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Alteration of Volumetric Bone Mineral Density Parameters in Men with Spinal Cord Injury

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Keywords

Spinal cord injury · 3D-DXA · 3D-SHAPER® · Volumetric bone mineral density · Areal bone mineral density · Trabecular bone · Cortical bone

Abstract

Spinal cord injury (SCI) induces severe losses of trabecular and cortical volumetric bone mineral density (vBMD), which cannot be discriminated with conventional dual-energy X-ray absorptiometry (DXA) analysis. The objectives were to: (i) determine the effects of SCI on areal BMD (aBMD) and vBMD determined by advanced 3D-DXA-based methods at various femoral regions and (ii) model the profiles of 3D-DXA-derived parameters with the time since injury. Eighty adult males with SCI and 25 age-matched able-bodied (AB) controls were enrolled in this study. Trabecular and cortical vBMD, cortical thickness and derived strength parameters were assessed by 3D-SHAPER® software at various femoral subregions. Individuals with SCI had significantly lower integral vBMD, trabecular vBMD, cortical vBMD, cortical thickness and derived bone strength parameters ($p < 0.001$ for all) in total proximal femur compared with AB controls. These alterations were approximately to the same degree for all three femoral subregions, and the difference between the two groups tended to be greater for cortical vBMD than trabecular vBMD. There were minor differences according to the lesion level (paraplegics vs tetraplegics) for all 3D-DXA-derived parameters. For total proximal femur, the decreasing bone parameters tended to reach a new steady state after 5.1 years for integral vBMD, 7.4 years for trabecular vBMD and 9.2 years for cortical vBMD following SCI. At proximal femur, lower vBMD (integral, cortical and trabecular) and cortical thickness resulted in low estimated bone strength in individuals with SCI. It remains to be demonstrated whether these new parameters are more closely associated with fragility fracture than aBMD.

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Introduction

Spinal cord injury induces bone loss through the acute and dramatic increase in bone resorption activity associated with almost normal bone formation during the first weeks following injury [1, 2]. Various studies using dual-energy X-ray absorptiometry (DXA), the conventional tool for measuring areal bone mineral density (aBMD, g/cm²), have demonstrated that the value decreases rapidly, with a loss of 30–40% at the femoral neck within the first 2 years after injury, followed by a new steady state [2, 3]. However, other studies have shown continuous bone loss beyond this period [4, 5]. The bone deterioration occurs exclusively below the level of injury with a maximum in regions initially subject to weight-bearing, such as hip or tibia [2].

Bone loss implies a significant weakening of skeletal integrity, which likely influences the 24- to 104-fold higher compared with the able-bodied population [6], even though their risk of trauma is reduced. The most frequent mechanisms identified for the low-energy lower extremity fractures are forced manoeuvres by the patient or a third party, falls and during transfers [7]. These fractures most commonly occur at the epiphysis or metaphysis of the distal femur or proximal tibia [7–9], where the bone loss is most severe [10, 11]. As fragility fractures result in increased healthcare costs, short-term hospitalisation, increased disability and mortality [12, 13], strategies for identifying those individuals at high risk of these fracture should be further developed. Although measurements around the knee seem to be more relevant for predictions of fracture risk in the SCI population [14], the absence of both a standardised protocol available for the DXA technique and reference values such as the T-score has limited its clinical utility.

Fragility fracture is due not only to a reduction in bone mass, but also to a specific alteration of bone geometry. However, the standard clinical DXA technique does not allow the quantification of volumetric bone density (vBMD) and bone geometry [15] and tends to underestimate bone loss due to SCI [16]. Consequently, these limitations have reduced its utility in providing detailed descriptions of the components of bone structure relevant to fracture risk [15]. Moreover, DXA does not distinguish between trabecular and cortical bone, a limitation that is particularly relevant in disuse osteoporosis due to the differences in the extent and time course of bone loss in these two components [4, 17, 18]. In addition, the percentage of bone loss (absolute change) in the trabecular bone response to disuse appears more pronounced and faster than in cortical bone [4, 17, 18]. On the other hand, peripheral quantitative computed tomography (pQCT) has unique capabilities to quantitatively assess vBMD, as well as microstructural cortical and trabecular features [19]. Assessment of these parameters may improve fracture risk prediction in both able-bodied men [20] and individuals with SCI [14]. However, although pQCT technique is widely used in research, it is still unsuitable for routine clinical use because it remains very expensive and the radiation dose delivered is relatively high (approximately 90 μ Sv) compared with DXA when scanning central sites (spine and hip) are performed [21].

To overcome this limitation, advanced DXA-based methods have been developed, such as the 3D modelling approach that evaluates vBMD and differentiates trabecular and cortical compartments at the proximal femur. The 3D-DXA-derived parameters were demonstrated to be highly correlated with equivalent measurements assessed by quantitative computed tomography (QCT) [22].

Therefore, the present study was conducted in order to (i) analyse the effect of SCI on 3D-DXA parameters by comparing values between patients and able-bodied controls and (ii) model the profiles of 3D-DXA-derived parameters according to the time since injury.

Subjects and Methods

Subjects

This study followed a cross-sectional design, and the protocol has been described in detail elsewhere [23]. Eighty individuals with SCI, having a neurological lesion exclusively due to trauma, were consecutively recruited from the Centre Mutualiste PROPARGA, a specialised spinal cord injury clinic (Montpellier, France). According to the American Spinal Injury Association Impairment Scale (ASIA), they were classified as complete (AIS A), incomplete with no motor function below the neurological level of injury (AIS B), or incomplete with incomplete motor recovery (AIS C and D). All skeletal fractures at SCI onset and post-SCI were recorded. In most cases, post-SCI fractures were reported during the anamnesis and were confirmed by radiography in our clinic or by checking the patient records. Spasticity and its location were also recorded. All individuals with SCI used a manual or electrically assisted wheelchair as their primary means of mobility. The physical activity of the patients was not recorded, but none was participating in a training program liable to modify bone components, such as functional electrical stimulation (FES) or whole-body vibration.

The individuals with SCI were compared to a control group of 25 healthy males with similar age. None of the participants had a history of a neuromuscular disease like multiple sclerosis, had an evident secondary cause of osteoporosis (i.e. osteogenesis imperfecta or known endocrine disorders associated with bone loss), presented current bone fractures, or was taking medication known to affect bone metabolism, including bisphosphonates, within the 3 years before inclusion. They had to be 18 years or older.

Study approval was obtained from the Regional Research Ethics Committee (Comite de Protection des Personnes Sud- Mediterranee IV, Montpellier, France). Participants were given oral and written information and then delivered written consent.

Methods

All participants were evaluated in a single session after an overnight fast. Height was measured with a stadiometer. Weight was determined using a weight scale with a precision of 0.1 kg. BMI was calculated as weight (kg) divided by the square of height (m).

Bone Mineral Density, Body Fat and Fat-Free Soft Tissues

DXA (Hologic QDR-4500A, Hologic, Inc., Waltham, MA) measured the aBMD (g/cm²) at specific bone sites: the anteroposterior lumbar spine (L1-L4), the dominant arm radius, and the hip. When an individual with SCI had a fracture, osteosynthesis material or heterotopic ossification, the contralateral hip and radius were assessed. All scanning and analyses were performed by the same operator to ensure consistency after following standard quality control procedures. Quality control for DXA was checked daily by scanning a lumbar spine phantom consisting of calcium hydroxyapatite embedded in a cube of thermoplastic resin (DPA/QDR-1; Hologic x-calibre anthropometric spine phantom). The least significant change (LSC) was

calculated in our Department of Nuclear Medicine (CHRU Montpellier, France) and was determined at 0.013 g/cm² for the lumbar spine and 0.018 g/cm² at the hip.

DXA -Based 3D Modelling

3D-Shaper® software (version 2.2, 3D-Shaper Medical, Spain) was used to assess the trabecular macrostructure and the cortex in 3D from DXA scans [22]. The method relies on a statistical shape and density model of the proximal femur built from a database of QCT images. The 3D statistical model is registered onto the DXA scan to obtain a 3D patient-specific model of the patient's proximal femur shape and BMD distribution. The cortical thickness and density are computed by fitting a mathematical function to the density profile computed along the normal vector at each node of the proximal femur surface mesh [24]. 3D-DXA measurements include the vBMD and bone mineral content (BMC) of the cortical, trabecular and integral (trabecular + cortical) bone compartments and the cortical thickness. The 3D-DXA measurements were performed at the total proximal femur, neck, trochanter and shaft (intertrochanteric) regions. The precise localisations of the 3D-DXA regions analysed by the software were previously described by Humbert et al. [22] and Clotet et al. [25]. The accuracy of the models and measurements provided by the 3D-DXA software algorithm was evaluated in a previous study by comparing 3D-DXA and QCT analyses [22]. As previously described in detail [25] for each region, the 3D-Shaper® software program computes the following variables to give an estimated strength of the femoral regions: (i) the bone cross-sectional area (CSA; in square centimetres), an index of resistance to axial forces; (ii) the section modulus (Z) (cubic centimetres), an index of strength in bending computed from the crosssectional moment of inertia (iii) that weights the area in the cross-section by the square of its distance from the centroid (CSMI; in cm⁴); and (iv) the buckling ratio (BR), an index of susceptibility to local cortical buckling under compressive loads. Higher values are associated with greater estimated femoral strength for CSA, Z and CSMI parameters except for BR, for which higher values estimated lower femoral strength.

Assays

Blood samples (25 ml) were collected in the morning (08h30-09h30) in sterile chilled tubes by standard venepuncture technique. The samples were allowed to clot at room temperature and were then centrifuged at 2500 rpm for 10 min at 4 °C. Concerning bone metabolism, serum samples were assayed by Cobas 6000 (Roche Diagnostic, Mannheim, Germany) for osteocalcin (OC), procollagen type I N-terminal propeptide (PINP) and type I-C telopeptide breakdown products (sCTX). The inter- and intra-assay CVs for the latter three parameters were lower than 7%.

Statistical Analysis

Characteristics are described with proportions for categorical variables and with means and standard deviations (SD) for quantitative variables. Controls were compared with paraplegic and tetraplegic subgroups, as well as with the group of all individuals with SCI (paraplegics and tetraplegics). Paraplegics were also compared with tetraplegics. Comparisons between groups were performed using Student's t-test for quantitative variables and the Chi-square or Fisher's exact test for qualitative variables. In order to quantify the effect size for each quantitative variable, we calculated Cohen's d (difference between the means of two groups divided by a pooled standard deviation), which is a standardised measure of the effect of a factor (here SCI) independent of the scale of the parameter under consideration [26]. As an

indication, a Cohen's d value of 0.2 corresponds to a small effect of the factor, a value of 0.5 to a medium effect, a value of 0.8 to a large effect, a value of 1.2 to a very large effect and a value of 2 to a huge effect [27].

We then examined the relationships between bone markers and time since injury by fitting a nonlinear segmented regression model [28]. For each bone marker, we defined two segments for which we estimated the parameters through iteration by minimising the sum of residual squares, using the NLIN procedure in SAS software. This method allowed us to identify a breakpoint or moment, at which the two segments connect, representing the time since injury when the bone markers stopped decreasing and stabilised at the plateau phase. After estimating the breakpoint, a graphic representation of bone marker evolution was achieved through monotonic B-spline regression with one knot, using the previously estimated breakpoint as the knot. All analyses were conducted using SAS Enterprise Guide software (V.7.15, SAS Institute, Cary, NC, USA). A two sided p-value of < 0.05 was considered significant.

Table 1 Clinical characteristics and biochemical profiles of individuals with spinal cord injury and able-bodied controls matched for age

Variables	Controls (n=25)	Individuals with SCI (n=80)	Cohen's d	p-values
Age, years	37.6 ± 12.0	43.0 ± 13.5	0.42	0.07
Weight, kg	75.8 ± 8.9	76.4 ± 15.2	0.04	0.85
Height, cm	177.4 ± 7.6	178.5 ± 7.2	0.15	0.51
BMI, kg/m ²	24.1 ± 2.5	24.0 ± 4.8	-0.02	0.94
Characteristics of SCI				
Duration of SCI, years	-	13.9 ± 12.1		
Paraplegia/tetraplegia (%)	-	78.8 / 21.2		
Complete injury, n (%)	-	71 (88.8)		
Spasticity, n (%)	-	52 (68.4)		
Post-SCI fracture history				
Fracture (n)	-	64		
Patients with 1 fracture, n(%)	-	20 (28.571)		
Patients with 2 fractures, n(%)	-	8 (11.429)		
Patients with 3 fractures, n (%)	-	3 (4.286)		
Post-SCI occurrence § (years) [min,max]	-	14.0 ± 13.2 [0.5;48.8]		
Fracture location				
Femur	-	21		
Tibia	-	13		
Other§	-	11		
aBMD				
Total hip ^a (g/cm ²)	1.010 ± 0.159	0.729 ± 0.213	-1.4	< .0001
Z-score total hip ^a (SD)	0.02 ± 1.04	-2.8 ± 1.4	-1.64	< .0001
Lumbar spine ^b (g/cm ²)	1.015 ± 0.195	1.063 ± 0.194	0.24	0.30
Z-score lumbar spine ^b (SD)	-0.51 ± 1.7	-0.07 ± 1.8	0.25	0.30
Radius ^c (g/cm ²)	0.636 ± 0.068	0.630 ± 0.064	-0.09	0.53
Z-score radius ^b (SD)	-0.41 ± 1.4	-0.57 ± 1.3	-0.13	0.65
Bone turnover markers				
Osteocalcin, ng/ml	26.5 ± 10.8	25.6 ± 9.5	-0.1	0.91
PINP, ng/ml	64.1 ± 21.7	78.7 ± 58.6	0.28	0.99
sCTX, ng/ml	0.5 ± 0.2	0.5 ± 0.3	-0.06	0.12

Data are presented as mean ± SD

SD standard deviation; SCI spinal cord injury; BMI body mass index; SD standard deviation; aBMD areal bone mineral density; PINP propeptide amino-terminal of type I procollagen; sCTX serum carboxy-terminal telopeptide of type I collagen

§ The post-SCI fracture occurrence is the time in years after injury when the fracture occurred. § other fractures included the following: scapula, sacrum, tarsus, ankle and pelvis

Cohen's d is a standardised measure of the effect of a factor (here SCI) independent of the scale of the parameter under consideration

Results

Subject Characteristics

Patient characteristics are shown in Table 1. There was no significant difference in mean age, weight or BMI between the healthy controls and the individuals with SCI. The time from the initial injury varied from 0.3 to 49.1 years with a median of 10.8 years. Most individuals with SCI presented a complete medullar motor lesion (AIS A or B, 88.8%); 78.8% were paraplegics and 21.2% were tetraplegics. Sixty-four post-SCI fractures were counted with a post-SCI occurrence of 14 years ranging from 0.5 to 48.8 years. Fractures were mostly observed in femoral and tibial regions.

Table 2 Comparison of 3D-DXA bone parameters between individuals with spinal cord injury and able-bodied controls matched for age

Variables	Control group (n=25)	Individuals with SCI (n=80)	Cohen's d	p-value
Total proximal femur				
Integral vBMD (mg/cm ³)	328.3 ± 63.0	235.2 ± 73.0	-1.31	<0.0001
Trabecular vBMD (mg/cm ³)	188.0 ± 53.4	135.4 ± 52.5	-1.00	<0.0001
Cortical vBMD (mg/cm ³)	838.6 ± 62.3	718.3 ± 74.5	-1.67	<0.0001
Mean cortical thickness (mm)	2.038 ± 0.181	1.686 ± 0.279	-1.36	<0.0001
Neck region				
Integral vBMD (mg/cm ³)	377.0 ± 93.1	280.6 ± 90.2	-1.06	<0.0001
Trabecular vBMD (mg/cm ³)	244.9 ± 75.8	167.6 ± 73.8	-1.04	<0.0001
Cortical vBMD (mg/cm ³)	856.6 ± 109.0	691.7 ± 105.4	-1.55	<0.0001
Mean cortical thickness (mm)	1.754 ± 0.238	1.715 ± 0.370	-0.11	0.6174
CSA, cm ²	1.34 ± 0.34	0.98 ± 0.46	-0.82	0.0006
CSMI, cm ⁴	2.10 ± 0.62	1.77 ± 1.01	-0.35	0.0303
Z, cm ³	1.07 ± 0.31	0.84 ± 0.43	-0.57	0.0138
BR,	10.15 ± 1.94	10.81 ± 2.52	-0.28	0.227
Trochanter region				
Integral vBMD (mg/cm ³)	259.5 ± 57.1	180.7 ± 65.3	-1.24	<0.0001
Trabecular vBMD (mg/cm ³)	166.2 ± 44.0	106.5 ± 46.7	-1.29	<0.0001
Cortical vBMD (mg/cm ³)	730.1 ± 99.7	564.8 ± 112.2	-1.51	<0.0001
Mean cortical thickness (mm)	2.013 ± 0.174	1.784 ± 0.279	-0.89	0.0002
CSA, cm ²	2.33 ± 0.52	1.50 ± 0.66	-1.31	<0.0001
CSMI, cm ⁴	9.10 ± 1.78	6.02 ± 3.51	-0.97	<0.0001
Z, cm ³	2.60 ± 0.50	1.67 ± 0.88	-1.16	<0.0001
BR,	16.72 ± 2.25	19.03 ± 3.67	0.69	0.0008
Shaft region				
Integral vBMD (mg/cm ³)	433.5 ± 87.5	302.3 ± 95.1	-1.41	<0.0001
Trabecular vBMD (mg/cm ³)	218.3 ± 62.7	143.0 ± 66.3	-1.15	<0.0001
Cortical vBMD (mg/cm ³)	943.2 ± 123.6	729.4 ± 131.4	-1.65	<0.0001
Mean cortical thickness (mm)	3.171 ± 0.214	2.666 ± 0.421	-1.32	<0.0001
CSA, cm ²	2.61 ± 0.37	1.87 ± 0.70	-1.17	<0.0001
CSMI, cm ⁴	4.24 ± 0.65	3.44 ± 2.40	-0.38	<0.0001
Z, cm ³	2.45 ± 0.35	1.87 ± 0.90	-0.72	<0.0001
BR,	3.06 ± 0.43	3.69 ± 0.70	0.99	<0.0001

Data are presented as mean ± SD

SD standard deviation; vBMD volumetric bone mineral density (mg/cm³); CSA bone cross-sectional area; CSMI the cross-sectional moment of inertia; Z the section modulus; BR the buckling ratio. Cohen's d is a standardised measure of the effect of a factor (here SCI) independent of the scale of the parameter under consideration

Comparison of Bone Mineral Density Between Healthy Controls and Individuals with SCI

Table 1 presents the aBMD for the two groups at various bone sites. The aBMD measurements were not available for 1 individual with SCI at the total hip, for 15 individuals at the lumbar spine and for 1 individual at the radius (Table 1). The main reasons were the presence of osteosynthesis material, osteoarthritis, vertebral fracture, heterotopic ossifications and muscle contractures. Compared with controls, individuals with SCI presented significantly ($p < 0.0001$) lower aBMD at the total hip (Cohen's $d = -1.4$), with a Z-score representing only -2.8 SD of normal values and ranging from -5.8 SD to $+1.1$ SD. Lumbar

spine and radius aBMD values in the individuals with SCI were similar to the values in healthy controls (Cohen's d 0.24 and -0.09 , respectively). No difference between the two groups was observed for bone turnover markers of bone formation or bone resorption.

Comparison of 3D-DXA Bone Parameters Between Healthy Controls and Individuals with SCI

The comparison of 3D-DXA parameters is presented in Table 2. Individuals with SCI had significantly lower 3D-DXA-derived parameters ($p < 0.001$ for all) in total proximal femur and at all femoral subregions, i.e. neck, trochanter and shaft regions, compared with healthy controls. For the total proximal femur, the Cohen's d values were -1.31 for integral vBMD, -1.00 for trabecular vBMD and -1.67 for cortical vBMD. The degree of alteration was approximately the same for all three femoral subregions. In total proximal femur and all femoral subregions, the difference between the two groups tended to be greater for cortical vBMD compared with trabecular vBMD (Cohen's d around -1.6 and -1.1 , respectively). The mean cortical thickness was also significantly lower ($p < 0.0001$) in men with SCI compared with healthy controls for total proximal femur (Cohen's $d = 1.36$) and for all femoral subregions (neck region excepted). Strength estimates (CSA, CSMI, Z) were lower and BR was higher in men with paraplegia, and tetraplegia indicated a fragility of the femur to withstand axial and compressive forces.

Bone Parameters According to the Time Since Injury

Figure 1 shows the variation of 3D-DXA-derived parameters at total proximal femur with the time since injury. The decreasing bone parameters tended to reach a new steady state after 5.1 years for integral vBMD, 7.4 years for trabecular vBMD and 9.2 for cortical vBMD, beyond which bone loss may continue but at a slower rate.

Bone Parameters According to the Lesion Level (paraplegia vs tetraplegia)

Data comparing the characteristics of men with paraplegia and men with tetraplegia are presented in Table 3. When the two subgroups were examined, the age and the time since injury were comparable, whereas weight and BMI were lower in the men with tetraplegia compared with paraplegia. All aBMD parameters were lower in individuals with tetraplegia than in those with paraplegia. When the data were compared with data from healthy controls, the reduced bone mass was regional: total hip aBMD involvement was universal in the two subgroups of men with SCI, despite being accentuated in those with tetraplegia, whereas radius aBMD involvement was only seen in association with tetraplegia. Last, lumbar spine aBMD was higher in persons with paraplegia compared with controls. Both subgroups presented similar normal values for markers of bone turnover (data not shown).

Concerning 3D parameters (Table 4), the total proximal femur of men with paraplegia and men with tetraplegia showed lower values of integral, cortical and trabecular vBMD and cortical thickness compared with healthy controls. With a few exceptions, these alterations were observed in all regions of the femur for the two SCI subgroups and were associated with significantly lower CSA, CSMI and Z and significantly higher BR in comparison with controls. Minor differences were observed according to the lesion level, mainly at the neck region, and characterised by lower trabecular vBMD, mean cortical thickness, CSA, CSMI

and Z in tetraplegics compared with paraplegics. Figure 2 shows a 3D reconstruction of the femoral cortical thickness in representative individuals with SCI (paraplegic and tetraplegic) and in controls.

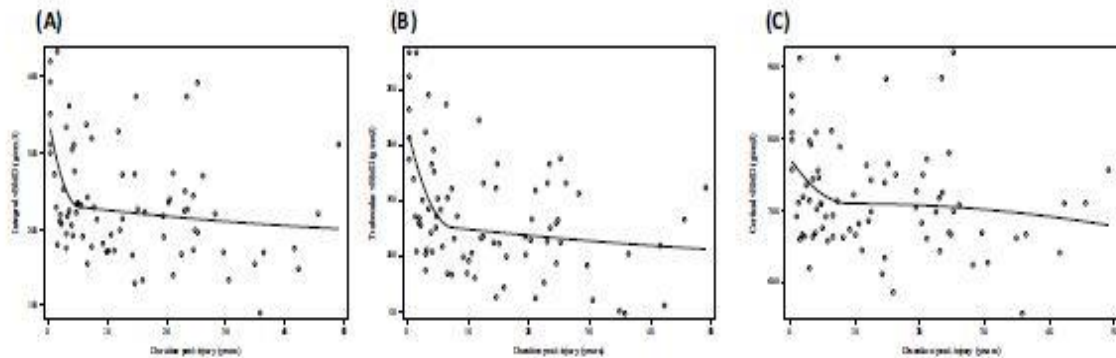


Fig. 1 Variation of integral A, trabecular B, and cortical C volumetric bone mineral density (vBMD) with the time since injury determined by 3D-DXA at the total proximal femur

Discussion

This study confirmed that SCI induces a decrease in aBMD in the sublesional area. In addition, 3D-DXA revealed a deterioration of integral, trabecular and cortical vBMD and cortical thickness at femoral regions in these patients. These findings may explain the reduction in estimated bone strength that predisposes this population to a high risk of fragility fractures.

It has been widely shown that SCI induces an extensive alteration of aBMD, mainly at weight-bearing bone sites [2, 23, 29]. Our results confirmed these findings, but additionally showed that tetraplegic patients presented a more extensive and accentuated loss of aBMD than paraplegic patients. The conventional DXA analysis used to determine the effect of SCI on bone tissue does not provide any information on the specific alteration of the trabecular and cortical bone compartments at femoral regions, although this would be useful for improving therapeutic targeting [30].

The 3D-DXA approach has been extensively used to characterize vBMD in various populations [31–33]. This study is the first to compare the vBMD between men with SCI and healthy controls. Our results demonstrated that at total proximal femur, a specific pattern of bone loss occurred after SCI, which was characterised by the concomitant deterioration of the trabecular and cortical compartments leading to a lower integral vBMD in individuals with SCI compared with controls. The lower trabecular density may be explained by a reduction in the trabecular numbers, which increases the trabecular separation associated with lower trabecular thickness [17]. It was proposed that the loss of cortical vBMD was due to an increase in cortical porosity [17] and/or a reduction in cortical thickness due to endocortical resorption [4, 34, 35].

Table 3 Clinical characteristics and biochemical profiles of individuals with spinal cord injury according to paraplegic or tetraplegic status

	Paraplegics (n=63)	Tetraplegics (n=17)	Controls (n=25)	Cohen's d P vs T	p-values P vs T	Cohen's d P vs CO	p-values P vs C	Cohen's d T vs CO	p-values T vs CO
Age, years	44.2±13.7	38.4±12.03	37.5±12.0	-0.44	0.1146	0.51	0.0337	0.07	0.7626
Weight, kg	78.7±14.4	68.0±15.4	75.8±8.7	-0.74	0.0087	0.22	0.3547	-0.66	0.0423
Height, cm	178.7±7.2	177.7±7.0	177.4±8.0	-0.13	0.6228	0.18	0.4526	0.04	0.8910
BMI, kg/m ²	24.7±4.6	21.5±4.5	24.1±2.5	-0.70	0.0124	0.15	0.5305	-0.75	0.0219
Characteristics of SCI									
Duration of SCI, years [min;max]	13.6±12.4	15.1±10.8		0.12	0.5402				
Complete injury, n (%)	54 (85.71)	17 (100)			0.0981				
Spasticity, n (%)	41 (68.3)	11 (68.8)			1				
Fracture, n	36	9			0.3196				
Fracture post-SCI occurrence § (years) [min;max]	12.2±13.5 [0.5; 48.8]	20.1±10.5 [0.3; 35.8]		0.61	0.0718				
Areal bone mineral density									
Total hip (g/cm ²)	0.761±0.188	0.612±0.261	1.010±0.159	-0.73	0.0182	-1.39	<.0001	-1.94	<.0001
Z-score total hip (SD)	-1.957±1.142	-3.006±2.014	0.024±1.039	-0.77	0.0078	-1.78	<.0001	-2.03	<.0001
Lumbar spine (g/cm ²)	1.106±0.172	0.941±0.206	1.015±0.195	-0.91	0.0020	0.5	0.0452	-0.37	0.2467
Z-score lumbar spine (SD)	0.329±1.571	-1.206±1.952	-0.508±1.695	-0.92	0.0019	0.52	0.0390	-0.39	0.2251
Radius (g/cm ²)	0.641±0.058	0.587±0.067	0.636±0.068	-0.90	0.0016	0.08	0.9525	-0.73	0.0291
Z-score radius (SD)	-0.372±1.020	-1.367±1.241	-0.412±1.434	-0.93	0.0037	0.03	0.8355	-0.7	0.0388

Data are presented as mean±SD.

SD standard deviation; SCI spinal cord injury; BMI body mass index; SD standard deviation; aBMD areal bone mineral density; P paraplegics; T tetraplegics; CO controls. Cohen's d is a standardised measure of the effect of a factor (here SCI) independent of the scale of the parameter under consideration

Table 4 (continued)

	Paraplegics (n=63)	Tetraplegics (n=17)	Controls (n=25)	Cohen's d P vs T	p-values P vs T	Cohen's d P vs CO	p-values P vs CO	Cohen's d T vs CO	p-values Tetra vs Con
Cortical vBMD (mg/cm ³)	559.4±91.9	584.6±169.3	730.1±99.7	0.22	0.8966	-1.81	<0.0001	-1.1	0.0011
Mean cortical thickness (mm)	1.815±0.273	1.672±0.281	2.013±0.174	-0.52	0.0617	-0.8	0.0012	-1.53	<.00001
CSA, cm ²	1.577±0.654	1.226±0.611	2.325±0.517	-0.54	0.0658	-1.21	<0.0001	-1.97	<0.0001
CSMI, cm ²	6.461±3.607	4.432±2.635	9.101±1.782	-0.59	0.0091	-0.83	<0.0001	-2.16	<0.0001
Z, cm ³	1.768±0.895	1.300±0.724	2.604±0.501	-0.54	0.0360	-1.04	<0.0001	-2.17	<0.0001
BR	18.895±3.007	19.521±5.44	16.720±2.251	0.17	0.8408	0.77	0.0004	0.73	0.1044
Shaft region									
Integral vBMD (mg/cm ³)	298.1±81.9	317.9±134.9	433.5±87.4	0.21	0.9435	-1.62	<.0001	-1.06	0.0016
Tra-becular vBMD (mg/cm ³)	143.6±63.3	141.2±78.5	218.3±62.7	-0.04	0.7229	-1.18	<.0001	-1.11	0.0011
Cortical vBMD (mg/cm ³)	723.7±113.3	750.6±186.0	943.2±123.6	0.2	0.8316	-1.89	<.0001	-1.27	0.0002
Mean cortical thickness (mm)	2.699±0.396	2.543±0.497	3.171±0.214	-0.37	0.2859	-1.33	<.0001	-1.77	<.0001
CSA, cm ²	1.918±0.722	1.669±0.579	2.607±0.368	-0.36	0.1893	-1.07	<0.0001	-2.03	<0.0001
CSMI, cm ²	3.662±2.559	2.601±1.324	4.244±0.653	-0.45	0.0253	-0.27	0.0003	-1.70	<0.0001
Z, cm ³	1.961±0.935	1.525±0.687	2.448±0.347	-0.49	0.0765	-0.6	<0.0001	-1.82	<0.0001
BR	3.701±0.643	3.654±0.899	3.055±0.434	-0.07	0.4935	1.09	<0.0001	0.92	0.0154

Data are presented as mean ± SD

SD standard deviation; vBMD volumetric bone mineral density (mg/cm³); CSA bone cross-sectional area; CSMI the cross-sectional moment of inertia; Z the section modulus; BR the buckling ratio P paraplegics; T tetraplegics; CO controls. Cohen's d is a standardised measure of the effect of a factor independent of the scale of the parameter under consideration

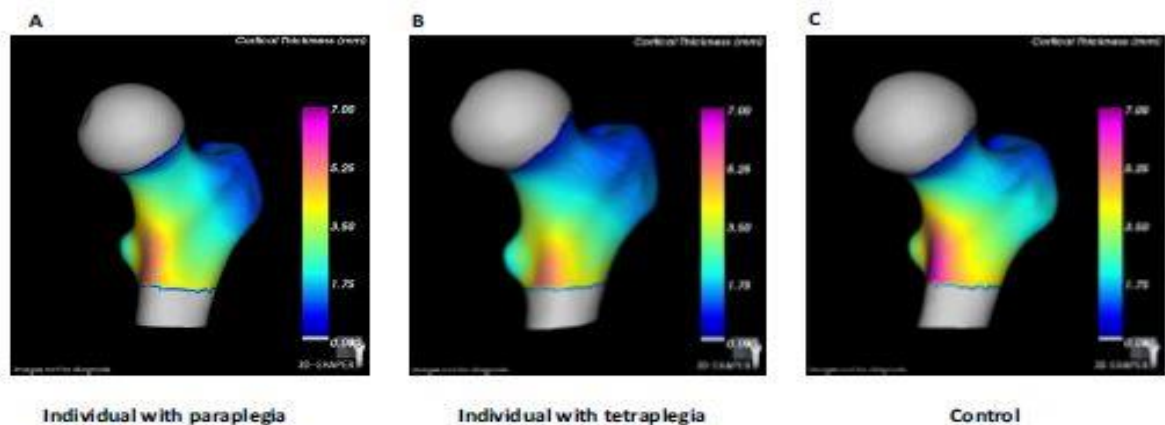


Fig. 2 Examples of a 3D reconstruction of DXA scans of the femoral cortical thickness in two representative individuals with spinal cord injury (**A**: individual with paraplegia; Age: 41.4 years;

12.5 years postinjury and **B**: individual with tetraplegia; Age: 45 years; 19.5 years postinjury) and from a control subjects (**C**: Age: 41.7 years)

Nevertheless, when we analysed our data in greater detail we found that, although a large effect size was observed for the two compartments (Cohen's $d > 1.2$) [27], cortical bone tended to be more affected by SCI (Cohen's $d = -1.67$) than trabecular bone (Cohen's $d = -1.00$) for total proximal femur. Interestingly, the magnitude differences for the two compartments between controls and individuals with SCI tended to be homogeneous for the three femoral subregions. Cortical thickness was also found to be significantly lower in SCI at the total hip, trochanter and shaft. At the neck, although lower in SCI (1.715 mm vs 1.754 mm in controls), the difference was not statistically significant. This could be explained by larger measurement errors at the neck, where the cortex is very thin, compared with other regions such as the shaft or the trochanter [22]. Consequently, the neurological lesion seems to have a similar detrimental effect along its proximal length. The concomitant alterations of trabecular and cortical bone density and geometry parameters (i.e. cortical thickness) may explain the estimated reduction in bone strength regarding axial and compressive forces, as indicated by the decrease in CSA, CSMI and the section modulus and the increase in the buckling ratio. The reduction in femoral bone strength that was previously reported [4, 36] may explain why fracture risk increases in this population. These findings strongly suggest that anti-resorptive treatments such as bisphosphonates should be proposed to prevent the rapid bone loss in the first months after injury [37].

To our knowledge, only Gifre et al. [38] investigated the effect of SCI in a small group of 16 males using a similar method [38]. In the first-year post-neurological injury, a decrease in trabecular (22%) and cortical (5%) vBMD, associated with a significant decrease in cortical thickness (11%), was reported. However, it is likely that the real bone loss was underestimated because the first measure was performed 93 ± 25 days after injury, which meant that the initial acute bone loss was not taken into account [1, 2, 39]. In addition, the lack of a control group makes it difficult to precisely determine the real impact of SCI on the 3D-Shaper® parameters. Although we should keep in mind that it is difficult to merge our results with those of Gifre et al. [38] due to the differences in the DXA device used and the population studied, the 3D-derived parameters were systematically lower in our chronic population. These results suggest that bone loss continues beyond the 1st year and can be identified with this method. However, it is difficult to precisely define the time course of bone loss in individuals with SCI because several studies have reported an early intense loss with stabilisation of bone mass at about 2 years [2, 3], whereas still others have suggested that bone mass continues to decline throughout the chronic phase [4, 5]. Part of this divergence may be attributed to (i) whether the study design was cross-sectional or longitudinal and whether inter-individual variations were taken into account, and (ii) the parameters evaluated by different techniques (DXA vs pQCT or HR-pQCT). Our modelling approach, which characterised the variation of integral and trabecular bone in terms of time since injury, demonstrated that new steady states tended to be reached at 5.1 and 7.3 years, respectively, and further showed a delay for cortical vBMD at 9.2 years since injury. The bone biochemical markers found within the reference values also corroborated the finding of no additional or limited bone loss in our individuals with SCI (mean time since injury: 14 years). In line with our results, Eser et al. [4] conducted a cross-sectional study in a comparable population of SCI (men with a mean 12 years since injury) and reported that bone geometry and BMD reached new steady states at values ranging from 25 to 75% lower than the values of the reference group within 3 to 8 years after onset of SCI. The time scale depended on the bone parameters and the measured site (femur or tibia) [4]. The same team later confirmed these findings with a longitudinal study [40].

In our study, we sought to determine whether the lesion level had an effect on the 3D parameters. Although our two subgroups of individuals with SCI presented similar characteristics in terms of age and time since injury, the tetraplegic individuals tended to present accentuated lower 3D-DXA derived parameters than the paraplegic subgroup, which confirmed some previous results [17, 41], but not all [36].

As above-mentioned, the data are very limited on the effects of SCI on cortical and trabecular compartments assessed by the same 3D-DXA method. We therefore attempted to draw a parallel with data obtained using pQCT or HR-pQCT, the gold standard technique for bone microstructural analysis. Nevertheless, due to technical constraints, only the distal or shaft regions of the tibia and femur can be analysed with these devices. This might constitute a greater bias, most likely because the proximal tibial region is more affected by loss, as estimated by aBMD or vBMD, than the femoral region following SCI [10, 11, 42]. Using pQCT, McCarthy et al. [43] investigated the proximal tibia of nine males with time since injury > 24 months (mean 77.1 ± 33.4 months) and found a reduction of almost 40% in trabecular BMD compared with in controls, while there were small but significant differences (~ 6%) in the cortical BMD only at the anterior aspect of the tibia. Interestingly, individuals with acute SCI (time since injury < 6 months) did not present significant alteration of either the trabecular or cortical compartment [43]. Ghasem-Zadeh et al. [17] recently used HR-pQCT and reported lower values of total (ranging from - 36.6 to - 30% for tetraplegics and paraplegics, respectively), cortical (- 16% and - 18%, respectively) and trabecular (- 42% and - 52%, respectively) vBMD at distal tibia in men with SCI and a mean 6.5 years since injury compared with healthy controls. In line with these findings, we calculated the percentage difference between controls and individuals with SCI (data not shown) and also observed a reduction of the same order of magnitude for total proximal femur (- 28.4% for total vBMD, - 14.3% for cortical vBMD and - 28% for trabecular vBMD). As expected, the vBMD loss observed in our population was more pronounced than during the 1st year after injury for cortical (2.5–7%) and trabecular (15–20%) components [36, 42] evaluated by pQCT at tibia or femur. The concordance between our and these previous results obtained with the reference techniques suggests the potential utility of 3D-DXA for accurate follow-up of bone status in populations with SCI. However, we must note that, although the decrease in trabecular vBMD seems to be unanimously observed [4, 17, 34–36, 42, 43], as is the reduction in cortical thickness [4, 34, 35], some studies have shown a relatively stable cortical vBMD after the injury [4, 34, 35, 42, 43].

Our study presents some limitations that should be noted. Its cross-sectional design did not allow us to follow the variation of 3D-DXA parameters in the same subjects over a long period, thus introducing inter-individual variability. However, the inclusion of patients with a wide range of times since injury and similar disease is the only method that can be used to assess the long-term consequences of SCI. Moreover, given the difficulties of recruiting from the SCI population [34], the constitution of a large group of individuals with SCI, as well as an age-matched uninjured control group to limit the effect of age-related bone loss, may be considered a notable strength of our study. In fact, it is probable that the bone loss was independent of age because bone structure is already adapted to minimal mechanical loading and no further reduction in mechanical loading due to ageing occurs in this population [40]. Finally, despite the evidence that hip aBMD is associated with fragility fractures [14], it will be necessary to determine whether the vBMD measured at the femoral proximal region is a predictive parameter of the fragility fractures that occur mostly in the distal femur and the tibial epiphyses [8, 44]. This would likely improve the medical care of patients because

measurement in the hip region is the standard procedure and not all clinical centres have standardised protocols for measuring aBMD around the knee [14].

In summary, this study showed that SCI induces a loss of vBMD for both cortical and trabecular compartments and a decrease in cortical thickness, resulting in low estimated bone strength. A new bone steady state tended to be reached between 5 and 9 years after SCI, and bone loss intensity tended to be higher in tetraplegics than in paraplegics. The close results obtained with 3D-DXA and those previously reported with the reference techniques (pQCT and HR-pQCT) suggest that this new approach may be useful in the SCI population to follow bone loss. Nevertheless, it remains to be demonstrated whether vBMD parameters are more sensitive than aBMD to discriminate between individuals with SCI at high or low risk of a fracture.

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Author Contributions

LM and DM-G contributed to conceptualisation. LM, CS and TM contributed to methodology. LM, LH, CS and TM contributed to software. LM, CS and TM contributed to validation. CS and TM contributed to formal analysis. LM, AG, VB, CF and DM-G contributed to investigation. LM, AG, PdS-B, CF contributed to resources. LM, CS and TM contributed to data curation. LM, DM-G contributed to writing—original draft. LM, AG, CS, TM, LH, VB, PdS-B, DL, CF and DM-G writing—review & editing. LM, CS and TM contributed to visualisation. LM, AG, CF and DM-G contributed to supervision. LM, AG, CF and DM-G contributed to project administration.

Declarations

Conflict of interest I certify that neither I (Laurent Maimoun) nor my co-authors (Anthony Gelis, Chris Serrand, Thibault Mura, Vincent Boudousq, Pascal de Santa-Barbara, Didier Laux, Charles Fattal, Denis Mariano-Goulart) have a conflict of interest that is relevant to the subject matter or materials included in this work. Ludovic Humbert is an employee and shareholder of 3D-Shaper Medical.

Human Rights and Informed Consent

Approval was obtained from Regional Research Ethics Committee (Comite de Protection des Personnes Sud-Mediterranee IV, Montpellier, France). All procedures used adhere to the tenets of the Declaration of Helsinki. Participants were given oral and written information and then delivered written informed consent.

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