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Reviews

Bone remodeling and calcium homeostasis in patients with spinal cord injury: a review

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ARTICLE INFO

Article history:
Received 7 December 2010
Accepted 16 April 2011

ABSTRACT

Patients with spinal cord injury exhibit early and acute bone loss with the major functional consequence being a high incidence of pathological fractures. The bone status of these patients is generally investigated by dual-energy x-ray absorptiometry, but this technique does not reveal the pathophysiological mechanism underlying the bone loss. Bone cell activity can be indirectly evaluated by noninvasive techniques, including measurement of specific biochemical markers of bone formation (such as osteocalcin or bone-alkaline phosphatase) and resorption (such as procollagen type I N- or C-terminal propeptide). The bone loss in spinal cord injury is clearly due to an uncoupling of bone remodeling in favor of bone resorption, which starts just after the injury and peaks at about 1 to 4 months. Beyond 6 months, bone resorption activity decreases progressively but remains elevated for many years after injury. Conversely, bone formation is less affected. Antiresorptive treatment induces an early and acute reduction in bone resorption markers. Level of injury and health-related complications do not seem to be implicated in the intensity of bone resorption. During the acute phase, the hypercalcemic status is associated with the suppression of parathyroid hormone and vitamin D metabolites. The high sensitivity of these markers after treatment suggests that they can be used for monitoring treatment efficacy and patient compliance. The concomitant use of bone markers and dual-energy x-ray absorptiometry may improve the physician's ability to detect patients at risk of severe bone loss and subsequent fractures.

1. Introduction

Patients with spinal cord injury (SCI) present with early and acute bone demineralization, which occurs exclusively below the level of injury (LOI) and predominantly in load-bearing parts of the skeleton [1-9]. The decrease in bone mineral content and bone mineral density (BMD) is associated with a deterioration in bone microarchitecture [10,11], geometric structure, and strength [12,13], as well as an altered degree of mineralization and collagen matrix composition [14]. These changes have major functional consequences, as demonstrated by the high incidence of pathological fractures of the lower limbs [15-18]. The predominance of bone demineralization at the distal femur and proximal tibia may explain why these are frequent fracture sites [8,18,19]. In the first 3 years postinjury, factures are quite rare, although a 40% decrease in trabecular bone is

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doi:10.1016/j.metabol.2011.04.005

noted. The median postinjury time of the first fragility fracture is 8.5 years [8]. These fractures are asymptomatic and carry the risk of several complications (eg, lengthy immobilization, heterotypic ossification, and pressures sores) [18]. Moreover, the porous nature of the bone means that surgical fixation is often difficult. Although neurological osteoporosis is a well-known chronic complication of SCI, its therapeutic management remains quite unsatisfactory. A better understanding of the pathophysiological mechanisms and kinetics of bone loss may optimize the treatment choices and refine the therapeutic window.

Dual x-ray absorptiometry (DXA) has been extensively used to evaluate BMD status in patients with SCI, and the data obtained with this technique were recently reviewed [20,21]. However, although DXA helps to evaluate the fracture risk, it cannot determine the mechanisms underlying bone loss. Bone histomorphometry has shown an uncoupling between bone formation and bone resorption [10] associated with an increase in osteoclast recruitment and subsequently eroded surfaces [22]. Nevertheless, biopsies do not provide information on the exact time sequence of these metabolic events. Bone cell activity can instead be evaluated indirectly with less invasive techniques, such as specific serum and urine biochemical markers of bone turnover. Bone resorption markers reflect osteoclast activity and are the product of the protein matrix degradation of type I collagen. At first, hydroxyproline, pyridinoline (PYD), and deoxypyridinoline (DPD) adjusted to creatinine (Cr) were used; but they were relatively nonspecific and have been largely replaced by new markers such as N- and C-telopeptide cross-links of type 1 collagen (NTx and CTx). The most frequently reported bone formation markers in the literature reflect osteoblast activity and are the products of collagen synthesis (procollagen type I N-terminal peptide or C-terminal peptide [PINP and PICP]), osteoblastic enzyme (bone-alkaline phosphatase [B-ALP]), or matrix protein (osteocalcin [OC]). It was noted that OC indicates not only bone formation by reflecting mature osteoblasts activity but also overall bone turnover [23].

These markers are reliable, noninvasive, and relatively cost-efficient for bone turnover assessment [24,25]. In addition, bone markers allow for monitoring minor and acute changes in bone turnover, which is not possible with DXA methods because the detection of BMD changes in this population requires a few months [9,26]. Although these bone markers are widely used in a variety of populations such as postmenopausal women [27], very few studies have reported bone marker changes after SCI in adult patients [5,6,8,9,26,28-34]. This may be due to the fact that there is little evidence to date that these markers can predict the future risk of fracture. Moreover, bone turnover changes have been evaluated using several markers, each having a different specificity and sensitivity; and the data have been reported from heterogeneous groups of patients (in terms of LOI, time since injury [TSI], complete or incomplete lesion, and degree of physical activity).

Lastly, it should be noted that analysis of other bone-related cytokines like osteoprotegerin (OPG) and rank-ligand (RANK-L), which are rarely evaluated in patients with SCI [9,32], may provide interesting information about the mechanisms of bone adaptation to neurological lesion.

The clinical applications of bone markers require knowledge of both their limitations and benefits. Bone markers are subject to preanalytical (biological) and analytical variability. Uncontrollable sources of preanalytical variability include age, sex, menopausal status, coexisting disease (eg, diabetes mellitus, impaired renal function, and liver disease), drugs (eg, glucocorticoids), immobilization, and recent fractures, which some patients with SCI may present [35]. The effects of controllable factors (circadian variations, seasonal rhythms, and fasting status) can be minimized by standardized sample collection [35]. Moreover, the currently used bone markers reflect only whole-body net changes. They thus cannot determine the specific bone sites affected by intense bone demineralization or discriminate between turnover changes in a specific skeletal envelope, that is, trabecular vs cortical.

Despite these limitations, studies with long-term follow-up in a large population with this pathology are called for to determine whether the use of bone markers would improve the assessment of fracture risk, as has been reported in other populations such as postmenopausal women [36,37].

The objective of this review was to integrate the various data concerning biochemical bone markers with the aim of clarifying the global effect of SCI on bone turnover. The effects of various factors directly related to the lesion (LOI, TSI), the degree of physical activity, and the treatments likely to affect bone remodeling were also taken into consideration. A better understanding of how SCI affects bone turnover would provide useful information for developing new therapeutic approaches and would help refine therapeutic windows. The calcium (Ca) homeostasis and calciotropic hormones, which are highly implicated in the regulation of bone remodeling, are reviewed in parallel.

2. Kinetics of bone remodeling after SCI

2.1. *Acute phase (<1 year)*

2.1.1. *Bone resorption*

During the acute phase, the early and intense bone loss [2-9] is due to intense bone resorption activity [6,8,26,28-30,34,38-41]. Bone mineral loss was first deduced from the observation of hypercalciuria, whether or not associated with hypercalcemia [38,42,43], with peak values 1 to 4 months postinjury [43]. The increase in bone resorption markers occurs very early on, from 1 to 2 weeks postinjury [6,41], with levels of DPD and NTx up to 10 times the normal values [6]. Similar increases in serum and urinary CTx and urinary NTx/Cr have been seen at 3 months postinjury [26,30,34]. In a large homogenous group of 100 male patients with paraplegia and complete motor loss, Zehnder et al [8] reported that bone resorption markers (DPD) had dramatically increased (5-fold) in patients with a TSI of less than 1 year. The longitudinal follow-up of 1 to 24 weeks in a population of 30 patients with paraplegia or quadriplegia demonstrated that the bone resorption peak occurred at about 10 to 16 weeks [6]. The values had not returned to baseline by the end of the study, indicating ongoing bone resorption [6]. In another longitudinal study of 7 patients with complete injury, we confirmed that this period was characterized by an

intensive bone degradation process because higher values for plasma and serum CTx were found at 16 weeks [9]. Beyond 6 months TSI, values for urinary NTx/Cr tended to decrease progressively, reaching normal levels at 12 months; but this was not the case for serum CTx [34]. There is a consensus regarding the dramatic increase in bone resorption during the acute phase (TSI <1 year) because all studies have reported elevated values for bone resorption markers [28,29,31,44-46].

2.1.2. *Bone formation*

Contrasting with the large increase in bone resorption markers, the changes in bone formation are modest and generally barely exceed the upper range for the reference values [6]. Osteocalcin levels were reported as normal at 1 month post-SCI for 6 patients but gradually increased over a 6-month period postinjury [28]. Similarly, we reported higher OC levels in young male patients with SCI and TSI of about 3 months [21,26]. The higher levels were observed at about 16 to 24 weeks and then decreased significantly, reaching normal levels after 48 weeks [9]. In the first 16 weeks, increased levels of total-ALP were also reported [6]. In patients with TSI of less than 3 months, PINP was also found to be higher than the reference values; and values returned to within the reference range after 12 months [34]. Zehnder et al [8] reported that total-ALP or OC in patients with TSI of less than 1 year were either within or slightly higher than the upper reference ranges, confirming the previous cross-sectional [39,47] and longitudinal studies on the period from 1 to 24 weeks [6]. Only Reiter et al [31] reported lower B-ALP values in patients with TSI of less than 1 year.

The modest increase in bone formation markers contrasts with the results from Minaire et al [10], who reported a decrease in bone formation surface from iliac crest biopsies. In this condition, the elevated OC levels reported in SCI patients during the acute phase [9,26,28,30] may not reflect the overall intensive bone formation activity but instead are more likely due to local bone repair processes at the site of the vertebral fracture [48]. Moreover, several experimental investigations have demonstrated that immobilization itself may also induce a rise in OC levels [49]; so it is quite difficult to estimate the relative effects of spine fracture and immobilization on bone formation markers [9]. Comparison of the data from a local biopsy and circulating bone markers is also difficult because the SCI may have a local impact on the activity of bone cells.

The intense demineralization observed in patients with SCI in this early phase is clearly due to the imbalance in bone cell activities in favor of bone resorption. Zehnder et al [8] found no correlation between resorption and formation parameters, pointing to an uncoupling between the 2 processes. Moreover, we can note that the bone resorption changes in patients with SCI are greater than those in healthy individuals submitted to experimental immobilization (bed rest) [50] or microgravity [51,52]. This suggests that other mechanisms, probably related to the neurological lesion itself, might be involved in this acute and early bone loss [21,53], in addition to bed confinement, lack of mobility, and malnutrition [54]. The bone loss associated with SCI is a complex clinical model, and the exact contribution of the various factors is difficult to ascertain.

2.2. *Chronic phase*

It is very difficult to clearly identify the time needed to normalize bone remodeling postinjury because of the lack of long-term longitudinal studies [6,9]. Most data have been obtained from cross-sectional studies on heterogeneous populations with several confounding factors such as LOI, complete or incomplete injury, and TSI. The potential effects of these factors on bone remodeling will be detailed below.

2.2.1. *Bone resorption*

Studies report that bone resorption stays elevated many years after the initial injury [7,8,28,31,33,40,55,56]. Jones et al [33] reported that bone resorption evaluated with DPD was higher than the reference ranges in 4 male patients with SCI and TSI of more than 5 years (mean, 27 years). These results were confirmed in 8 male patients with TSI of more than 5 years who showed quite elevated PYD, DPD, and NTx [31]. In an extensive study including a homogeneous population of 100 men with paraplegia, Zehnder et al [8] reported that bone resorption estimated by DPD remained elevated in 50% of patients with TSI ranging from 1 to 9 years and in 30% of patients with TSI of more than 10 years. The authors also found that the latter presented lower BMD z scores at the tibial sites and had approximately 4 times the number of fragility fractures compared with patients with chronic paraplegia and normal DPD [8].

2.2.2. *Bone formation*

Most patients injured more than a year earlier have presented normal values for bone formation [7,8,55], but lower [31] or higher [28,56] levels of bone formation markers have also been reported. The degree of alteration was nevertheless lower compared with bone resorption; and in most cases, the values were close to the reference ranges.

During the chronic stage, very few studies have reported the lack of SCI impact on bone remodeling [5,57]. Kannisto et al [5] reported that the bone formation and resorption markers in a population of 35 adult patients who had been injured in childhood (range, 1.5-17 years) were within the reference ranges, whereas BMD loss was observed.

3. OPG/RANK-L system

Rank-ligand is produced by osteoblasts and binds to its receptor, RANK, on the surface of osteoclasts and their precursors. This process regulates the differentiation of precursors into multinucleated osteoclasts, as well as osteoclast activation and survival. Osteoprotegerin, which is also secreted by osteoblasts, protects the skeleton from excessive bone resorption by binding to RANK-L and preventing it from interacting with RANK [58,59]. Although the OPG/RANK-L system is essential for bone regulation, these cytokines have received limited attention [9,32]. Patients with recent SCI presented lower serum RANK-L levels and higher serum OPG levels than able-bodied individuals. An increase in the OPG/RANK-L ratio could modulate the bone resorption process in favor of a reduction in osteoclast differentiation and activity. No significant variation with TSI (16-71 weeks) was observed

for any cytokine [9]. In chronic patients (TSI >2 years), Morse et al [32] reported increased OPG levels with age modulated by the level and severity of the injury. In agreement with this study [9], no relationship between OPG/RANK-L values and TSI was found.

Nevertheless, blood measurement of OPG/RANK-L concentrations at a single point in time may underestimate the changes in local OPG/RANK-L production within the microenvironment of bone cells [60].

4. Factors with a potential impact on bone remodeling

4.1. *Duration of injury*

As noted, the level of bone resorption decreases with TSI [6,8,9,31]. However, some studies have found a negative linear relationship between markers like Hyd/Cr [28] or B-ALP [33] and TSI, whereas others did not [8,32]. These discrepancies may be related to the studied population (whether or not the TSI ranges are wide), as well as to the markers used [28]. It is possible that the markers, particularly those reflecting bone resorption, decline following a logarithmic time curve after an intense phase, with bone resorption tending to progressively return to reference ranges [8].

4.2. *Level of injury*

Given the small number of patients that are often available, the studies that have tried to evaluate the impact of LOI on bone remodeling have generally settled for an arbitrary comparison of 2 large categories of patients classified as paraplegic or quadriplegic. During the acute phase, we reported no difference between male patients with paraplegia (n = 7) and quadriplegia (n = 9) with complete traumatic injury. In both SCI groups, the values of bone resorption markers were systematically higher compared with the values in an able-bodied group [30]. Similarly, Pietschman et al [28] observed no differences in OC or Hyd/Cr between chronic SCI patients with paraplegia (n = 7) and quadriplegia (n = 6). Roberts et al [6] also reported no differences for total-ALP, DPD, and NTx during the first 24 weeks between the 2 SCI groups. Only a slightly higher total PYD value was observed in patients with quadriplegia compared with paraplegia when values were expressed as the percentage of basal values, suggesting greater bone resorption in patients with quadriplegia. However, the authors highlighted that PYD is less specific than DPD and NTx; and because a limited number of subjects (9 patients with paraplegia and 10 with quadriplegia) were investigated, it was not possible to conclude a bone remodeling difference according to the LOI. Last, Morse et al [32] also found that LOI was not correlated with CTx or OC values.

It is surprising that a clear bone remodeling profile cannot be identified according to the LOI (paraplegia vs quadriplegia) because, although the neurological LOI does not determine the degree of bone loss, it does have an impact on the extent of the alteration [3,7]. As has been noted, bone markers give a global but not site-specific evaluation of bone turnover. The lack of differences between the 2 groups may reflect the heterogeneity of these populations; and functionally, some patients with paraplegia and quadriplegia might not be so different, thus showing bone turnover that is quite similar [6].

4.3. *Physical activity*

Physical activity in able-bodied individuals is known to induce changes in bone remodeling [61], and most persons with SCI present a sedentary lifestyle [62]. Jones and Legge [33] compared 2 groups of male patients: an active group that reported a mean physical activity volume of 12.2 h/wk (±6.0) and a sedentary group that reported no significant physical activity. The authors found that B-ALP was significantly higher in the sedentary patients compared with the active group, whereas DPD tended to be lower. This suggested that physical activity in this population may modulate bone remodeling. However, the number of subjects was limited (sedentary, n = 4; active, n = 11); and the population showed differences in TSI and age, 2 confounding factors that could affect bone remodeling. Conversely, Roberts et al [6] found no relationships between the levels of physical activity and bone markers; and Morse et al [32] reported no correlations between OC and CTx concentrations and the ambulation mode (from motorized wheelchair ambulation to independent walking) in patients with TSI of more than 2 years.

4.4. *Other factors*

In addition to bone demineralization, SCI induces a dramatic alteration in body composition [63,64], health-related complications such as diabetes mellitus [65], and lifestyle changes [62]. It is thus important to better understand the effects of these parameters on bone remodeling. Morse et al [32] studied 82 male patients with TSI of more than 2 years and found no relationships between OC and CTx values and factors like body mass index, smoking history, history of heart disease, high blood pressure, and diabetes [32]. Roberts et al [6] confirmed that weight and nutrition do not affect biochemical bone markers. In able-bodied individuals, numerous studies have reported that bone remodeling is affected by age [66]. The impact of age on patients with SCI can be debated, probably because injury causes a greater alteration in bone loss than age. Nevertheless, it was noted that the studies were generally conducted in a subgroup of adult patients with a relatively narrow age range (20-45 years), a period where bone turnover is relatively stable. In this population, CTx was found to increase significantly with age [32], whereas OC decreased [8] and no variation for DPD or total-ALP was reported. More extensive study in other age groups may improve our knowledge on the relationship between age/SCI and bone turnover, with particular focus on childhood and adolescence, as these 2 periods have not been investigated.

After controlling for age and TSI, patients with a history of fracture had significantly lower OC ($P < .05$) and significantly higher DPD ($P < .05$) concentrations compared with the group with no fractures [8].

Other factors like the severity of the neurological lesion (complete or incomplete) should be investigated, and a more refined analysis of the impact of the LOI could be conducted to better appreciate its effect on bone remodeling.

5. Ca homeostasis

5.1. *Calcium*

As previously mentioned, hypercalciuria associated with abnormally high ionized calcium (iCa) levels with or without abnormal elevated total Ca was reported in patients during the acute SCI phase [6,26,28,38,40,42,43,47,67-71]. Pietschmann et al [28] reported that urinary Ca/Cr was higher than normal in patients during the first 6 months postinjury. Values tended to return to normal during the chronic phase and were not affected by the LOI [28]. Ionized Ca and urinary Ca excretion rose soon after the initial SCI, and they remained elevated for the 24-week study duration [6]. Moreover, in this period, increased phosphorus (P) values were also reported [6,8,26,38,47,67,69,71]. This increase could be explained by the loss of P from bones and muscle tissues [7] and results from the relative hypoparathyroidism (see below). Secondarily, it can directly inhibit the 1,25(OH)D synthesis [71].

5.2. *Parathyroid hormone*

During the acute SCI stage, the release of minerals (Ca, P) from bone tissue into the blood circulation causes a profound alteration in calciotropic hormone secretion, which finely regulates Ca homeostasis. In this phase, the secretion of parathyroid hormone (PTH) drops quickly [6,9,26,28,43,67,68]. Our group reported that PTH was reduced by more than 80% in 7 patients in the acute SCI stage (TSI <3 months) compared with values from an able-bodied group [26]. This initial suppression seemed to be transitory because it tended to level off after 6 months, as demonstrated in 3 longitudinal studies [6,9,28]; but values did not always return to normal 71 weeks postinjury [9]. The inhibition of PTH biosynthesis coincides with the rise in iCa [6,8,9,26,46], but not with the high concentration of 1,25-dihydroxy-vitamin D ($1,25[OH]_2D$) because this synthesis is also suppressed [9,26].

Parathyroid hormone tended to increase during the chronic SCI phase compared with the acute phase [8]; yet in most cases, values remained less than or within the lower reference ranges [72]. Vaziri et al [73] showed persistent PTH suppression in a cross-sectional study of 40 patients with TSI ranging from 3 to 50 years. The lower PTH value was observed despite the presence of normal iCa and lower total Ca, suggesting that the decreased PTH values in the SCI group may have been due to an increase in Ca release into the extracellular matrix, most likely from the skeleton. Persistent PTH inhibition in individuals with chronic SCI seems to indicate that low-grade net bone resorption continues for many years after the initial injury. As mentioned above, the maintenance of high levels of bone resorption markers during this chronic phase may point toward this hypothesis. Conversely, Pietschmann et al [28] reported no differences between PTH levels in patients and able-bodied individuals; but the population presented a wide TSI range (4-812 weeks). The TSI can be considered as a confounding factor because PTH levels were found to be positively and significantly correlated with TSI and higher values were reported in patients with a TSI of more than 1 year [28]. The increase in PTH with TSI was also reported by other authors [8]. Patient age may also interfere with PTH levels [8]. The LOI, especially paraplegia or quadriplegia, did not seem to have an impact on PTH levels [28,30]. However, when the LOI was properly classified as sacral, thoracic, or cervical, PTH levels were inversely related to the LOI; and the values were higher in the sacral group [73]. Parathyroid hormone suppression was also associated with the degree of neurological impairment (complete or incomplete SCI) rather than the LOI itself [71]. Various interventional programs such as functional electrical stimulation and stationary biking increased PTH levels [74].

The decreased PTH levels in patients with SCI may have 2 major consequences: (1) a decrease in Ca reabsorption at a distal nephron site and (2) a reduction in $1,25(OH)_2D$ synthesis that indirectly induces a decrease in intestinal Ca absorption. These mechanisms presumably serve as a protective shield, minimizing the possibility that skeletal Ca loss will lead to hypercalcemia [43].

5.3. *Vitamin D metabolites*

In addition to the decrease in PTH levels, vitamin D metabolites were found to be altered. In fact, patients with SCI have been reported to have a higher prevalence of vitamin D deficiency than the able-bodied population [9,26,30,43,46,73,75].

Stewart et al [43] reported that during the first or second week postinjury, a suppression of the parathyroid–vitamin D axis was the result of bone resorption and hypercalciuria. In a recently injured group of patients (TSI ≈3 months), we confirmed these results [26]. Vitamin D deficiency was also reported in persons with chronic SCI [73]; but in fact, it seems that only $1,25(OH)_2D$ was specifically altered. Afterward, despite plasma 25-hydroxy-vitamin D (25[OH]D) values that tend to decrease with TSI, these values remained within reference ranges, indicating the presence of normal vitamin D stores [6,43,71]. Other studies demonstrated that the proportion of subjects with a 25(OH)D defect was significantly greater in individuals with chronic SCI (32%) than in able-bodied populations (16%) [75] and that 25(OH)D levels were negatively correlated with PTH levels [75]. In fact, it is likely that 25(OH)D deficiency occurs more often in severe cases, such as patients with quadriplegia hospitalized for pressure ulcers over long periods of time [76]. Conversely, for $1,25(OH)_2D$ concentrations, the active hormonal forms are generally reduced [9,26,30,43,73]. Only Bauman et al [75] reported that values of $1,25(OH)_2D$ were higher in a population of 100 patients with chronic SCI than in controls, which may have reflected an increased effect on 1-α-hydroxylase activity in renal tubular cells. Differences in racial origin, diet, and sunlight exposure may provide some insight [75]. The $1,25(OH)_2D$ levels may be modulated by the LOI because patients with quadriplegia were found to have significantly lower values than patients with paraplegia [73]. In addition, an opposite correlation between 25(OH)D levels and $1,25(OH)_2D$ was reported in patients with paraplegia and quadriplegia, suggesting that the LOI might act on renal $1,25(OH)_2D$ formation or the inhibition of hepatic 25(OH)D synthesis [71]. However, in a more recent study, we could not confirm the effect of LOI on vitamin D metabolism [21].

The $1,25(OH)_2D$ biosynthesis deficit generally observed is probably due to several factors, including lower PTH values

that stimulate 1-hydroxylation of 25(OH)D and limited sunlight exposure due to physical disability and prolonged hospital stays [76]. 1,25-Dihydroxy-vitamin D synthesis suppression may have several negative physiological effects because it facilitates active Ca absorption in a population whose Ca intake is generally quite restricted [43]. However, in a very limited number of patients, Ca absorption was found not to be clearly altered [38]. Taking into account the suppression of $1,25(OH)_2D$ secretion, vitamin D supplements may improve bone health in this population. Bauman et al [75] supplemented individuals with chronic SCI with 800 IU 1,25 (OH)D per day over a 12-month period and found a doubling of vitamin D levels and a one-third decrease in PTH levels. However, vitamin D deficiency persisted in some patients [75].

5.4. *Calcitonin*

In patients with SCI, calcitonin (CT)-related data are quite scarce but do not seem to differ between patients with SCI and able-bodied individuals [28,73]. Pietschmann et al [28] reported that the LOI had no impact on CT concentration, whereas Vaziri et al [73] found higher values in patients with quadriplegia than in patients with paraplegia. The authors suggest that this may indicate a compensatory response to the ongoing Ca loss from the skeletal site of paralyzed structures, which covers a greater area in quadriplegics [73].

6. Effect of treatment on bone remodeling

6.1. *Ca injection*

Bolus injection of Ca gluconate (0.025 mmol elemental Ca per kilogram) in 8 men with chronic SCI (6 patients with paraplegia and 2 with quadriplegia) with a TSI of 12 ± 8 years (range, 3-27 years) decreased PTH and NTx concentrations over the following 6 hours. In this study, a low 25(OH)D (<20 ng/mL) and/or elevated serum PTH (>55 pg/mL) at basal level was a prerequisite for inclusion. This result suggests that, in addition to the well-known negative effect induced by loss of mechanical constraints and the neurological lesion, Ca alterations may contribute to promoting an adverse context for bone turnover [77].

6.2. *Vitamin D supplementation*

In a randomized, placebo-controlled trial, Bauman et al [78] reported that the administration of 4 μg 1-α-hydroxyvitamin D2 (a vitamin D analog) to patients with chronic SCI for 24 months induced a small increase in leg BMD. This improvement was probably due to a decrease in bone resorption activity, as demonstrated by the significant reduction of urinary NTx without modification of bone formation (OC and PINP). Nevertheless, the response of bone mass and markers to 1-α-hydroxyvitamin D2 was dependent on the smoking status.

6.3. *Bisphosphonates*

Analysis of biochemical bone markers demonstrated that bone resorption is the most affected bone cell activity post-SCI. Taking into account this pathophysiological finding, various interventional studies have attempted to demonstrate the positive effect of bisphosphonates, a safe and effective treatment of osteoporosis in postmenopausal women [79]. Bisphosphonates play a crucial role in bone resorption by reducing osteoclast recruitment, activity, and life span. In a nonrandomized study, Nance et al [44] reported the positive effects of 30 mg (every 4 weeks for 24 weeks) of intravenous pamidronate administered to 14 patients in the acute SCI stage (TSI <6 weeks), which is the period when bone resorption is most affected. The high excretion of urinary NTx observed in patients within 6 weeks of their injury decreased by approximately 60% after the first treatment, and values remained low throughout the follow-up. In the same acute period, 3 studies confirmed the positive effect of pamidronate on bone resorption markers, whether or not it was combined with daily administration of calcitriol and Ca [40,45,46]. In a retrospective study, Mechanick et al [46] demonstrated that, after 2 weeks of treatment, a single dose of 90-mg pamidronate injection had triggered a greater decrease in NTx than 3 doses of 30 mg [46]. Chen et al [45] reported that 30-mg pamidronate for 3 days significantly reduced NTx levels in patients with SCI. In patients with TSI of less than 10 days, the use of alendronate (70 mg once weekly) prevented bone loss during the 12-month treatment period; and this effect was sustained for 6 months after stopping the treatment. The positive effect on bone mass was correlated with the early inhibition of intense bone resorption and was confirmed by the dramatic decrease in CTx and calciuria values. These values were back to normal after 3 months as opposed to the still high values in the placebo group. However, there was no difference in values between the 2 groups 6 months after completing the treatment of alendronate and placebo administration.

In the acute SCI phase, most patients are bedridden; and therefore, administration of oral bisphosphonates immediately after injury is more difficult than administration of intravenous drugs such as zoledronic acid [34]. Bubbear et al [34] reported that patients treated with a single dose of 4-mg intravenous zoledronic acid presented total preservation of hip BMD at 12 months postinjury and normalization of bone markers (PINP, CTx, or NTx/Cr) after 6 weeks to 3 months. In the control group, this normalization occurred only after 12 months. The decrease in bone resorption markers for patients treated with bisphosphonates is similar to the results obtained from transiliac bone biopsies, where decreased histomorphometry measures of bone resorption (number of osteoclasts) were reported after treatment [22].

In a 2-year, randomized, controlled, and open-label study, Zehnder et al [55] reported that patients in the chronic phase treated with alendronate (10 mg daily) and Ca (500 mg) had a significant reduction in bone turnover as determined by DPD, OC, and total-ALP compared with patients who were only supplemented with Ca. The patients treated with alendronate also showed relative BMD preservation associated with the bone remodeling changes.

Because bisphosphonates were found to reduce bone resorption in both acute and chronic stages, the benefits of these drugs appear less obvious many years after the SCI, probably because the most severe bone loss has been reached

by this stage and bone resorption is reduced. Moreover, the response to bisphosphonates may also vary according to the complete or incomplete nature of the SCI [44].

Other drugs such as human recombinant PTH, which has proven its efficacy in postmenopausal osteoporosis [80], should be considered for the treatment of osteoporosis after SCI. A more recent drug, denosumab [81], a human monoclonal antibody that binds to RANKL, should also be evaluated.

6.4. *Physical therapy methods*

In 5 patients with TSI of less than 6 months, 48 sessions of body weight–supported treadmill training did not prevent bone loss [39]. Despite the absence of a control group, the authors noted that the patients presented the same small fluctuations in bone markers [39] normally observed after acute SCI in the absence of any intervention [6]. The patients' compliance with this type of exercise affected the bone remodeling response [39]. The impact of this same type of training (144 sessions of body weight–supported treadmill training) was evaluated in 14 patients in the chronic phase of incomplete trauma SCI for an average follow-up of 12 months (mean, 7.7 ± 6.7 years) [56]. No changes in BMDs at the femur or tibia after weight-supported treadmill training were observed; and in parallel, no changes were found for DPD or OC.

A 9-month program of functional electrical stimulation on a stationary bicycle ergometer (TSI, 6 ± 1.2 years) induced a parallel increase in lumbar spine BMD and OC (+78%) in 9 chronic patients, without any change in hydroxyproline/Cr [74].

A 12-month functional electrical stimulation upright cycling program for 30 min/d, 3 d/wk in 10 patients showed that the increase in tibial BMD was not associated with changes in OC or DPD. The authors suggested that the affected bone mass was too small to cause measurable systemic changes in bone markers [57].

7. Conclusion

In conclusion, this review clearly demonstrates that the extensive and acute bone loss after SCI is induced by an uncoupling of bone remodeling in favor of bone resorption. This imbalance takes place right after the initial injury and persists for many years. Osteoclasts appear to be the major therapeutic target, and antiresorptive drugs should be considered as the best treatment option today. Moreover, as calciotropic hormones are also modified, vitamin D supplementation may improve Ca reabsorption in these patients and subsequently contribute to reducing bone loss, particularly during the chronic phase when hypercalcemic status is not noted. During the acute phase, questions about supplementation and/or the dose to be used remain unresolved because of concerns about the increased risk of renal tract calculi following SCI. The high sensitivity of the response to these therapeutic interventions suggests that bone markers should be systematically evaluated in patients to determine whether the treatment is appropriate.

More studies on large groups of patients are needed to determine the impact of confounding factors like the LOI on bone markers levels. Lastly, the concomitant use of bone markers and the DXA technique may improve the physician's ability to detect patients at risk of severe bone loss and subsequent fractures.

Funding

Financial support was provided by Roche Diagnostic.

Acknowledgment

The authors would like to thank Mrs Bénédicte Clement for her medical editing in the English language.

Conflict of interest

None.

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