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Bone loss and mechanical properties of tibia in spinal cord injured men

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Abstract

Aim: The effects of Spinal Cord Injury (SCI) on bone in paralyzed areas are well documented but there are few data for the importance of the level of injury in the decrease of mechanical strength in paralyzed legs. The aim of the present study was to describe bone loss of the separate compartments of trabecular and cortical bone in spinal cord injured men and to compare possible changes in mechanical properties of tibia with the neurological level of injury. **Materials and methods:** Fifty men were included in this study: 39 had complete SCI in chronic stage. As chronic stage, we considered paraplegia >1.5 years (yrs). Men were separated as follows: Group A (18 men, high paraplegia: Thoracic (T)4-T7 level, mean age: 33 yrs, duration of paralysis: 5.9 yrs) and group B (21 men, low paraplegia: T8-T12 level, mean age: 39 yrs, duration of paralysis: 5.6 yrs) in comparison with 11 healthy men as a control group (C) of similar age, height, and weight. None of the subjects was given bone acting drugs. The neurological profile of each patient was assessed according to the American Spinal Injury Association (ASIA). All subjects were measured by peripheral quantitative computed tomography (pQCT). Measurements were performed at the tibia with a Stratec XCT 3000 (Stratec Medizintechnik, Pforzheim, Germany) scanner. The distal end of the tibia was used as an anatomical marker. The bone parameters, bone mass density (BMD) trabecular, BMD total, BMD cortical, and cortical thickness have been measured at 4% and 38%, respectively, of the tibia length proximal to this point, and the periosteal and endocortical was measured at 14% of the tibia. We calculated stress strain index (SSI), a bone strength estimator derived from the section modulus, and the volumetric density of the cortical area at 14% (SSIPol2) and 38% (SSIPol3) of the tibia length proximal to the distal end of the tibia. **Results:** In both groups A and B most bone mass parameters were statistically decreased in comparison with controls. In each group we calculated the median $\delta SSI_{3\text{-}2}$ (SSIPol3 – SSIPol2). In the paraplegic groups Spearman correlation coefficient between duration of paralysis and $\delta SSI_{3\text{-}2}$ was in group A: r=-0.178, p=N.S. and group B: r=0.534, p=0.027, respectively. **Conclusion:** Despite the similar paralytic effect on bone in all paraplegic patients in our study and because of the non-significant duration of paralysis between paraplegic groups (p=0.87), the two paraplegic groups act differently in mechanical properties of the tibia. In addition, group A patients in respect to the level of injury, are susceptible to autonomic dysreflexia as a result of the disruption of the autonomic nervous system pathways. These results suggest that neurogenic factors are influencing geometric bone parameters.

Keywords: Spinal Cord Injury, Osteoporosis, Men, Peripheral Quantitative Computed Tomography (pQCT)

The authors have no conflict of interest.

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Introduction

Paraplegia causes an extreme and sudden immobilization of lower limbs that results in bone loss and an increased risk of fractures. The pathophysiology of osteoporosis in spinal cord injured patients is complex[1]. Disuse may play an important role. Paraplegics unable to bear weight on their limbs (sitting in the

wheelchair) are not exposed to forces to stimulate bone formation[2]. The loss of mechanical stimuli to the bone is considered a powerful influence in sustaining bone integrity. Immobility leads to a changing pattern of loading in the paralysed areas, which respond by alteration in skeletal structure. Bone loss in the literature of the spinal cord injured population is explained using various concepts focusing on impaired calcium and phosphate metabolism and the parathyroid hormone (PTH)-vitamin D axis, hypercortisolism, poor nutritional status, venous and capillary vascular stasis, neural factors and gonadal function[3-5]. The predominant finding of Spinal Cord Injury (SCI) on bone is a large loss of bone during the first year of injury due to disuse osteoporosis[6-8], predisposing to an increased prevalence of fractures[9,10]. The effects of SCI on bone in paralyzed areas are well documented[1,11,12]. No significant difference between paraplegics and tetraplegics was found for tibia cortical or trabecular BMD[13]. The importance of the neurological level of injury (NLoI) among paraplegic patients in the decrease of mechanical strength in paralyzed legs is not fully explained because there are no studies investigating the mechanical strength after separation of paraplegics according to the NLoI[5,14].

Nowdays there is evidence that the nervous system participates in skeletal development and bone turnover[15]. Clinical studies also indicated that neurological injuries are associated with the development of a rapid and severe osteoporosis that is not only due to a compromised biomechanical function but can have a central nervous system origin[8]. The most commonly existing studies on bone loss in SCI patients have employed dual energy X-ray absorptiometry (DXA)[9,16]. Some authors have published data in the study of long bones with the peripheral quantitative computed tomography (pQCT) in SCI patients[13,14]. Peripheral quantitative computed tomography allows the measurements of true volumetric densities at a minimum exposure to X-rays and to assess cortical and trabecular bone density separately, as well as to evaluate the geometrical properties of long bones non-invasively[17]. Given that fractures in spinal cord injured patients do often occur in the tibia this skeletal site provides an excellent specimen for the study of pathologic bone in SCI, for assessing bone geometry and the effect of mechanical loading[2].

The aim of the present study was to use peripheral quantitative computed tomography (pQCT): 1) to describe bone loss of the separate compartments of trabecular and cortical bone, as well as changes in bone geometry of the tibia in spinal cord injured (SCI) men with long-term (>1.5 yr) complete SCI above thoracic T12 neurological level of injury (NLoI) and able-bodied controls; 2) to compare possible changes in bone parameters in SCI injured patients with the neurological level of injury (NLoI) >T7 with patients with NLoI between T7 and T12.

Method and material

This study was carried out in the Laboratory for Research of the Musculoskeletal system in the University of Athens, in KAT Hospital in Kifissia, Greece in co-operation with the 2nd Rehabilitation Department of the National Rehabilitation Center in Athens, Greece. The protocol was designed according to the Declaration of Helsinki and approved by the Ethics Committee of Athens University. All subjects gave written informed consent.

Fifty men were included in this study. The neurological profile of each paraplegic subject was assessed according to the international standards for neurological and functional classification of spinal cord injury defined by the American Spinal Injury Assosiation (ASIA)[18]. Thirty-nine men had complete spinal cord injury (an absence of sensory or motor function below the neurological level, including the lowest sacral segment) in chronic stage. As chronic stage we considered the neurological stabilization and the absence of spinal shock (>1.5 years). Men were separated as follows: Group A (18 men, high paraplegia: T4-T7 neurological level of injury (NLoI), mean age: 32.88±15.6 yrs, Duration of Paralysis (DoP): 5.97±5.9 yrs) and group B (21 men, low paraplegia: T8-T12 NLoI, mean age: 39.47±13.81 yrs, DoP: 5.65±5.8 yrs) in comparison with 11 healthy men as the control group of similar age, height and weight. The control population was recruited from volunteers. Controls were considered healthy after physical examination and comprehensive medical history review, which was free of any previous fracture, endocrine or metabolic bone disease, malignancy, drug abuse, alcoholism and hepatic or renal disorders. Each subject was interviewed and examined by the first author by a baseline personal data questionnaire designed for this study and based on anthropometric and clinical information. Anthropometric factors, including age, height, weight, BMI (in both paraplegic groups and controls) and clinical parameters such as age at injury, duration of paralysis, and the level of injury were recorded in all paraplegics after the interview and the complete physical examination. All spinal cord subjects underwent vertebral fixation procedures and followed rehabilitation programs after injury (mean time 5 months). A possible explanation for the late onset of rehabilitation is the lack of specialization in SCI rehabilitation departments in Greece in past years[19]. After hospitalization in the rehabilitation unit some patients followed rehabilitation programs at home. None of the spinal cord injured subjects was younger than 25 years at the time of examination or suffered from heterotopic ossifications. We also excluded spinal cord patients with chronic administration of bone acting drugs, which promote the bone loss and coexisting diseases that impair bone tissue. In Table 1 we present the anthropometric data and the clinical parameters of the study population. All paraplegics were wheelchair-bound, not bedridden at the time of examination. All men were examined by peripheral quantitative computed tomography (pQCT). Measurements were performed with a Stratec XCT 3000 (Stratec Medizintechnik, Pforzheim, Germany) scanner. A pQCT scanner provides the benefits of the large clinical QCT systems but at a lower cost and radiation exposure[17]. It also allows for distinction between the effects of bone size and changes in bone mass per unit volume. Therefore, pQCT has the potential to improve the diagnostic utility of densitometry in the skeleton. Measurements were per-

SUBJECTS Parameters	**Control s n=*11*** mean ± sd	**Group A n=*18*** mean±sd	**Group B n=*21*** mean±sd	**p-value (N.S.)**
Age (years)	33.9±3.81	32.88±15.6	39.47±13.81	0.3
Weight (kg)	80±6.5	72.88±8.16	76.82±8.33	0.08
Height (m)	1.79±0.05	1.74±0.07	1.75±0.04	0.09
BMI (kg/m^2)	24.91±2.06	24.11±2.55	25.09±2.5	0.4
Age at injury (years)	●	26.63±14.35	33.57±12.3	0.118
Duration of Paralysis (years)	●	5.97±5.9	5.65±5.8	0.87

Table 1. The anthropometric data and the clinical parameters of controls and paraplegic population.

Tibia Slices pQCT	**Bone Mass Parameter**	**Control Group** n=11 mean±sd	**Group A** n=18 mean±sd	**Group B** n=21 mean n=21 sd	**Difference Control to group A**	**Difference Control to group B**	**ANOVA *p* value**
4%	BMDtrb (mg/cm^3)	264.15±39.49	110.09±59.91***	134.58±68.53***	-58.32%	-49.05%	<0.0005
	BMDtot (mg/cm^3)	342.01±41.75	181.61±48.75***	187.59±64.79***	-46.90%	-45.15%	<0.0005
14%	SSIPol2 mm^3	2128.51±179.35	1820.84±387.16	1603.64±245.53**	-14.45%	-24.66%	0.009
38%	BMDcort (mg/cm^3)	1108.75±23.79	1087.90±19.97	1057.30±46.65*	-1.88%	-4.64%	0.029
	SSIPol3 mm^3	2318.64±156.95	1876.14±240.31*	1920.84±141.57*	-19.08%	-17.16%	0.003
	THIcort (mm)	6.42±0.42	5.15±1.08*	5.33±0.77*	-19.78%	-16.98%	0.019

p-value<0.05, **p-value<0.005, ***p-value<0.0005 of Bonferroni- tests for control group vs. NLI>T7 group and vs. T7<NLI<T12 group; BMDtrb: Bone Mass Density trabecular, BMDtot: BMD total, BMDcort: BMD cortical, THIcort: Cortical Thickness, SSIPol 2: Stress Strain Index 14% tibia, SSIPol 3: Stress Strain Index 38% tibia.

Table 2. Reduced pQCT parameters of the study population.

formed on the left tibia (one leg study). The subject sat on the scanner chair with the extended lower limb resting inside the concentric acrylic cylinder at the central gantry. Before taking slices, a 30 mm plannar scoutview over the joint line of interest was performed. The appropriate location of the reference line was visually verified. After reference verification, 4 slices were taken at 4%, 14%, 38% and 66% of the tibia length, distance from the reference line.

From the epiphyseal scans, trabecular and total bone parameters and mineral density (BMDtrab and BMDtot) were calculated, and from the shaft scans, cortical BMD (BMDcort), endocortical circumference, periosteal circumference and thickness (endo c, peri c, thickness) were determined. The distal end of the tibia was used as an anatomical marker. The bone parameters were measured at 4%, 14%, and 38% of the tibia length proximal to this point.

Stress-strain index (SSI) parameter, a bone strength estimator, was derived from the section modulus and the volumetric density of the cortical area at 14% (SSI Pol 2) and 38% (SSI Pol 3) of the tibia length proximal to the distal end of the tibia.

Statistical Analysis

All variables are represented by the number of patients (n), mean value (mean), and standard deviation (sd). Comparisons of variables among the 3 groups were performed using the one factor analysis of variance with no repeated measurements model (One way ANOVA) and Bonferroni test for pairwise comparisons. Comparison of variables among the 2 paraplegic groups were performed using analysis of covariance model (ANCOVA) controlling for age at injury and duration of paralysis, respectively. All tests are two-sided; $p<0.05$ was defined as significant. All data analysis was performed using the Statistical Package for Social Sciences (version 10.0) software (SPSS Inc., Chicago, IL).

Results

In both groups A and B most bone mass parameters were significantly reduced (Table 2) in comparison with controls, which indicate severe bone loss after injury. Paraplegic

pQCT	Bone Mass Parameter	Controls	Paraplegics (group A)	Paraplegics (group B)	Difference Control to group A	Difference Control to group B	ANOVA *p* value
Tibia Slice	***subjects***	***11*** mean±sd	*18* mean±sd	*21* mean±sd			
14%	Peri C (mm)	82.33±6	85.67±7.8	85.30±7.5	0.96%	0.95%	p=0.45
	Endo C (mm)	63.57±6.17	72.12±10.1	73.8±9.4	8.80%	8.60%	p=0.012

p-value<0.05, **p*-value<0.005, ***p*-value<0.0005 of Bonferroni-tests for control group vs. NLI>T7 group and vs. T7<NLI<T12 group, peri c: periosteal circumference, endo c: endocortical circumference.

Table 3. Periosteum and endocortical circumference pQCT parameters of the study population.

groups' losses in BMDtrab and BMDtot compared to controls were higher than in BMDcort meaning that the trabecular bone was more affected from the spinal lesion during the years of paralysis. Trabecular BMD of the epiphyses was reduced by 57.5% in high and 51% in low paraplegics. Cortical thickness decreased by 21.44% vs. 23.2% in the paraplegic groups, respectively. Cortical BMD of the shaft was decreased by 3.6% and 6.5% ($p=0.029$) in comparison with controls. SSIPol 2 decreased by 14.45% and 24.66% in high paraplegics and low paraplegics, respectively, while SSIPol 3 decreased by 19.8% and 17.16%. SSIPol and cortical thickness deficit were parallel. Periosteal circumference was similar ($p=0.45$) in controls and paraplegics (controls 82.33±6 vs. high paraplegics 85.67±7.8 vs. low paraplegics 85.3±7.5) but in contrast endosteal resorption was significant (controls 63.57±6.17 vs. low paraplegics 73.8±9.4, $p=0.012$ and controls vs. high paraplegics 72.12±10.1 $p=0.054$) (Table 3). We also calculated in each group the mean difference between SSI in tibial 14% and 38% sites (δSSI_{3-2}). In group A mean δSSI_{3-2} was found to be 236.47±229, and in group B increasing to 277.87±164 (control group: 190.13±61.33). Comparison of the mean δSSI_{3-2} of the paraplegic groups was statistically significant ($p=0.05$) vs. controls but not with each other ($p=0.55$). Because of the high SD in the group of high paraplegics we calculated in both groups the median difference δSSI_{3-2}. Using this parametric analysis we found in the group of high paraplegics δSSI_{3-2}: 174.7 (min 2.41-max 717.70) and in the group of low paraplegics δSSI_{3-2}: 236.5 (50.32-573.9). The results were non-significant again ($p=0.2$). Trying to understand the meaning of this difference we searched correlations and p-values between δSSI_{3-2} difference and anthropometric and clinical parameters. δSSI_{3-2} was strongly correlated with the age of the low paraplegics ($r=0.5$, $p=0.04$), age at injury in both paraplegic groups ($r=0.387$, $p=0.02$) and the duration of paralysis in low paraplegics ($r=0.534$, $p=0.27$). In contrast, in the high paraplegic group Spearman correlation coefficient between age, duration of paralysis and δSSI_{3-2} was non-significant: $r=0.056$, $p=0.83$ and $r=-0.178$, $p=0.5$, respectively. We did not find any correlation between δSSI_{3-2} with height and weight in the two paraplegic groups.

Paraplegics	δSSI_{3-2}	Total	High	Low
Age	r	0.344	0.056	0.505
	p-value	0.046	,830	0.039
Age at injury	r	0.387	0.130	0.393
	p-value	0.024	0.620	0.119
Duration of paralysis	r	0.071	-0.178	0.534
	p-value	0.688	0.495	0.027
Height	r	-0.027	-0.053	0.009
	p-value	0.881	0.839	0.973
Weight	r	0.045	0.129	-0.253
	p-value	0.801	0.621	0.327

Table 4. *p*-value and correlations of δSSI_{3-2} with clinical parameters and subjects' characteristics.

Discussion

Before the analysis of our results, we need to declare the difficulties in completing such a study because of the small population of high-level paraplegics in comparison with low-level paraplegics in a general paraplegic population. Therefore in our paraplegic group we were not able to have exactly the same mean ages between the two paraplegic groups but similar ($p=0.3$). High-level paraplegic subjects were younger. According to many authors and the general literature on osteoporosis in men, peak bone mass is reached at 25 years, criterion which we included in our study[20]. Biering-Sörensen et al. demonstrated an ongoing demineralization 3 years after trauma in the proximal tibia[6]. According to Lazo et al., the bone loss in SCI is progressing over 12 to 16 months prior to stabilization[9]. Bone loss after SCI is reported to reach fracture threshold at 1 to 5 years after injury[12]. These studies on bone loss in SCI have employed DXA. The approach of pQCT allows evaluation of the geometrical properties of bones non-invasively and regionally.

Paraplegic groups' losses in BMDtrab and BMDtot com-

pared to controls were higher than in BMDcort, meaning that the trabecular bone was more affected from the spinal lesion in our study population with duration of paralysis 5.7 years. In the study of Eser et al. in the group of paraplegic patients with duration of paralysis 14±11.5 years it is shown that only trabecular BMD decreased, while the cortical wall of the bones (femur and tibia) of the paralyzed legs became thinner but no less dense. When the authors analyzed data with time post-injury of less than 5 years, they found a significant linear decrease of BMDcort with time post-injury (at the tibia was $r=0.379$, $p=0.003$)[14]. In addition Frey-Rindova et al. in another study including paraplegic patients pointed out that loss of cortical BMD began later than trabecular and was significant 12 months after SCI. These authors also support the "relative stability" of the cortical bone in subjects with SCI[21].

The similar losses in BMD trab (58.32% in group A and 49.05% in group B in comparison with controls) and BMDtot 46.90% and 45.15%, respectively, suggest that in the epiphyseal area an homogenously deficit pattern occurs, especially in the group of low paraplegics because the central and the peripheral of the cross-sectional area of bone were similarly affected. On the contrary, in the high paraplegic group the trabecular bone loss was higher suggesting that an increasing intracortical remodeling was responsible for keeping the total BMD similar.

The findings of our study are in line with Eser et al. regarding the decrease in BMD total and cortical thickness[13,14]. Decrease of mean cortical thickness in our population is 0.28 mm/year in SCI tibial finding first described in the previous studies of Eser et al. in paraplegic subjects[14]. Our results show the non-significant difference in periosteal circumference between both paraplegic groups and controls and the increase in endosteal circumference. Concerning cortical geometric properties, a striking abnormality was the significant increase of endosteal circumference, $p=0.054$, in the group of high and $p=0.012$ in the group of low paraplegics, whereas periosteal circumference was comparable ($p=0.45$). That led to reduction of cortical thickness 19.78% and 16.98% in the two groups, respectively.

Stress strain index polar (SSI Pol) is an important validated biomechanical strength bone parameter because it is related to bone breaking force, an explanation why people with chronic spinal cord injury are prone to bone fractures[13]. The change of the SSIPol between the two paraplegic groups versus controls was: 1) less in comparison with other bone parameters, and 2) paralleled to the deficit of cortical thickness finding which is also found by other authors[14]. Furthermore, the $\delta SSI_{3\text{-}2}$ of high paraplegics in absolute values was small and/or the difference between the paraplegic groups in tibia slices 38% and 14% of pQCT ($\delta SSI_{3\text{-}2}$) was higher in the low paraplegic group. Because of the non-significant duration of paralysis ($p=0.87$) and despite the similar paralytic effect on bone in all paraplegic patients in our study between the two groups, we needed to explore other factors influencing this result. Could this difference be a possibe result of higher incidence of standing in the group of low paraplegics and indirect effect of loading on the mechanical parameters of lower tibia? We can make only speculations. Loading is associated with ambulation and normal physical function is critical to maintaining both trabecular connectivity and bone mineral mass[22]. Moreover, it is known that dynamic mechanic stimulation is more efficacious for bone formation, since under static loads bone cells become less responsive to stimuli[23]. After the acute immobilization period, patients performed standing using various standing devices, long leg braces and a standing frame in the hospital. Standing was continued at home after discharge from the hospital. The main reason for not performing standing was mostly the unwillingness of the patient, rather than the functional level. The effect of standing and the influence of the mechanical forces were beyond the scope of this paper. It is well known that after spinal injury onset rehabilitation efforts are very strong but patients lose their faith and motives during aging in paralysis. This means that they do not follow the suggestions from the physicians and do not perform among other things standing or walking with leg braces orthoses. Low paraplegics act in their lifestyle like high paraplegics after the first years of paralysis, losing the indirect effects of loading on the mechanical parameters of the lower tibia.

An interesting question arises from this result as to why high paraplegics had a similar paralytic effect in 14% of the tibia (larger surface of trabecular compared to cortical bone), and in 38% of the tibia. This homogenous result could not be easily explained. According to the duration of paralysis the two paraplegic groups act differently in mechanical properties of the tibia ($\delta SSI_{3\text{-}2}$ was in group A: $r=-0.178$, $p=$N.S. and group B: $r=0.534$, $p=0.027$, respectively).

All paraplegics were in a chronic stage, which suggests that not only the mechanical (forces-standing), but the neurogenic factor seems to co-exist as an influential regulator in osteoporosis during the years of paralysis. The recent scientific finding[24] of a sympathetic innervation of bone tissue and its role in the regulation of bone remodeling[25], is of major interest in situations where uncoupling between osteoclasts and osteoblasts occurs. The authors believe that we need to consider paraplegic subjects as a superfast bone loser population to understand better the pathophysiology of osteoporosis in paraplegia.

Maintenance of homeostasis within the body is a function of the autonomic nervous system and is interrupted when the central nervous system (CNS) communications are interrupted. With high-level spinal cord injuries the sympathetic nervous system (SNS) is disproportionately involved when compared with the parasympathetic nervous system. In a complete high-level SCI, functioning in the isolated spinal cord below the lesion becomes independent of supraspinal control and has been termed "decentralization" of the SNS[26]. Today there is clinical evidence that the sympathetic regulation of bone does exist in humans and plays a clinically important role in diseases characterized by excessive sympa-

thetic activity[27]. SCI is a dynamic process that is related to alterations in both the central and peripheral SNS. Also, changes in the autonomic nervous system are proposed to cause attrition of SCI bone, via changes in vascular tone and flow. Sympathetic denervation in SCI may cause arteriovenous shunts and a slowdown of intraosseous blood flow, thus increasing bone resorption[3,23]. Group A patients in respect to the Neurological Level of Injury (NLoI), are susceptible to autonomic dysreflexia as a result of the disruption of the autonomic nervous system pathways. In high level paraplegia SNS dysfunction after SCI is attributable to loss of supraspinal control that occurs with disruption of spinal cord pathways. Loss of supraspinal control leads to dysregulation of those homeostatic mechanisms normally influenced by the SNS through loss of facilitation or lack of inhibition[26]. In addition, in those with SCI above thoracic level 6 (T6) appears the clinical sequelae of autonomic dysreflexia, although autonomic dysreflexia has been reported in some individuals with lesions as T8 to T10[28,29]. SCI subjects of group A (paraplegia above T7 level) in our study are associated with significant dysfunction of the sympathetic nervous system (autonomic dysreflexia) as another possible parameter for the statistically significant result[30].

Conclusion

Despite the small number of our population, by employing pQCT as a measuring methodology in paraplegic patients we are able to assess separately cortical, trabecular and various geometric properties in high risk fracture sites of the paralyzed lower extremities like the distal tibia. These results suggest that neurogenic factors are influencing geometric bone parameters and the prognostic importance of the neurological level of injury in the decrease of mechanical strength in high risk fracture sites of the paralyzed lower extremities like the distal tibia. These findings give to the clinician the possibility of a new therapeutic intervention regarding the risk of fracture in SCI patients, because pQCT is a volumetric, quantitative, non-ivasive and regional measurement.

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