J Musculoskelet Neuronal Interact 2011; 11(3):257-265

Review Article

Hylonome

Spinal cord injury-related bone impairment and fractures: An update on epidemiology and physiopathological mechanisms

Y. Dionyssiotis

Rehabilitation Department, Physical and Social Rehabilitation Center Amynteo, Florina, Greece

Abstract

A sudden loss of motor function in segments of the spinal cord results in immobilisation and is complicated by bone loss and fractures in areas below the level of injury. Despite the acceptance of osteoporosis and fractures as two major public health problems, in people with spinal cord injuries, the mechanisms are not adequately investigated. Multiple risk factors for bone loss and fractures are present in this disabled population. This review is an update on the epidemiology and physiopathological mechanisms in spinal cord injury-related bone impairment and fractures.

Keywords: Spinal Cord Injury, Bone, Fractures, Physiopathology, Epidemiology

Introduction

Osteoporosis is a systemic skeletal disease characterised by reduced bone strength predisposing a person to an increased risk of fracture. Bone strength incorporates bone mineral density and bone quality[1]. The World Health Organisation (WHO) created an operational definition of postmenopausal osteoporosis based on a bone mineral density (BMD)-based T-score measurement at any point of the frame[2]. The ranking system of the WHO is commonly used in the literature and in all discussions with respect to bone diseases. According to WHO criteria, the general categories for making a diagnosis are the following: 1) normal: BMD of not less than one standard deviation (SD) than the average young adult (T-score>-1), 2) osteopenia: BMD between one and 2.5 SD below the average for young adults (-1<T-score< -2.5), 3) osteoporosis: BMD 2.5 SD or more below the average for young adults (T-score>-2.5) and 4) severe or established osteoporosis: BMD 2.5 SD or more below the average for young adults and the presence of one or more fractures[2,3].

As efforts to identify clinical signs of low bone density have focused mainly on able-bodied people, many factors which make a disabled person at increased risk of osteoporosis were not taken into account. The clinical usefulness of the T-score in diagnosing spinal cord injury (SCI) patients with low BMD remains unclear. Despite the increased number of risk factors in SCI, guidelines are not available on BMD measurements and, as well, virtually no ranking system exists similar to the one already mentioned for postmenopausal women. For this reason, we believe that it would be more appropriate for people with SCI and various disabilities to use the Z-score obtained from the measurement of bone densitometry. The Z-score is the number of standard deviations above or below what is normally expected for someone of similar age, sex, weight and race in question. In clinical practice, it is useful because a Z-score of below -1.5 SD probably indicates secondary causes of osteoporosis[4].

Proposing a new terminology to describe bone loss in spinal cord injury

Frost et al. explained in 1997 that the traditional definitions of osteoporosis and osteopenia are not appropriate for describing bone loss in SCI[5]. In the international literature on disability and SCI, most authors use these terms and subjects are classified according to WHO criteria for postmenopausal

The author has no conflict of interest.

Corresponding author: Yannis Dionyssiotis, MD, PhD, Physical and Social Rehabilitation Center Amynteo, 53200, Florina, Greece
E-mail: yannis_dionyssiotis@hotmail.com

Edited by: F. Rauch
Accepted 4 July 2011

women. On the other hand, the term "bone loss" is probably not specific enough, and might imply that the change in bone status is being recorded over time.

Generally, there are differences in traumatic and pathological lesions of the spinal cord accompanied by ongoing bone loss: the progression or not of the disease (i.e. progressive multiple sclerosis vs. complete paraplegia), the type of injury (i.e. lesion with a level of injury vs. upper motor neuron pyramidal lesion), life expectancy, residual mobility and functionality, the ability to walk and stand (i.e. incomplete paraplegia vs. tetraplegia vs. high-low paraplegia) and drug treatment (i.e. frequent corticosteroid therapy in multiple sclerosis vs. long-term therapy with anticoagulants in paraplegia) vary. In addition, there are differences in the degree of spasticity (i.e. flaccid vs. spastic paralysis) and it is necessary to take into account the issue of fatigue and muscle weakness in disabilities. Moreover, patients with motor disorders often face problems of depression which can make it difficult to comply with the proposed treatments by the physicians and limit mobility. In terms of physical disability, there are differences between complete (an absence of sensory or motor function below the neurological level, including the lowest sacral segment) and incomplete lesions (partial preservation of motor and/or sensory function below the neurological level, including the lowest sacral segment). Patients with complete injuries have greater bone loss than those with an incomplete injury[6], as has already been shown in Brown-Sequard subjects (incomplete SCI), where BMD of the more paretic knee was lower than that of the stronger knee[7]. However, in spinal cord lesions, there are also similarities; for example, the clinical equivalence of diseases with different physiopathology, location, evolution, etc. A severe form of multiple sclerosis (MS) can result in a wheelchair-bound patient having a clinical outcome equivalent to paraplegia. One patient with MS may have a better walking gait pattern in comparison with a patient with incomplete paraplegia, but may also be unable to walk and vice versa.

In addition to these differences/similarities, the role of factors which do not change, i.e., race or gender of the patient, is inadequately clarified. Few studies on women with disabilities debate whether their bones are more affected than those of men with disabilities. There is a tendency for chronic SCI women to have lower bone mass than men[8]. Moreover, higher rates of lower bone mass with lower T-scores have been reported in women with SCI compared to women with other disabilities[9]. Because a large proportion of spinal cord injuries occur before achieving peak bone mass, and because the rate of bone resorption and formation is reduced, particularly below the level of injury, low values of BMD and increased risk of fracture in people with impaired spinal cord are not surprising[10]. Studies in paraplegics have found that the age at injury can affect bone loss[6]. The term "osteoporosis" below the level of injury must be used with caution, especially in tetraplegia, paraplegia and/or equivalent diseases. This concept is supported by the maintenance of bone in the spine in regions below the level of the lesion because of weight bearing in the seated position (i.e. in a wheelchair), and compressive stress of the fusion materials used following injury in the injured area (i.e. in traumatic paraplegia). Force exerted by orthopaedic materials in the surrounding muscles may affect the BMD of the spine, but there are no studies to support this hypothesis.

Because of the unique and individually-based approach needed in the management of each disabled subject with a spinal cord lesion and their complications according to bone loss the new term "spinal cord injury-related bone impairment, (SCI-related BI)" is used throughout this paper.

Epidemiology

According to the literature, spinal cord injury-related bone impairment occurs in 75% of patients with complete spinal cord injury (SCI)[11]. Lazo et al. showed that 25 out of 41 patients with SCI (61%) met WHO criteria for osteoporosis; eight (19.5%) were osteopenic and only eight (19.5%) showed normal values[6]. In SCI children (boys and girls), values for BMD at the hip were approximately 60% of normal, or had a Z-score that indicated a 1.6-1.8 SD reduction in BMD compared with age- and sex-matched peers[12]. The decrease in BMD was probably the dominant cause for the high prevalence of SCI-related BI in the long femur or proximal tibia and explains why these areas are often fracture sites[6,13,14]. For example, a reduction in bone mineral density in the femoral neck of about 0.1 g/cm^2 increases fracture risk by 2.2 times. This decrease in bone mass is associated with alterations in bone material, reduced bone elasticity and is connected to the origin of pathological fractures with minimal injury, in which these patients are vulnerable and exposed[13,15-17]. Fractures are very common in patients with SCI. Ragnarsson and Sell retrospectively studied more than 3000 SCI subjects admitted over five years and found 1.8% of men and 2.5% of women had fractured[13]. Mulsow et al. recently found a 5% lower limb fracture incidence in patients with complete SCI in line with previously publications which reported rate of fractures between 1%-6%, but this number was probably underestimated[18]. Lazo et al. reported a higher frequency of history of fractures in patients with SCI (34% of patients)[6]. Epidemiological data from the U.S. (Model SCI Systems) reported that 14% of SCI suffer a fracture during the first five years after injury. The percentage increases to 28% at 10 years and 39% after 15 years. The incidence of fractures increases with age and is higher in complete lesions (10 times higher compared to incomplete lesions), in paraplegics compared to tetraplegics (due to greater mobility and participation in physical activity) and in women than in men[19]. Fractures often occur in the long femur and the proximal end of the tibia and, because of their increased frequency in those areas, are characterised as "paraplegic" fractures[20]. In a retrospective analysis performed by Logan in a subset of the 1996 Veterans Health Administration (VHA) National Spinal Cord Dysfunction Registry, from which 8150 patients were identified with either MS (n=1789) or SCI (n=6361), it was found that, in subjects with spinal cord disease, there were significant differences in the risk of fracture according to causal disease, controlling for motor impairment and duration,

whereas trauma-related SCI increased the relative risk (RR) of fracture by 80% (RR=1.82, p<.001) compared with MS[21]. Vestergaard et al. reported significantly increased fracture rates in SCI patients especially leading to low-energy fractures of the lower extremities which increased from the time of the injury to a stable level from the third year onwards. Fractures of the forearms were rare because of bone loss protection from using manual wheelchairs and in subjects with tetraplegia because of their inability to use their forearms to prevent falls and traumas which thus affects other parts of the body. It also seems that female gender is a specific factor associated with an increased fracture risk. High energy fractures resulting from bicycle or motor vehicle accidents are unusual in the chronic phase in SCI patients, but occur at the time of injury[22]. Wang et al. have stated that the incidence of extra-spinal fractures was 28% at the same time as SCI, and most frequently involved the chest (52%), followed by the lower extremities (25%), upper extremities (24%), head (17%), other (11%) and pelvis (9%)[23]. In chronic SCI, Morse et al. stated that the most common cause of fractures was falling from the wheelchair (51%), followed by fractures during transferring like twisting or catching a lower extremity (14%), and catching a lower extremity on a doorframe while operating a wheelchair (6%)[24]. Others showed that fractures are also common while turning in bed and transferring from the wheelchair to the car. Incorrect placement of the feet and hip during turning also increases pressure on the leg and causes fractures[25]. Hospitalisation is often required most commonly for tibia/fibula fracture (47.5%) followed by the distal femoral metaphysis (20%), the proximal femur (15%) and then less common fractures of the humerus (5%), metatarsals (5%) and phalanges (7.5%)[24].

Physiopathology

Physiopathology of spinal cord injury-related bone impairment in SCI is multifactorial in the acute and chronic phases. The main cause of SCI-related BI is not sufficiently understood, although the problem was detected 50 years ago[26-28]. Disuse seems to play a role, but most specialists believe that immobilisation of these patients is a minor factor in the aetiology of SCI-related BI below the neurological level of injury[29]. The loss of mechanical stimuli in bone is a major challenge and has an effect on bone integrity. In individuals with SCI, bone loss begins immediately after injury[30,31]. SCI-related BI below the level of injury is much greater compared with other conditions (i.e. age, immobilisation, bed rest, lack of gravity environment).

Bone loss and deterioration of bone structure according to the neurological level of injury

During the first months, demineralisation occurs exclusively in the areas below the level of the lesion and especially in the weight-bearing parts of the skeleton such as the distal end of the femur and the proximal tibia, which are rich in cancellous bone, while the region of the diaphysis of the femur and tibia, which are areas rich in cortical bone, are partially preserved. Using the method of dual-energy X-ray absorptiometry (DXA), Wilmet et al. reported a reduction in bone mineral content during the first years after the injury at a rate of 4% per month in regions rich in cancellous bone, and 2% per month at sites containing mainly cortical bone[26]. The largest decrease in bone mass occurred during the first six months after injury and stabilised after 12-16 months, at which point around 2/3 of the original bone mass was close to the threshold for pathological fracture[32]. On the other hand, Szollar et al., employing DXA, indicated that the loss of bone mass approached the fracture threshold one to five years after injury[33]. In SCI-related BI, bone loss differs even in the same bone[34]. Recently, Eser et al. using peripheral quantitative computed tomography (pQCT) in SCI subjects, specified the chronic SCI bone steady-state as occurring at around three to seven years post-SCI, and found that bone loss in the epiphyses was 50% in the femur and 60% in the tibia, while loss was 35% and 25% in the femoral and tibial shafts, respectively. They also found that bone loss between the trabecular and cortical bone compartments differed in mechanism, i.e. in the epiphyses, bone was lost due to a decrease in trabecular bone, while in the diaphysis, cortical bone density was maintained and bone was lost due to endocortical resorption[35]. In line with the previous study, another pQCT study of the tibia included chronic complete paraplegic men classified according to the neurological level of injury (above and below thoracic 7), and found a loss of trabecular bone in all paraplegics (57.5% vs. 51% in high and low paraplegics, respectively) and cortical bone (3.6% and 6.5%, respectively), suggesting that trabecular bone is more affected during years of paralysis[36] (Figure 1). Another finding in this study was that both paraplegic groups had a similar loss of total BMD (46.90% vs. 45.15% in high and low paraplegics, respectively), suggesting that a homogenous deficit pattern occurs in the epiphyseal area, especially in the group of low paraplegics, because the centre and periphery of the cross-sectional area of bone were similarly affected. On the contrary, in the group of high paraplegics, trabecular bone loss was higher, suggesting increased endocortical remodeling while keeping the total BMD similar. Concerning cortical geometric properties, the results showed an increased endosteal circumference between both paraplegic groups vs. controls leading to a reduction in cortical thickness, 19.78% vs. 16.98% in the paraplegic groups respectively, whereas periosteal circumference was comparable to controls[36]. Surprisingly, the lumbar spine bone, which mainly consists of spongy bone, did not show a reduction in bone density regardless of the level of injury or duration of the traumatic period[37]. Nevertheless, it should be noted that in certain cases, the BMD at the lumbar spine may be increased due to neuropathic spondylarthropathies[38]. Deformities that reduce the physiological load of the vertebral bodies put a person with SCI at greater risk of BMD loss in the spine. In the absence of bone resorption, a significant loss of bone density in patients with an impaired spinal cord is not expected in the spine and therefore should differentiate secondary causes of osteoporosis[39].

Regarding tetraplegic patients in the study by Tsuzuku et al., statistically significant differences were found in the BMD of the spine, trochanteric region and upper limbs between paraplegic and tetraplegic patients, but not in the femoral neck, pelvis and

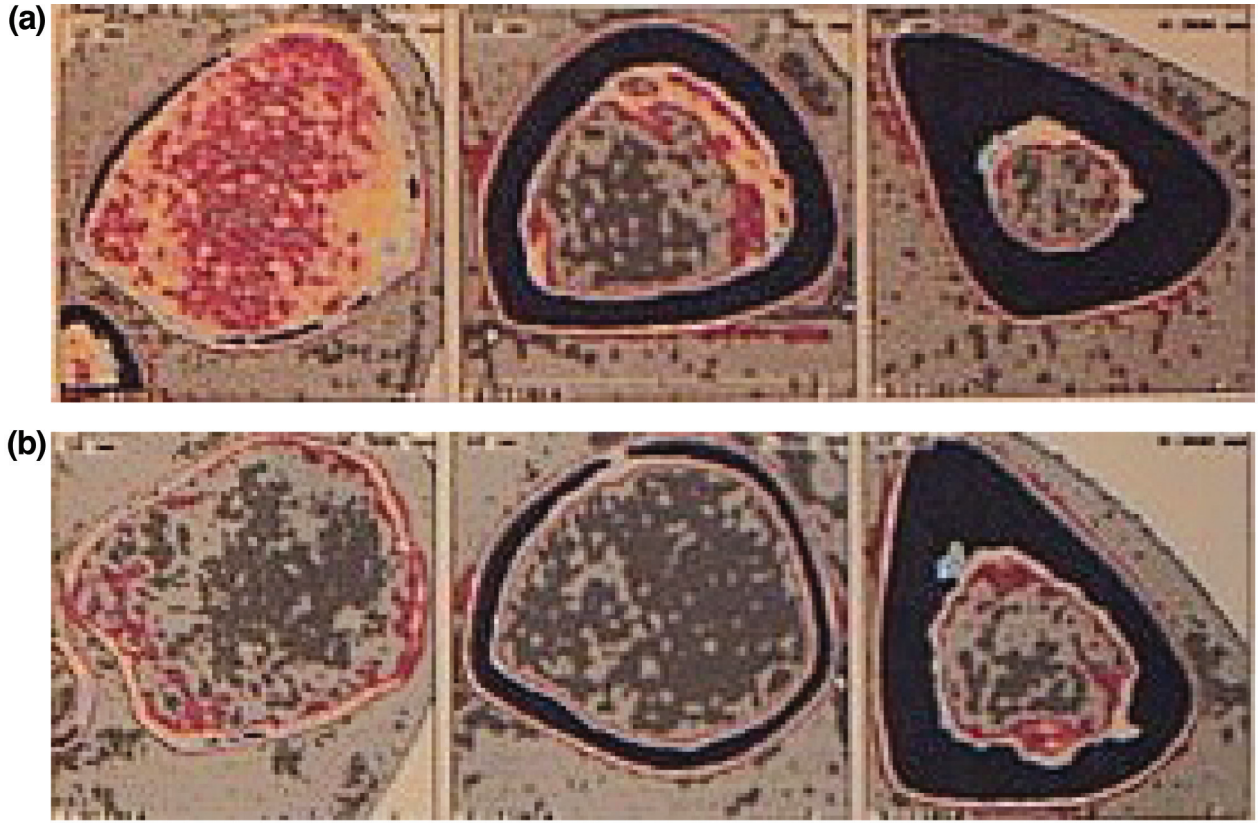

Figure 1. Figure represents peripheral quantitative computed tomography (p QCT) tibia slices in control (**a**) and spinal cord injured subject with paraplegia (**b**), (scanner XCT 3000 Stratec Medizintechnik, Pforzheim, Germany). Bone loss is evident in the paraplegic subject. Areas in red represent trabecular bone, while areas in grey represent fat. (a) Tibia p QCT from a control 39 years old man, slices: 4%, 14%, 38%. (b) Tibia pQCT from a spinal cord injured paraplegic T12 24 years old man, slices: 4%, 14%, 38%.

lower extremities[40]. Indeed, the effects on spinal BMD differed from previously published work in which the investigation mainly focused on paraplegics[41-43]. The importance of mechanical loading and site specificity to maintain or increase BMD is already shown[44]. Transferring these results to a spinal cord population, the level of neurological injury affects BMD and the magnitude of mechanical loading on the spine. The mechanical model of force in the spine is different when sitting in a wheelchair with a slight inclination of the torso forward, which is the most common position at work. To maintain a constant inclination of the trunk, force needs to be exerted in the opposite direction. The contraction of the dorsal muscles provides the power to maintain force in the balanced position and is retained in partially paraplegic patients, depending on the level of injury. On the contrary, tetraplegics cannot use the erector spinal muscle group or the multifidus muscle because of their injury level, and are seated at the back of the wheelchair. As a result, the compressive force applied to paraplegics does not exist in tetraplegics. This analysis explains how mechanical loading affects the lumbar BMD. Differences in BMD of the spine may be also due to muscle stretching/loading[40]. Moreover, an increase in BMD of the trochanter region in paraplegics compared to tetraplegics is due to the inclination of the trunk in the wheelchair during transfers and cannot be explained by immobilisation or muscle loading/stretching.

The additional risk factor of feminine gender

Women with disabilities have a higher risk of losing bone mass compared to men because of the inevitable reduction in oestrogen levels that occurs at menopause. Findings that women with serious disabilities have low bone density are not surprising and are probably related to the lack of activity (reduced mobility, reduced loading on bone) and worsening of the disability[9]. Regarding women with complete SCI, the initial bone loss in the lumbar spine is negligible. Post-injury over a period of years, BMD in SCI women is maintained or increases compared with non-injured age-matched women, in whom BMD decreases during aging. Fracture risk in the lumbar spine in women with spinal cord injury without pre-existing osteoporosis is low and fractures above the level of the lesion require an examination in detail[45,46]. SCI women reach the fracture threshold earlier compared to able-bodied women because BMD in the knee decrease to 40-45% of that seen in able-bodied women. Fracture risk increases with age depending on how close the age of the subject at the time of injury is to the age associated with peak bone mass[47,48].

Biochemical changes in bone after spinal cord injury

After SCI, osteoblast activity slightly increases, while a significant increase in osteoclast activity within a maximum of 10 weeks after injury and at level up to 10 times greater than normal is present. The imbalance between bone resorption and bone formation below the level of the lesion or injured area may be due to decreased blood flow and venous stasis, arteriovenous anastomoses and tissue oxidation[37,49]. SCI-related BI can be enhanced by a lack of muscular tension on bone or other neuronal factors associated with the lesion. The parathyroid glands are inactive with low levels of parathyroid hormone (PTH) observed up to one year after injury. The hypercalcemia that occurs immediately after injury is responsible for low levels of PTH. Gradually, in a range of one to nine years after injury, the function of the parathyroid is restored. The result is an increase in bone resorption associated with dysfunction of the parathyroid glands in the chronic phase of injury. This mechanism of SCI-related BI during the chronic phase tends to be balanced by an increase in bone mineral density (BMD) in areas of the body with increased loading (upper limbs, spinal column) and adds bone density (transferring bone mineral) compared to a loss in the chronic non-loadable areas of the skeleton (pelvis, lower limbs and upper limbs in tetraplegics). Hormonal changes (parathyroid hormone, glucocorticoids and calcitonin) and metabolic disorders (increased alkaline phosphatase, hypercalcemia/hypercalciuria and hydroxyproline excretion) may be secondary to the loss of bone density[30,33,49-53]. Hypercalciuria is seen in the first 10 days after neurological injury and reaches its maximum value after one to six months and is two to four times greater that the hypercalciuria observed after prolonged bed rest. The significant increase of calcium in the urine is the result of an imbalance between bone formation and bone resorption[32,54]. The rate of formation or resorption of bone matrix can be determined by quantifying the enzyme activity of bone cells or by measuring the components of the matrix that are released into the circulation during the process of absorption. It should be noted that these indices of bone activity are somewhat non-specific. The intact procollagen I N-terminal propeptide (PINP) molecule is the amino end of type I procollagen before excision and the formation of fibrils and is a measure of the total synthesis of collagen in the body, all of which is related to bone matrix[55,56]. Osteocalcin is a non-collagen protein which is a primary constituent of osteoblasts, and may also be released during apoptosis of osteoclasts and indicates either formation when resorption and formation are coupled or turnover in decoupling[55-57]. Urinary excretion of cross-linked pyridoline type I collagen is recognised as a sensitive marker of bone resorption, and pyridoline quality tests including measurement of the aminoterminal (NTx) and carboxyterminal (CTx) intermolecular cross-linking domain of bone type-1 collagen provide a good indicator of bone resorption[58-60]. Roberts et al. studied markers of bone metabolism for six months after acute spinal cord injury and observed an increase in ionised serum calcium above the upper limit of normal and suppression of serum PTH[60]. The indices of bone resorption (total pyridoline, deoxypiridoline [total and free] and NTx) recorded a significant increase (even 10 times above the upper limit of normal) after acute immobilisation, with the highest values found 10 to 16 weeks after injury. The markers of bone formation (total alkaline phosphatase and osteocalcin) showed an insignificant increase, which remained within the normal limits[60]. Moreover, Nance et al. observed that values of NTx in the urine were lower during the first months in patients receiving pamidronate compared with the control group, but this finding did not reach significance[61]. Regarding the lack or insufficiency of vitamin D, it has been reported that 64% of paraplegics are deficient (<15 ng/ml)[62].

The effect of neurogenic factor

The autonomic nervous system maintains homeostasis within the body, a function which is disturbed when central nervous system (CNS) communications are interrupted[51]. Spinal cord injury is a dynamic process that is related to alterations in both the central and peripheral sympathetic nervous system (SNS). Sympathetic denervation in SCI may cause arteriovenous shunts and a slowdown of intraosseous blood flow, thus increasing bone resorption[63]. With high-level spinal cord lesions, the SNS is disproportionately involved when compared to the parasympathetic nervous system. In a complete high-level SCI, functioning in the isolated spinal cord below the lesion becomes independent of supraspinal control and has been termed "decentralisation" of the SNS[64]. Loss of supraspinal control leads to dysregulation of those homeostatic mechanisms normally influenced by the SNS through loss of facilitation or lack of inhibition[65]. In those with SCI above thoracic level 6 (T6), the clinical sequelae of autonomic dysreflexia appear, although autonomic dysreflexia has been reported in some individuals with lesions from T8 to T10[66]. Today, there is clinical evidence that the sympathetic regulation of bone does exist in humans and may play a clinically important role in diseases characterised by excessive sympathetic activity[67]. The recent scientific finding by Takeda et al. suggesting sympathetic innervations of bone tissue[68,69] and its role in the regulation of bone remodelling could be of major interest in situations where uncoupling between osteoclasts and osteoblasts occurs[70].

Duration of paralysis and bone loss

The duration of paralysis affects the degree of bone loss in regions below the level of injury. Clasey et al. studied 21 men with SCI for an average duration of 10.6 years, using DEXA, and expressed at various levels of injury an inverse relationship between BMD in the legs and the duration of the lesion ($r=0.76$, $p<0.01$)[71], while Modlesky et al. found a weaker relationship regarding the microarchitecture of the distal end of the tibia[72]. Eser et al., in a study which included paraplegics with paralysis 14±11.5 years in duration, found a positive correlation between the duration of paralysis and the degree of bone loss[35]. Dauty et al. stated that the length of immobilisation in the acute post-traumatic period increased bone loss in the legs, particularly in the proximal tibia; over 50% of bone mass was lost (in the affected areas) in the period ten years after injury[73]. Szollar et al. categorised subjects depending on the duration of the lesion (0-1, 1-5, 6-9, 10-19, 20-29, 30-39, 40-49

and 50-59 years after injury), and found in all age groups that bone loss in the hip area occurred one year after injury[33]. Zehnder et al., using DXA and QUS (quantitative ultrasound) measurements in 100 men with SCI, aged 18 to 60 years, found that bone density decreased over time in all measured points ($r=0.49$ to 0.78, $p<0.0001$). In the femoral neck and distal epiphysis, bone loss followed a linear pattern which stabilised within three years after injury. On the contrary, Z-scores of the distal region of the diaphysis of the tibia continued to decrease even beyond ten years after injury[74].

Bauman et al. reported that the duration of paralysis was related to bone loss in the legs of monozygotic twins with chronic paraplegia in comparison with their able-bodied cotwins[75]. The results of a comparison of chronic complete paraplegic men vs. controls in another study found a reduction in BMD in paraplegics' legs independent of the neurological level of the lesion. The BMD of the legs was negatively correlated with the duration of paralysis in the total paraplegic group, but after an investigation into the neurological level of the lesion, this correlation was due to the strong correlation of high paraplegics' leg BMD with the duration of paralysis, suggesting a possible influence of the neurological level of injury on the extent of bone loss[76]. Clasey et al. analysed varying levels of SCI and found a significant inverse relationship between percentage-matched BMD leg, arm and trunk values and time since injury[77].

The influence of spasticity

So far, spasticity has been considered by many researchers as a prophylactic factor for bone. It is well known that voluntary muscle contraction is effective in the prevention of osteoporosis[78,79]. Although muscle loading plays a vital role in maintaining bone density, conflicting results regarding the effect of muscle spasms in the form of spasticity have been reported in SCI patients[80-82]. Demirel et al. found that the decline in bone density was lower in paraplegics with spasticity compared to those subjects with flaccid paralysis (Z-score, 0.078 ± 0.62 vs. 0.118 ± 0.46, $p<0.05$)[80]. This result is consistent with the findings of Eser et al.[82] Rittweger et al. in their study suggested that muscle spasms can slow bone loss based on the theory of a single basic muscle/bone unit[83]. Muscle spasms and muscle tension in the presence of spasticity put force on bone. This is likely to play a regulatory role in maintaining bone density. These studies concluded that spasticity may be a protective factor against bone loss in SCI. Other researchers, however, could not find a correlation between bone density and spasticity[81,84]. Moreover, Löfvenmark et al. in 18 motor complete SCI men matched for time since injury, gender and age (nine had severe spasticity and nine had spasticity that was either mild or not present) found no difference in BMD depending on the level of spasticity[85]. A pQCT study investigating the tibia in complete paraplegics above the thoracic 12 (T12) level with various degrees of spasticity found no effect on volumetric BMD measurements[86]. Others have reported that spasticity may be protective against bone loss in SCI patients, however, without any preserving effect on the tibia[82]. A possible explanation for this could lie in the fact that studies include various SCI subjects with various degrees of spasticity. In addition, in studies examining the lower leg, muscle spasms affecting the lower leg would mainly be extension spasms resulting in plantar flexion, thus creating little resistance to the contracting muscles. Furthermore, the measuring sites of the tibia did not include any muscle insertions of either the knee or the ankle extensor muscles. Patients without spasticity usually have more fractures. At the same time, excessive spasticity may cause fractures through uncontrolled limb movements, i.e. in a wheelchair. Therefore, the effect of spasticity on bone is probably two-sided: a low grade of spasticity is beneficial while a high grade is harmful[84,87].

Conclusions

Despite the fact that the design of studies has been mostly cross-sectional, including a small number of subjects, mixed populations of tetraplegics and paraplegics or subjects with incomplete and complete injuries, it is clear that spinal cord injury induces bone loss. A decline in bone mineral density, bone mineral content, as well as geometric characteristics of bone is expected in paralysed limbs. The duration of paralysis is positively correlated with the degree of bone loss. Neurogenic factors and central control of bones seem to co-exist as influential regulators in SCI-related bone impairment during the years of paralysis. Understanding the physiopathological context is the cornerstone to developing treatments for SCI-related BI in the future.

References

1. NIH Consensus Development Panel on Osteoporosis JAMA 285(2001):785-95.
2. World Health Organisation. Assessment of fracture risk and its implication to screening for postmenopausal osteoporosis: Technical report series 843. Geneva: WHO, 1994.
3. Sambrook P, Schrieber L, Taylor T, Ellis A (2001). The musculoskeletal system. Edinburgh: Churchill Livingstone.
4. Bone density test: Measure your risk of osteoporosis. MayoClinic.com. Available online at http://www.mayoclinic.com.http://www.mayoclinic.com/health/bone-density-tests/WO00024
5. Frost HM. Defining osteopenias and osteoporoses: another view (with insights from a new paradigm). Bone 1997;20:385-91.
6. Lazo MG, Shirazi P, Sam M, Giobbie-Hurder A, Blacconiere MJ, Muppidi M. Osteoporosis and risk of fracture in men with spinal cord injury. Spinal Cord 2001;39:208-14.
7. Garland DE, Foulkes GD, Adkins RH, Stewart CA, Yakura JS. Regional osteoporosis following incomplete spinal cord injury. Contemporary Orthopaedics 1994; 28:134-9.
8. Coupaud S, McLean AN, Allan DB. Role of peripheral quantitative computed tomography in identifying disuse os-

teoporosis in paraplegia. Skeletal Radiol 2009;38:989-95.
9. Smeltzer SC, Zimmerman V, Capriotti T. Osteoporosis risk and low bone mineral density in women with physical disabilities. Arch Phys Med Rehabil 2005;86:582-6.
10. Garland DE, Stewart CA, Adkins RH, Hu SS, Rosen C, Liotta FJ, Weinstein DA. Osteoporosis after spinal cord injury. J Orthop Res 1992;10:371-8.
11. Claus-Walker J, Halstead LS. Metabolic and endocrine changes in spinal cord injury: IV. Compounded neurologic dysfunctions. Arch Phys Med Rehabil 1982;63:632-8.
12. Lauer R, Johnston TE, Smith BT, Mulcahey MJ, Betz RR, Maurer AH. Bone mineral density of the hip and knee in children with spinal cord injury. J Spinal Cord Med 2007; 30(Suppl.1):S10-4.
13. Ragnarsson KT, Sell GH. Lower extremity fractures after spinal cord injury: a retrospective study. Arch Phys Med Rehab 1981;62:418-23.
14. Nottage WM. A review of long-bone fractures in patients with spinal cord injuries. Clin Orthop 1981;155:65–70.
15. Keating JF, Kerr M, Delargy M. Minimal trauma causing fractures in patients with spinal cord injury. Disabil Rehab 1992;14:108-9.
16. Ingram RR, Suman RK, Freeman PA. Lower limb fractures in the chronic spinal cord injured patient. Paraplegia 1989;27:133-9.
17. Freehafer AA, Mast WA. Lower extremity fractures in patients with spinal-cord injury. J Bone Joint Surg Am 1965; 47:683-94.
18. Mulsow J, O'Toole GC, McManus F. Traumatic lower limb fractures following complete spinal cord injury. Ir Med J 2005;98:141-2.
19. Northwest Regional Spinal Cord Injury System (NWRSCIS) SCI Forum Reports http://www.depts.washington.edu/rehab/sci/ms01.html
20. Freehafer AA. Limb fractures in patients with spinal cord injury. Arch Phys Med Rehab 1995;76:823-7.
21. Logan WC Jr, Sloane R, Lyles KW, Goldstein B, Hoenig HM. Incidence of fractures in a cohort of veterans with chronic multiple sclerosis or traumatic spinal cord injury. Arch Phys Med Rehabil. 2008;89:237-43.
22. Vestergaard P, Krogh K, Rejnmark L, Mosekilde L. Fracture rates and risk factors for fractures in patients with spinal cord injury. Spinal Cord 1998;36:790-6.
23. Wang CM, Chen Y, DeVivo MJ, Huang CT. Epidemiology of extraspinal fractures associated with acute spinal cord injury. Spinal Cord 2001;39:589-94.
24. Morse LR, Battaglino RA, Stolzmann KL, Hallett LD, Waddimba A, Gagnon D, Lazzari AA, Garshick E. Osteoporotic fractures and hospitalization risk in chronic spinal cord injury. Osteoporos Int 2009;20:385-92.
25. McKinley WO, Jackson AB, Cardenas DD, DeVivo MJ. Long-term medical complications after traumatic spinal cord injury: A regional model systems analysis. Arch. Phys. Med. Rehabil 1999;80:1402-10.
26. Wilmet E, Ismail AA, Heilporn A, Welraeds D, Bergmann P. Longitudinal study of bone mineral content and of soft tissue composition after spinal cord injury. Paraplegia 1995;33:674-7.
27. Chantraine A. Actual concept of osteoporosis in paraplegia. Paraplegia 1978;16:51-8.
28. Chantraine A, Heynen G, Franchimont P. Bone metabolism, parathyroid hormone, and calcitonin in paraplegia. Calcif Tissue Int 1979;27:199-204.
29. Elias AN, Gwinup G. Immobilization osteoporosis in paraplegia. J Am Paraplegia Soc 1992;15:163-70.
30. Uebelhart D, Demiaux-Domenech B, Roth M, Chantraine A. Bone metabolism in spinal cord injured individuals and in others who have prolonged immobilisation. A review. Paraplegia 1995;33:669-73.
31. Bauman WA, Garland DE, Schwartz E. Calcium metabolism and osteoporosis in individuals with spinal cord injury. Top Spinal Cord Inj Rehabil 1997;2:84-96.
32. Naftchi NE, Viau AT, Sell GH, Lowman EW. Mineral metabolism in spinal cord injury. Arch Phys Med Rehabil 1980;61:139-42.
33. Szollar SM, Martin EM, Sartoris DJ, Parthemore JG, Deftos LJ. Bone mineral density and indexes of bone metabolism in spinal cord injury. Am J Phys Med Rehabil 1998;77:28-35.
34. Rauch F, Rittweger J. What is new in neuro-musculoskeletal interactions? J Musculoskelet Neuronal Interact 2005;5:91-4.
35. Eser P, Frotzler A, Zehnder Y, Wick L, Knecht H, Denoth J, Schiessl H. Relationship between the duration of paralysis and bone structure: a pQCT study of spinal cord injured individuals. Bone 2004;34:869-80.
36. Dionyssiotis Y, Trovas G, Galanos A, Raptou P, Papaioannou N, Papagelopoulos P, Petropoulou K, Lyritis GP. Bone loss and mechanical properties of tibia in spinal cord injured men. J Musculoskelet Neuronal Interact 2007;7:62-8.
37. Maimoun L, Fattal C, Micallef JP, Peruchon E, Rabischong P. Bone loss in spinal cord-injured patients: from physiopathology to therapy. Spinal Cord 2006; 44:203-10.
38. Jaovisidha S, Sartoris DJ, Martin EME, De Maeseneer M, Szollar SM, Deftos LJ. Influence of spondylopathy on bone densitometry using dual energy X-ray absorptiometry. Calcif Tissue Int 1997;60:424-9.
39. Healey JH, Lane JM. Structural scoliosis in osteoporotic women. Clin Orthop Relat Res 1985;195:216-23.
40. 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.
41. Biering-Sorensen F, Bohr HH, Schaadt OP. Longitudinal study of bone mineral content in the lumbar spine, the forearm and the lower extremities after spinal cord injury. Europ J Clin Invest 1991;20:330-5.
42. Biering-Sorensen F, Bohr HH, Schaadt OP. Bone mineral content of the lumbar spine and lower extremities years after spinal cord lesions. Paraplegia 1988;26:293- 301.
43. Leslie WD, Nance PW. Dissociated hip and spine dem-

ineralization: a specific finding in spinal cord injury. Arch Phys Med Rehabil 1993;74:960-4.
44. Lanyon LE, Rubin CT, Baust G. Modulation of bone loss during calcium insufficiency by controlled dynamic loading. Calcif Tissue Int 1986;38:209-16.
45. Lee TQ, Shapiro TA, Bell DM. Biochemical properties of human tibias in long-term spinal cord injury. J Rehab Res Dev 1997;34:295-302.
46. Weeks C. Women, spinal cord injury and osteoporosis. Top Spinal Cord Injury Rehab 2001;7:53-63.
47. Garland DE, Adkins RH, Stewart CA, Ashford R, Vigil D. Regional osteoporosis in women who have a complete spinal cord injury. J Bone Joint Surg Am 2001;83 A:1195-200.
48. Garland DE, Foulkes G, Adkins RH, Hu SS, Rosen C, Liotta FJ, Weinstein DA. Regional osteoporosis following incomplete spinal cord injury. J Orthop Res 1992;10:371-8.
49. Jiang SD, Dai LY, Jiang LS. Osteoporosis after spinal cord injury. Osteoporos Int 2006;17:180-92.
50. Claus-Walker J, Carter RE, Di Ferrante M, Singh J. Immediate endocrine and metabolic consequences of traumatic quadriplegia in a young woman. Paraplegia 1977; 15:202-8.
51. Claus-Walker J, Scurry M, Carter RE, Campos RJ. Steady state hormonal secretion in traumatic quadriplegia. J Clin Endocrinol Metab 1977;44:530-5.
52. Claus-Walker J, Spencer WA, Carter RE, Halstead LS, Meier RH 3rd, Campos RJ. Bone metabolism in quadriplegia: dissociation between calciuria and hydroxyprolinuria. Arch Phys Med Rehabil 1975;56:327-32.
53. Claus-Walker J, Carter RE, Compos RJ, Spencer WA. Hypercalcemia in early traumatic quadriplegia. J Chronic Dis 1975;28:81-90.
54. Bauman WA, Wecht JM, Kirshblum S, Spungen AM, Morrison N, Cirnigliaro C, Schwartz E. Effect of pamidronate administration on bone in patients with acute spinal cord injury. J Rehabil Res Dev 2005;42:305-13.
55. Delmas PD. Markers of bone formation and resorption. In: Favus MJ, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. 2nd ed. New York: Raven Press; 1993. p. 108-12.
56. Raisz LG, Kream BE, Lorenzo JA. Metabolic bone disease. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, editors. Williams textbook of endocrinology. 9th ed. Philadelphia (PA): W.B. Saunders Company; 1998. p. 1220-21.
57. Christenson RH. Biochemical markers of bone metabolism: an overview. Clin Biochem 1997;30:573-93.
58. Rosen HN, Dresner-Pollak R, Moses AC, Rosenblatt M, Zeind AJ, Clemens JD, Greenspan SL. Specificity of urinary excretion of cross-linked N-telopeptides of type I collagen as a marker of bone turnover. Calcif Tissue Int 1994;54:26-9.
59. Gertz BJ, Shao P, Hanson DA, Quan H, Harris ST, Genant HK, Chesnut CH 3rd, Eyre DR. Monitoring bone resorption in early postmenopausal women by an immunoassay for cross-linked collagen peptides in urine. J Bone Miner Res 1994;9:135-42.
60. Roberts D, Lee W, Cuneo RC, Wittmann J, Ward G, Flatman R, McWhinney B, Hickman PE. Longitudinal study of bone turnover after acute spinal cord injury. J Clin Endocrinol Metab 1998;83:415-22.
61. Nance PW, Schryvers O, Leslie W, Ludwig S, Krahn J, Uebelhart D. Intravenous pamidronate attenuates bone density loss after acute spinal cord injury. Arch Phys Med Rehabil 1999;80:243-51.
62. Bauman WA, Zhong YG, Schwartz E. Vitamin D deficiency in veterans with chronic spinal cord injury. Metabolism 1995;44:1612-6.
63. Chantraine A, van Ouwenaller C, Hachen HJ, Schinas P. Intra-medullary pressure and intra-osseous phlebography in paraplegia. Paraplegia 1979;17:391-9.
64. Karlsson AK, Friberg P, Lonnroth P, Sullivan L, Elam M Regional sympathetic function in high spinal cord injury during mental stress and autonomic dysreflexia. Brain 1998;121:1711-9.
65. Teasell RW, Arnold JM, Krassioukov A, Delaney GA. Cardiovascular consequences of loss of supraspinal control of the sympathetic nervous system after spinal cord injury. Arch Phys Med Rehabil 2000;81:506-16.
66. Gimovski ML, Ojeda A, Ozaki R, Zerne S. Management of autonomic hyperreflexia associated with a low thoracic spinal cord lesion. Am J Obstet Gynecol 1985;153:223-4.
67. Schwarzman RJ. New treatments for reflex sympathetic dystrophy. N Engl J Med 2000;343:654-6.
68. Takeda S, Elefteriou F, Levasseur R, Liu X, Zhao L, Parker KL, Armstrong D, Ducy P, Karsenty G. Leptin regulates bone formation via the sympathetic nervous system. Cell 2002;111:305-17.
69. Kondo H, Nifuji A, Takeda S, Ezura Y, Rittling SR, Denhardt DT, Nakashima K, Karsenty G, Noda M. Unloading induces osteoblastic cell suppression and osteoclastic cell activation to lead to bone loss via sympathetic nervous system. J Biol Chem 2005;280:30192-200.
70. Levasseur R, Sabatier JP, Potrel-Burgot C, Lecoq B, Creveuil C, Marcelli C. Sympathetic nervous system as transmitter of mechanical loading in bone. Joint Bone Spine 2003;70:515-9.
71. 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.
72. Modlesky CM, Bickel CS, Slade JM, Meyer RA, Cureton KJ, Dudley GA. Assessment of skeletal muscle mass in men with spinal cord injury using dual-energy X-ray absorptiometry and magnetic resonance imaging. J Appl Physiol 2004;96:561-5.
73. Dauty M, Perrouin Verbe B, Maugars Y, Dubois C, Mathe JF. Supralesional and sublesional bone mineral density in spinal cord-injured patients. Bone 2000;27:305-9.
74. Zehnder Y, Lüthi M, Michel D, Knecht H, Perrelet R, Neto I, Kraenzlin M, Zäch G, Lippuner K. 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.
75. Bauman WA, Spungen AM, Wang J, Pierson RN Jr, Schwartz E. Continuous loss of bone during chronic immobilization: a monozygotic twin study. Osteoporos Int 1999;10:123-7.
76. Dionyssiotis Y, Petropoulou K, Rapidi CA, Papagelopoulos P, Papaioannou N, Galanos A, Papadaki P, Lyritis GP. Body composition in paraplegic men. J Clin Densitom 2008;11:437-43.
77. 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.
78. Engelke K, Kemmler W, Lauber D, Beeskow C, Pintag R, Kalender WA. Exercise maintains bone density at spine and hip EFOPS: a 3-year longitudinal study in early postmenopausal women. Osteoporos Int 2006;17:133-42.
79. Kraemer WJ. Endocrine responses and adaptations to strength training. In: Strength & Power in Sport, P.V. Komi (Editor). Oxford: Blackwell Scientific Publications, 1992; p. 291-304.
80. Demirel G, Yilmaz H, Paker N, Onel S. Osteoporosis after spinal cord injury. Spinal Cord 1998;36:822-5.
81. Frey-Rindova P, de Bruin ED, Stussi E, Dambacher MA, Dietz V. 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.
82. Eser P, Frotzler A, Zehnder Y, Schiessl H, Denoth J. Assessment of anthropometric, systemic, and lifestyle factors influencing bone status in the legs of spinal cord injured individuals. Osteoporos Int 2005;16:26-34.
83. Rittweger J, Gerrits K, Altenburg T, Reeves N, Maganaris CN, de Haan A. Bone adaptation to altered loading after spinal cord injury: a study of bone and muscle strength. J Musculoskelet Neuronal Interact 2006;6:269-76.
84. Panin N, Gorday WJ, Paul BJ. Osteoporosis in Hemiplegia. Stroke 1971;2:41-7.
85. Löfvenmark I, Werhagen L, Norrbrink C. Spasticity and bone density after a spinal cord injury. J Rehabil Med 2009; 41: 1080- 4.
86. Dionyssiotis Y, Lyritis GP, Mavrogenis AF, Papagelopoulos PJ. Factors influencing bone loss in paraplegia Hippokratia 2011;15:54-9.
87. Ramnemark A, Nyberg L, Lorentzon R, Olsson T, Gustafson Y. Hemiosteoporosis after severe stroke, independent of changes in body composition and weight. Stroke 1999;30:755-60.