent for total FM and  $2.1 \pm 0.4$  percent for total LM. The basic principles of pQCT and DEXA are described elsewhere [14,19–20].

### Statistical Analysis

All variables are represented by the number of subjects ( $n$ ) and mean value  $\pm$  SD. We performed comparisons of variables among the groups using one-factor analysis of variance (ANOVA) with no repeated measurements model (one-way ANOVA) and Bonferroni test for pair-wise comparisons. We performed comparisons of variables among groups with paraplegia using the analysis of covariance model, controlling for age at injury and DOP, respectively. All tests are two-sided; we defined  $p < 0.05$  as significant. We performed all data analysis using SPSS version 10.0 (SPSS, Inc; Chicago, Illinois).

## RESULTS

BMI values for the groups with paraplegia were statistically lower ( $p = 0.02$ ) than group C. SSI<sub>2</sub> decreased by 14.45 and 24.66 percent in groups A and B, respectively ( $p = 0.001$ ), while SSI<sub>3</sub> decreased by 19.08 and 17.16 percent ( $p = 0.001$ ) compared with group C (Table 2). Figures 1 and 2 depict the linear and logarithmic correlations between SSI<sub>2</sub> and DOP and the best-fit equations in both groups with paraplegia. The correlation between SSI<sub>2</sub> and DOP was negatively high in both groups with paraplegia together and separately (Table 3). However, we found a similar correlation in only group A between SSI<sub>3</sub> and DOP (Table 3). Figures 3 and 4 depict the linear cor-

relations and the best-fit equations at SSI<sub>3</sub> for both groups with paraplegia. According to these findings, we calculated the difference between SSI<sub>3</sub> and SSI<sub>2</sub> (SSI<sub>3-2</sub> [SSI<sub>3</sub> – SSI<sub>2</sub>]) between the groups with paraplegia. Comparison of the mean SSI<sub>3-2</sub> of the groups with paraplegia was statistically significant ( $p = 0.05$ ) versus group C, but not between groups with paraplegia ( $p = 0.55$ ). Evaluating further correlations and  $p$ -values between mean SSI<sub>3-2</sub> and clinical parameters, we found a strong correlation with the DOP in group B ( $r = 0.534$ ,  $p = 0.03$ ). On the contrary, we found no significant correlation in group A ( $r = -0.178$ ,  $p = 0.5$ ) (Table 4).

We observed a statistically significant reduction in lower limbs of both groups with paraplegia in comparison with group C in BMC ( $886 \pm 178$  vs  $1,214 \pm 149$ ,  $p < 0.001$ ) and LM ( $11,094 \pm 2,174$  vs  $19,693 \pm 3,242$ ,  $p < 0.001$ ). However, we found no difference in FM between groups A and B and group C and in the above parameters after analysis according to NLOI between the groups with paraplegia. Table 5 presents the values.

We found the lower-limb BMC to be negative when correlated with the DOP in both groups with paraplegia ( $r = -0.46$ ,  $p = 0.01$ ), but according to the NLOI, we found this to be due to the strong correlation with group A ( $r = -0.658$ ,  $p = 0.01$ ) (Table 4). DOP was strongly correlated with FM in group A's lower limbs ( $r = 0.5$ ,  $p = 0.05$ ). We found no significant relationship between the intensity of bone loss and spasticity (data not shown).

## DISCUSSION

We found BMI values to be statistically reduced in both groups with paraplegia compared with group C. Bone strength parameters, BMC, and LM were statistically decreased, but we found no difference in FM compared

**Table 2.** Peripheral quantitative computed tomography (pQCT) parameters of subjects.

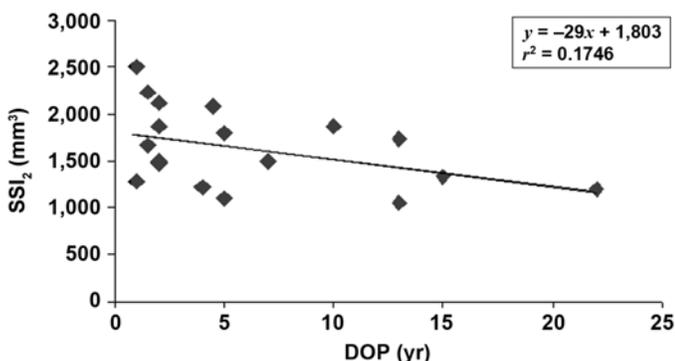
Tibia Point (%)	Bone Parameter	Groups (Mean $\pm$ SD)			Difference Between Groups (%)		ANOVA $p$ -Value
		Control ( $n = 33$ )	High-Level Paraplegia ( $n = 15$ )	Low-Level Paraplegia ( $n = 15$ )	Control and High-Level Paraplegia	Control and Low-Level Paraplegia	
14	SSI <sub>2</sub>	2,128.51 $\pm$ 179.35	1,820.84 $\pm$ 387.16	1,603.64 $\pm$ 245.53*	-14.45	-24.66	0.009
38	SSI <sub>3</sub>	2,318.64 $\pm$ 156.95	1,876.14 $\pm$ 240.31 <sup>†</sup>	1,920.84 $\pm$ 141.57 <sup>†</sup>	-19.08	-17.16	0.003

\* $p$ -value  $< 0.005$ .

<sup>†</sup> $p$ -value  $< 0.05$ .

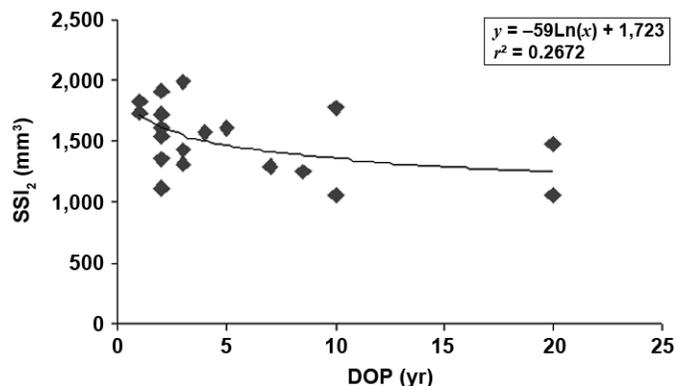
Note: Bonferroni tests for control group versus high-level paraplegic group and versus low-level paraplegic group.

ANOVA = analysis of variance, SD = standard deviation, SSI<sub>2</sub> = stress-strain index at 14% of tibia length, SSI<sub>3</sub> = stress-strain index at 38% of tibia length.



**Figure 1.**

We found linear correlation between stress-strain index (SSI) at 14% of tibia length ( $SSI_2$ ) and duration of paralysis (DOP) in group with high-level paraplegia (range: 1.5–22.0 yr) to best fit our data. Decay equations refer to best-fit SSI data of subjects with paraplegia regarding tibia.  $r^2$  = goodness of fit of equation (Pearson partial correlation squared),  $x$  = DOP in years ( $x$ -axis),  $y$  =  $SSI_2$  in  $mm^3$  ( $y$ -axis).



**Figure 2.**

We found logarithmic correlation between stress-strain index (SSI) at 14% of tibia length ( $SSI_2$ ) and duration of paralysis (DOP) in group with low-level paraplegia (range: 1.5–20.0 yr) to best fit our data. Decay equations refer to best-fit SSI data of subjects with paraplegia regarding tibia.  $\ln(x)$  = logarithmic of  $x$ ,  $r^2$  = goodness of fit of equation (Pearson partial correlation squared),  $x$  = DOP in years ( $x$ -axis),  $y$  =  $SSI_2$  in  $mm^3$  ( $y$ -axis).

with group C. The correlation of BMI with FM was statistically significant in groups B and C. In a correlation between DOP and BMI, we found  $SSI_{3-2}$  in group B and between BMC and FM in group A.

BMI values in all subjects were below the BMI signifying obesity (BMI > 27.8) [21]. Furthermore, in both groups with paraplegia we found lower values of BMI than in group C. BMI is a value that relates body weight to body

**Table 3.**

Correlation and statistical significance in total and within paraplegic groups between duration of paralysis (DOP),  $SSI_2$  (stress-strain index at 14% of tibia length), and  $SSI_3$  (stress-strain index at 38% of tibia length).

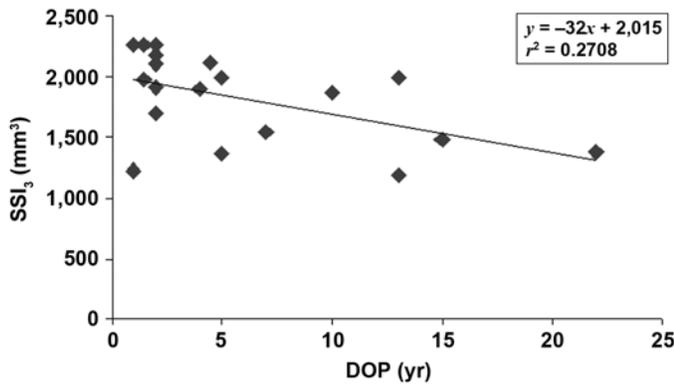
pQCT Variables	DOP	Groups with Paraplegia		Total ( $n = 30$ )
		High-Level ( $n = 15$ )	Low-Level ( $n = 15$ )	
$SSI_2$	$r$	-0.419	-0.473	-0.423
	$p$	0.074	0.041	0.008
$SSI_3$	$r$	-0.475	0.097	-0.266
	$p$	0.040	0.692	0.106

Note: Data are presented as correlation coefficients ( $r$ ).

$p = 0.05$  (we defined  $p < 0.05$  as significant), pQCT = peripheral quantitative computed tomography,  $r \geq 0.4$  medium ( $r > 0.6$  strong).

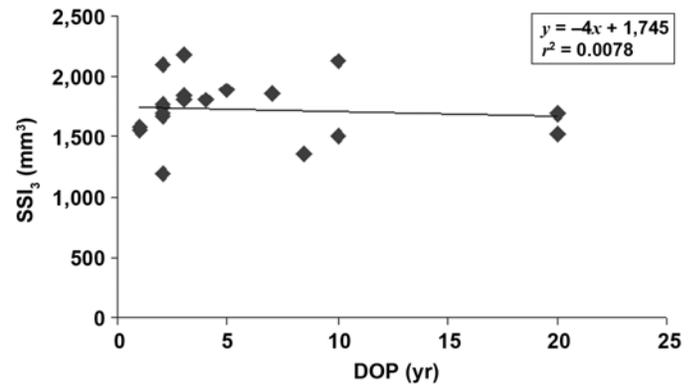
size and does not distinguish between subjects' component of weight (LM and FM). Studies in the literature have proven that FM and body fat percent are greater in paraplegics [8–9]. In a former study, we show that the values of FM in total body composition of a subject with paraplegia compared with a control subject (using whole-body DEXA) were increased. We found BMI to be related to FM in all groups; however, after analysis according to the NLOI, only group B showed significant correlation between BMI and FM. Group B had more FM at any given BMI value than group C [9]. Spungen et al. and Dionyssiotis et al. also found a relationship between total body fat percent and BMI for a SCI and control group, but our finding that the correlation depends on the values of the groups with low-level paraplegia is new [8–9]. An explanation may lie in the specific alterations to body composition of patients with paraplegia and the effect of factors such as immobilization, damage to the sympathetic nervous system (SNS), and hormonal status. Measuring fat with BMI in subjects with chronic paraplegia is not enough to determine a subject's body fat percentage. According to our results, the reduced BMI in the groups with paraplegia is the result of a reduced LM.

According to Spungen et al., the predominant finding regarding bone in subjects with SCI is a large loss during the first year of injury due to disuse osteoporosis, predisposing the subject to an increased prevalence of fractures [8]. Biering-Sørensen et al. demonstrated an ongoing demineralization in the tibia 3 years after trauma [3]. Bauman et al. reported DOP-related bone loss in the lower limbs of monozygotic twins with chronic paraplegia in comparison with their nondisabled cotwins [22]. The results of the



**Figure 3.**

We found linear correlation between stress-strain index (SSI) at 38% of tibia length ( $SSI_3$ ) and duration of paralysis (DOP) in group with high-level paraplegia (range: 1.5–22.0 yr) to best fit our data. Decay equations refer to best-fit SSI data of subjects with paraplegia regarding tibia.  $r^2$  = goodness of fit of equation (Pearson partial correlation squared),  $x$  = DOP in years ( $x$ -axis),  $y$  =  $SSI_3$  in  $mm^3$  ( $y$ -axis).



**Figure 4.**

We found linear correlation between stress-strain index (SSI) at 38% of tibia length ( $SSI_3$ ) and duration of paralysis (DOP) in group with low-level paraplegia (range: 1.5–20.0 yr) to best fit our data. Decay equations refer to best-fit SSI data of subjects with paraplegia regarding tibia.  $r^2$  = goodness of fit of equation (Pearson partial correlation squared),  $x$  = DOP in years ( $x$ -axis),  $y$  =  $SSI_3$  in  $mm^3$  ( $y$ -axis).

comparison between all groups in this study suggest a reduction of lower-leg BMC in subjects with paraplegia independent of the NLOI. BMC in the lower limbs negatively correlated with the DOP in the groups with paraplegia, but after investigating according to the NLOI, we found this correlation to be due to the strong correlation of group A's lower-limb BMC with DOP, meaning that the NLOI determines the extent of bone loss. SSI is an important validated biomechanical strength bone parameter because it is related to bone breaking force, an explanation of why people with chronic SCI are prone to bone fractures [23]. A recent publication found different DOP until steady state for different parameter and scan sites [24]. Based on previously published cross-sectional data from a large number of subjects with paraplegia and tetraplegia [7], Frotzler et al. performed all statistical analyses of tibial and femoral bone data, including only subjects with a lesion duration of at least the time to reach bone steady state ( $t$ ) for each particular bone parameter calculated from bone measurements at  $t0$  [24]. They chose the cutoff point of 8 years because this was the maximum time required for the femur and tibia to reach the new steady state [7]. This was not the case in our study. Instead, we cross-section analyzed a more homogenous sample of subjects. We did not include tetraplegics or subjects with flaccid paralysis, and we performed the analysis with mean DOP  $\pm$  SD ( $5.65 \pm 5.80$  yr vs  $12.0 \pm 10.8$  yr [7]). Only  $SSI_3$  in group B did not depend on the DOP, whereas  $SSI_3$  in group A and  $SSI_2$  in both groups with paraplegia

depended on the DOP.  $SSI_3$  is a value measured in the bone shaft at 38 percent of the tibia length, and according to Eser et al., the cortical wall of the long bones of the paralyzed lower limbs thins but is no less dense (except for a transient decrease during increased intracortical remodeling during the first 5 years after injury), and reaches a new steady state at a higher relative level in the diaphyses than in the epiphyses [7]. Together with the finding that the  $SSI_3$  and BMC in group B were decreased compared with group C means that this parameter was already in a steady state.

The strong correlation of  $SSI_{3-2}$  with DOP in group B could not be easily explained because of the similar paralytic effect on bone in both groups with paraplegia despite the nonsignificant DOP between them. This difference could possibly be a result of the higher incidence of standing in group B and a direct effect of loading on the mechanical parameters of the lower tibia. Paraplegics stand using various devices, long leg braces, and standing frames, although some lose their motivation to use such devices over age. According to DOP, the two groups with paraplegia have different mechanical properties of the tibia. All subjects of both paraplegic groups were in chronic stage which suggests that not only the mechanical (forces-standing) but also the neurogenic factor seems to coexist as an influential regulator in osteoporosis during paralysis. The recent scientific finding of a sympathetic innervation of bone tissue and its role in the regulation of bone remodeling is of major interest in situations where

**Table 4.**

*p*-Value and correlation between duration of paralysis (DOP), difference between stress-strain index at 38 and 14 percent of tibia length (SSI<sub>3-2</sub>), and lower-limb bone mineral content (BMC) parameters in paraplegic groups.

Parameter	DOP	Groups with Paraplegia		Total ( <i>n</i> = 30)
		High-Level ( <i>n</i> = 15)	Low-Level ( <i>n</i> = 15)	
Lower-Limb	<i>r</i>	-0.658	-0.140	-0.460
BMC	<i>p</i>	0.006	0.617	0.009
SSI <sub>3-2</sub>	<i>r</i>	-0.178	0.534	0.071
	<i>p</i>	0.495	0.027	0.688

Note: Data are presented as correlation coefficients (*r*).

*p* = 0.05 (we defined *p* < 0.05 as significant), *r* ≥ 0.4 medium (*r*) > 0.6 strong.

uncoupling between osteoclasts and osteoblasts occurs [13]. Subjects with paraplegia lose bone extremely fast and the SNS is disproportionately involved when compared with the parasympathetic nervous system at high-level SCI [9]. Clinical evidence exists that the sympathetic regulation of bone does occur in humans and plays a clinically important role in diseases characterized by excessive sympathetic activity [25]. In high-level paraplegia, we can attribute SNS dysfunction after SCI to loss of supraspinal control that occurs with the disruption of spinal cord pathways. In addition, in those with SCI above T6, the clinical sequelae of autonomic dysreflexia appear. We associated group A with significant dysfunction of the SNS (autonomic dysreflexia) as another possible parameter for this statistically significant result.

Wilmet et al. found a 15.1 percent LM reduction in lower limbs 1 year after injury [2]. Maggioni et al. found that the total FM was significantly higher in paraplegics and the LM significantly lower compared with controls [26]. In our study, the subjects with paraplegia had significantly lower LM in the lower limbs. According to the NLOI, FM values in group A and B's lower limbs were increased but not significant compared with group C (9%

and 28%, respectively). In high-level paraplegia, impaired or reduced activity of SNS may put paraplegics at a higher risk for developing obesity. Decentralization and impairment of SNS may interrupt the pathway of leptin, described by Jeon et al., and we expected increased FM in group A [13]. However, we found opposite results. This paradoxical finding could possibly be explained as follows: (1) in the chronic injury phase, low-level paraplegics have a similar lifestyle as high-level paraplegics (wheelchair users) and do not use orthoses for lower-limb mobility; (2) some of our subjects with paraplegia were using orthoses to ambulate, so the load and intensity of this locomotion might not be enough to reduce FM in the lower limbs; (3) the role of hormonal mechanisms, particularly leptin, is inadequately explained in paraplegia; and (4) our study did not include the analysis of the paraplegic groups' trunks and total body composition for methodological reasons. This finding needs further investigation but is supported by a strong correlation of DOP with FM in group A's lower limbs, suggesting that this population clearly reflects the neurogenic consequences after SCI.

## CONCLUSIONS

We recognize the possibility of increased mobility using walking orthoses in our study's low-level subjects with paraplegia, which could result in increased energy expenditure and reduced adiposity. The low number of subjects with paraplegia in this study may be considered a limitation; we believe that a similar large-scale study could increase the statistical power of our results. Another study limitation is that the NLOI was at the T12 level or higher in all subjects with paraplegia, with various degrees of spasticity according to the Ashworth Scale. This limitation may have precluded our results regarding the effect of spasticity on bone parameters of the lower limbs.

**Table 5.**

Parameters measured with dual-energy X-ray absorptiometry in lower limbs of subjects.

Parameter (g)	Groups (Mean ± SD)			<i>p</i> -Value
	Control ( <i>n</i> = 33)	High-level Paraplegia ( <i>n</i> = 15)	Low-level Paraplegia ( <i>n</i> = 15)	
BMC	1,213.84 ± 149.37	898.14 ± 202.88	873.60 ± 155.21	0.001
Lean Mass	19,692.73 ± 3,242.00	11,739.38 ± 1,843.39	10,406.33 ± 2,347.39	0.001
Fat Mass	6,909.91 ± 2,497.00	7,552.44 ± 2,832.65	8,897.53 ± 3,956.94	0.11

BMC = bone mineral content, SD = standard deviation.

We must also consider that muscles and bones act as a unit and are related tissues. Therapeutic strategies that help patients with paraplegia bear weight, stand, or walk should be added early in a rehabilitation program to gain muscle and bone benefit.

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### Author Contributions:

*Study concept and design:* Y. Dionyssiotis.

*Acquisition, analysis, and interpretation of data:* Y. Dionyssiotis.

*Drafting of manuscript:* Y. Dionyssiotis, G. P. Lyritis.

*Critical revision of manuscript for important intellectual content:*

G. P. Lyritis, N. Papaioannou, P. Papagelopoulos, T. Thomaidis.

*Study supervision:* G. P. Lyritis.

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