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Bone Loss in Spinal Cord Injury and Multiple Sclerosis

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Introduction

Osteoporosis is characterized by low bone mass and destruction of the microarchitecture of bone tissue, resulting in increased bone fragility and susceptibility to fractures (NIH 2001). The clinical usefulness of T-score at disabled people on the recognition of people with low BMD remains unclear according to ranking system of the World Health Organization (WHO 1994). Despite the increased number of risk factors in people with disabilities no guidelines are available on BMD measurements; so it would be more appropriate to use the term low bone mass instead of osteoporosis or osteopenia and also take into account the Z-score obtained from the measurement of bone densitometry which is the number of standard deviations above or below that normally expected for someone of similar age, sex, weight and race in question. In disabilities there are differences among subjects according to the type of lesion; complete (an absence of sensory or motor function below the neurological level, including the lowest sacral segment) vs. incomplete lesions (partial preservation of motor and/or sensory function below the neurological level, including the lowest sacral segment), the neurological level of lesion, the progress of the disease (i.e in complete spinal cord injury vs. progressive multiple sclerosis), the residual mobility, walking-standing ability, functionality and degree of spasticity.

Physiopathology of bone loss in spinal cord injury

Bone loss in spinal cord injury (SCI) is a multifactorial disease in acute and chronic phase and can be enhanced by the lack of weight bearing, muscular tension on bone or other neural factors associated with the injury. Moreover, differentiation of the sympathetic nervous system after SCI is leading to venous and capillary vascular stasis. Some additional non-mechanical factors to stimulate bone loss include poor nutritional adequacy, gonadal changes and other endocrine disorders (Chantraine 1978; Chantraine and others 1979b; Jiang and others 2007; Maimoun and others 2006).

A reduction in bone density about 4% per month in the first year was estimated in areas rich in trabecular bone, such as the tibial and femoral epiphyses and about 2% per month in areas with predominantly compact bone (Wilmet and others 1995). In studies with peripheral quantitative computed tomography (p QCT) in paraplegics bone loss in the epiphyses was 50% in the femur and 60% in the tibia, while in the

diaphyses of these bones was 35% and 25%, respectively, meaning that bone loss in the epiphyses almost doubled the loss in the diaphyses (Figure 1). According to bone loss there are some interesting features; demineralization in spinal cord injured subjects is area dependent, occurs exclusively in the areas below the level of injury (Dauty and others 2000), 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 (Eser and others 2004; Kiratli and others 2000). 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 (Dionyssiotis et al 2007; Eser et al 2004). Studies are supporting the concept of a new steady state at 16-24 months after injury, especially for bone metabolic process (Bauman WA 1997; Demirel et al 1998; Szollar et al 1998), 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 (Coupaud et al 2009; Dionyssiotis et al 2008; Eser et al 2004) (Figure 2). 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 (Garland et al 2001; Weiss 2003). Loss of bone is closing fracture threshold from 1 to 5 years after injury (Szollar et al 1998) 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 (Garland et al 2004; Garland et al 1992; Lazo et al 2001).

Management of bone loss in spinal cord injury

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 (Goemaere et al 1994). 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 showed benefits concerning the reduction of cancellous bone loss compared to immobilized subjects (de Bruin et al 1999; Frey-Rindova et al 2000), while no correlation for passive standing-training to bone status was found in another p QCT study (Eser et al 2005). 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 remodelling reaches faster cortical bone (Frost 1992; Frost 2001; Frost 2003). Others also supported the concept of different strain thresholds bone remodelling control (Gutin and Kasper 1992; LeBlanc et al 2007; Smith et al 2009). 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 (Eser et al 2003). 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 (Chen et al 2005). 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 (Giangregorio et al 2009).

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) (Chantraine et al 1979a; Minaire P 1987). 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 (Roux et al 1998); whereas tiludronate appeared effective in reducing bone resorption and preserving bone mass in a histomorphometric study in 20 paraplegic patients (Chappard et al 1995). Intravenous pamidronate has been shown to attenuate bone loss in SCI and normalize serum calcium in immobilization hypercalcemia (Bauman et al 2005). 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 (Moran de Brito et al 2005; Zehnder et al 2004). 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 (Bubbear et al; Shapiro et al 2007).

Physiopathology of bone loss in Multiple Sclerosis

Reduced mobility has been implicated as an important factor in bone loss in patients suffering from multiple sclerosis (MS) and it seems to greatly influence the BMD of the femur. However, the high proportion of ambulatory patients with bone loss suggest additional non-mechanical factors (Cosman et al 1998). There is a high incidence of vitamin D deficiency in MS patients and is determined by levels of 25-hydroxy vitamin D <20ng/ml (Nieves et al 1994). The reasons might be due to a combination of low dietary vitamin D intake and avoiding of sun exposure, and that because of MS symptoms may worsen after sun exposure (fatigue-related heat) leading these patients to avoid sun. Low testosterone alone in these populations does not explain bone loss and no clear effect of smoking or alcohol abuse to decreased bone mass could be established (Weinstock-Guttman et al 2004). Glucocorticoid (GC)-induced osteoporosis (OP-GC) is the main type of secondary osteoporosis (Canalis et al 2004; Canalis et al 2007; Lakatos et al 2000; Mazziotti et al 2006; Schwid et al 1996; Shuhaibar et al 2009). The mechanism is that excess GC causes a rapid and significant damage to bone quality. Now days we know that GCs act direct on bone mainly to the stromalosteoblastic lineage and at high concentrations alter differentiation, survival, and function of them causing a shift from osteoblastic to

adipocytic differentiation of precursors; inducing apoptosis of mature osteoblasts; and inhibition of synthesis and secretion of bone components (Manolagas 2000; Pereira et al 2002). Finally, GCs promote ostoclasts and stimulate bone resorption (Weinstein et al 2002). The mechanisms of GCs action in bone has been studied extensively. In patients receiving chronic per os GC, bone loss is admitted rapidly and is evident within 6 or even 3 months (Cosman et al 1998). A study investigated the effect of intravenously (i.v.) administration of glucocorticoids in MS patients found no clear effect on bone loss: on the contrary they reported an increase in BMD of the lumbar spine (Schwid et al 1996). Prolonged treatment with glucocorticoids results in increased risk of fractures, evident at 3 months, regardless of changes in BMD. High dose, short-term i.v. treatment with GCs leads directly to reduction of bone formation and increased bone resorption, as indicated by markers of bone turnover (De Vries et al 2007; Van Staa et al 2000). In the study of Zorzon et al osteopenia not osteoporosis was significantly more frequent in patients with MS compared with controls, especially in women who received high dose methylprednisolone pulses (HDMP) in relapses period making important the regularly monitoring of BMD in these patients. The authors concluded that disability and the subsequent immobilization osteoporosis is the more serious factor in this group and treatment with repeated HDMP pulses did not cause osteoporosis in MS subjects followed-up for almost 8 years unlike chronic corticosteroid therapy which induces osteoporosis and/or recovery of BMD is permitted without permanent skeletal damage (Zorzon et al 2005). The lack of physical activity exacerbates osteoporosis.

Management of bone loss in multiple sclerosis

All MS patients should be considered high risk for osteoporosis. Prevention with calcium rich foods and dietary supplements containing vitamin D and antiosteoporotic drugs is necessary for these patients. Particular attention should be paid to transfers and falls prevention in this population to prevent fractures which occur easily and heal slowly (Cattaneo et al 2007). Subjects with multiple sclerosis are not the best candidates for bisphosphonates because of swallowing difficulties. Selective Estrogen Receptor Modulators (SERMs) and strontium ranelate could be an alternative for effective treatment of MS-related osteopenia-osteoporosis.

Conclusions

Despite the fact that the design of studies is mostly cross-sectional, it is clear that spinal cord injury and multiple sclerosis induce bone loss. The neurogenic factor seems to co-exist as an influential regulator in disabilities related bone loss during the years. Understanding the central control of bones is the cornerstone to develop treatments for neurological osteoporosis in the future.

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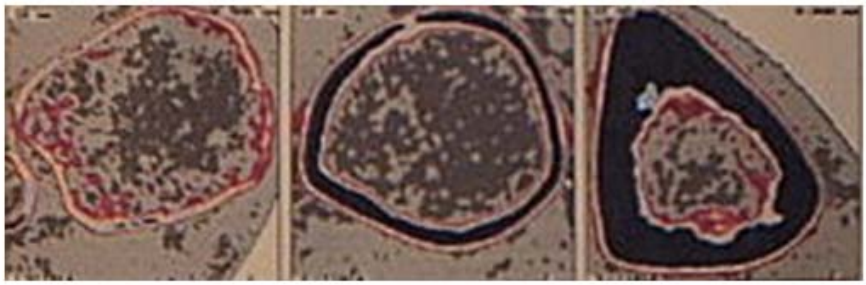
Figures and Tables

Figure 1

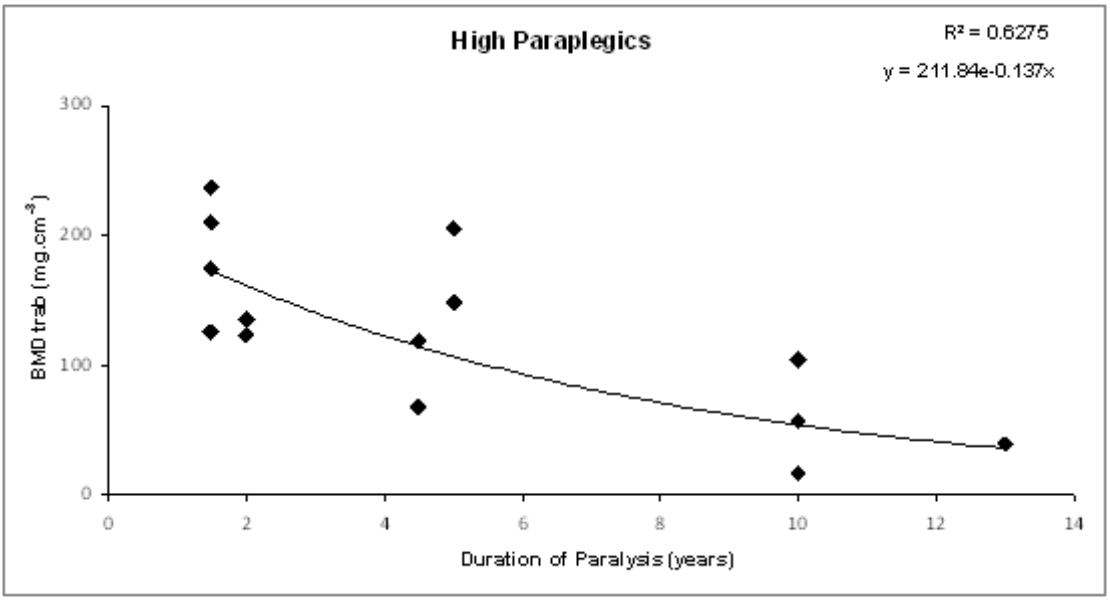
p QCT in the tibia of control subject 39 years old man, slices: 4%,14%,38%



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

Figures represent 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, Trovas G, Galanos A, Raptou P, Papaioannou N, Papagelopoulos P, Lyritis GP. Bone Loss and Mechanical Properties of Distal Tibia in High and Low Level Spinal Cord Injured Men (SA331) Abstracts ASBMR, 28th Annual Meeting, 2006, Philadelphia, Pennsylvania, USA.

Figure 2



The duration of paralysis was inversely related with bone loss in spinal cord injured subjects. Exponential correlation between volumetric trabecular bone mineral density BMDtrab and duration of paralysis in high paraplegics was found to fit best.

Table: 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).

Clinical examination and management of bone loss in SCI ***(Dionyssiotis 2009)***	
Medical Evaluation	**Treatments**
• 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** • counselling 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.