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Bridging the bone gap: a prospective study protocol on osteoporosis risk in Portuguese patients with spinal cord injury

Abstract

Spinal Cord Injury is associated with a decrease in bone mineral density and consequently an increased risk of fragility fractures. This prospective study protocol, aims to investigate the risk factors and prevalence of osteoporosis in a Portuguese population of spinal cord injured patients. By analyzing a range of variables, including not only personal and family history, lifestyle factors, and injury severity, but also bone mineral density and biochemical markers of bone resorption, the research seeks to enhance our understanding of osteoporosis in spinal cord injury patients and improve preventive measures. The effectiveness of pharmacological interventions is greater when started soon after the injury, therefore, prompt diagnosis and treatment of osteoporosis are essential to prevent the complications associated with this condition, particularly osteoporotic fractures.

Volume 11 Issue 3 - 2023

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Received: October 16, 2023 | **Published:** October 27, 2023

Introduction

Spinal Cord Injury (SCI) is associated with a decrease in bone mineral density (BMD) and consequently an increased risk of fragility fractures. The loss of bone mass (BM) is more pronounced in the first 2 years after SCI. This results in an estimated loss of 7 to 15% of trabecular and endocortical bone in the epiphyses of the long bones of the lower limbs, in the first year post-injury.[1,2] BM reduction below the level of the injury has been described in the literature for up to about 7 to 8 years after SCI, with an estimated rate of 2 to 5% per year after the second year of injury, contributing to a high prevalence of osteoporosis observed in SCI patients, which can affect 61% of patients.[3,4]

The pathogenesis underlying osteoporosis in this patient group is complex and remains unclear. The primary cause described for the initial and excessive loss of bone mass is the reduction in mechanical loading in the context of muscle weakness and immobility, associated with sympathetic nervous system dysfunction. Metabolic, autoimmune, vascular, nutritional, and hormonal alterations are also suggested as potential causes of bone mass loss; however, the relative contribution of these factors remains unknown.[5]

Corticosteroid-induced osteoporosis is a common form of secondary osteoporosis, especially in young adults. Soon after starting corticosteroid therapy, there's an early onset of bone loss and a heightened frequency of fractures, with these occurrences closely tied to the dosage and duration of treatment. The use of methylprednisolone was suggested to potentially enhance neurological outcomes in individuals with acute, non-penetrating traumatic SCI. However, the available evidence supporting its effectiveness is restricted and there is conflicting data whether its use is associated with the development of medical complications, leading to substantial debate regarding its utilization. As a result, the majority of authors do not find compelling or consistent evidence in current literature to support the idea that administering high doses of methylprednisolone improves outcomes in traumatic spinal cord injury. Despite recommendations against it, the continued use of high-dose methylprednisolone remains a common practice in the treatment of spinal cord injury in the acute phase, contributing to the occurrence of osteoporosis in affected patients.[5–7]

SCI results in an immediate lack of mechanical stress on bones, which is a critical factor in the bone remodeling process regulated by osteocytes. This absence of mechanical loading triggers an adaptive response characterized by a reduction in osteoblastic bone formation and an increase in osteoclastic bone resorption, leading to demineralization. In some cases, the imbalance between bone formation and resorption is significant and sustained, resulting in severe bone loss. This phenomenon has been well-documented in both acute and chronic SCI.[5–8]

Assessment of BMD through hip and femur bone densitometry is considered a simple and effective method for identifying patients with decreased bone mass and quantifying the risk of fragility fractures.[7]

Biomarker measurements of bone formation and absorption, aimed at providing information about bone metabolic activity, may be an option in future clinical practice.[9,10] Biochemical markers of bone resorption in blood and urine, such as total deoxypyridinoline (DPD), N-telopeptide (NTx), serum and urinary type I collagen C-telopeptide (CTx), and hydroxyproline, have been found to be significantly elevated in both acute and chronic SCI. However, in chronic SCI, these markers tend to be lower than in acute SCI. Nevertheless, it's worth noting that elevated levels of DPD have been observed in 30% of patients who are 10 years or more post-injury. This substantial increase in bone resorption rates after SCI has also been associated with a slight rise in osteoblastic bone formation activity, as indicated by minor increases in serum osteocalcin and total alkaline phosphatase. However, there is no consensus on the significance of these modest increases in osteoblastic activity, with some studies reporting them as minor while others consider them substantial.[11–13] A study conducted by Gifre and colleagues revealed that individuals with SCI who have baseline total femur BMD values below 1 g/cm² and lumbar BMD values less than 1.2 g/cm² are at an elevated risk for osteoporosis. Furthermore, in addition to BMD findings, the researchers identified that higher baseline values of bone turnover markers, specifically bone-specific alkaline phosphatase (bone ALP) and serum type-1 procollagen N-terminal peptide (P1NP), also indicate a greater risk for osteoporosis.[14]

The International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC-IOF) Working Group for Standardization of Bone Marker Assays, along with the National Bone Health Alliance (NBHA), recommend CTx and P1NP as reference bone markers for assessing fracture risk and evaluating the effectiveness of osteoporosis treatment. This recommendation is based on several factors, including their low inter-individual variability, relatively stable characteristics in serum at room temperature, and the availability of reference intervals for these biomarkers in different geographic regions and individual assays.[15]

Hypercalciuria is prevalent in the acute phase of SCI due to abnormally high ionized calcium levels, which eventually return to normal during the chronic phase. These changes observed during the acute phase are followed by alterations in calcium regulatory hormone levels. In particular, serum intact parathyroid hormone (iPTH) levels tend to be suppressed during the acute and sub-acute phases of SCI, as expected in this negative feedback loop, which typically spans 1 to 4 months. iPTH levels increase in the chronic phase compared to the acute phase but usually remain within or below the lower reference range.[16] Changes in vitamin D levels in acute SCI are often characterized by reduced levels of 1,25(OH)2 vitamin D, which is the biologically active form of vitamin D. This reduction is attributed to the increased bone resorption and the suppression of parathyroid hormone (PTH).[11–13,17]

Within the literature, fragility fractures in this patient group are reported to have incidences ranging from 1% to 34%. These fractures share common characteristics, such as their location in the distal femur and/or proximal tibia (around the knee joint) and their origin in low-impact traumas. They often occur, for example, in wheelchair falls, during transfers or in activities involving minimal or no trauma, sometimes going unnoticed by patients.[6]

Risk factors associated with fragility fractures following SCI include: female gender, age at the time of injury, time since injury, neuromotor status of paraplegia (defined by the ASIA International Standards for Neurological Classification of Spinal Cord Injury - ISNCSCI), low body mass index (BMI), low bone mineral density in the lower limbs, and the use of anticonvulsants, anticoagulants, and/or opioid analgesics. Patients with complete spinal cord injuries tend to experience more substantial bone mass loss compared to those with incomplete injuries. Furthermore, it appears that patients with paraplegia face a greater risk of fragility fractures compared to tetraplegics, which may be attributed to their greater level of activity and independence.[7]

Patients with SCI who sustain fragility fractures appear to experience a greater incidence of complications than the general population. These complications include an elevated risk of delayed or absent fracture healing, along with a heightened susceptibility to deep venous thrombosis, pressure ulcers and local infections.[5,8]

Although fragility fractures are not typically observed until up to 3 years after SCI, according to the literature, the effectiveness of pharmacologic interventions is greater when administered soon after the injury, within a narrow therapeutic window of weeks to months. Treatment with bisphosphonates in the first year following the injury has been shown to significantly reduce bone mass loss. Some studies have observed a lack of efficacy of pharmacologic-based therapeutic interventions in chronic spinal cord injury patients.[13,15,18,19]

Fragility fractures following SCI are associated with a loss of independence in activities of daily living, increased morbidity and mortality, as well as an increase in direct and indirect medical expenses. Preserving bone mass and architecture is crucial for reducing the risk of fragility fractures in this patient group, making it essential to better understand the pathogenesis and associated risk factors. However, studies on the incidence and risk factors for fragility fractures in SCI are often limited in sample size, have short follow-up periods, and are primarily cross-sectional. Likewise, data related to complications and the therapeutic approach to fractures in these patients are limited.[2,3,12,15]

Methods

The aim of this study is to assess the development of osteoporosis during the first year after a traumatic spinal cord injury and the associated risk factors.

This is a prospective study that includes patients admitted to a Rehabilitation Center between January 2022 and January 2023, with recent traumatic spinal cord injuries (less than 6 months since the injury) and aged 18 years or older. Patients with BMD at admission suggestive of osteoporosis, a personal history of fragility fractures, or an obvious secondary cause of osteoporosis, severe liver or kidney disease, or those currently undergoing anti-osteoporotic treatment at the time of study inclusion were excluded.

Evaluations were conducted at admission and 12 months later, including clinical assessment, and BMD measurements. Laboratory tests were performed at admission. Risk factors for osteoporosis were assessed in all patients, including personal and family histories of fragility fractures, tobacco and alcohol consumption, age at menopause in female patients, and associated comorbidities. Additionally, the level of spinal cord injury, changes in muscle tone (spastic/flaccid injury), time since the injury and classification according to the ISNCSCI score were also recorded, as well as gender, age, weight, height, and body mass index.

Biochemical assessment

Blood and urine samples were obtained between 8:00 and 10:00 in the morning after an overnight fast, on the same day as the first bone densitometry, including complete blood count, serum creatinine, serum calcium, phosphate, PTH, 1,25(OH)2 vitamin D, bone formation markers, in particular, bone ALP and P1NP, and bone resorption markers, namely CTx and DPD.

Bone mineral density assessment

Bone mineral density of the lumbar spine and proximal femur will be measured by Dual X-ray Absorptiometry at the time of admission and at the 12-month follow-up.

Results

While the period of patient's inclusion in our study has already ended, we are currently awaiting the final DEXA scans for a subset of participants.

Out of the 23 patients initially included in the study, 3 were excluded due to initial DEXA scans indicative of osteoporosis. Among the remaining 20 patients, 85% were male, with an average age of 47 ± 18.41 years. Their primary causes of spinal cord injury were as follows: 10 (50%) due to falls, 2 (10%) resulting from bicycle accidents, 7 (35%) due to motorcycle or automobile accidents and 1 (5%) from a diving accident. Half of the patients were tetraplegic, while the other half were paraplegic. Of these, 4 had complete spinal

Citation: Xénia V, António P, Carolina P, et al. Bridging the bone gap: a prospective study protocol on osteoporosis risk in Portuguese patients with spinal cord injury. *Endocrinol Metab Int J.* 2023;11(3):57–59. DOI: 10.15406/emij.2023.11.00333

cord injuries (20%), and 9 (45%) had spastic injuries, with most having limited or no walking ability. Upon admission, 65% exhibited significant functional impairment, with an average Functional Independence Measure (FIM) score of 80 and a standard deviation of ±24.43. Only 6 reported a history of smoking or past smoking habits, and 4 had notable alcohol consumption. The majority indicated adequate calcium intake (65%). The average body mass index (BMI) was 24.07 ± 4.4. Most patients were not on anticonvulsant medication, opioid analgesia, or anticoagulants, apart from prophylactic doses of enoxaparin.

Conclusion

In the face of the challenges posed by SCI the confluence of physical, physiological, and psychological consequences often overshadows a less visible yet equally significant issue—osteoporosis. The reduced bone mineral density and heightened fracture risk associated with SCIs represent a substantial threat to the long-term well-being of affected individuals.

Monitoring this decline and by exploring risk factors, prevalence and potential preventive measures, we have taken a substantial step towards enhancing the quality of life and overall health of SCI patients. Preventive strategies are essential to avoid the complications of osteoporosis, particularly osteoporotic fractures. To the best of the authors' knowledge, this is the first study conducted in a Portuguese population of spinal cord injury patients with the objective of not only monitoring bone mineral density and bone activity biomarkers but also evaluating patient and injury-related risk factors.

Our ongoing study is currently in progress, with dedicated efforts from our research team to gather and analyze valuable data. Once our study reaches completion, authors are committed to publishing the results. In summary, this study protocol intends to not only contribute to the scientific understanding of osteoporosis in the context of SCIs but also foster the hope of reducing the burden of this condition on the lives of those individuals. It is our fervent wish that the research outlined in this article serves as a catalyst for further advancements in this field and, ultimately, an improved quality of life for SCI patients.

Acknowledgement

None.

Conflicts of interest

Authors declare that there is no conflict of interest exists.

Funding

None.

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