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REVIEW

Osteoporosis after spinal cord injury

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Abstract Osteoporosis is a known consequence of spinal cord injury (SCI) and occurs in almost every SCI patient. It manifests itself as an increase in the incidence of lower extremity fractures. The pattern of bone loss seen in SCI patients is different from that usually encountered with endocrine disorders and disuse osteoporosis. In general, there is no demineralization in supralesional areas following SCI. Several factors appear to have a major influence on bone mass in SCI individuals, such as the degree of the injury, muscle spasticity, age, sex and duration after injury. At the lumbar spine, bone demineralization remains relatively low compared to that of the long bones in the sublesional area. A new steady state level between bone resorption and formation is reestablished about 2 years after SCI. SCI may not only cause bone loss, but also alter bone structure and microstructure. Trabecular bone is more affected than cortical bone in the SCI population. Numerous clinical series have reported a high incidence ranging from 1 to 34% of lower extremity fractures in SCI patients. The pathogenesis of osteoporosis after SCI remains complex and perplexing. Disuse may play an important role in the pathogenesis of osteoporosis, but neural factors also appear to be important. SCI also leads to impaired calcium and phosphate metabolism and the parathyroid hormone (PTH)-vitamin D axis. Pharmacologic intervention for osteoporosis after SCI includes calcium, phosphate, vitamin D, calcitonin and biphosphonates. However, the concomitant prescription of bone-active drugs for the prevention and treatment of osteoporosis remains low, despite the availability of effective therapies. Functional stimulated exercises may contribute to the prevention of bone loss to some extent. In addition, many unanswered questions remain about the pathogenesis of osteoporosis and its clinical management.

Keywords Bone mineral density · Osteoporosis · Paraplegia · Spinal cord injuries

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Introduction

Osteoporosis, a condition characterized by low bone mass and deterioration of the skeletal microarchitecture, is a known consequence of spinal cord injury (SCI). The significance of osteoporosis after SCI is that it results in skeletal fragility and an increased risk of fractures. Complications from fractures lead to an increase not only in the associated morbidity and mortality, but also in the health care costs that they generate. The pattern of bone loss seen in SCI patients is different from that in osteoporosis, which occurs as a result of other etiologies such as endocrine diseases, nutritional disorders and drug-related factors. In this paper, the clinical data, pathophysiology and treatment of osteoporosis after SCI are reviewed.

Clinical evidence

SCI and BMD

SCI induces bone loss, thereby increasing the fracture risk. A decline in bone mineral density (BMD) and bone mineral content (BMC) has been detected radiologically in the paralyzed limbs of patients as early as 6 weeks after SCI [1], and the dramatic reduction in BMD or BMC has been amply documented in chronic SCI patients [2, 3, 4, 5, 6, 7]. Osteoporosis generally involves the pelvis and lower extremities in persons with paraplegia, whereas bone loss is also noted in the upper extremities in tetraplegic patients in addition to the pelvis and lower

extremities [8, 9]. SCI patients display a specific form of demineralization typified by an exclusively sublesional topography in which the head of tetraplegics (impairment of the arms, trunk and legs) and the upper limbs of paraplegics (lower body segment paralysis) are preserved. In SCI patients, the demineralization predominates on the long bones of the lower limbs. The most affected sites are the trabecular metaphysical-epiphyseal areas of the distal femur and the proximal tibia. In a cross-sectional study of 31 SCI patients more than 1 year after injury, Dauty et al. [10] demonstrated a significant demineralization at the distal femur (−52%) and the proximal tibia (−70%), respectively, and this is in accordance with the findings of Biering-Sorensen et al. [11] and Finsen et al. [12]. SCI always results in substantial and rapid bone loss. A longitudinal study of 15 acute SCI patients revealed that BMD in the calcaneus and proximal tibia was decreased by 7.5 and 5.3% in 6 weeks after injury, respectively [6]. Cancellous bone is more affected than cortical bone after SCI. In a prospective study, six acute tetraplegics were followed up for 12 months, and the trabecular and cortical BMDs of

Table 1 Sublesional bone mineral density in spinal cord-injured patients

Author	Type of study	Duration after injury	Males	Females	Age	Skeletal site measured	BMD (Z-score, SD or % loss or reduction of BMD)
Bauman et al. [26]	Prospective	3–26 years	8		25–58 years	Lower limb	−35%
						Pelvis	−29%
Biering et al. [11]	Prospective	9 days–53 months	8			Femoral neck	−30∼40%
						Distal femur	−48%
						Proximal tibia	−45%
						Femur diaphysis	−25%
						Tibia diaphysis	−25%
Clasey et al. [24]	X-sectional	0.6–35.3 years	21	8	23–56 years	Lower extremity	−28.20%
Dauty et al. [10]	X-sectional	>1 years	31		18–60 years	Femoral neck	−30%
						Femoral trochanter	−39%
						Distal femur	−70%
						Proximal tibia	−52%
de Bruin et al. [31]	Prospective	3.5 years	9	1	19–81 years	Distal tiabial trabecular bone	−40%
						Distal tiabial compact bone	−11%
Demirel et al. [16]	X-sectional	2–30 months	32	9	19–49 years	Lower extremity	−2.19 ± 3.5 SD
Finsen et al. [12]	X-sectional	7 months–33 years	19		15–64 years	Tibia distal diaphysis	−26%
						Tibia distal metaphysic	−45%
Frey-Rindova et al. [13]	Prospective	12 months	27	3	19–59 years	Tibia trabecular bone	−15%
						Tibia cortical bone	−7%
Garland et al. [32]	Prospective		6			Distal femur	−27%
						Proximal tibia	−32%
						Os calcis	−38%
Garland et al. [8]	X-sectional	2–8 years		6	20–30 years	Knee	−37.90%
						Hip	−17.50%
		3–30 years		16	31–50 years	Knee	−41.30%
						Hip	−25%
		9–44 years		9	53–77 years	Knee	−47%
						Hip	−25.50%
Jones et al. [33]	X-sectional	7–372 months	20 (total)		17–52 years	Femur	−27%
						Hip	−37%
Kiratli et al. [25]	X-sectional	0.1–51 years	239	7	27–78 years	Femoral neck	−27%
						Femoral midshaft	−25%
						Distal femur	−43%
Sabo et al. [4]	X-sectional	1–26 years	46		<50 years	Proximal femur	−24.50%
Uebelhart et al. [34]	Prospective	>6 months	6			Lower extremity	−6.40%
Warden et al. [6]	Prospective	1–6 months	15		19–40 years	Calcaneus	−7.5 ± 3.0%
						Proximal tibia	−5.3 ± 4.2%
Zehnder et al. [35]	X-sectional		100		18–60 years		
		<1 year	16			Femoral neck	−0.03 ± 0.25 SD
		<1 year	16			Tibia epiphysis	−0.34 ± 0.22 SD
		1–9 years	38			Femoral neck	−1.65 ± 0.17 SD
		1–9 years	38			Tibia epiphysis	−3.81 ± 0.13 SD
		10–19 years	31			Femoral neck	−1.76 ± 0.25 SD
		10–19 years	31			Tibia epiphysis	−4.00 ± 0.21 SD
		20–29 years	13			Femoral neck	−1.76 ± 0.28 SD
		20–29 years	13			Tibia epiphysis	−4.12 ± 0.24SD

the tibia were found to be decreased by 15 and 7% [13]. Similarly, in another cross-sectional study of eight SCI patients, a change of 35.3% in BMD of the tibial trabecular bone occurred within the first 2 years after SCI, whereas there was only a 12.9% reduction in tibial cortical bone [14]. Before an equilibrium is reestablished between bone resorption and formation, bone loss seems to progress. Bone loss in the proximal tibia of acute SCI patients is about 5.3–15%, whereas in chronic SCI patients a range of 15 to 52% was reported [6, 10, 11, 13].

Several factors appear to have an influence on bone mass in SCI individuals. The level of the lesion and thus the extent of impairment of motor and sensory function may be taken into account first, because tetraplegics are more likely to lose more bone mass throughout the skeleton than paraplegics [9, 10, 15, 16] (Table 1, Table 2). However, the similar severity of demineralization in the sublesional area was shown between paraplegics and tetraplegics, and the extent of the bone loss may be variable [10, 13, 15]. In addition, bone mass loss may be more severe in SCI individuals with complete lesions (an absence of sensory or motor function below the neurological level, including the lowest sacral segment) than in those with incomplete lesions (partial preservation of motor and/or sensory function below the neurological level, including the lowest sacral segment) [4, 9, 15, 17]. In a cross-sectional study of 11 patients with complete SCI and 30 patients with incomplete SCI, Demirel et al. [15] noticed a significant difference in BMD between the two groups of SCI patients. Osteopenia was more apparent when defined as a decreased Z-score (-2.29 ± 0.51 versus 0.12 ± 0.22) in patients with complete SCI than in patients with incomplete SCI ($P < 0.05$). In another cross-sectional study of 46 male SCI patients, BMD in the lumbar spine of patients with complete lesions was significantly lower than that of patients with incomplete lesions (Z-score, -1.47 ± 0.55 versus 0.02 ± 0.58).

Muscular loading of the bones has been thought to play a role in the maintenance of bone density. Controversial results have been reported regarding the effect of muscle spasms on BMD in SCI patients. The decrease in BMD was less in the spastic SCI patients than in the flaccid SCI patients (Z-score, 0.078 ± 0.62 versus -0.118 ± 0.46, $P < 0.05$) in a cross-sectional study of 41 SCI patients [15]. This result is consistent with the finding of Eser et al. [18]. Thus, it was concluded that spasticity may be protective against bone loss in SCI patients. But other investigators have not been able to establish a correlation between BMD and muscle spasticity [2, 11, 14, 19, 20, 21].

The duration of injury has also been shown to affect the degree of bone loss in the sublesional areas [11, 22]. Clasey et al. [23] noted that there were significant inverse relationships between duration after injury with leg percentage-matched BMD ($r^2 = -0.76$, $P < 0.01$) and trunk percentage-matched BMD ($r^2 = -0.38$, $P < 0.05$). Also, the duration of acute post-traumatic immobilization increased the loss of bone mass in the lower limbs, particularly in the proximal tibia [10].

Aging is considered to be another contributing factor to bone loss in complete SCI patients. In a cross-sectional case control study of 31 complete SCI women 2 to 44 years after injury, Garland et al. [8] stratified the patients into three groups according to their age: the youngest, middle, and oldest. The reduction of BMD in

Table 2 Superlesional bone mineral density in spinal cord-injured patients

Author	Type of study	Duration after injury	Males	Females	Age	Skeletal site measured	BMD (Z-score, SD or % loss or reduction of BMD)
Clasey et al. [24]	X-sectional	0.6–35.3 years	21	8	23–56 years	Upper extremity	+11.10%
Dauty et al. [10]	X-sectional	>1 year	20		18–60 years	Upper extremity	+6%
de Bruin et al. [31]	Prospective	3.5 years	9	1	19–81 years	Distal radius trabecular bone	−10∼+14%
Demirel et al. [16]	X-sectional	2–30 months	32	9	19–49 years	Upper extremity	+0.09 ± 0.15 SD
Finsen et al. [12]	X-sectional	7 months-33 years	19		15–64 years	Forearm distal diaphysis	−5%
						Forearm distal metaphysis	−13%
Frey-Rindova et al. [13]	Prospective	12 months	27	2	19–59 years	Radius trabecular bone	−8%
						Radius cortical bone	0%
						Ulna trabecular bone	−4%
						Ulna cortical bone	−1%
Sabo et al. [4]	X-sectional	1–26 years	46		<50 years	Distal forearm	−6.10%
Zehnder et al. [35]	X-sectional		100		18–60 years		
		<1 year	16			Ultradistal radius	+0.02 ± 0.24 SD
		<1 year	16			Radius shaft 1/3	+0.00 ± 0.41 SD
		1–9 years	38			Ultradistal radius	+0.01 ± 0.15 SD
		1–9 years	38			Radius shaft 1/3	+0.40 ± 0.17 SD
		10–19 years	31			Ultradistal radius	+0.52 ± 0.20 SD
		10–19 years	31			Radius shaft 1/3	+0.97 ± 0.20 SD
		20–29 years	13			Ultradistal radius	+0.44 ± 0.32 SD
		20–29 years	13			Radius shaft 1/3	+0.27 ± 0.31 SD

the knee in the youngest, middle and oldest SCI groups was 38, 41 and 47% compared with that in the corresponding control age groups. Also, the mean reduction of BMD in the hips of the youngest, middle and oldest SCI groups was 18, 25 and 25% compared with the densities in the control subjects in the respective age groups. Furthermore, the oldest injured group had a mean reduction of knee BMD of 54% compared with the youngest control group. Similarly, moderate correlation between age and femoral BMD was observed in a cross-sectional study of 30 patients with SCI of 1-year duration or less [24]. Bauman et al. [25] reported that bone loss in eight pairs of identical male twins with SCI of a duration ranging from 3 to 26 years appeared to be independent of age, and this is consistent with the finding of Wood et al. [26]. Initial bone loss in the knee of an injured woman is approximately 5 to 10% greater than that in injured men [8, 9]. Demirel et al. [15] found no correlation between the age and sex of the patients and BMD when they measured BMD in 41 SCI patients at 2 to 30 months post injury The authors believed the results could be explained by the youth of their patients or the premenopausal status of their female patients.

Unlike the situation in able-bodied women, body weight does not influence BMD in the proximal part of the femur in SCI patients [8]. The ability to stand or ambulate itself does not improve BMD and does not prevent osteoporosis after SCI, although exercise increases site-specific osteogenesis in able-bodied individuals [4, 27]. There was only one study demonstrating that standing might reduce the loss of trabecular bone after SCI. In this prospective study of 19 acute SCI patients, the patients involved in early loading intervention exercise lost almost no bone mineral, whereas the immobilization patients lost 6.9 to 9.4% of trabecular bone [28]. Increased intramedullary fluid pressure providing a stimulus for bone maintenance may be the underlying mechanism [29].

Is there a time after injury where bone loss ceases? Some authors reported that approximately 2 years after SCI, a new steady state level between bone resorption and formation would be reestablished [1, 11], whereas de Bruin et al. [30] found that there was no sign of a new steady state in bone formation in the lower extremities 2 years after the SCI. Whether a new steady state of bone remodeling is reestablished after SCI still remains controversial.

There is no demineralization of the upper limbs in paraplegics. On the contrary, a minor increase of BMD (6%) in the humerus was reported in a cross-sectional study of 31 male chronic paraplegics 1 year post injury [10]. With reliance on the upper limbs to provide movement for activities of daily living in the SCI population, this area could be subjected to greater site-specific loading, and thus increasing osteogenesis, than in the corresponding able-bodied population.

At the lower third of the femur and the upper third of the tibia, the bone demineralization is considerable (about a 24.5 to 70% reduction in BMD [4, 8, 12, 31, 32]), whereas at the lumbar spine, the trabecular bone demineralization remains relatively low compared to the cortical bone demineralization of long bones [10]. Normal [1, 2, 27] or even higher than normal [9, 27, 35, 36] values of BMD in the lumbar spine have been reported (Table 3). This phenomenon is named dissociated hip and spine demineralization [25, 37]. Most authors admit that bone mass in the vertebral column is generally spared because of its continued weight-bearing function in paraplegics, but there is no correlation between the daily duration of sitting and BMD in the lumbar spine [10]. In a cross-sectional study of 135 SCI men, BMD in the lumbar spine was found to be stable with an insignificant decline in the tetraplegic population at 1 ± 5 years post injury in the 20–39-year age group, whereas in the 40-59-year age group and the 60 + -year age group, bone mass in the lumbar spine remained unchanged or even increased with age [38]. However, Liu et al. [39] investigated BMD in the lumbar spine of 64 patients with longstanding SCI using quantitative computed tomography (QCT) and demonstrated osteoporosis (Z-score, -2.0 ± 1.2,) in the spine of these patients, whereas DXA lumbar spine BMD for the same population showed an opposite result (Z-score, 1.3 ± 2.3). These discrepancies might be explained by the

Table 3 Bone mineral density of lumbar spine in spinal cord-injured patients

Author	Type of study	Duration after injury	Males	Females	Age	BMD (Z-score, SD or % increase or reduction of BMD)
Clasey et al. [24]	X-sectional	0.6–35.3 years	21	8	23–56 years	2%
Dauty et al. [10]	X-sectional	> 1 year	31		18–60 years	−11%
Garland et al. [8]	X-sectional	2–8 years		6	20–30 years	2%
		3–30 years		16	31–50 years	8.10%
		9–44 years		9	53–77 years	14.80%
Liu et al. [40]	X-sectional		64		20–98 years	−2.0 ± 1.2 SD
Sabo et al. [4]	X-sectional	1–26 years	46		< 50 years	−3.80%
Zehnder et al. [35]	X-sectional		100		18–60 years	
		< 1 year	16			−0.43 ± 0.19 SD
		1–9 years	38			+ 0.11 ± 0.15 SD
		10–19 years	31			+ 1.09 ± 0.23 SD
		20–29 years	13			+ 1.00 ± 0.42 SD

difficulties of analysis of the lumbar spine BMD in SCI patients. Several factors may affect the results of BMD measurement: lumbar spine arthrosis, bone callus, vertebral fracture, aortic calcification, osteosynthesis material, etc. Among them, degenerative changes in the spine may be the most possible reason to give falsely higher values of BMD [10]. This raises some questions: does SCI accelerate the development of degenerative spine joint disease? If BMD is falsely increased, why don't we see osteoporotic vertebral fractures in SCI patients to the extent it occurs in post-menopausal osteoporotic women or senile osteoporotic men? Does degenerative spine joint disease provide stability, thus preventing osteoporotic vertebral fractures? These questions still remain unresolved.

SCI and bone structure and microarchitecture

SCI may not only cause bone loss, but also alter the bone structure and microarchitecture. Trabecular bone is more deteriorated than cortical bone in SCI patients. Minaire et al. [40] showed a 33% decrease in iliac crest trabecular bone volume in a cross-sectional case control study at 25 weeks post injury. Modlesky et al. [41] reported that men with long-term (more than 2 years post injury) complete SCI ($n = 10$) had markedly deteriorated trabecular bone microarchitecture in the knee, which might contribute to their increased fracture incidence (Table 4). The deterioration of sublesional trabecular bone in SCI patients is more significant than in patients with other forms of osteoporosis, such as postmenopausal osteoporosis. Middle-aged postmenopausal, ambulatory women not taking estrogen or medications that affect bone did not show the deteriorated trabeculae that were evident in women with SCI [42]. Interaction on bone loss between SCI and an estrogen deficit may exist in postmenopausal women with SCI. Slade et al. [42] investigated the trabecular bone microarchitecture of the knee in a cross-sectional study of 20 pre- and postmenopausal women with complete SCI at more than 2 years post injury and found that postmenopausal women with SCI had 34% greater trabecular spacing in the tibia than the 40-year-old premenopausal women with SCI. The deterioration of trabecular connectivity may be, to some extent, independent of bone mineral loss. This notion is supported by a recent study by Warden et al. [6] in which changes in the speed of sound and broadband ultrasound attenuation of the calcaneus were not correlated with changes of BMD in the calcaneus or proximal tibia in SCI patients.

SCI and fractures

Osteoporosis has moved from a disease of fractures to a disease of fracture risks [43, 44, 45]. An inverse relationship exists between BMD and fracture risk. It has been shown that BMD is a significant predicator of an increased frequency of fractures in patients with SCI when age, the duration after SCI and level of SCI were simultaneously considered [5].

Numerous clinical series have reported a high incidence ranging from 1 to 34% of lower extremity fractures in SCI patients [46, 47, 48, 49, 50]. Vestergaard et al. [49] showed that, in a cross-sectional case control study of 438 SCI patients and 654 normal controls, fractures were more frequent in female patients ($P = 0.008$) and in male patients with a family history of fractures ($P = 0.004$) than in controls. It was demonstrated that the completeness of injury dictates and overrides most modifiable and nonmodifiable risk factors for bone loss at the knee leading to pathologic fractures in a cross-sectional study of 152 chronic SCI patients by logistic regression [17]. Patients with complete SCI have a lower BMD than those with incomplete lesions. In a cross-sectional study of 46 male SCI patients, it was demonstrated that the fracture threshold is exceeded at the proximal femur (−2.41), reflecting the high fracture rate in patients with complete lesions [4].

The absence of published reports of vertebral compression fractures suggests that they are rare in SCI-related osteoporosis in contrast to their frequency in other forms of osteoporosis. Trauma plays a relatively minor role in SCI-related fractures as most of them occur following minimal or no injury [47]. Comarr et al. [48] believed that supracondylar fractures of the distal femur were so characteristic of this population that they were labeled the "the paraplegic fracture." This predilection is explained by studies that show sites adjacent to

Table 4 Fracture incidence in spinal cord-injured patients

Author	Type of study	Duration after injury	Males	Females	Age	Fracture incidence
Comarr et al. [49]	X-sectional		1,363 (total)			11%
Frisbie et al. [51]	X-sectional	21.1 ± 12.1 years	120		20–79 years	33%
Ingram et al. [48]	X-sectional	> 1 years	526 (total)		13–70 years	5%
Lazo et al. [5]	X-sectional	1.1–43.1 years	49		27–83 years	34%
Ragnarsson et al. [47]	X-sectional	9 years (mean)	578 (total)		4–71 years	4%
Vestergaard et al. [50]	X-sectional		309	129	17–80 years	2%/year
Zehnder et al. [35]	X-sectional		100		18–60 years	
		< 1 year	16			1%/year
		1–9 years	38			1.3%/year
		10–19 years	31			3.4%/year
		20–29 years	13			4.6%/year

the knee (such as the proximal tibia) are more severely affected than even the hip or femoral shaft. This is in line with autonomic nervous system disorders and venous stasis after SCI [1, 51]. The mechanism that causes the knee region to be far more affected by rapid bone loss than the proximal femur or lower tibia still is not understood.

Although BMD is currently the best in vivo surrogate of fracture risk widely available, estimating 50–80% of the variance in bone strength [52, 53], and a predictor of fracture in patients with SCI, there is substantial overlap in those who do and do not experience skeletal fracture. It has been hypothesized that the unexplained variability is caused by other skeletal features, such as trabecular bone microarchitecture [54, 55, 56, 57, 58]. This notion is supported by studies showing an improvement in the prediction of strength and fracture when bone mineral measures are combined with trabecular bone microarchitecture [58, 59]. Advances in the application of high-resolution magnetic resonance imaging has made it feasible to conduct previously impossible studies of human trabecular bone microarchitecture.

Also, geometric properties of cortical bone in SCI patients change significantly. De Bruin et al. [60] reported that SCI patients with a lower extremity pathologic fracture history had a substantial decline in the area moment of inertia of the tibia with respect to the first main axis and the second main axis at diaphysis, indicating that the distribution of bone mineral around the bone's bending axis is decreased in the SCI patients with fracture history when compared to that in the SCI patients without fracture history and normal controls. A change of geometric properties after SCI may contribute to the high fracture incidence of the lower extremities.

Therefore, a structural analysis of bone, combined with the measurement of bone density, may improve the ability to assess fracture risk in patients with SCI. Although lower-limb bone mass is reduced in SCI individuals, this reduction is not detectable with ultrasound measurements at the mid-tibia [61]. It remains to be determined whether ultrasound measurements can predict fracture in the SCI population.

Pathophysiology

Factors involved in the development of osteoporosis after SCI are complex. Disuse may play an important role in the pathogenesis of osteoporosis, but factors that are independent of mechanical loading of the skeleton also appear to be important. Possible nonmechanical factors may include poor nutritional status, disordered vasoregulation [62, 63, 64], hypercortisolism (either therapeutic or stress-related), alterations in gonadal function [65, 66, 67] and other endocrine disorders. The mechanisms that underlie osteoporosis after SCI remain poorly elucidated and controversial.

Effect of disuse on bone tissue

Mechanical stress is one of the determinants of BMD, bone morphology and bone strength. Therefore, disuse accelerates bone resorption, especially of cancellous bone, and the bone becomes atrophic and fragile. Osteocytes embedded in the bone matrix respond to the mechanical load and changes of bone metabolism [68, 69, 70]. The gap junction of the long processes of osteocytes plays an important role in transmitting the mechanical load through intracellular signal transmitters (cAMP and cGMP) and extracellular signal transmitters (PGE_2, IGF-I, IGF-II and TGF-β) to induce bone formation by osteoblasts, inhibition of bone resorption by osteoclasts or a combination of the two [71, 72, 73]. In a prospective pilot study, Leblanc et al. [74] reported that maximal bone loss was involved in the calcaneus (−10.4%) and hip (−3.6%), with less involvement of the tibia after 17 weeks of continuous bed rest. This differs from SCI patients where tibial demineralization is much more severe than that in the hip [2]. Recumbency for 1 week induced a 1% decrease of bone mineral content of the vertebral body [75], whereas the bone mineral content of the lumbar spine in SCI patients was relatively preserved. Vertical positioning of the patient lacks a protective effect on bone mineralization [27, 76, 77]. Also, the expected benefits on bone from gait with orthosis have not been confirmed [2, 11, 78]. The role of the voluntary muscular contractions on a possible prevention of bone demineralization remains more difficult to evaluate. A prospective study following up eight patients for 31–53 months after SCI found a femoral preservation when hip voluntary contractions were preserved. Against the purely mechanical hypothesis, we can note the data from the literature, such as the lack of efficiency of reflex contractions [11, 20, 77] or of electrostimulated contractions on bone demineralization [36, 79]. In contrast, mechanical constraints seem to improve the BMD in healthy areas, as is shown by the significant increase of BMD in the upper limbs of paraplegics. This phenomenon is well known in tennis players, who present a 15% increase of bone mass in the dominant upper limb [80]. Taken together, these findings demonstrate from the pathophysiological point of view the major role played by the neurological lesion on bone demineralization in SCI patients. It is certain that disuse plays a role in the pathogenesis of osteoporosis after SCI, but the significance of disuse in this process after SCI still remains controversial.

Effect of neural factors on bone tissue

Deafferentation of the sympathetic nervous system after SCI causes the opening of the bone intravenous shunts, thus leading to a venous and capillary vascular stasis [1, 51]. Vascular modifications below the neurological lesion have an influence on osteoporosis in SCI patients. This plays a role in the bone resorption after

SCI by inducing a local modification of the endosteal surface. The decrease of gas exchanges and blood nutritive supplies to the bone due to venous stasis could promote osteoclast formation because of local hyperpressure, thus accelerating bone resorption [64]. This clear predominance of bone demineralization in the highly vascularized metaphyseal-epiphyseal areas of the long bones constitutes an additional argument. However, there is indeed a significant local vascularization at the level of these areas, which would be particularly affected by a secondary intramedullary blood stasis due to the sublesional vasomotor disorder. The significance of automatic nerve disorders after SCI in the pathogenesis of osteoporosis remains to be further elucidated.

Effect of calcium and phosphate homeostasis

In the early stage of SCI (less than 6 months post injury), serum phosphate and ionized calcium significantly increase in SCI patients, whereas serum calcium remains normal. Urinary calcium excretion also increased after SCI. One cross-sectional study found urinary calcium excretion, serum phosphorus and ionized calcium were significantly higher in acute SCI patients ($n = 7$) who had sustained injury an average of 3 months earlier than normal controls ($n = 10$), whereas serum calcium was normal [81]. The same result was shown in two other longitudinal studies by Roberts et al. [82] and Bergmann et al. [83] in acute SCI patients. These findings may reflect the release of the mineral phase of bone tissue into the blood circulation because of accelerated bone resorption with decreased calcium absorption [84]. However, serum total calcium concentration in long-standing SCI patients (more than 2 years post injury) was significantly lower. This was associated at least in part with the reduced albumin-bound fraction in the long-standing SCI population that showed a reduced serum albumin concentration. In fact, the serum concentration of ionized calcium in the long-standing SCI population was normal [85]. This indicates a new balance of bone formation, and resorption may be reestablished in long-standing SCI patients.

Generally, hypercalciuria is a common metabolic complication following the acute phase of SCI [84, 85]. Calciuria increases in 10 days, reaching a maximum between 1 and 6 months after injury [66, 86, 87]. The maximum urinary calcium level in those with SCI was between two and four times that of able-bodied subjects who were voluntarily placed on prolonged bed rest. Also, calciuria was not reduced by passive weight-bearing exercise or wheelchair activity [87]. These indicate the pathogenesis of osteoporosis after SCI may be different from that of disuse osteoporosis due to bed rest, space flight, etc. Hypercalcemia can occur in adults with acute SCI when bone resorption is accelerated in association with an impaired fractional excretion of calcium by the kidney.

Multiple fractures place adults with SCI at increased risk for hypercalcemia. Children and adolescents with acute SCI may be particularly susceptible to hypercalcemia because of preexisting rapid bone turnover and elevated bone resorption [88]. Other risk factors for hypercalcemia include recent paralysis, male gender, complete neurological injury, high cervical cord injury, dehydration and prolonged immobilization [86]. Although urinary calcium was markedly elevated on a low-calcium diet (400 mg/day), increased dietary calcium (to at least 1,160 mg/day) in acute SCI patients did not further increase either urinary or serum calcium concentrations in one longitudinal study [84]. The finding of hypercalciuria and hypercalcemia after acute SCI has led to the misguided clinical practice of a dietary restriction of calcium intake at the time of acute injury, an invalid and unnecessary intervention, which thus further worsens the calcium and phosphate metabolism.

Since $1,25(OH)_2$ vitamin D formation is principally governed by the parathyroid hormone (PTH) stimulation of renal 1α-hydroxylation of 25(OH) vitamin D, serum $1,25(OH)_2$ vitamin D levels may be decreased with the suppression of PTH. After acute SCI, the PTH-vitamin D axis is suppressed with depressed PTH and $1,25(OH)_2$ vitamin D [84]. In a cross-sectional study, it was demonstrated that PTH and $1,25(OH)_2$ vitamin D levels were suppressed in acute SCI patients by 80.6 and 66%, respectively [81]. Also, PTH suppression in SCI patients is associated with the degree of neurological impairment. Mechanick et al. [89] investigated serum PTH and $1,25(OH)_2$ vitamin D levels in SCI patients that were tested at a mean of 76.5 days post injury in a cross-sectional retrospective study and found that patients with complete SCI, when compared to those with incomplete injury, had a greater suppression of the PTH-vitamin D axis. Inconsistencies exist among studies of the PTH-vitamin D axis in chronic SCI patients.

Long-standing SCI is associated with a significant depression of $1,25(OH)_2$ vitamin D and PTH concentrations [85]. Persistent inhibition of PTH in individuals with chronic SCI seems to indicate that low-grade net bone resorption continued for many years. This may be caused by a persistent reduction in the mechanical stresses, the direct action of $1,25(OH)_2$ vitamin D at high concentrations on parathyroid tissue and changes in cytokine regulation. However, in another cross-sectional study of 100 chronic SCI patients, no difference of serum PTH levels between SCI patients and controls was shown, and serum $1,25(OH)_2$ vitamin D levels were higher in the SCI group [90]. This apparent difference in physiology in the two studies is not easily explained. Differences in the racial mix, diet, sunlight exposure and duration of SCI may provide some insight. Because of the tendency to calcium nephrolithiasis soon after acute SCI, individuals with chronic SCI are often instructed to restrict their calcium intake, chiefly dairy products. This dietary restriction may also result in vitamin D deficiency because dietary products, especially milk, are fortified with vitamin D and generally serve as the main

source of dietary intake of vitamin D. In addition, those with SCI may have reduced sunlight exposure or may receive anticonvulsants or other medications that induce hepatic microsomal enzymes, accelerating vitamin D metabolism [91, 92, 93].

Reduced calcium and vitamin D intake would be expected to lower the serum calcium concentration and stimulate the release of PTH, resulting in increased bone resorption and accentuation of osteopenia. However, only approximately one third of chronic SCI patients had secondary hyperparathyroidism with vitamin D deficiency [90]. In chronic SCI patients, as in the general population, secretion of PTH and the increase of circulating $1,25(OH)_2$ vitamin D are subject to control by negative feedback mechanisms related to the serum calcium level, which is in turn influenced by the 25(OH) vitamin D level. The serum calcitonin concentration in SCI patients was higher [85]. This may represent a compensatory response to ongoing calcium efflux from the skeleton of the paralyzed structures. Regardless of its mechanism, an elevated endogenous calcitonin level may help to mitigate the rate of bone resorption [85].

Effect of bone turnover

After SCI, there is an increased turnover of bone tissue. In the mean time, bone formation and bone resorption remain uncoupling, thus leading to bone loss. SCI may cause the bone microenvironment to secrete compounds that stimulate osteoclastogenesis. Demulder et al. [94] reported that a higher number of osteoclast-like cells formed in iliac bone marrow culture compared with sternal bone marrow culture for paraplegic patients approximately 6 weeks after their lesion. IL-6 was found to be significantly higher in iliac conditioned media compared to sternal conditioned media in most paraplegic patients. Paraplegia may induce an increase in the capacity of progenitors to form osteoclast-like cells in the long-term bone marrow cultures. This may contribute to the dramatic bone loss after SCI.

Biochemical markers reflect the process involved in remodeling and can reveal acute changes in bone turnover. A prospective study following up 30 acute SCI patients for 6 months has demonstrated a dramatic increase in bone resorption markers, such as urinary deoxypyridinoline and urinary N-telopeptide of type I collagen, beginning within the 1st week after injury and peaking around 10 to 16 weeks. The peak was as high as ten times the upper limit of normal, and these markers did not return to normal values at the end of study. Pietschmann et al. [95] showed that urinary hydroxyproline/creatinine ratios were significantly higher in SCI patients 1 month after injury than those in controls in a cross-sectional study. Similarly, in another cross-sectional study [81], the levels of urinary and serum type I collagen C-telopeptide (CTXu and CTXs) were substantially increased in the SCI patients approximately 3 months after injury by a factor of 5 and 2.5, respectively, compared with controls. Zehnder and associates [34] investigated bone turnover biochemical markers in a cross-sectional study of paraplegic men stratified by the time since injury: less than 1 year (stratum I), 1 to 9 years (stratum II), 10–19 years (stratum III) and 20–29 years (stratum IV). Markers of bone resorption (D-pyr/Cr and Ca/Cr) dramatically increased in recently injured paraplegics, whereas bone resorption estimated by the D-pyr/Cr ratio remained elevated in 50 and 30% of paraplegics in stratum II and strata III-IV, respectively [34]. The extremely high values of bone resorption markers, in comparison with those reported in short- [96, 97] and long-duration [96, 98] bed rest investigations, support the assumption that immobilization is not the only factor affecting bone metabolism.

In contrast to the resorption markers, the bone formation markers showed a different variation rate. In a prospective study, Roberts et al. [82] found a minor rise of serum osteocalcin concentrations of acute SCI patients in a 6-month follow-up after injury. This increase in serum osteocalcin could be partly explained by the low level of $1,25(OH)_2$ vitamin D concentration, as it has been shown that osteocalcin is directly stimulated by $1,25(OH)_2$ vitamin D in osteoblasts and osteosarcoma cells [99]. The changes observed in osteocalcin concentration cannot be related to a modification of glomerular filtration, since no variation in urinary creatinine concentration was demonstrated. Maimoun et al. [81] reported serum osteocalcin levels that were significantly higher in SCI patients 3 months after injury than in controls in a cross-sectional study. A similar finding was found in another longitudinal study in which the serum osteocalcin levels in six acute SCI patients was normal and then continuously increased until the end of the study 6 months later [34]. However, Maimoun et al. [81] reported that serum bone alkaline phosphatase (B-ALP) levels remained unchanged in the SCI patients approximately 3 months after injury in a cross-sectional study. Osteocalcin and B-ALP could reflect different aspects of bone formation. The majority of chronic SCI patients showed a normal bone formation marker in a cross-sectional study [34]. The results of bone turnover markers suggest that an imbalance between elevated bone resorption and normal (or minor elevated) bone formation after SCI plays a role in the pathogenesis of bone loss and fracture in SCI patients.

Treatment and prophylaxis

Functional exercise

Some studies have reported the reversal of osteopenia resulting from bed rest or weightlessness by ambulation or a return to normal gravity [100, 101]. However, a cross-sectional study demonstrated that intensive exercise regimens might contribute to the preservation of arm bone mass loss, but did not prevent demineralization in the lower body [32]. Contrarily, Goemare et al.

[102] reported that standing might partially prevent bone loss in the region of the femoral shaft, but not at the proximal hip. Functional electrical stimulation (FES) cycle ergometry, which produces active muscle contractions in the paralyzed limb, was expected to elevate BMD in SCI patients. However, inconsistencies exist among studies of FES-induced cycling on the BMD of SCI patients. With chronic adult SCI patients, several studies found no difference in the BMD of the lower limbs before and after the FES-cycling intervention of 3–12 months in observational studies [103, 104, 105]. The effect of FES cycle ergometry on BMD was investigated in an observational study of six quadriplegic men more than 2 years post injury, and it was demonstrated that 6 months of FES cycle ergometry did not produce an increase in BMD of the femoral neck, Ward triangle and trochanter [104]. However, in another observational study of ten SCI patients undergoing FES-cycling training, it was found that there was a 10% increase in BMD at the proximal tibia after 1 year of training, while no change was observed in the lumbar spine and femoral neck in response to training [106]. Similarly, Bloomfield et al. [107] measured BMD in a randomized controlled trial and found that in SCI patients treated with FES, BMD is increased by 0.047 ± 0.010 g/cm^2 at the lumbar spine, but changes in BMD at the femoral neck, distal femur and proximal tibia were not significant. In the SCI patients without FES, there was no significant change in BMD at any site over 6 months. Meanwhile, an 18% increase in BMD was found in the distal femur in four patients training at a higher intensity of the stimulus for at least 3 months, but no increase was found in other patients with lower power output. Taken together, the efficiency of FES on bone in SCI patients may be site-specific and related to the magnitude and frequency of FES. Because many studies suggest the rate of bone mineral loss is greatest within the first 2 years after the injury [9, 108], a loading-imposing intervention may have a greater effect sooner after the injury rather than later. But Eser et al. [109] reported that FES-cycling applied in 19 acute SCI patients did not attenuate bone loss in a randomized study of 38 SCI patients by investigating BMD of tibial diaphysis. This indicates that the effect of FES on cortical and cancellous bone is different. Adults and children may be differently susceptible to FES. In a pilot randomized controlled trial of 20 children with SCI, volumetric trabecular BMD in the proximal tibia of the SCI patients who stood on active devices increased by 17.7% after 6 months of low magnitude mechanical loading, while there was a decrease of 11.9% in the other SCI patients who stood on placebo devices. This result shows that low-magnitude, high-frequency mechanical stimuli are anabolic to trabecular bone in children with SCI, possibly by providing a surrogate for suppressed muscular activity in the disabled [110]. The same result was demonstrated when the BMD of electrically stimulated limbs decreased significantly less than that of the non-stimulated limbs in a paralyzed rabbit experiment [111]. Ultrasound, a high-frequency acoustic energy traveling in the form of a mechanical wave, represents a potential site-specific intervention for osteoporosis. However, Warden et al. [112] found that low-intensity pulsed ultrasound was unable to protect against SCI-induced calcaneal bone change in a pilot randomized controlled trial of 15 acute SCI patients. This may be primarily related to the inability of ultrasound to effectively penetrate the outer cortex of bone because of its acoustic properties [112].

Pharmacologic treatment

Pharmacologic intervention on osteoporosis after SCI includes calcium, phosphate, vitamin D, calcitonin and biphosphonates. Urinary calcium increases rapidly after SCI, and the calcium balance becomes negative. To some extent, supplementation of calcium and vitamin D may contribute to calcium homeostasis, but cannot prevent osteoporosis after SCI [113]. Similarly, phosphate supplementation can reduce urinary calcium excretion, but does not prevent bone loss after SCI [114]. In paraplegic rats, calcitonin is ineffective on osteoporosis [115]. However, in SCI patients, calcitonin has been shown to counteract the early increase in bone resorption following SCI [116]. Because of the limited number of studies, the preferred dosage regimen, therapy duration and administration route for adequate efficacy in SCI patients still remain unclear.

In a case report, Carey et al. [117] suggested that combination therapy with calcitonin and glucocorticoids should be utilized in severe hypercalcemia after SCI in order to take advantage of the rapid effect of calcitonin and the more sustained effect of glucocorticoids. Calcitonin and etidronate have a rapid and combined effect on the treatment of hypercalcemia after SCI [118].

Biphosphonates strongly inhibit bone resorption and have been administered to treat primary osteoporosis and secondary osteoporosis, including osteoporosis after SCI. In a randomized controlled trial of acute SCI patients treated with cyclical etidronate (800 mg orally, once per day for 2 weeks, repeated once) for 30 weeks, a protective effect of etidronate on bone loss was not observed. The patients who became ambulatory and received etidronate treatment had a preservation of bone density as compared to all other patients who showed a loss of bone density over time [119]. Merli et al. [120] reported that etidronate could treat hypercalcemia in SCI patients, but the inhibitory effects on bone formation limited its usefulness during recovery from a fracture. In another randomized controlled trial of 20 SCI patients, tiludronate at a higher dose than tested (400 mg/d) produced a slight increase in the bone volume/total volume of a transiliac bone biopsy, supporting the evidence that a high-potency biphosphonate would be generally effective in reducing bone density loss after SCI [121]. Nance et al. [122] reported that patients treated with intravenous pamidronate had significantly less bone density loss

compared with those who did not receive pamidronate. Also, ambulatory subjects had significantly less bone density loss than nonambulatory subjects. In a prospective randomized controlled trial of 65 men with complete SCI (0.1 to 27.2 years post injury), alendronate plus calcium was effective in preventing tibial trabecular bone loss of more than 10% over 24 months; in addition, alendronate was effective in preventing cortical tibial bone loss [123]. However, the changes in BMD of SCI patients with alendronate were below what was observed in postmenopausal women or in osteoporotic men at the standard treatment dose of 10 mg daily [124, 125]. One possible explanation is that 10 mg daily dosing of alendronate, which is the recommended dosage in postmenopausal osteoporosis, is too low in paraplegics to inhibit the osteoclastic activity at all resorption pits, because there is extremely high infralesional bone turnover in SCI patients. In addition, the result of a patient with incomplete SCI showed a greater increase in BMD in the weaker lower extremity compared with the stronger one after 2 years of alendronate treatment [126]. The use of alendronate had a positive effect on bone mineral density in SCI patients and therefore represents a potential tool for the prevention and treatment of osteoporosis in this population [127].

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