Bone Turnover and Spinal Cord Injury

42

Roop Singh

Contents

R. Singh (✉)
Department of Orthopaedics, Pandit B. D. Sharma PGIMS, Rohtak, Haryana, India
e-mail: drroopsingh@rediffmail.com; drroopsingh08@gmail.com

V.B. Patel, V.R. Preedy (eds.), *Biomarkers in Bone Disease*, Biomarkers in Disease: Methods, Discoveries and Applications, DOI 10.1007/978-94-007-7693-7_3

Abstract

Spinal cord injury (SCI) causes rapid, severe osteoporosis with increased fracture risk. The pathogenesis of osteoporosis after SCI is a complex process and is usually attributed to "disuse" or "immobilization." However, the exact pathophysiology of osteoporosis after SCI is still not clear. In SCI, bone remodeling becomes uncoupled with an initial decrease in bone formation and steadily increasing bone resorption. Osteoporosis after SCI can be evaluated by measuring BMD using DEXA, pQCT, and MRI; and estimating biochemical markers of bone turnover. Bone cell activity can be evaluated indirectly with techniques, such as specific serum and urine biochemical markers of bone turnover. An improved understanding of the natural history and risk factors for chronic bone loss following SCI is essential to designing therapies to reduce the rate of bone loss, define fracture risk, and ultimately prevent osteoporotic fractures and their associated morbidity. In conclusion, we are of the opinion that prospective randomized controlled trials should be conducted to evaluate, standardize, and find bone-specific biochemical marker of bone turnover, for the better understanding of the pathophysiology of osteoporosis in SCI.

Keywords

Spinal cord injury • Bone turnover • Osteoporosis • Bone mineral density • Biochemical marker

List of Abbreviations

ALP	Alkaline phosphatase
B-ALP	Bone-specific alkaline phosphatase
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
CGRP	Calcitonin gene-related polypeptide
Cre	Creatinine
CTx	C-Telopeptide cross-link of type I collagen
DEXA	Dual energy X-ray absorptiometry
DPD	Deoxypyridinoline
HYPRO	Hydroxyproline
IL-6	Interleukin-6
LHRH	LH-releasing hormone
NDY	Neuropeptide Y
NTx	N-Telopeptide cross-link of type I collagen
OC	Osteocalcin
OPG	Osteoprotegerin
PICP	Procollagen type I C-terminal peptide
PINP	Procollagen type I N-terminal peptide
pQCT	Peripheral quantitative computed tomography
PTH	Parathyroid hormone

PYD	Pyridinoline
RANKL	NF-κB ligand
SCI	Spinal cord injury
TSH	Thyroid-stimulating hormone
VIP	Vasoactive intestinal polypeptide

Key Facts of Spinal Cord Injury

- The term "spinal cord injury" (SCI) refers to damage to the spinal cord resulting from trauma or from disease or degeneration.
- Every year, around the world, between 250,000 and 500,000 people suffer a SCI.
- There is no reliable estimate of global prevalence, but estimated annual global incidence is 40–80 cases per million population.
- The majority of spinal cord injuries are due to preventable causes such as road traffic crashes, falls, or violence.
- People with a spinal cord injury are two to five times more likely to die prematurely than people without a spinal cord injury, with worse survival rates in low- and middle-income countries.
- Spinal cord injury is associated with lower rates of school enrollment and economic participation, and it carries substantial individual and societal costs.
- Spinal cord injury is associated with a risk of developing secondary conditions that can be debilitating and even life-threatening – e.g., deep vein thrombosis, urinary tract infections, muscle spasms, osteoporosis, pressure ulcers, chronic pain, and respiratory complications.

Definition of Words and Terms

Bone mineral density (BMD)	It is a measure of bone density, reflecting the strength of bones as represented by calcium content.
Bone turnover markers	Markers of bone turnover are biochemical products measured usually in blood or urine that reflect the metabolic activity of bone but which themselves have no function in controlling skeletal metabolism.
Osteopenia	Mild thinning of the bone mass and represents a low bone mass. Osteopenia results when formation of new bone (osteoid synthesis) is not sufficient to offset normal bone loss (osteoid lysis).
Osteoporosis	Thinning of the bones, with reduction in bone mass, due to depletion of calcium and bone

	protein. Osteoporosis predisposes a person to fractures.
Paraplegia	When the paralysis affects all or part of the trunk, legs, and pelvic organs.
Spinal cord	The spinal cord encased by vertebral column functions primarily in the transmission of neural signals between the brain and the rest of the body. It gives rise to 31 pairs of nerves.
Spinal cord injury	Damage to any part of the spinal cord or nerves in the spinal canal – often causes permanent changes in strength, sensation, and other body functions below the site of the injury.
Tetraplegia	Also known as quadriplegia, this means your arms, hands, trunk, legs, and pelvic organs are all affected by your spinal cord injury.

Introduction

Spinal cord injury (SCI) leads to sudden disruption of flow of information from the central nervous system. It has wide-ranging psychological and pathological effects those including an increase in bone resorption (Biering-Sorensen et al. 1988; Roberts et al. 1998; Maimoun et al. 2005; Singh et al. 2014a), hormonal alterations (Shetty et al. 1993; Bauman et al. 1994; Maimoun et al. 2005), and modification of body composition (Wilmet et al. 1995; Maimoun et al. 2005; Singh et al. 2014b). It is well known that SCI is accompanied by less bone mass caused by accelerated bone remodeling, with bone resorption exceeding bone formation. This situation causes a net bone loss and ultimately leads to osteoporosis (de Bruin et al. 2005). Osteoporosis in SCI occurs predominantly in the pelvis and the lower extremities (Garland et al. 1992; Demirel et al. 1998; Lazo et al. 2001; Maimoun et al. 2002; Zehnder et al. 2004). The neuronal lesion and subsequent immobilization create a unique form of early and severe bone loss in SCI persons (Chantraine et al. 1986; Garland et al. 1992; Leslie and Nance 1993; Hill et al. 1993; Uebelhart et al. 1995), characterized by a specific pattern of bone loss below the level of lesion (Finsen et al. 1992; Garland et al. 1994; Biering-Sorensen et al. 1988). Development of severe osteoporosis in the paralyzed part of the body is accompanied by the loss of biomechanical strength. In addition, the biosynthesis of structurally modified matrix is unable to sustain normal mechanical stress. Therefore, the risk of fracture is dramatically increased (Szollar et al. 1998; Dauty et al. 2000). Typically up to 33% of the bone mass is lost within first 6 months of injury, stabilizing to approximately 66% of the bone mass by 12–16 months post injury, which is considered to be close to the fracture threshold of the bone (Garland et al. 1992; Garland and Adkins 2001). The time course of bone loss may depend on the bone compartment; at sites within a high proportion of trabecular bone, bone loss followed a log curve leveling off from 1 to

3 years post injury, whereas at the tibial diaphysis, a cortical bone site, bone mass appeared to decrease progressively beyond 10 years post injury (Zehnder et al. 2004). During the first month post injury, demineralization occurs exclusively in the sublesional areas and predominantly in weight-bearing skeletal sites such as the distal femur and proximal tibia which are trabecular-rich site (Chantraine et al. 1986; Garland et al. 1992; Biering-Sorensen et al. 1998; Maimoun et al. 2005), while the diaphyseal area of the femur and the tibia, which are cortical-rich sites, are relatively spared (Dauty et al. 2000). Tibial trabecular bone losses within 2 years of SCI ranged from 0.4% to 80%, and cortical changes ranged from 1.7% increase to 32.7% decrease (de Bruin et al. 2005).This clear dissociation of the bone mineral density (BMD) loss between the trabecular and cortical compartments has been confirmed using the pQCT techniques (Frey-Rindova et al. 2000; Eser et al. 2004).

Various prospective longitudinal and cross-sectional studies using dual energy X-ray absorptiometry (DEXA) and peripheral quantitative computed tomography (pQCT) have described the magnitude of bone lost in the lower limbs (Table 1) and upper limbs (Table 2) following SCI.

Paradoxically, at the lumbar spine, which is mainly constituted of trabecular bone, no reduction in BMD usually occurs. This phenomenon is named dissociated hip and spine demineralization (Leslie and Nance 1993; Bauman et al. 1999). In the lumbar spine, the trabecular bone demineralization remains relatively low compared to the cortical bone demineralization of long bones (Dauty et al. 2000). Various studies have reported a normal (Chantraine et al., 1986; Biering-Sorensen et al., 1988) or even higher than normal (Garland et al., 1992; Kunkel et al., 1993; Ogilvie et al., 1993; Sloan et al., 1994; Singh et al., 2014a) BMD in the lumbar spine. Table 3 shows BMD of lumbar spine in SCI patients reported in various studies.

The decrease in bone mineral content (BMC) and BMD is associated with a deterioration in bone microarchitecture (Minaire et al. 1974; Modlesky et al. 2004), geometric structure, and strength (Modlesky et al. 2005; Rittweger et al. 2010), as well as an altered degree of mineralization and collagen matrix composition (Chantraine et al. 1986). Minaire et al. (1974) 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. (2004) 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 the increase in fracture incidence. Slade et al. (2005) investigated the trabecular bone microarchitecture of the knee in 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. Modlesky et al. (2005) reported that the medullary cavity had 53% more volume and was 21–25% wider in the SCI group ($p < 0.05$) compared to the men without SCI. In contrast, the cortical wall in the SCI group had a 24% lower volume and was 27–47% thinner ($p < 0.05$). Calculated cross-sectional moment of inertia, section modulus, and polar moment of inertia were lower in the SCI group. Rittweger et al. (2010) suggested that the anatomical

Table 1 Sublesional bone mineral density of lower limbs in spinal cord injury patients

Author	Type of study	Duration after injury	Males	Females	Age	Skeletal site measured	BMD (Z-score, SD or % loss or reduction of BMD or total BMD)
Bauman et al. 1999	Prospective	3–26 years	8		25–58 years	Lower limb Pelvis	−35% −29%
Biering-Sorensen et al. 1990	Prospective	9 days–53 months	8			Femoral neck Distal femur Proximal tibia Femur diaphysis Tibia diaphysis	−30_40% −48% −45% −25% −25%
Chow et al. 1996	X-sectional	Three groups <0.25 years 0.25–1 year 1–35 years	19	12	19-58 years	Pelvis Proximal femur Leg	−2% −6% −28%
Clasey et al. 2004	X-sectional	0.6–35.3 years	21	8	23–56 years	Lower extremity	−28.20%
Dauty et al. 2000	X-sectional	>1 year	31		18–60 years	Femoral neck Femoral trochanter Distal femur Proximal tibia	−30% −39% −70% −52%
de Bruin et al. 2005	Prospective	3.5 years	9	1	19–81 years	Distal tibial Trabecular bone Distal tibial Compact bone	−40% −11%
Demirel et al. 1998	X-sectional	2–30 months	32	9	19–49 years	Lower extremity	−2.19 ± 3.5 SD
Eser et al. 2004	X-sectional	0.17–50 years	89		41.5 ± 14.2 years	Femur shaft Distal femur Tibia shaft Distal tibia	−1.4% −45% −57% −2.6%

Finsen et al. 1992	X-sectional	7 months–33 years	19		15–64 years	Tibia distal diaphysis Tibia distal metaphysis	−26% −45%
Frey-Rindova et al. 2000	Prospective	12 months	27	3	19–59 years	Tibia trabecular bone Tibia cortical bone	−15% −7%
Garland et al. 1992	Prospective	114 ± 8.6 days	12		28 ± 0.8	Proximal femur Distal tibia	−13% −13%
Garland et al. 2004	Prospective		6			Distal femur Proximal tibia Os calcis	−27% −32% −38%
Garland et al. 2001	X-sectional	20–30 years 31–50 years 50+ years		31	5.7 ± 2.3 years 16.1 ± 9.4 years 28.9 ± 11.4 years	Knee, hip	−38%, −18% −41%, −25% −47%, −25%
Garland et al. 2001	X-sectional	2–8 years 3–30 years 9–44 years	6 16 9		20–30 years 31–50 years 53–77 years	Knee Hip Knee Hip Knee Hip	−37.90% −17.50% −41.30% −25% −47% −25.50%
Jones et al. 1998	X-sectional	1–30 years	5		32.6 ± 6.3 years	Femur neck Leg BMC	−26% −30%
Jones et al. 2002	X-sectional	7–372 months	20 (total)		17–52 years	Femur Hip	−27% −37%
Kannisto et al. 1998	X-sectional	1–30 years	25	10	1.5–57 years	Proximal femur	−26%

(*continued*)

Table 1 (continued)

Author	Type of study	Duration after injury	Males	Females	Age	Skeletal site measured	BMD (Z-score, SD or % loss or reduction of BMD or total BMD)
Kiratli et al. 2000	X-sectional	0.1–51 years	239	7	27–78 years	Femoral neck Femoral midshaft Distal femur	−27% −25% −43%
Leslie and Nance 1993	X-sectional	1–17 years	14		20–41 years	Femur neck	−26%
Maimoun et al. 2005	Prospective		7		31.3 ± 9.5 years	16 weeks Total proximal femur Femoral neck Trochanter Intertrochanter 71 weeks Total proximal femur Femoral neck Trochanter Intertrochanter	1.014 (1.030 ± 0.188) 1.005 (0.992 ± 0.185) 0.718 (0.769 ± 0.167) 1.163 (1.187 ± 0.211) 0.741 (0.799 ± 0.151) 0.795 (0.780 ± 0.095) 0.570 (0.616 ± 0.133) 0.847 (0.945 ± 0.198)
Modlesky et al. 2004	X-sectional	8.7 ± 7.5 years	10		34 ± 10 years	Proximal tibia	−43%
Moynahan et al. 1996	X-sectional		30	21	3–20 years	Femur neck Ward's triangle Intertrochanter	−36% −36% −44%
Paker et al. 2007	X-sectional	24.52 ± 20.9 months	33	15	38.47 ± 15.88 years	Injury duration < one year Femur neck Total femur	0.954 ± 0.195 0.992 ± 0.182 −0.766 ± 1.46 −0.5 ± 1.45 0.785 ± 0.146

						Femur neck T score Total femur T score Injury duration > one year Femur neck Total femur Femur neck T score Total femur T score	0.762 ± 0.136 −2.088 ± 1.03 −2.258 ± 1.09
Reiter et al. 2007	Prospective						
Sabo et al. 2001	X-sectional	1–26 years	46		<50 years	Proximal femur	−24.50%
Singh et al. 2014	Prospective	0–12 months	71	24	33.3 years	Initial Hip Proximal tibia Tibial diaphysis Distal tibial epiphysis 12 months Hip Proximal tibia Tibial diaphysis Distal tibial epiphysis	0.968 1.02 1.11 0.985 0.77 0.74 1.005 0.75

(*continued*)

Table 1 (continued)

Author	Type of study	Duration after injury	Males	Females	Age	Skeletal site measured	BMD (Z-score, SD or % loss or reduction of BMD or total BMD)
Uebelhart et al. 1994	Prospective	>6 months	6			Lower extremity	−6.40%
Warden et al. 2001	Prospective	1–6 months	15		19–40 years	Calcaneus Proximal tibia	−7.5 ± 3.0% −5.3 ± 4.2%
Wilmet et al. 1995	Prospective	Within 56 days	24	7	18–66 years	Pelvis, leg	Complete −40%−45%, −25% Incomplete −30%, −10%
Zehnder et al. 2004	X-sectional	<1 year <1 year 1–9 years 1–9 years 10–19 years 10–19 years 20–29 years 20–29 years	100 16 16 38 38 31 31 13 13		18–60 years	Femoral neck Tibia epiphysis Femoral neck Tibia epiphysis Femoral neck Tibia epiphysis Femoral neck Tibia epiphysis	−0.03 ± 0.25 SD −0.34 ± 0.22 SD −1.65 ± 0.17 SD −3.81 ± 0.13 SD −1.76 ± 0.25 SD −4.00 ± 0.21 SD −1.76 ± 0.28 SD −4.12 ± 0.24 SD

Some of the data are from the Jiang et al. (2006b), Copyright(2005), with permission from "Springer Science and Business Media"

Table 2 Sublesional bone mineral density of upper limbs in spinal cord injury patients

Author	Type of study	Duration after injury	Males	Females	Age	Skeletal site measured	BMD (Z-score, SD or % loss or reduction of BMD or total BMD)
Clasey et al. 2004	X-sectional	0.6–35.3 years	21	8	23–56 years	Upper extremity	+11.10%
Dauty et al. 2000	X-sectional	>1 year	31		18–60 years	Upper extremity	+6%
de Bruin et al. 2005	Prospective	3.5 years	9	1	19–81 years	Distal radius trabecular bone	−10̃ to + 14%
Demirel et al. 1998	X-sectional	2–30 months	32	9	19–49 years	Upper extremity	+0.09 ± 0.15 SD
Finsen et al. 1992	X-sectional	7 months–33 years	19		15–64 years	Forearm distal diaphysis Forearm distal metaphysis	−5% −13%
Frey-Rindova et al. 2000	Prospective	12 months	27	3	19–59 years	Radius trabecular bone Radius cortical bone Ulna trabecular bone Ulna cortical bone	−8% 0% −4% −1%
Maimoun et al. 2005	Prospective		7		31.3 ± 9.5 years	16 weeks Distal radius 71 weeks Distal radius	0.667 (0.654 ± 0.058) 0.640 (0.633 ± 0.052)
Sabo et al. 2001	X-sectional	1–26 years	46		<50 years	Distal forearm	−6.10%

(*continued*)

Table 2 (continued)

Author	Type of study	Duration after injury	Males	Females	Age	Skeletal site measured	BMD (Z-score, SD or % loss or reduction of BMD or total BMD)
Singh et al. 2014	Prospective	0–12 months	71	24	33.3 years	Initial Distal radius 12 months Distal radius	0.61 0.57
Zehnder et al. 2004	X-sectional	<1 year <1 year 1–9 years 1–9 years 10–19 years 10–19 years 20–29 years 20–29 years	100 16 16 38 38 31 31 13 13		18–60 years	Ultra distal radius Radius shaft 1/3 Ultra distal radius Radius shaft 1/3 Ultra distal radius Radius shaft 1/3 Ultra distal radius Radius shaft 1/3	+0.02 ± 0.24 SD +0.00 ± 0.41 SD +0.01 ± 0.15 SD +0.40 ± 0.17 SD +0.52 ± 0.20 SD +0.97 ± 0.20 SD +0.44 ± 0.32 SD +0.27 ± 0.31 SD

Some of the data are from the Jiang et al. (2006b), Copyright (2005), with permission from "Springer Science and Business Media"

Table 3 Sublesional bone mineral density of lumbar spine in spinal cord injury patients

Author	Type of study	Duration after injury	Males	Females	Age	BMD (Z-score, SD or % loss or reduction of BMD or total BMD)
Clasey et al. 2004	X-sectional	0.6–35.3 years	21	8	23–56 years	2%
Dauty et al. 2000	X-sectional	>1 year	31		18–60 years	−11%
Garland et al. 2001	X-sectional	2–8 years 3–30 years 9–44 years	6 16 9		20–30 years 31–50 years 53–77 years	2% 8.10% 14.80%
Liu et al. 2000	X-sectional		64		20–98 years	−2.0 ± 1.2 SD
Maimoun et al. 2005	Prospective		7		31.3 ± 9.5 years	16 weeks 1.023 (1.017 ± 0.094) 71 weeks 1.044 (1.051 ± 0.109)
Sabo et al. 2001	X-sectional	1–26 years	46		<50 years	−3.8%
Singh et al. 2014	Prospective	0–12 months	71	24	33.3 years	1.21
Zehnder et al. 2004	X-sectional	<1 year 1–9 years 10–19 years 20–29 years	100 16 38 31 13		18–60 years	−0.43 ± 0.19 SD +0.11 ± 0.15 SD +1.09 ± 0.23 SD +1.00 ± 0.42 SD

Some of the data are from the Jiang et al. (2006b), Copyright (2005), with permission from "Springer Science and Business Media"

variation in the geometry, rather than in the bone mass, can explain differential (endocortical vs. periosteal) rate of bone of loss after SCI. Chantraine et al. (1986) reported a large increase in the proportion of little calcified bone in the cortical as well as in the cancellous bone. They also reported a decreased number in hydroxyproline (HYPRO) residue in the newly synthesized organic matrix from paraplegia bone resulting either from an alteration of the prolyl hydroxylation or from the presence of an excess of non-collagen polypeptide.

Pathophysiology of Bone Turnover After SCI

The exact pathophysiology of osteoporosis after SCI is still not clear. The pathogenesis of osteoporosis after SCI is generally considered disuse. Mechanical loading is known to be a crucial stimulus for bone formation and resorption, thereby controlling bone mass, structure, and strength. The skeleton possess an inherent biological control system that directs bone formation in response to high mechanical stresses (or strains), thus strengthening skeleton in highly stress regions. This system, sometimes called the "Mechanostat," involves the resident cells within bone tissue that detect and respond to mechanical loads (Jiang et al. 2006a). According to Frost's Mechanostat Theory, bone adapts their structure that bone strength ensures strains caused by physiological loads remain within narrow window. In particular, bone strength and mass normally adapt to the largest voluntary loads on bones, whereby under physiological conditions, the largest loads are produced by muscle forces (Frost 1987, 1997, 2003). At the other end of the spectrum, immobilization due to paralyses leads to the absence of voluntary muscle contractions and hence to the absence of muscle loads. Under this condition bone "disuse-mode" is turned on, causing a distinct bone loss (Frost 1998). The findings of Frotzler et al. (2008) study support this theory. After complete SCI, bone mass and strength are lost within first years post injury until the concerned skeletal parts have adapted to the new level of mechanical loading (Rittweger et al. 2006). In SCI subject with strong muscle spasms, bone strength at the femur has been found to be greater than in subjects with weak or no muscle spasm (Eser et al. 2004).

Disuse may play an important role in the pathogenesis of the osteoporosis, but the factors that are independent of mechanical loading of the skeleton also appear to be important (Jiang et al. 2006a). Possible nonmechanical factors may include poor nutritional status (Bauman et al. 1995, 2005), lesion-induced blood circulation abnormalities at the sublesional levels that affects bone cell differentiation (Chantraine et al. 1979), alteration in gonadal functions (Morley et al. 1979; Naftchi et al. 1980; Nance et al. 1985), hypercortisolism (either therapeutic or stress related) (Bugaresti et al. 1992), and other endocrine disorders (Bauman et al. 1994). Recent work suggests that bone remodeling is regulated by nerve-derived signals, such as vasoactive intestinal polypeptide (VIP), calcitonin gene-related polypeptide (CGRP), neuropeptide Y (NPY), and substance P, as well as classical neuromediators such as noradrenaline, serotonin, and glutamate (Elefteriou 2005). It has also been reported that there is a marked modification in the osteoprotegerin/

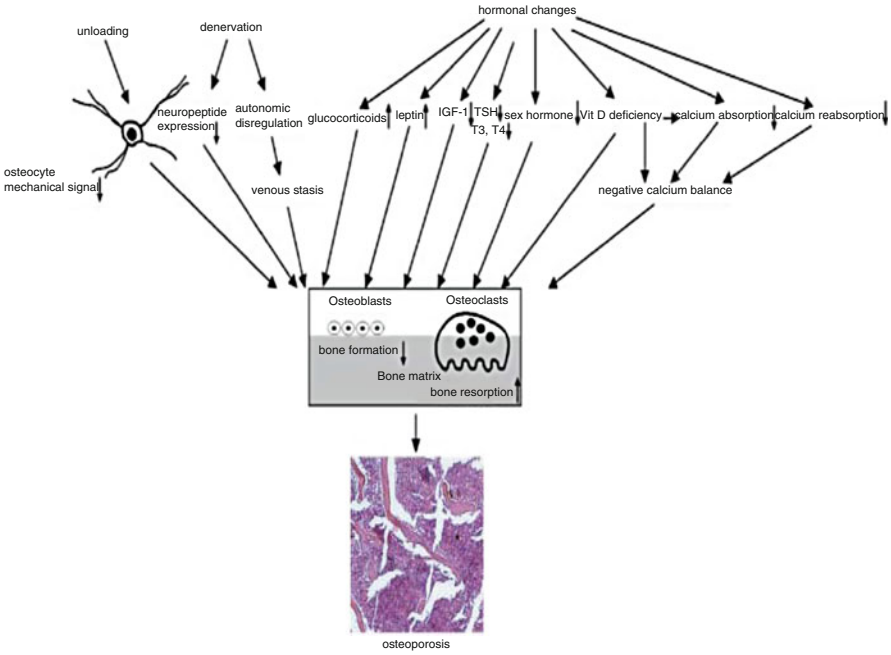

Fig. 1 A schema outlining the pathways implied in the pathogenesis of osteoporosis after SCI (Figure is from Jiang et al. (2006a), Copyright (2006), with permission from "Wiley")

RANKL system in recent SCI patients (Maimoun et al. 2005). Jiang et al. (2006a) outlined the pathways in the pathogenesis of osteoporosis after SCI (Fig. 1). The mechanism that underlies osteoporosis after SCI remains poorly elucidated and controversial (Jiang et al. 2006a).

Biochemical Markers of Bone Turnover in SCI

Bone cell activity can be evaluated indirectly with techniques, such as specific serum and urine biochemical markers of bone turnover. Biochemical markers reflect the process involved in bone turnover (Jiang et al. 2006b). Bone resorption markers reflect osteoclast activity and are the products of the protein matrix degradation of type I collagen, but noncollagenous proteins such as the enzyme of osteoclast origin tartrate-resistant acid phosphatase 5b (TRACP) and helical peptide 620–623 have also been investigated as resorption markers. At first hydroxyproline, pyridinoline (PYD), and deoxypyridinoline (DPD) adjusted to creatinine (Cre) were used; but they were relatively nonspecific and have been largely replaced by new markers such as N- and C-telopeptide cross-link of type I collagen (NTx and CTx) (Maimoun et al. 2011; Vasikaran et al. 2011). SCI is found to promote human osteoclast formation ex vivo (Demulder et al. 1998). The key molecule of osteoclast

development is the receptor activator of the NF-κB ligand (RANKL) (Lacey et al. 1998). There is evidence that bone-resorbing cytokines, such as interleukin (IL)-6, may be a potential candidate for mediating the bone loss following SCI (Demulder et al. 1998). Recent studies suggest that sclerostin is a key mediator of SCI-induced bone loss. Sclerostin, encoded by the sost gene, is produced primarily by osteocytes and is a potent inhibitor of bone formation and growth (Balemans et al. 2001; Staehling-Hampton et al. 2002). Mechanical unloading causes upregulation of sclerostin, leading to reduced Wnt/β-catenin signaling in osteoblasts. While the anti-anabolic role of sclerostin has been well characterized, recent evidence indicates that sclerostin also has catabolic activity. In fact, sclerostin causes upregulation of RANKL and downregulation of OPG expression by osteocytes, increasing osteoclast differentiation and activity, ultimately leading to bone resorption (Wijenayaka et al. 2011).

"The bone formation markers" reflect osteoblast activity and are the products of collagen synthesis (procollagen type I N-terminal peptide or C-terminal peptide [PINP & PICP], osteoblastic enzyme, i.e., bone-alkaline phosphatase [B-ALP], or matrix protein (osteocalcin [OC]) (Maimoun et al. 2011; Vasikaran et al. 2011). Type I collagen is an important component of bone matrix, and osteoblasts secrete its precursor procollagen molecule during bone formation. The extension peptides at each end of the procollagen molecule, PINP and PICP, are cleaved by enzymes during bone matrix formation and released into the circulation. Osteocalcin, one of the most abundant noncollagenous proteins in bone matrix, is also produced by osteoblasts during bone formation, and some proportion finds its way into the extracellular compartment where it can be measured. It is excreted by the kidneys and its fragments may also be measured in urine. Newly formed osteoid undergoes maturation followed by mineralization, and during this phase, alkaline phosphatase (ALP) is secreted by osteoblasts into the extracellular fluid and can be measured in serum. However, only about half of the ALP activity in blood of healthy adults derives from the bone, the other half being predominately of hepatic origin. Assays are available that detect more specifically the B-ALP (Vasikaran et al. 2011). After SCI, there is an increased turnover of bone tissue. In the meantime, bone formation and bone resorption remain uncoupling, thus leading to bone loss (Jiang et al. 2006a).

Increased bone resorption after SCI has been demonstrated clinically. After SCI, notable increase in bone resorption markers have been reported to occur as early as 2 weeks, reaching peak value 2–4 months after injury onset (Bergmann et al. 1977; Uebelhart et al. 1994; Roberts et al. 1998; Maimoun et al. 2002). However, bone formation markers remain normal or elevated (Roberts et al. 1998; Maimoun et al. 2002). Table 4 shows biochemical markers of bone turnover reported in various studies. The currently used bone markers reflect only whole-body net changes. They thus cannot determine the specific bone site affected by the intense bone demineralization or discriminate changes in a specific skeletal envelope, that is, trabecular versus cortical (Maimoun et al. 2011).

Table 4 Showing biochemical biomarkers of bone turnover reported in various studies in SCI population

	Parameters								
	Bone formation markers				Bone resorption markers				
Studies	OC	ALP	B-ALP	OPG	Serum CTx	Urinary CTx	sRANKL	HYPRO	DPD
Bagis et al. 2002 Paraplegia Tetraplegia	3.51 ± 2.07 ng/dL 3.18 ± 1.26 ng/dL	168.5 ± 44.6U/L 121.7 ± 0.1 U/L			0.49 ± 0.009 ng/mL 0.63 ± 0.12 ng/mL				
Hummel et al. 2012					263.6 ± 145.2 ng/L				
Kannisto et al. 1998 Males Females	7.2 ± 5.2 ug/L 3.8 ± 2.5 ug/dL	170 ± 86 U/L	68 ± 33 U/L		4.4 ± 2.5 ug/L	18–20 years 0.28 ± 0.2 mmol/L 21–65 years 0.12 ± 0.11 mmol/L			5.8 ± 1.8 nmol/L 8.3 ± 5.5 nmol/L
Kaya et al. 2006		100.05 ± 36.98 U/L							
Maimoun et al. 2002	24 ± 8 ng/mL		13.8 ± 5.5 ng/mL		13,340 ± 4,921 pmol/L	894 ± 371 μg. mmol/LCr			
Maimoun et al. 2005	16 weeks 25.6 (24 ± 7.9) mg/mL 71 weeks 15.3 (15.1 ± 2.44) mg/mL		16 weeks 14.5 (13.8 ± 5.5) ng/mL 71 weeks 21.7 (22 ±) mg/mL	16 weeks 7.8 (8.6 ± 1.5) U/L 71 weeks 8.4 (8.7 ± 1.5) U/L	16 weeks 13,500 (13,340 ± 4,921) pmol/L 71 weeks 3,171 (6,369 ± 5,093) pmol/L	16 weeks 849 (894 ± 371) μg. mmol/LCr 71 weeks 331 (404 ± 197) μg. mmol/LCr	16 weeks 0.13 (0.29 ± 0 30) pmol/L 71 weeks 0.25 (0.37 ± 0.33) pmol/L		
Morse et al. 2008	21.54 [17.82–28.63] ng/mL			58.39 [43.93–79.60] pg/mL	0.20 [0.15–0.31] ng/mL		0.07 [0.04–016] pg/mL		
Paker et al. 2007	23.60 ± 10.73 ng/mL	118.75 ± 84.53 U/L			1.37 ± 0.60 ng/mL				

(*continued*)

Table 4 (continued)

	Parameters								
	Bone formation markers				Bone resorption markers				
Studies	OC	ALP	B-ALP	OPG	Serum CTx	Urinary CTx	sRANKL	HYPRO	DPD
Pietschmann et al. 1992	10.5 ± 3.3 ng/mL								
Sabour et al. 2014 Male Female	17.26 ± 9.84 ng/mL 14.70 ± 6.96 ng/mL		15.0 ± 6.03 ng/mL 14.6 ± 7.72 ng/mL		0.91 ± 0.62 ng/mL 0.549 ± 0.26 ng/mL				
Singh et al. 2014 Initial 1 year		195.2 ± 47.1 U/L 231.3 ± 30.5 U/L							

Factors Affecting the Bone Turnover After SCI

Various factors may have a potential impact on bone remodeling after SCI. These include duration of injury, level of injury, physical activity, body composition, health-related complications such as diabetes mellitus, and lifestyle changes.

Duration of Injury

A positive correlation exists between the time following injury and degree of bone loss. Bone resorption decreases with post injury duration (Roberts et al. 1998; Zehnder et al. 2004; Maimoun et al. 2005; Reiter et al. 2007). However, some studies have found a negative linear relationship between markers like hydroxyproline/creatinine (Pietschmann et al. 1992) or bone alkaline phosphatase (Jones and Legge 2009). Sabour et al. (2014) and Bagis et al. (2002) found that post injury duration did not have any effect on CTx levels. Bone mineral content at the femoral shaft reaches a new steady-state at a mean 6.8 years post injury, and BMD cortical is reduced during the first 2–5 years when increased intracortical remodeling is present and recovers to normal values thereafter (Frotzler et al. 2008).

Level of Injury

SCI patients are classified into two large categories, i.e., paraplegia and quadriplegia. No significant difference in BMD is usually found between paraplegic and quadriplegic individuals (Tsuzuku et al. 1999; Demirel et al. 1998; Singh et al. 2014a). No difference in the bone resorption markers are usually observed between the two groups (Pietschmann et al. 1992; Roberts et al. 1998; Maimoun et al. 2006; Morse et al. 2008).

According to Maimoun et al. (2011), it is surprising that a clear bone remodeling profile cannot be identified according to the level of injury (paraplegia and quadriplegia) because, although the neurological level of injury does not determine the degree of bone loss, it does have an impact on the extent of alteration (Garland et al. 1992; Dauty et al. 2000). As has been noted, bone markers give a global but not site-specific evaluation of bone turnover. The lack of difference between the two groups may reflect the heterogenecity of these populations; and functionally, some patients with paraplegia and quadriplegia might not be so different, thus showing bone turnover that is quite similar (Roberts et al. 1998).

Age

In trabecular bone compartment, thinning and loss of trabeculae lead to reduced BMD with age (Inceoglu et al. 2005). This was also found in people with SCI

(Kiratli et al. 2000). Frotzler et al. (2008) reported no significant age-related changes after completion of initial bone loss and reaching of bone steady-state in the SCI population. Age-related bone adaptation may be absent when bone structure already adapted to minimal mechanical loading due to aging. They also reported no periosteal diameter at the tibial or femoral shaft to increase, indicating that there is no generalized age-related periosteal expansion in people with chronic SCI.

Age has no significance on CTx levels (Bagis et al. 2002; Savour et al. 2014). Morse et al. (2008) showed that CTx is increased by age in chronic SCI that cannot be justified with reduction of BMD loss through time. The impact of age on patients with SCI can be debated, probably injury causes a greater alteration in bone loss than age (Maimoun et al. 2011).

Complete Versus Incomplete SCI

Motor-complete (ASIA A and B) patients have significantly lower BMD than motor-incomplete (ASIA C and D) patients (Demirel et al. 1998; de Bruin et al. 2005; Singh et al. 2014). Individuals with incomplete SCI tended to lose less bone than individuals with complete SCI. The degree of mobility may be important; a cross-sectional study demonstrated that BMD in SCI patients were positively correlated with their mobility with a mobility index ranging from complete paralyses to unlimited ambulation (Saltzstein et al. 1992). However, Kaya et al. (2006) could not find significant difference in BMD values between these two groups.

Physical Activity

Physical activity in able-bodied individual is known to induce changes in bone remodeling (Maimoun and Sultan 2011), and most persons with SCI present a sedentary lifestyle (Noreau and Shephard 1995). Various studies vary in exercise modality, training duration and/or intensity, and participant level and duration of injury reveal no change (Giangregorio et al. 2005), increased (Belanger et al. 2000) or diminished BMD (Clark et al. 2007), at various sites in response to exercise training. Completion of 6 months of activity-based therapy was unable to ameliorate bone loss of the total body and hip, but reduce the expected magnitude of bone loss seen after SCI. Spine BMD was increased, and markers of bone formation and resorption were unchanged with training (Astorino et al. 2013). Jones and Legge (2009) compared two groups of male patients with SCI: an active group and a sedentary group. No difference was found for the bone resorption markers between these two groups ($p > 0.05$). Deoxypyridinoline concentration in active group (16.8 nmol/mmol creatinine $\pm$ 10.3) was higher in sedentary group (11.8 nmol/mmol creatinine $\pm$5.4). Bone alkaline phosphatase (bone formation marker) activity in sedentary SCI men was significantly higher than those of active group (sedentary, 28.0 $\pm$ 6.4 U/L; active, 14.0 $\pm$ 3.6 U/L, $p < 0.01$). Roberts et al. (1998) found no

relationship between the levels of physical activity and bone markers; and Morse et al. (2008) reported no correlation between osteocalcin and CTx concentration and ambulation mode in patients with duration of injury more than 2 years. In a cross-sectional study (Chain et al. 2012), no difference in urinary CTx was revealed between sedentary and active men with chronic SCI.

Other Factors

Individual with SCI not only lose motor and/or sensory, they experience dramatic muscle and bone changes (Giangregorio and McCartney 2006; Singh et al. 2014a). It also induces health-related complications (Bauman et al. 1994) and lifestyle changes (Noreau and Shephard 1995). Morse et al. (2008) studied 82 male patients with duration of injury more than 2 years and found no relationship between OC and CTx values and factors like body mass index (BMI), smoking history, history of heart disease, high blood pressure, and diabetes. Roberts et al. (1998) confirmed that weight and nutrition do not affect biochemical bone markers.

Effects of Hormones on Bone Turnover After SCI

Bone remodeling is a process of bone renewal accomplished by two opposing activities of bone cells: bone resorption by osteoclast and bone formation by osteoblasts. Systemic hormones such as parathyroid, vitamin D, sex steroids, thyroid hormones, and leptin may also be involved in bone loss following SCI (Jiang et al. 2006a). Table 5 shows biochemical parameters of bone turnover reported in various studies in SCI population and Table 6 various methods of assaying these parameters.

Calcium and Phosphate Homeostasis

Hypercalciuria associated with abnormally high ionized calcium (iCa) level with or without abnormal elevated total calcium was reported in patients during the acute SCI phase (Bergmann et al. 1977; Naftchi et al. 1980; Uebelhart et al. 1994; Mechanick et al. 1997; Roberts et al. 1998; Maimoun et al. 2002). The increased osteoclastic bone resorption is mainly responsible for hypercalciuria following SCI. In addition, reduced renal function has been observed in acute SCI patients (Maynard and Imai 1977), and the increased urinary elimination of calcium that occurs in response to SCI may be related to diminished renal tubular reabsorption. Urinary calcium excretion, serum phosphorous, and ionized calcium were significantly higher in acute SCI patients (Bergmann et al. 1977; Roberts et al. 1998; Maimoun et al. 2002). Serum concentration of ionized calcium in long-standing SCI population was normal (Vaziri et al. 1994). This indicates a new balance of bone formation,

Table 5 Showing biochemical parameters of bone turnover reported in various studies in SCI population

	Parameters					
	Serum					
Studies	Total calcium	Ionized calcium	Phosphorus	Proteins	Albumin	PTH
Bagis et al. 2002 Paraplegia Tetraplegia	9.21 ± 0.66 mg/dL 8.60 ± 0.58 mg/dL	1.14 ± 0.07 mmol/L 1.16 ± 0.08 mmol/L	4.06 ± 0.39 mg/dL 4.27 ± 0.26 mg/dL			41.72 ± 7.55 pmol/L 37.6 ± 8.25 pmol/L
Hummel et al. 2012		1.24 ± 0.04 mmol/L				4.4 ± 2.4 pmol/L
Kaya et al. 2006	9.60 ± 0.56 mg/dL		4.38 ± 0.70 mg/dL			2.23 ± 1.27 pmol/L
Maimoun et al. 2002	2.42 ± 0.09 mmol/L	1.27 ± 0.05 mmol/L	1.45 ± 0.24 mmol/L			5.14 ± 1.2 pmol/L
Maimoun et al. 2005	16 weeks 90.3 (90.7 ± 3.4) mg/L 71 weeks 82.8 (83 ± 3.1) mg/L				16 weeks 42 (40.1 ± 5.9) g/L 71 weeks 49 (49 ± 5) g/L	16 weeks 5 (5.1 ± 1.2) pg/mL 71 weeks 15 (16.6 ± 3.2) pg/mL
Paker et al. 2007	8.87 ± 0.57 mg/dL		4.20 ± 0.90 mg/dL			
Pietschmann et al. 1992						61.5 ± 33.0 pmol/L
Sabour et al. 2014 Male Female						3.22 ± 6.90 pg/mL 2.27 ± 1.05 pg/mL
Singh et al. 2014 Initial 1 year	8.8 ± 1.2 mg/dL 8.3 ± 0.8 mg/dL		3.8 ± 1.2 mg/dL 4.2 ± 0.8 mg/dL	6.24 ± 0.6 mg/dL 6.4 ± 1.0 mg/dL		

					Urine		
CT	T3	T4	TSH	1,25(OH) D3	24-h calcium	24-h phosphorus	Calcium/ creatinine
					288.2 ± 139.5 mg/ dL 259.5 ± 119.3 mg/ dL		0.3 ± 0.1 0.2 ± 0.001
				86.6 ± 37.8 nmol/L			
7.84 ± 3.15 mg/dL	2.47 ± 0.61 pg/mL	1.2 ± 0.23 ng/mL	1.45 ± 1.04 μIU/mL		238.81 ± 153.6 mg/ dL		0.3 ± 0.18
				13.57 ± 7.8 pg/mL		1.81 ± 1.23 mmol. mmol/Cr	0.76 ± 0.37
				16 weeks 11 (13.5 ± 7.8) pg/mL 71 weeks 24 (22.8 ± 6.6) pg/mL			16 weeks 0.72 (0.76 ± 0.37) 71 weeks 0.21 (0.23 ± 0.1)
48.3 ± 14.8 pg/mL							
	10.62 ± 9.84 pg/mL 9.64 ± 26.03 pg/mL						
					109.5 ± 24.5 mg/day 120.7 ± 39.0 mg/day	1.06 ± 0.16 mg/day 1.08 ± 0.03 mg/day	

Table 6 Showing various methods of assessment of various parameters of bone turnover

Parameter	Method of assay
Serum	
Calcium (Ca)	Colorimetric technique
Phosphorous (P)	Colorimetric technique
Ionized calcium (iCa)	Ion-specific electrode
Alkaline phosphatase (ALP)	Spectrophotometry
Bone specific alkaline phosphatase (B-ALP)	Human immunoradiometeric assay (IRMA) using two monoclonal antibodies; Scandinavian method and polyacrylamide gel electrophoresis for isoenzymes; competitive immunosorbent assay
Osteocalcin (OC)	Radioimmunoassay (RIA); human immunoradiometeric assay (IRMA)
Parathyroid hormone (PTH)	Human immunoradiometeric assay (IRMA) using two different polyclonal antibodies; solid-phase, two-site chemiluminescentimmunometeric assay; radioimmunoassay (RIA)
C-telopeptide cross-link of type I collagen (CTx)	Enzyme-linked immunosorbent assay (ELISA); radioimmunoassay (RIA); electrochemiluminescence
Procollagen type I N-terminal peptide (PINP)	Enzyme-linked immunosorbent assay (ELISA)
$1,25(OH)_2$ vitamin D_3	Radioimmunoassay (RIA) using polyclonal 1,25 vitamin D antibody; column chromatography; chemiluminescence immunoassay
RANKL: NF-κB ligand	Enzyme-linked immunosorbent assay (ELISA)
Osteoprotegerin (OPG)	Enzyme-linked immunosorbent assay (ELISA)
Urine	
Calcium (Ca)	Colorimetric technique
Creatinine (Cre)	Colorimetric technique; modified Jaffe method
Hydroxyproline (HYPRO)	Spectrophotometry
Deoxypyridinoline (DPD)	Immunoassay; high-performance liquid chromatography
C-telopeptide cross-link of type I collagen (CTx)	Radioimmunoassay (RIA); electrochemiluminescence

and resorption may be reestablished in long-standing SCI patients (Jiang et al. 2006b). Absorption of calcium from gastrointestinal tract has been found to decrease in acute phase following SCI (Zhou et al. 1993). Risk factors for hypercalcemia include children and adolescent, recently paralyzed, male gender, complete neurological injury, high cervical cord injuries, dehydration, and prolonged immobilization (Maynard 1986).

Soon after initial SCI, increased phosphorus values were reported (Bergmann et al. 1977; Naftchi et al. 1980; Roberts et al. 1998; Maimoun et al. 2002; Zehnder et al. 2004; Kaya et al. 2006). The increase could be explained by the loss of phosphorus from bone and muscle tissues (Dauty et al. 2000) and result from relative hypoparathyroidism. Secondarily, it can directly inhibit the $1,25(OH)_2$ vitamin D_3 synthesis (Mechanick et al. 1997).

Parathyroid Hormone (PTH)

In the acute phase of SCI, secretion of parathyroid hormone drops quickly (Claus-Walker et al. 1977; Chantraine et al. 1979; Pietschmann et al. 1992; Roberts et al. 1998; Maimoun et al. 2002, 2005). After acute SCI, the PTH-vitamin D axis is suppressed with depressed PTH and $1,25(OH)_2$ vitamin D_3 (Stewart et al. 1982). The initial suppression seems to be transitory because it tended to level off after 6 months (Pietschmann et al. 1992; Roberts et al. 1998; Maimoun et al. 2005); but value did not return to normal 71 weeks post injury (Maimoun et al. 2005). Hypercalcemia after injury may lead to PTH-vitamin D axis suppression in acute phase of SCI. PTH suppression in SCI patients is associated with the degree of neurological impairment. Mechanick et al. (1997) investigated serum PTH and $1,25(OH)_2$ vitamin D_3 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 PTH-vitamin D axis. Dysfunction of this axis soon after SCI is unlikely to be involved in the pathogenesis of bone loss after the injury (Jiang et al. 2006b).

Long-standing SCI is associated with a significant depression of $1,25(OH)_2$ vitamin D_3 and PTH concentration (Vaziri et al. 1994). 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 persistent reduction in the mechanical stresses, the direct action of $1,25(OH)_2$ vitamin D_3 at high concentration on parathyroid tissue and changes in cytokine regulation (Jiang et al. 2006b). Approximately one-third of chronic SCI patients showed secondary hyperparathyroidism with vitamin D deficiency (Bauman et al. 1995).

Vitamin D

Patients with SCI have been reported to have higher prevalence of vitamin D deficiency than able-bodied population (Stewart et al. 1982; Vaziri et al. 1994; Bauman et al. 1995; Maimoun et al. 2002, 2005, 2006; Mechanick et al. 2006). In acute SCI, $1,25(OH)_2$ vitamin D_3 levels were suppressed compared with controls by 66% (Maimoun et al. 2002).

Findings on vitamin D metabolites in chronic SCI patients are less consistent (Jiang et al. 2006a). Vitamin D deficiency was reported in persons with chronic SCI (Vaziri et al. 1994); but in fact, it seems that only $1,25(OH)_2$ vitamin D_3 was specifically altered. Afterward, despite plasma 25-hydroxy vitamin D (25[OH]D) values that tend to decrease with duration of injury, these values remained within reference range, indicating the presence of normal vitamin D store (Stewart et al. 1982; Mechanick et al. 1997; Roberts et al. 1998). Other studies demonstrated that a proportion of subjects with 25(OH)D defect was significantly greater in individuals with chronic SCI (32%) than in able-bodied population (16%) and that 25(OH)D levels were negatively correlated with PTH levels (Bauman et al. 1995). In fact, it is likely that 25(OH)D deficiency occurs more

often in severe cases, such as patients with quadriplegia hospitalized for pressure ulcers over a long period of time (Zhou et al. 1993). Conversely, for 1,25$(OH)_2$ vitamin D_3, concentrations are generally reduced (Stewart et al. 1982; Vaziri et al. 1994; Maimoun et al. 2002, 2005, 2006).

Reduced calcium and vitamin D intake would be expected to lower the serum calcium concentrations and stimulate the release of PTH, resulting in increased bone resorption and accentuation of osteopenia. In a randomized, placebo-controlled trial of 40 chronic SCI patients, a vitamin D analogue [1-alpha D(2)] was demonstrated to increase leg BMD 24 months after treatment, and urinary N-telopeptide, a marker of bone resorption, was significantly reduced during treatment 1-alpha D(2), but not in the placebo group (Bauman et al. 2005). Bauman et al. (1995) supplemented individuals with chronic SCI with 800 IU 1,25$(OH)_2$ vitamin D_3 per day over a 12-month period and found a doubling of vitamin D levels and one-third decrease in PTH levels.

Calcitonin

The calcitonin concentration in SCI patient was higher. This may represent a compensatory response to ongoing calcium reflex from the skeleton of the paralyzed structure. Regardless of its mechanism, an elevated endogenous calcitonin may help to mitigate the rate of resorption (Vaziri et al. 1994). Pietschmann et al. (1992) reported that level of injury had no impact on calcium concentration.

Growth Hormone

Insulin resistance may be a contributing factor leading to osteoporosis following SCI. In addition, growth factors and their second messengers, such as IGF-I, have been reported to be depressed in patients with chronic SCI (Jiang et al. 2006a). Shetty et al. (1993) reported that the average plasma IGF-I level in patients with tetraplegia was depressed when compared with ambulatory controls. However, Maimoun et al. (2006) did not demonstrate a role of growth factor in accelerated bone resorption following SCI.

Gonadal Hormones

The inhibitory effect of SCI on the synthesis and secretion of sex steroids contributes to pathogenesis of SCI-induced osteoporosis (Jiang et al. 2006a). The literature provides the conflicting data: there are subsets of SCI men with relative and absolute androgen deficiency (Naftchi et al. 1980; Nance et al. 1985; Maimoun et al. 2005). Maimoun et al. (2006) reported that total testosterone and free androgen index were significantly lower in SCI patients than able-bodied controls. No significant change in serum gonadotropin concentration was observed in SCI men by Wang

et al. (1992) and Tsitouras et al. (1995), while in another cross-sectional study, it was demonstrated that there was high prevalence of low serum gonadotropins and a delayed appearance of gonadotropin peak response tKo LH-releasing hormone (LHRH) in SCI men (Naderi and Safarinejad 2003). These studies suggest that SCI may suppress the hypothalamic-pituitary-testis axis at different levels, including the hypothalamus, the anterior pituitary gland, and the gonads. The endocrine abnormalities may be the mechanism contributing to the development after SCI (Jiang et al. 2006a).

Serum estrogen levels in SCI women are also significantly lower than in controls (Rosenquist 1950). An enhanced gonadotropin response to LHRH has been reported in a group of SCI women, indicating a hypothalamic disorder within the hypothalamus-pituitary-ovary axis (Huang et al. 1996). These studies suggest that there is a high prevalence of hypothalamus-pituitary-ovary axis disorders in SCI women, and these disorders may be involved in the pathogenesis of osteoporosis after SCI (Jiang et al. 2006a).

Leptin

SCI results in progressive loss of percentage of total lean body mass and increase in percentage of fat mass (Wilmet et al. 1995; Kaya et al. 2006; Singh et al. 2014). Plasma leptin concentration is markedly elevated in SCI patients compared with able-bodied controls (Huang et al. 2000; Hjeltnes et al. 2005; Wang et al. 2005; Maimoum et al. 2004). The increased plasma concentration of leptin in SCI patients and the accompanying augmented circadian variation might distort the normal turnover of bone tissue in SCI patients, leading to osteoporosis (Hjeltnes et al. 2005).

Thyroid Hormone

Serum T3 and T4 levels remain depressed in acute SCI patients (Bugaresti et al. 1992; Claus-Walker et al. 1977). After acute stress, there may also be associated changes in thyroid hormone binding that could lower serum thyroid hormone levels (Bermudez et al. 1975). Similarly, in chronic SCI patients, serum T3 and T4 were also reduced compared to controls (Cheville and Kirshblum 1995). Patients with tetraplegia had lower serum T3 levels than did those with paraplegia (Wang et al. 1992). These data suggest a thyroid disorder within the hypothalamic-pituitary-thyroid axis (Jiang et al. 2006a).

In the literature, many studies reported normal concentration of TSH in chronic SCI patients (Prakash 1983; Huang et al. 1996). Zeitzer et al. (2000) investigated the 24 h average and circadian amplitude of TSH rhythm in the chronic SCI patients and found that they were within the low end of normal range. These data suggest that a small decline in TSH amplitude in chronic SCI patients may be a contributing factor in the pathogenesis of osteoporosis (Jiang et al. 2006b).

Glucocorticoids

Hypercortisolism found in acute SCI patients may be therapeutic or stress related (Bugaresti et al. 1992). Therefore, glucocorticoids may contribute to bone loss following SCI. However, findings on the effect of chronic SCI on serum cortisol level are less consistent. The current balance of evidence does not support the idea that the changes in serum cortisol level may be a contributing factor in the pathogenesis of osteoporosis in chronic SCI patients (Jiang et al. 2006a).

Potential Application of Bone Turnover Markers to Prognosis, Other Disease, or Conditions

Osteoporosis is a major health problem worldwide, especially in postmenopausal women. The clinical consequences of osteoporosis reside in the fracture risk. Technological developments for the measurement of bone mineral density (BMD) have led to diagnostic criteria that are widely applied (Vasikaran et al. 2011).The World Health Organization diagnostic criterion for osteoporosis is a BMD measurement equal to or more than 2.5 standard deviations (SD) below the young female (age 20–29 years) reference mean (T-score ≤ -2.5 SD) (Kanis et al. 2008). There has been interest in the clinical potential of bone turnover markers, both as tools to assess fracture risk and for monitoring treatment, to thereby aid intervention strategies (Szulc and Delmas 2008; Vasikaran 2008; Bergmann et al. 2009).

Estrogen deficiency, associated with menopause, results in a generalized increase in bone remodeling and an imbalance between bone formation and resorption (Darby and Meunier 1981; Jilka 2003). Bone turnover marker levels are also influenced by factors that are not easily modified. In postmenopausal and elderly women, the major uncontrollable factors are diseases and associated bed rest and immobility, medications, nutritional status, and recent fractures (Szulc and Delmas 2008).Increased bone turnover marker levels, especially bone resorption, are found in the institutionalized elderly and in patients with chronic diseases associated with prolonged bed rest and limited mobility such as dementia, Alzheimer's disease, stroke, hemiplegia, and Parkinson's disease(Szulc and Delmas 2008).

High levels of bone turnover markers may predict fracture risk independently from bone mineral density in postmenopausal women. They have been used for this purpose in clinical practice for many years, but there is still a need for stronger evidence on which to base practice. Bone turnover markers hold promise in fracture risk prediction and for monitoring treatment (Vasikaran et al. 2011). We need more bone turnover markers reflecting the action of enzymes involved in the catabolism of bone matrix, e.g., cathepsin K, metalloproteinases. They would be useful to assess enzymatic mechanisms of bone matrix degradation and the efficacy of drugs acting on certain metabolic pathways, e.g., cathepsin K inhibitors (Szulc and Delmas 2008).

Summary Points

- This chapter focuses on the bone turnover after spinal cord injury.
- Osteoporosis is one of the most frequent complications following SCI, resulting from uncoupling of bone remodeling in favor of bone resorption.
- This imbalance takes place right after the initial injury and persists for many years.
- Development of severe osteoporosis in the paralyzed part of the body is accompanied by the loss of biomechanical strength, and the biosynthesis of structurally modified matrix unable to sustain normal mechanical stress. Therefore, the risk of fracture is dramatically increased.
- The exact pathophysiology of osteoporosis after SCI is still not clear. The pathogenesis of osteoporosis after SCI is generally considered disuse. Mechanical loading is known to be a crucial stimulus for bone formation and resorption, thereby controlling bone mass, structure, and strength.
- The factors that are independent of mechanical loading of the skeleton also appear to be important.
- Recent works suggest that bone remodeling is regulated by nerve-derived signals, sclerostin, and that there is a marked modification in the osteoprotegerin/RANKL system in recent SCI patients.
- Biochemical bone markers of bone turnover are shown to reflect dynamic skeletal status and may help to identify increased bone loss and fracture risk.
- An improved understanding of the natural history and risk factors for chronic bone loss following SCI is essential to designing therapies to reduce the rate of bone loss, define fracture risk, and ultimately prevent osteoporotic fractures and their associated morbidity.
- We are of the opinion that prospective randomized controlled trials should be conducted to evaluate, standardize, and find bone-specific biochemical marker of bone turnover in SCI.

References

Astorino TA, Harness ET, Witzke KA. Effect of chronic activity based therapy on bone mineral density and bone turnover in persons with spinal cord injury. Eur J Appl Physiol. 2013;113:3027–37.

Bagis S, Sahin G, Aybay C, Karag€oz A. Bone metabolism in patients with spinal cord injury. Turkish J Rheumatol. 2002;17:168–73.

Balemans W, Ebeling M, Patel N, et al. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). Hum Mol Genet. 2001;10:537–43.

Bauman WA, Spungen AM, Flangan S, et al. Blunted growth hormone response to intravenous arginine in subjects with a spinal cord injury. Horm Metab Res. 1994;26:152–6.

Bauman WA, Zhong YG, Schwartz E. Vitamin D deficiency in veterans with chronic spinal cord injury. Metabolism. 1995;44(12):1612–6.

Bauman WA, Spungen AM, Wang J, et al. Continuous loss of bone during chronic immobilization: a monozygotic twin study. Osteoporos Int. 1999;10:123–7.

Bauman WA, Morrison NG, Spungen AM. Vitamin D replacement therapy in persons with spinal cord injury. J Spinal Cord Med. 2005;28(3):203–7.
Belanger M, Stein RB, Wheeler GD, et al. Electrical stimulation: can it increase muscle strength and reverse osteopenia in spinal cord injured individuals? Arch Phys Med Rehabil. 2000;81:1090–8.
Bergmann P, Heilporn A, Schoutens A, et al. Longitudinal study of calcium and bone metabolism in paraplegic patients. Paraplegia. 1977;15 suppl 2:147–59.
Bergmann P, Body JJ, Boonen S, et al. Evidence-based guidelines for the use of biochemical markers of bone turnover in the selection and monitoring of bisphosphonate treatment in osteoporosis: a consensus document of the Belgian Bone Club. Int J Clin Pract. 2009;63:19–26.
Bermudez F, Surks MI, Oppenheimer JH. High incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease. J Clin Endocrinol Metab. 1975;41:27–40.
Biering-Sorensen F, Bohr H, Schaadt O. Bone mineral content of the lumbar spine and lower extremities years after spinal cord lesion. Paraplegia. 1988;26:293–301.
Biering-Sorensen F, Bohr H, Schaadt O. Longitudinal study of bone mineral content in the lumbar spine, the forearm and the lower extremities after spinal cord injury. Eur J Clin Invest. 1990;20:330–5.
Bugaresti JM, Tator CH, Silverberg JD, et al. Changes in thyroid hormones, thyroid stimulating hormone and cortisol in acute spinal cord injury. Paraplegia. 1992;30(6):401–9.
Chain A, Koury JC, Bezerra FF. Physical activity benefits bone density and bone-related hormones in adult men with cervical spinal cord injury. Eur J Appl Physiol. 2012;112:3179–86.
Chantraine A, Heynen G, Franchimont P. Bone metabolism, parathyroid hormone, and calcitonin in paraplegia. Calcif Tissue Int. 1979;27:199–204.
Chantraine A, Nusgens B, Lapiere CM. Bone remodeling during the development of osteoporosis in paraplegia. Calcif Tissue Int. 1986;38:323–7.
Cheville AL, Kirshblum SC. Thyroid hormone changes in chronic spinal cord injury. J Spinal Cord Med. 1995;18:227–32.
Chow YW, Inman C, Pollintine P, et al. Ultrasound bone densitometry and dual energy X-ray absorptiometry in patients with spinal cord injury: a cross-sectional study. Spinal Cord. 1996;34 suppl 12:736–41.
Clark JM, Jelbart M, Rischbieth H, et al. Physiological effects of lower extremity functional electrical stimulation in early spinal cord injury: lack of efficacy to prevent bone loss. Spinal Cord. 2007;45:78–85.
Clasey JL, Janowiak AL, Gater DR. Relationship between regional bone density measurements and the time since injury in adults with spinal cord injuries. Arch Phys Med Rehabil. 2004;85:59–64.
Claus-Walker J, Carter RE, Di Ferrante M, et al. Immediate endocrine and metabolic consequences of traumatic quadriplegia in a young woman. Paraplegia. 1977;15:202–8.
Darby AJ, Meunier PJ. Mean wall thickness and formation periods of trabecular bone packets in idiopathic osteoporosis. Calcif Tissue Int. 1981;33:199–204.
Dauty M, Perrouin-Verbe B, Maugars Y, et al. Supralesional and sublesional bone mineral density in spinal cord-injured patients. Bone. 2000;27:305–9.
de Bruin ED, Vanwanseele B, Dambacher MA, et al. Long-term changes in the tibia and radius bone mineral density following spinal cord injury. Spinal Cord. 2005;43:96–100.
Demirel G, Yilmaz H, Paker N, et al. Osteoporosis after spinal cord injury. Spinal Cord. 1998;36:822–5.
Demulder A, Guns M, Ismail A, et al. Increased osteoclast-like cells formation in long-term bone marrow cultures from patients with a spinal cord injury. Calcif Tissue Int. 1998;63:396–400.
Elefteriou F. Neuronal signaling and the regulation of bone remodeling. Cell Mol Life Sci. 2005;62:2339–49.
Eser P, Frotzler A, Zehnder Y, et al. Relationship between the duration of paralysis and bone structure: a pQCT study of spinal cord injured individuals. Bone. 2004;34:869–80.
Finsen V, Indredavik B, Fougner KJ. Bone mineral and hormone status in paraplegics. Paraplegia. 1992;30:343–7.

Frey-Rindova P, De Bruin ED, Stussi E, et al. Bone mineral density in upper and lower extremities during 12 months after spinal cord injury measured by peripheral quantitative computed tomography. Spinal Cord. 2000;38:26–32.
Frost HM. Bone "mass" and the "mechanostat": a proposal. Anat Rec. 1987;219:1–9.
Frost HM. On our age-related bone loss: insights from a new paradigm. J Bone Miner Res. 1997;12:1539–46.
Frost HM. Osteoporosis: a rationale for further definitions? Calcif Tissue Int. 1998;62:89–94.
Frost HM. Bone's mechanostat: a 2003 update. Anat Rec A Discov Mol Cell Evol Biol. 2003;275:1081–91.
Frotzler A, Berger M, Knecht H, et al. Bone steady-state is established at reduced bone strength after spinal cord injury: a longitudinal study using peripheral quantitative computed tomography (pQCT). Bone. 2008;43:549–55.
Garland DE, Adkins RH. Bone loss at the knee in spinal cord injury. Top Spinal Cord Inj Rehabil. 2001;6 suppl 3:37–46.
Garland DE, Stewart CA, Adkins RKH, et al. Osteoporosis after spinal cord injury. J Orthop Res. 1992;10:371–8.
Garland DE, Foulkes GD, Adkins RH, Stewart CA, Yakura JS. Regional osteoporosis following incomplete spinal cord injury. Contemporary Orthop. 1994;28(suppl 2):134–139.
Garland DE, Adkins RH, Stewart CA, et al. Regional osteoporosis in women who have a complete spinal cord injury. J Bone Joint Surg Am. 2001;83:1195–200.
Garland DE, Adkins RH, Scott M, et al. Bone loss at the os calcis compared with bone loss at the knee in individuals with spinal cord injury. J Spinal Cord Med. 2004;27:207–11.
Giangregorio L, McCartney N. Bone loss and muscle atrophy in spinal cord injury: epidemiology, fracture prediction, and rehabilitation strategies. J Spinal Cord Med. 2006;29: 489–500.
Giangregorio LM, Hicks AL, Webber CE, et al. Body weight supported treadmill training in acute spinal cord injury: impact on muscle and bone. Spinal Cord. 2005;43:649–57.
Hill EL, Martin RB, Gunther E, et al. Changes in bone in a model of spinal cord injury. J Orthop Res. 1993;11:537–47.
Hjeltnes N, De Groot P, Birkeland KI. Tetraplegic subjects have hyperleptinaemia with marked circadian variation. Clin Endocrinol. 2005;62:223–7.
Huang TS, Wang YH, Lai JS, et al. The hypothalamus–pituitary–ovary and hypothalamus–pituitary–thyroid axes in spinal cord-injured women. Metabolism. 1996;45:718–22.
Huang TS, Wang YH, Chen SY. The relation of serum leptin to body mass index and to serum cortisol in men with spinal cord injury. Arch Phys Med Rehabil. 2000;81:1582–6.
Hummel K, Craven BC, Giangregorio L. Serum 25(OH)D, PTH and correlates of suboptimal 25 (OH)D levels in persons with chronic spinal cord injury. Spinal Cord. 2012;50:812–6.
Inceoglu S, Burghardt A, Akbay A, et al. Trabecular architecture of lumbar vertebral pedicle. Spine. 2005;30:1485–90.
Jiang SD, Jiang LS, Dai LY. Mechanism of osteoporosis in spinal cord injury. Clin Endocrinol. 2006a;65:555–65.
Jiang SD, Dai LY, Jiang LS. Osteoporosis after spinal cord injury. Osteoporos Int. 2006b;17:180–92.
Jilka RL. Biology of the basic multicellular unit and the pathophysiology of osteoporosis. Med Pediatr Oncol. 2003;41:182–5.
Jones LM, Goulding A, Gerrard DF. DEXA: a practical and accurate tool to demonstrate total and regional bone loss, lean tissue loss and fat mass gain in paraplegia. Spinal Cord. 1998;36 suppl 9:637–40.
Jones LM, Legge M, Goulding A. Intensive exercise may preserve bone mass of the upper limbs in spinal cord injured males but does not retard demineralisation of the lower body. Spinal Cord. 2002;40:230–5.
Jones LM, Legge M. Biochemical markers of bone activity in active and sedentary spinal cord injured men. N Z J Med Lab Sci 2009; 63: 40–43.

Kanis JA, McCloskey EV, Johansson H, et al. A reference standard for the description of osteoporosis. Bone. 2008;42:467–75.
Kannisto M, Alaranta H, Merikanto J, et al. Bone mineral status after pediatric spinal cord injury. Spinal Cord. 1998;36 suppl 9:641–6.
Kaya K, Aybay C, Ozel S, et al. Evaluation of bone mineral density in patients with spinal cord injury. J Spinal Cord Med. 2006;29:396–401.
Kiratli BJ, Smith AE, Nauenberg T, et al. Bone mineral and geometric changes through the femur with immobilization due to spinal cord injury. J Rehabil Res Dev. 2000;37:225–33.
Kunkel CF, Scremin AM, Eisenberg B, et al. Effect of "standing" on spasticity, contracture, and osteoporosis in paralyzed males. Arch Phys Med Rehabil. 1993;74:73–8.
Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell. 1998;93:165–76.
Lazo MG, Shirazi P, Sam M, et al. Osteoporosis and risk of fracture in men with spinal cord injury. Spinal Cord. 2001;39:208–14.
Leslie WD, Nance PW. Dissociated hip and spine demineralization: a specific finding in spinal cord injury. Arch Phys Med Rehabil. 1993;74:960–4.
Liu CC, Theodorou DJ, Theodorou SJ, et al. Quantitative computed tomography in the evaluation of spinal osteoporosis following spinal cord injury. Osteoporos Int. 2000;11:889–96.
Maimoun L, Sultan C. Effects of physical activity on bone remodeling. Metabolism. 2011;60:373–88.
Maimoun L, Couret I, Micallef JP, et al. Use of bone biochemical markers with dual-energy x-ray absorptiometry for early determination of bone loss in persons with spinal cord injury. Metabolism. 2002;51:958–63.
Maimoun L, Puech AM, Manetta J, et al. Circulating leptin concentrations can be used as a surrogate marker of fat mass in acute spinal cord injury. Metabolism. 2004;53:989–94.
Maimoun L, Couret I, Mariano-Goulart D, et al. Changes in osteoprotegerin/RANKL system, bone mineral density and bone biochemical markers in patients with recent spinal cord injury. Calcif Tissue Int. 2005;76:404–11.
Maimoun L, Lumbroso S, Paris S, et al. The role of androgens or growth factors in the bone resorption process in with recent spinal cord injured patients: a cross-sectional study. Spinal Cord. 2006;44:791–7.
Maimoun L, Fattal C, Sultan C. Bone remodeling and calcium homeostasis in patients with spinal cord injury: a review. Metabolism. 2011;60:1655–63.
Maynard FM, Imai K. Immobilization hypercalcaemia in spinal cord injury. Arch Phys Med Rehabil 1977; 58: 16–24.
Maynard FM. Immobilization hypercalcemia following spinal cord injury. Arch Phys Med Rehabil. 1986;67:41–4.
Mechanick JI, Pomerantz F, Flanagan S, et al. Parathyroid hormone suppression in spinal cord injury patients is associated with the degree of neurologic impairment and not the level of injury. Arch Phys Med Rehabil. 1997;78:692–6.
Mechanick JI, Liu K, Nierman DM, Stein A. Effect of a convenient single 90-mg pamidronate dose on biochemical markers of bone metabolism in patients with acute spinal cord injury. J Spinal Cord Med. 2006;29:406–12.
Minaire P, Neunier P, Edouard C, et al. Quantitative histological data on disuse osteoporosis: comparison with biological data. Calcif Tissue Res. 1974;17:57–73.
Modlesky CM, Majumdar S, Narasimhan A, et al. Trabecular bone microarchitecture is deteriorated in men with spinal cord injury. J Bone Miner Res. 2004;19:48–55.
Modlesky CM, Slade JM, Bickel CS, et al. Deteriorated geometric structure and strength of the midfemur in men with complete spinal cord injury. Bone. 2005;36:331–9.
Morley JE, Distiller LA, Lissoos I, et al. Testicular function in patients with spinal cord damage. Horm Metab Res. 1979;11:679–82.
Morse LR, Nguyen HP, Jain N, et al. Age and motor score predict osteoprotegerin level in chronic spinal cord injury. J Musculoskelet Neuronal Interact. 2008;8:50–7.

Moynahan M, Betz RR, Triolo RJ, et al. Characterization of the bone mineral density of children with spinal cord injury. J Spinal Cord Med. 1996;19 suppl 4:249–54.
Naderi AR, Safarinejad MR. Endocrine profiles and semen quality in spinal cord injured men. Clin Endocrinol. 2003;58:177–84.
Naftchi NE, Viau AT, Sell GH, et al. Pituitary-testicular axis dysfunction in spinal cord injury. Arch Phys Med Rehabil. 1980;61:402–5.
Nance PW, Shears AH, Givner ML, et al. Gonadal regulation in men with flaccid paraplegia. Arch Phys Med Rehabil. 1985;66:757–9.
Noreau L, Shephard RJ. Spinal cord injury, exercise and quality of life. Sports Med. 1995;20:226–50.
Ogilvie C, Bowker P, Rowley DI. The physiological benefits of paraplegic orthotically aided walking. Paraplegia. 1993;31:111–5.
Paker N, Bugdaycı D, Ersoy S, et al. Bone loss and bone turnover in acute and chronic spinal cord injured patients. Neurosciences (Riyadh). 2007;12:232–5.
Pietschmann P, Pils P, Woloszczuk W, et al. Increased serum osteocalcin levels in patients with paraplegia. Paraplegia. 1992;30:204–9.
Prakash V. Low serum 3,3′,5-triiodothyronine (T3) and reciprocally high serum 3,3′, 5′-triiodothyronine (reverse T3) concentration in spinal cord injury patients. J Am Paraplegia Soc. 1983;6:56–8.
Reiter AL, Volk A, Vollmar J, et al. Changes of basic bone turnover parameters in short-term and long-term patients with spinal cord injury. Eur Spine J. 2007;16:771–6.
Rittweger J, Gerrits K, Altenburg T, et al. Bone adaptation to altered loading after spinal cord injury: a study of bone and muscle strength. J Musculoskelet Neuronal Interact. 2006;6:269–76.
Rittweger J, Goosey-Tolfrey VL, Cointry G, et al. Structural analysis of the human tibia in men with spinal cord injury by tomographic (pQCT) serial scans. Bone. 2010;47:511–8.
Roberts D, Lee W, Cuneo RC, et al. Longitudinal study of bone turnover after acute spinal cord injury. J Clin Endocrinol Metab. 1998;83:415–22.
Rosenquist RC. Evaluation of 17-ketosteroid, oestrogen and gonadotrophin excretion in patients with spinal cord injury. Am J Med. 1950;8:534–5.
Sabo D, Blaich S, Wenz W, et al. Osteoporosis in patients with paralysis after spinal cord injury: a cross-sectional study in 46 male patients with dual-energy X-ray absorptiometry. Arch Orthop Trauma Surg. 2001;121(suppl 1–2):75–8.
Sabour H, Javidan AN, Latifi S. Bone biomarkers in patients with chronic traumatic spinal cord injury. Spine J. 2014;14:1132–8.
Saltzstein RJ, Hardin S, Hastings J. Osteoporosis in spinal cord injury: using an index of mobility and its relationship to bone density. J Am Paraplegia Soc. 1992;15 suppl 4:232–4.
Shetty KR, Sutton CH, Mattson DA, et al. Hyposomatomedinemia in quadriplegic men. Am J Med Sci. 1993;305:95–100.
Singh R, Rohilla RK, Saini G, et al. Bone mineral density and biochemical markers of bone turnover during first year of injury in SCI patients. J Orthop Trauma Rehabil. 2014a;18:2–6.
Singh R, Rohilla RK, Saini G, et al. Measurements of body composition in spinal cord injury patients during first year of injury. Indian J Orthop. 2014b;48(2):168–77.
Slade JM, Bickel CS, Modlesky CM, et al. Trabecular bone is more deteriorated in spinal cord injured versus estrogen-free postmenopausal women. Osteoporos Int. 2005;16:263–72.
Sloan KE, Bremner LA, Byrne J, et al. Musculoskeletal effects of an electrical stimulation induced cycling programme in the spinal injured. Paraplegia. 1994;32:407–15.
Staehling-Hampton K, Proll S, Paeper BW, et al. A 52-kb deletion in the SOST-MEOX1 intergenic region on 17q12-q21 is associated with van Buchem disease in the Dutch population. Am J Med Genet. 2002;110:144–52.
Stewart AF, Adler M, Byers CM, et al. Calcium homeostasis in immobilization: an example of resorptive hypercalciuria. N Engl J Med. 1982;306:1136–40.
Szollar SM, Martin EME, Sartoris DJ, et al. Bone mineral density and indexes of bone metabolism in spinal cord injury. Am J Phys Med Rehabil. 1998;77:28–35.

Szulc P, Delmas P. Biochemical markers of bone turnover: potential use in the investigation and management of postmenopausal osteoporosis. Osteoporos Int. 2008;19:1683–704.
Tsitouras PD, Zhong YG, Spungen AM, et al. Serum testosterone and growth hormone/insulin-like growth factor-I in adults with spinal cord injury. Horm Metab Res. 1995;27:287–92.
Tsuzuku S, Ikegami Y, Yabe K. Bone mineral density differences between paraplegic and quadriplegic patients: a cross-sectional study. Spinal Cord. 1999;37:358–61.
Uebelhart D, Hartmann D, Vuagnat H, et al. Early modifications of biochemical markers of bone metabolism in spinal cord injury patients: a preliminary study. Scand J Rehabil Med. 1994;26:197–202.
Uebelhart D, Demiaux-Domenech B, Roth M, Chantraine A. Bone metabolism in spinal cord injured individuals and in others who have prolonged immobilization. A review. Paraplegia. 1995;33:669–673.
Vasikaran SD. Utility of biochemical markers of bone turnover and bone mineral density in management of osteoporosis. Crit Rev Clin Lab Sci. 2008;45:221–58.
Vasikaran S, Eastell R, Bruyere O. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int. 2011;22:391–420.
Vaziri ND, Pandian MR, Segal JL, et al. Vitamin D, parathormone and calcitonin profiles in persons with long-standing spinal cord injury. Arch Phys Med Rehabil. 1994;75:766–9.
Wang YH, Huang TS, Lien IN, et al. Hormone changes in men with spinal cord injuries. Am J Phys Med Rehabil. 1992;71:328–32.
Wang YH, Huang TS, Liang HW, et al. Fasting serum levels of adiponectin, ghrelin, and leptin in men with spinal cord injury. Arch Phys Med Rehabil. 2005;86:1964–8.
Warden SJ, Bennell KL, Matthews B, et al. Efficacy of low intensity pulsed ultrasound in the prevention of osteoporosis following spinal cord injury. Bone. 2001;29(5):431–6.
Wijenayaka AR, Kogawa M, Lim HP, et al. Sclerostin stimulates osteocyte support of osteoclast activity by a RANKL-dependent pathway. PLoS One. 2011;6:e25900.
Wilmet E, Ismail AA, Heilporn A, et al. Longitudinal study of the bone mineral content and of soft tissue composition after spinal cord section. Paraplegia. 1995;33:674–7.
Zehnder Y, Luthi M, Michel D, et al. Long-term changes in bone metabolism, bone mineral density, quantitative ultrasound parameters, and fracture incidence after spinal cord injury: a cross-sectional observational study in 100 paraplegic men. Osteoporos Int. 2004;15:180–9.
Zeitzer JM, Ayas NT, Shea SA, et al. Absence of detectable melatonin and preservation of cortisol and thyrotropin rhythms in tetraplegia. J Clin Endocrinol Metab. 2000;85:2189–96.
Zhou XJ, Vaziri ND, Segal JL, et al. Effects of chronic spinal cord injury and pressure ulcer on 25 (OH)-vitamin D levels. J Am Paraplegia Soc. 1993;16:9–13.