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Paraplegia Related Osteoporosis

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1. Introduction

Osteoporosis is characterized by low bone mass and destruction of the micro architecture of bone tissue, resulting in increased bone fragility and susceptibility to fractures. [1]

The World Health Organisation (WHO) created an operational definition of postmenopausal osteoporosis based on a bone mineral density (BMD)-based T-score measurement. The most widely validated technique to measure BMD is dual energy X-ray absorptiometry (DXA), and diagnostic criteria based on the T-score for BMD are a recommended entry criterion for the development of pharmaceutical interventions in osteoporosis. (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]

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 "paraplegia-related bone impairment, (Para-related BI)" is used throughout this chapter. The term bone impairment is more appropriate than bone disorder because includes terminology from Rehabilitation Science a specialty which interferes with all complications of spinal cord injury (SCI) and follows these patients during aging with paralysis. It is not used here for the 1st time. Very experienced scientists and researchers chose this term to describe "osteoporosis" in SCI. [4]

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2. Paraplegia related bone impairment
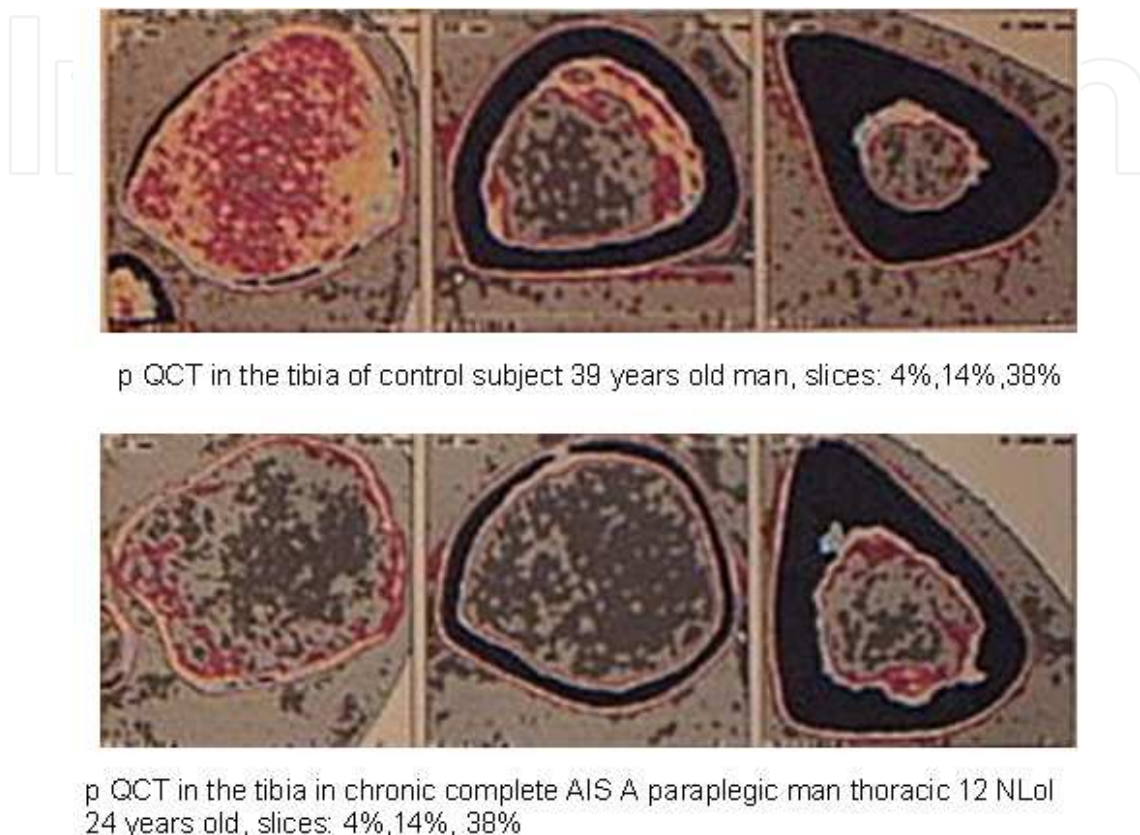
2.1. Epidemiology

According to the literature, spinal cord injury-related bone impairment (SCI-related BI) occurs in 75% of patients with complete SCI. [5] Twenty five 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. [7] 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 site. [6, 8, 9] 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. [8, 9]

2.2. Bone mineral density

In individuals with SCI bone loss begins immediately after injury. [10, 11] SCI-related BI below the level of injury is much greater compared with other conditions (i.e. age, immobilization, bed rest, lack of gravity environment). A reduction of bone mineral content during the first years after the injury of 4% per month in regions rich in cancellous bone, and 2% per month on sites containing mainly cortical bone is reported. [12] According to another study 25 out of 41 patients with SCI (61%) met WHO's 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. [7]

Bone loss measured with peripheral quantitative computed tomography (p QCT) in SCI subjects in the femur's and tibia's epiphyses was 50% and 60% vs. 35% and 25% in the diaphyses, respectively, meaning that bone loss in the epiphyses almost doubled the loss in the diaphyses. [13] This study also showed that bone loss between trabecular and cortical bone compartment differs in mechanism, i.e. in the epiphyses bone is lost due to the decrease in trabecular, while in diaphysis, the cortical bone density is maintained and bone is lost due to endocortical resorption. In line with the previous study, another p QCT study, performed in complete paraplegics with high (thoracic 4-7) and low (thoracic 8-12) neurological level of injury at the tibia, found a loss of trabecular (57.5% vs. 51%, in high vs. low paraplegics, respectively) and cortical bone (3.6% and 6.5%, respectively), suggesting that trabecular bone is more affected during the years of paralysis in comparison with cortical bone. [14] In the same study both paraplegic groups had a similar loss of total BMD (46.90% vs. 45.15%, in high vs. low paraplegics, respectively) suggesting that a homogenously deficit pattern occurs in the epiphyseal area, especially in the group of low paraplegics because the central and the peripheral of the cross sectional area of bone were similarly affected. On the contrary, in high paraplegics' group trabecular bone loss was higher suggesting an increasing endocortical

remodeling keeping the total BMD similar. Concerning cortical geometric properties the results had shown an increased endosteal circumference between both paraplegic groups vs. controls leading to reduction of cortical thickness, 19.78% vs. 16.98% in paraplegic groups respectively, whereas periosteal circumference was comparable to controls (Fig. 1).

p QCT in the tibia of control subject 39 years old man, slices: 4%,14%,38%

p QCT in the tibia in chronic complete AIS A paraplegic man thoracic 12 NLol 24 years old, slices: 4%,14%, 38%

Figure 1. Peripheral quantitative computed tomography (p QCT) tibia slices in control (a) and paraplegic subject (b), (scanner XCT 3000 Stratec, Medizintechnik, Pforzheim, Germany). Areas in red represent trabecular bone, while areas in grey represent fat; pQCT allows the measurements of true volumetric densities at a minimum exposure to X-rays, assess cortical and trabecular bone density separately as well as to evaluate the geometrical properties of long bones non-invasively, adapted from: Dionyssiotis Y. (15) (with permission).

Regarding tetraplegic patients statistically significant differences were found in BMD of the spine, trochanteric region and upper limbs between paraplegic and tetraplegic patients but not in the femoral neck, pelvis, and lower extremities. [16] Indeed, the effects on spinal BMD differed from previously published work in which the investigation was mainly focused in paraplegics. [17-19]

The importance of mechanical loading and site specificity to maintain or increase BMD is already shown. [20] According to bone loss there are some interesting features in spinal cord injured subjects; demineralization is area dependent, occurs exclusively in the areas below the level of injury, affecting mainly paralyzed extremities and increasing from proximal to distal regions i.e. in paraplegics weight bearing skeleton regions, as the distal end of femur and proximal tibia, which are rich in cancellous bone, while region of the diaphysis of the femur

and tibia, rich in cortical bone is reserved. [13, 14, 21] Moreover, bone loss between trabecular and cortical bone compartment differs in mechanism, i.e. in the epiphyses is due to decrease in trabecular but in diaphysis cortical bone is maintained and bone is lost through endocortical resorption by reducing cortical wall thickness. [13, 14]

2.2.1. 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 estrogen 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. [22] 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.

2.2.2. 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. [23] 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. [10, 24] 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. [25] 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. Osteocalcin is a non-collagen protein which is a primary constituent of osteo-blasts, and may also be released during apoptosis of osteoclasts and indicates either formation when resorption and formation are coupled or turnover in decoupling. [26, 27] 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. [28, 29] Others 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. [30] 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. [10] 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. [31] Regarding the lack or insufficiency of vitamin D, it has been reported that 64% of paraplegics are deficient (<15ng/ml). [32]

Mechanical unloading (paralysis) in acute SCI subjects causes greater sclerostin levels than those observed in the able bodied. This increase is associated with reduced bone formation during the acute phase of SCI. The ability to walk (mechanical loading) modulates the response of bone to paralysis by causing a smaller increase in sclerostin levels, thereby partially protecting against bone loss. In the chronic phase, bone wasting results in lower sclerostin levels than those observed in the able bodied. This effect is due to the reduction of sclerostin-producing osteocytes in the osteoporotic bone. In the chronic phase, similar to the acute phase, the ability to walk partially protects against bone loss. Sclerostin causes up-regulation of RANKL (key factor that promotes the differentiation of osteoclasts) and down regulation of osteoprotegerin (a key inhibitor of osteoclast differentiation) expression in osteocytes, which leads to increased osteoclast activity and bone resorption. [33]

2.2.3. Duration of paralysis and bone steady state

The duration of paralysis affects the degree of bone loss in regions below the level of injury. A study of 21 men with SCI with an average duration of 10.6 years, using DEXA, expressed at various levels of injury an inverse relationship between BMD in the legs and the duration of the lesion, while others found a weaker relationship regarding the microarchitecture of the distal end of tibia. [34, 35]

In a study which included paraplegics with duration of paralysis of 14 ± 11.5 years a positive correlation between the duration of paralysis and the degree of bone loss was found. [13] The length of immobilization in the acute posttraumatic 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 of ten years after the injury. [21] When subjects categorized depending on the length of the lesion (0-1, 1-5, 6-9, 10-19, 20-29, 30-39, 40-49, and 50-59 years after the injury), in all age

groups bone mineral density of the proximal femur declined and was detected a year after the injury. [24]

Using DXA and QUS (quantitative ultrasound) measurements in 100 men with SCI, aged 18 to 60 years, it was found that bone density decreases over time in all measured points, while bone loss followed a linear pattern in the femoral neck and distal epiphysis, stabilized within three years after the injury. On the contrary, Z-scores of the distal region of the diaphysis of the tibia continued to decrease even beyond ten years after the injury. [36] Duration of paralysis related bone loss in the legs of monozygotic twins with chronic paraplegia in comparison with their able-bodied co-twins has been also reported. [37]

The results of a comparison of chronic complete paraplegic men vs. controls in another study found a reduction of BMD in paraplegics' legs independent of the neurological level of lesion. BMD of the legs was negatively correlated with the duration of paralysis in the total paraplegic group, but after investigation according to the neurological level this correlation was due to the strong correlation of high paraplegics' legs BMD with the duration of paralysis, suggesting a possible influence of the neurological level of injury on the extent of bone loss. [38] A significant inverse relationship between percentage-matched in BMD leg, arm and trunk values and time since injury was found when varying levels of SCI were analyzed. [34]

Studies are supporting the concept of a new bone steady state at 16-24 months after injury, especially for bone metabolic process, but BMD decreases over the years at different areas and is inversely related to the time of the injury, which means continuous bone loss beyond the first two years after the injury (Fig. 2). [11, 13, 14, 24, 38-41]
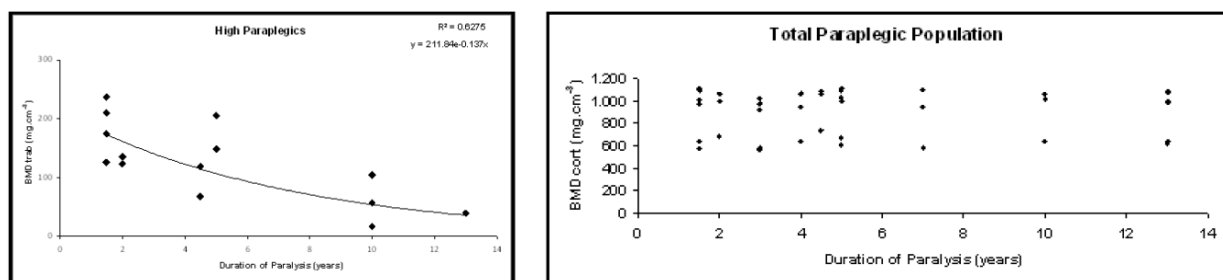
Figure 2. The duration of paralysis was inversely related with trabecular bone loss in spinal cord injured subjects. Exponential correlation between volumetric trabecular bone mineral density BMD trab and duration of paralysis in high paraplegics was found to fit best. On the contrary no significant decrease in BMD cort of the diaphyses was found in total paraplegic group. BMD parameters were measured by pQCT in 31 paraplegic men in chronic stage (>1.5 years of injury). Spinal cord injury paraplegic men were allocated into 2 subgroups based on the neurological level of injury; subgroup A (n=16, Thoracic (T) 4 –T 7 neurological level of injury) and subgroup B (n=15, T8-T12 neurological level of injury). BMDtrab: BMD trabecular; BMDcort: BMD cortical; (adapted from Dionyssiotis et al. [41] with permission).

The role played by factors such as race or gender of patients is not yet clear documented, but studies indicated more loss in women than men. [42] Loss of bone is closing fracture threshold from 1 to 5 years after injury and risk factors for fractures after spinal cord injury are gender (women are more at risk than men), age and duration of injury (increasing age and duration of injury increases the risk of fracture with a statistically significant increase in 10 years after

injury), the type of injury (complete SCI subjects have more fractures than incomplete), low body mass index (BMI) and low bone density in the tibia. [6, 24, 43]

2.2.4. The role of central nervous system

2.2.4.1. Sympathetic denervation in SCI

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. [44] With high-level spinal cord lesions the SNS is disproportionately involved when compared with the parasympathetic nervous system. In a complete high-level SCI, functioning in the isolated spinal cord below the lesion becomes independent of supraspinal control and has been termed "decentralization" of the sympathetic nervous system. [45]

Loss of supraspinal control leads to dysregulation of those homeostatic mechanisms normally influenced by the SNS through loss of facilitation or lack of inhibition. [46] Today there is clinical evidence that the sympathetic regulation of bone does exist in humans and plays a clinically important role in diseases characterized by excessive sympathetic activity. [47] The scientific finding about sympathetic innervations of bone tissue and its role in the regulation of bone remodelling is of major interest in situations where uncoupling between osteoclasts and osteoblasts occurs. [48-50]

2.2.4.2. 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. [51, 52] 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. [53-56] Controversial results have also been reported regarding the effect of spasticity on BMD in paraplegics. A cross-sectional study of 41 paraplegics reported less reduction of BMD in the spastic compared to the flaccid paraplegic SCI patients. [53-55] Other investigators suggested that muscle spasms can slow bone loss based on the theory of a single basic muscle/bone unit. [56] 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. [55] Moreover, 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) no difference was found in BMD depending on the level of spasticity. [57] A pQCT study investigating the tibia in complete paraplegics above the thoracic 12 (T12) level with various degrees of spasticity according to the Ashworth scale found no effect on volumetric BMD measurements.[41] Others have reported that spasticity may be protective against bone loss in SCI patients, however, without any preserving effect on the tibia. [55] 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. [41]

3. Interventions for prevention of bone impairment

3.1. Weight bearing activities – Body weight supported treadmill – Cycling

The effect of standing in bone after SCI has been investigated by many researchers. A beneficial effect on bone mass using passive mechanical loading has been shown on preservation of bone mass in the region of the femoral shaft, but not at the proximal hip of standing and non-standing patients and relatively better-preserved densities in patients standing with braces than in those using a standing frame or standing wheelchair. [58] A slower rate of bone loss in paraplegic subjects who did standing was expressed in a prospective study of 19 patients in acute SCI phase participated in early standing training program which showed benefits concerning the reduction of cancellous bone loss compared to immobilized subjects, while no correlation for passive standing-training to bone status was found in another p QCT study. [59, 60] Protection afforded by standing in the femoral diaphysis stands in contrast with the loss of bone in the proximal femur. This suggests that the transmission of forces through trabecular and cortical bone varies; so the less effective strain for the initiation of bone remodeling reaches faster cortical bone. [61] Others also supported the concept of different strain thresholds during bone remodeling control. [62-64] There is level 2 evidence (from 1 non-randomized prospective controlled trial) that Functional Electrical Stimulation (FES)-cycling did not improve or maintain bone at the tibial midshaft in the acute phase. [65] Moreover, there is level 4 evidence (from 1 pre-post study) that 6 months of FES cycle ergometry increased regional lower extremity BMD over areas stimulated. [66] Body weight supported treadmill training (BWSTT) did not alter the expected pattern of change in bone biochemical markers over time and bone density at fracture-prone sites. [67]

3.2. Whole body vibration

At a meeting of the American Society for Bone and Mineral Research the results of a small randomised, placebo-controlled study among 20 children with cerebral palsy who used a similar, commercially available vibrating platform for 10 min per day, 5 days per week for 6 months, reported a significant increase in tibial, but not lumbar-spine bone density in the treated group despite the simplicity, short duration of the "vibration, the young age of the children and the poor compliance. [68, 69]

After 6 months of whole body vibration (WBV) therapy in twenty children (14 boys-6 girls) with cerebral palsy (age 6.2 to 12.3 years) randomized to either continue their school physio-

Figure 3. Weight bearing in disabled subjects; using standing frames, functional walking with orthoses between bars and crutches, even push-ups in the wheelchair (in case of multiple sclerosis with a clinical equivalent like tetraplegia) bone can be loaded and bone loss rate would be slower (unpublished photos of Dionyssiotis Y).

therapy program unchanged or to receive 9 minutes of side-alternating WBV (Vibraflex Home Edition II®, Orthometrix Inc) no effect on areal BMD at the lumbar spine was observed, while areal BMD seemed to decrease somewhat in the cortical region of the femoral diaphysis. Authors explained that mechanical stimulation increases intracortical bone remodeling and thereby cortical porosity; moreover changes occurred in ways that are not reflected by areal BMD, but might be detectable by more sophisticated techniques such as such as peripheral quantitative computed tomography. [70] Low-intensity vibration (LIV) has shown to be associated with improvement in bone mineral density in post-menopausal women and children with cerebral palsy. Seven non-ambulatory subjects with SCI and ten able-bodied controls underwent transmission of a plantar-based LIV signal (0.27+/-0.11 g; 34 Hz) from the feet through the axial skeleton as a function of tilt-table angle (15, 30, and 45 degrees). SCI subjects and controls demonstrated equivalent transmission of LIV, with greater signal transmission observed at steeper angles of tilt which supports the possibility of the utility of LIV as a means to deliver mechanical signals in a form of therapeutic intervention to prevent/ reverse skeletal fragility in the SCI population. [71]

Figure 4. The Galileo Delta A TiltTable offers a wide variety of applications from relaxation to muscle training for a diverse range of patients who are unable to stand without support. The motor driven adjustable tilt angle of the Galileo Delta TiltTable (90°) allows vibration training with reduced body weight from 0 to 100%. This is ideal for deconditioned and disabled patients for gradually increasing training weights up to full body weight. System for application in adults (max. body height: 1.90 m) and children (max. body height: 1.50 m).The Galileo Delta A TiltTable is exclusively available from the manufacturer Novotec Medical GmbH. (published with permission).

3.3. Pulsed Electromagnetic Fields (PEMF)

Huang et al recently reviewed the effects of low-frequency pulsed electromagnetic fields (PEMFs) on chronic bony pain, bone mineral density (BMD), bone strength and biochemical markers of bone metabolism in the patients of osteoporosis. [72] Two studies are analyzed in SCI subjects: In a study that consisted of 6 male patients with complete spinal cord injury of a minimum of 2 years duration the time of therapy of PEMFs continued for 6 months and at 3 months BMD increased in the stimulated knees by 5.1% and declined in the control knees by 6.6% (P <0.05 and P <0.02, respectively). By 6 months the BMD returned to near baseline values and at 12 months both knees had lost bone at a similar rate. It was demonstrated that PEMFs can delay bone loss and there may exist both a local and a systemic response. [73] Another study consisted of 24 patients with SCI who were then divided into two groups, BMD of the total proximal femur and trochanter of patients in the treatment group were increased significantly compared with the control group. [74] Both of the trials indicated that the increase

in BMD effects of PEMFs may relate to the features of the subjects. People with spinal cord injury are younger than osteoporosis patients, the osteoblasts and osteoclasts of patients with spinal cord injury may be more sensitive to the PEMFs stimulation than that of the old people.

Clinical examination and management of bone loss in paraplegia	
• history of the patient (co morbidities, neurologic complications, use of drugs which impair bone metabolism, alcohol, smoking and information about the level of injury, duration of paralysis, immobilization period, onset of rehabilitation, use of assistive devices and orthoses).	• pharmacological treatment with bisphosphonates p.os and i.v. that have been studied in patients with spinal cord injuries and had positive effects on bone parameters. • Use of calcium supplements (monitoring renal function) and vitamin D.
• anthropometric parameters (age, weight, body mass index, BMI)• clinical examination (level of injury according to American Spinal Injury Association Impairment Scale, AIS) and assessment of spasticity)	• Education on falls prevention • Counseling regarding osteoporosis and related factors and identification of fractures in regions of impaired sensation.
• imaging (bone densitometry by DXA at the hip and spine, and if possible, p QCT at the the tibia or femur)	• physical therapy including: a) range of motion exercises, b) loading of the skeleton to reduce bone loss, d) therapeutic standing-walking with orthoses, e) passive-active cycling
• measurement of bone turnover indices in the serum (parathyroid hormone, alkaline phosphatase, calcium, vitamin D, PINP molecule, osteocalcin) and urinary excretion of 24 hour (calcium, hydroxyproline, aminoterminal (NTx) and carboxylterminal (CTx) intermolecular cross-linking domain of bone type-1 collagen), which provide a good indicator of bone resorption.	• dietary interventions to improve dietary intake of calcium and nutrition indices.

Table 1. An algorithm for the screening and management of osteoporosis in subjects with spinal cord injury (should be read top to bottom starting with the left column); adapted from: Dionyssiotis Y. (84) (with permission).

3.4. Drugs

Calcitonin in varying doses and methods of administration has given variable results in paraplegia (preferred dosage regimen, treatment duration, and administration route for adequate efficacy in SCI patients' remains unclear). [75, 76] Likewise, the outcome using bisphosphonates has been variable. Etidronate produced long-term benefit in lower limb bone mineral density (BMD) in selected walking SCI patients; whereas tiludronate appeared effective in reducing bone resorption and preserving bone mass in a histomorphometric study in 20 paraplegic patients. [77, 78] Intravenous pamidronate has been shown to attenuate bone loss in SCI and normalize serum calcium in immobilization hypercalcemia. [79] Alendronate

(1000 times more potent than etidronate), in an open observational study, reversed BMD loss in men with established SCI increased both axial and trabecular bone density and has proven efficacy and safety in men treated for osteoporosis, prevents hypercalciuria and bone loss after bed rest and lower leg fracture. [80, 81] Six months after using zolendronic acid in the treatment group BMD showed differences in the response to treatment between the mixed trabecular/cortical regions (narrow neck and intertrochanteric) and the purely cortical shaft. With respect to cross-sectional geometry, bone cross-sectional area and sectional modulus (indices of resistance to axial and bending loads, where higher values would indicate a positive effect of treatment) increased at the hip and buckling ratio (an index of the instability of thin-walled cross sections, where lower values would suggest that the treatment is improving stability) decreased consistent with improved bone outcomes; at 12 months, narrow-neck femur values declined and intertrochanteric and femoral shaft BMD was maintained vs. placebo group which showed a decrease in bone outcomes and an increase in buckling ratio at the hip at 6 and 12 months, while with respect to bone prevention 4 mg i.v. were effective and well-tolerated to prevent BMD loss at the total hip and trochanter for up to 12 months following SCI. [82, 83]

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