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Osteoporosis, Spinal Cord Injury

Authors

Matthew Varacallo[1]; Peter Pizzutillo.

Affilations

[1] Department of Orthopaedic Surgery, University of Kentucky School of Medicine

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Introduction

Osteoporosis is a condition describing a spectrum of overall compromised skeletal microarchitecture with clinical manifestations related to decreasing levels of bone mineral density (BMD).[1],[2] Spinal cord injuries (SCIs) vary significantly in terms of the range of clinical impact and overall compromise to a patient's functional outcomes and quality of life. SCIs have long been recognized as a clinical culprit that ultimately leads to osteoporosis.[3] Clinicians are encouraged to recognize and appreciate the similarities and subtle nuances differentiating SCI-induced osteoporosis as a separate and distinct clinical sub-entity of the broader more generalized osteoporosis diagnosis.

Etiology

SCIs involve a classic bimodal distribution pattern.[4]

Younger patients are injured via high-energy mechanisms with the following approximate associated incidence rates[4],[5],[6]:

- Motor Vehicle Accidents - 50% to 75%
- Falls - 10% to 15%
- Gunshot wounds - 10% to 15%
- Sports - 10% to 15%
- Iatrogenic - estimated incidence ranges from 3% to 25% of all SCIs occurring secondary to improper immobilization and patient transport

The elderly patient population sustains the majority of SCIs via minor trauma or mechanical falls. Elderly patients are predisposed to injury secondary to an underlying degenerative spine and associated spinal stenosis.[6]

Epidemiology

The prevalence of SCIs in the United States (US) increased by 30% from 1994 to 2012[3] In 2016, it was estimated that approximately 17,000 new SCI cases occurred in the US alone, representing an annual incidence of 54 cases per million population.[4] The prevalence of osteoporosis in the US is 10 million, with an additional 34 million considered to be at-risk and given a diagnosis of osteopenia, a term used to describe patients with BMD levels between that of normal reference range values but not low enough to be diagnostically considered osteoporotic.[2]

These aforementioned epidemiologic trends and patterns merge to result in over 50% of patients with a complete SCI developing osteoporosis by 1 year after the injury.[7] Long-term follow-up increases the prevalence rate to greater than 80%.[7] However, the most devastating complication secondary to osteoporosis developing after an SCI is the fragility fracture. Over half of these patients at long-term follow-up will sustain at least one low-impact fracture at some point after the SCI.[3]

Pathophysiology

Disuse Osteoporosis and Osteopenia

Patients sustaining SCIs are predisposed to disuse osteopenia from prolonged immobilization and overall decreased mobility and independent functional capabilities. Normal bone physiology relies on a process of active remodeling in a constant cycle of bone formation and bone resorption. In SCI, the generalized loss of mobility and ability to perform normal weight-bearing activities of daily living eventually uncouples the active remodeling process. The first 2 weeks after the initial injury is recognized as the most vulnerable period for decreased bone formation.[8]

Sclerostin, Vitamin D, Parathyroid Hormone

Recent studies suggest that sclerostin plays a critical role in SCI-induced bone loss. Sclerostin is produced primarily by osteocytes and inhibits bone formation via multiple mechanisms, including the up-regulation of receptor activator of nuclear factor-kappa B ligand (RANKL) and down-regulation of osteoprotegerin (OPG).[9] The end result of these pathways yields a net increase in bone resorption.

Several studies have demonstrated increased levels of sclerostin in patients afflicted with clinical conditions resulting in disability and immobility. In addition to SCI patients, stroke patients are considered particularly vulnerable and at risk for acute and chronic compromise to BMD levels. Moreover, sclerostin levels appear to be highest during the initial post-injury phase, followed by decreasing levels detected in chronic SCI osteoporosis patients.[3]

SCI patients typically have abnormally low levels of vitamin D and parathyroid hormone (PTH) levels in both the acute and chronic phases of SCI injury and recovery. Acutely, PTH levels are low secondary to the initial hypercalcemia resulting from the sclerostin-induced bone resorption.[3]

Long-Term Implications

After the initial 2 weeks following SCI, studies have suggested that, while bone formation rates can return to normal levels, the regions of the body below the level of the lesion (i.e., sublesion levels) continue to experience a 4% per month reduction in BMD. In addition, trabecular BMD is decreased by 40% by 2 years after the injury. Similarly, the long bones in the lower extremity undergo appreciable cortical thinning following SCI, predisposing to low-energy impact fractures.[10]

Beyond 2 to 5 years post-SCI, controversy remains in the literature with respect to ongoing decremental BMD rates into perpetuity. Some reports suggest that bone loss plateaus after 3 to 5 years, while others demonstrate a steady decremental loss in BMD.[3]

Fragility Fractures

SCIs represent conditions of significant morbidity and mortality. With respect to osteoporosis, the most obvious and devastating clinical manifestation is the fragility fracture.[1] The initial rapid decrease in BMD levels, even in the youngest of patients, can yield multiple ensuing fragility fractures. It is worth noting that many of these fractures can occur spontaneously, leading to missed or delayed diagnoses.[3]

Histopathology

Histologic osteoporotic specimens demonstrate thinning of the trabeculae, decreased osteon size, and enlarged haversian and marrow spaces.[11]

History and Physical

History

Clinicians should first consider the presentation of the patient with a history of SCI and note the time that elapsed between the present clinical evaluation and the original index injury. As mentioned earlier, the first 2 weeks after the SCI represents the most vulnerable time period for rapid decreases in BMD levels.

As part of a comprehensive history, the clinician should also consider predisposing conditions and the patient's age; these could potentially compound conditions of already compromised BMD levels. For example, elderly patients presenting 2 weeks after an SCI were likely previously diagnosed with osteoporosis or osteopenia before the injury. In effect, these patients are at the highest risk of developing spontaneous fractures without an appreciable underlying mechanism.

Other pearls for history taking include the following[1]:

- History of fragility fractures (e.g., hip fractures, vertebral compression fractures)
- Predisposing chronic medical conditions (e.g., eating disorders, asthma, malignancy, inflammatory conditions, endocrinopathies, malnutrition states)
- Medication use (e.g., anti-seizure medications, chronic steroid use, proton-pump inhibitors, methotrexate)
- History of early menopause or current post-menopausal status for female patients
- History of anti-osteoporosis medication treatment(s)

A comprehensive history includes eliciting potential risk factors attributable to secondary bone loss. A thorough social history also should be obtained with attention to smoking history and chronic alcohol consumption. The physician should note the patient's presenting overall nutritional status as well as any ongoing or previous calcium and/or vitamin D supplementation. A family history of osteoporosis also should be noted. The patient should be asked about any prior fractures, with focus given to low-energy ground-level fall mechanisms and any fractures after the age of 40.[2] Studies have demonstrated greater trabecular deterioration in post-menopausal women with a complete SCI compared to post-menopausal, ambulatory women.[2]

Physical Exam[12],[13]

Patients with SCI will present with varying clinical pictures, depending on the level of the injury. The clinician should note the specific injury type and classification. Descriptive categories include:

- Paraplegia
    - SCI causing dysfunction from the trunk/pelvic regions to the lower extremities
    - Patients have spared upper extremity function which preserves varying levels of independent mobility
- Tetraplegia
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    - SCI injuries at the level of the cervical spine, leading to dysfunction of the upper extremities, trunk/pelvic regions, and lower extremities
    - Patients are particularly susceptible to progressive losses in BMD as well as spontaneous VCFs without an apparent mechanism
- Complete SCI
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    - Patient is diagnosed with a complete SCI in the acute setting after resolution of the spinal shock state (i.e., after the return of the patient's bulbocavernosus reflex)
    - Patients have no spared motor or sensory function below the defined level of injury (i.e., American Spinal Injury Association [ASIA] A injuries)
- Incomplete SCI
-
    - Injuries are subdivided into syndromes of clinical manifestation based on the anatomic area of injury to the spinal cord

- All of these syndromes demonstrate some preserved motor or sensory function below the defined level of injury
- Syndromes include the following:
- - Anterior cord
  - Posterior cord
  - Central cord
  - Cauda equina
  - Conus medullaris
  - Brown-Sequard

In addition to documenting a comprehensive motor and sensory exam, careful palpation and heightened clinical suspicion for spontaneous/occult fractures are critical. The most common location for spontaneous fractures is in the sublesion regions, especially the lower extremity long bones.[14] The clinician should note any focal or diffuse areas of swelling, including deformity and overall limb alignment.

Much attention should be given to the patient sustaining a fragility fracture, and early follow-up with an appropriate practitioner is highly encouraged to initiate treatment. Unfortunately, osteoporosis follow-up rates, even after fragility fractures have occurred, remain relatively low. Automated follow-up systems and fracture liaison services are two increasingly popular strategies to help improve on the historically reported and strikingly low follow-up rates of 1% to 10%.[15]

Evaluation

In general, osteoporosis follow-up trends and patterns have received increasing attention over the last 5 to 10 years, but SCI-induced osteoporosis follow-up patterns and treatment recommendations lag behind that of the more generalized osteoporosis diagnostic category. These issues are further propagated secondary to the overall complexity of the SCI injury in addition to those previously mentioned and notoriously low follow-up rates for treatment of osteoporosis in general.

Osteoporosis Evaluation[1],[2]

The WHO has established dual-energy x-ray absorptiometry (DXA) scans as the gold standard for assessing BMD levels. DXA scans utilize an x-ray beam to measure calcified tissue in targeted regions in the body. DXA scans are reported to be the most accurate diagnostic imaging modality with the least amount of radiation exposure. The lumbar spine (L2 to L4), the hip (compiled from the femoral neck, trochanters, and intertrochanteric regions), and the wrist are routinely included in the scan. The BMD reported reflects the absolute, patient-specific score determined from these measured anatomic areas.

In addition, the scan also reports a t-score and a z-score. The t-score is measured in standard deviations and reflects the difference between the patient's measured BMD and the mean value of BMD in healthy, young, matched controls (e.g., 30-year-old women). By definition, a normal BMD measurement is within one standard deviation of the young adult mean. The WHO defines t-scores between -1 and -2.5 as osteopenic and scores below -2.5 as osteoporotic. The z-score is also measured in standard deviations, but the z-score is compared to a healthy, age-matched control group. The z-score is most clinically relevant when obtaining a DXA scan in younger patients when secondary osteoporosis is being considered. A z-score less than -1.5 warrants a comprehensive secondary osteoporosis workup.

Standard laboratory workup includes checking calcium, phosphorus, albumin, alkaline phosphatase, liver function tests, creatinine (serum and urine), 25 hydroxyvitamin D, thyroid-stimulating hormone (TSH) and free T4, and intact parathyroid hormone (PTH) levels. Males should have a free testosterone level checked to rule out hypogonadism.

The routine use of checking bone turnover markers (BTM) is debated. The utility of obtaining markers of bone resorption can be considered if it is being considered the possible underlying cause of secondary osteoporosis. Although reports question the reproducibility of such values, available tests include checking serum or urinary cross-links of type I collagen (deoxypyridinoline), N-telopeptide of type I collagen (NTx), or C-telopeptide of type I collagen (CTx).

The WHO created a fracture risk assessment tool (FRAX score) to predict the 10-year risk of sustaining a hip or other major osteoporotic fracture. These other major fragility fractures include fractures of the spine, wrist, forearm, or humerus. The assessment includes 12 questions weighted by the relative risk associated with a future fragility fracture event. Assessment includes age, sex, personal history of fracture, low BMI, oral steroid use, secondary osteoporosis, parental history of hip fracture, smoking status, and alcohol intake. In addition, optional BMD measurement values can be included from a prior DXA scan (if available) to provide a more comprehensive score report.

The utility of the FRAX score is emphasized, especially in the osteopenic patient. Although fracture risk increases with decreases in BMD, the concept that the vast majority of these fragility fractures occur in osteopenic (as opposed to osteoporotic) patients poses a conflicting treatment paradigm. Thus, clinicians rely on the FRAX score to stratify which osteopenic patients exceed the risk threshold to warrant more aggressive pharmacologic treatments. [16],[17]

Treatment / Management

Clinicians are encouraged to recognize the similarities and subtle differences when managing osteoporotic patients versus SCI-induced osteoporotic patients. While some general underlying principles in treatment exist, there is an evolving treatment paradigm to be recognized in the SCI-induced osteoporosis subgroup of patients.

Mechanical Loading

Weight-bearing activity stimulates and creates an ideal stress environment to promote physiologic bone remodeling according to the Wolff law. Mechanical loading has demonstrated reversal capabilities in the SCI-induced osteoporotic process in long bones in the lower extremity. Specifically, cortical thickening is noted in response to applied mechanical stress and strain even after disuse osteopenia has ensued. However, studies have demonstrated the most ideal environment to maximize osteogenic potential and create a net anabolic activity in bone turnover comes from intermittent force application. Constant stimulation can lead to desensitization of the bone to the applied mechanical forces. [3],[17]

Vibration Therapy

Low magnitude mechanical signals (LMMS) as a therapeutic modality has demonstrated bone formation capabilities in both human and rodent models. However, beyond limited case reports there is little evidence available to advocate its definitive therapeutic potential. Similarly, low-intensity vibration treatment protocols have shown some promising results in a small case series of SCI-induced osteoporotic patients. [17],[18]

Calcium and Vitamin D

Without question, all patients should be taking calcium and vitamin D supplementation. Patients should be educated on the recommended daily intake for calcium and vitamin D. The National Osteoporosis Foundation (NOF) recommends 1200 to 1500 mg of calcium per day and 800 to 1000 IUs of daily vitamin D for adults over the age of 50. In the setting of SCI-induced osteoporosis, all patients should begin supplementation regardless of age at presentation. [19]

Anti-Osteoporotic Pharmacotherapy Options

Pharmacotherapy agents work through either anti-resorptive or anabolic means. In general, bisphosphonates are the most commonly prescribed medication class for osteoporosis treatment. These drugs are divided into non-nitrogen and nitrogen-containing compounds. The latter are considered first-line therapy for osteoporosis.[2] However, a major concern with SCI-induced osteoporosis coupled with the bisphosphonate anti-resorptive mechanism on bone is the inability to actually demonstrate measurable increases in BMD levels.[3]

In one study, alendronate was able to prevent further bone loss in 55 patients with chronic SCI-induced osteoporosis at the 2-year follow-up. However, this is a stark contrast to alendronate's proven track record and documented capabilities to increase BMD values measured in ambulatory (i.e., not SCI-induced), post-menopausal women with osteoporosis. [3]

While alendronate, risedronate, and intravenous zoledronic acid have all demonstrated reduced fragility fracture rates in the general osteoporosis population, the clinical evidence has yet to be demonstrated in the SCI-induced osteoporosis population.[20] Clinicians are encouraged to recognize the subtle differences in efficacy and evidence-based approaches for the pharmacologic management of these vulnerable patients.

Denosumab

Denosumab, a monoclonal antibody against receptor activator of nuclear factor kappa-? ligand (RANKL), has recently been studied specifically in patients afflicted with SCI-induced osteoporosis. In 2016, one study demonstrated increases in lumbar and femoral BMD values as measured by DXA scans after 1 year of treatment compared to baseline BMD values. Denosumab was administered in a 60 mg every 6 months protocol during the study period. [3]

Anabolic Agents and Emerging Pharmacotherapy Agents

Teriparatide is a recombinant form of PTH that stimulates osteoblasts to produce more bone. Teriparatide is now FDA approved for osteoporosis treatment in males and females, but more studies are needed in order to improve our understanding of its effects on BMD levels and clinical outcomes in SCI-induced osteoporotic patients. [18],[21]

Activins are a group of agents belonging to the transforming growth factor-beta family and are highly expressed in bone. Studies have demonstrated that blocking the type II activin receptor, promotes bone formation secondary to the inhibition of activin A ligand signaling. In similar fashion, studies have also suggested the same conclusion when targeting cathepsin-K inhibitors. To date, there is little if any literature specifically targeting patients with SCI-induced osteoporosis. Future studies are warranted to delineate clinical efficacy. [3]

Differential Diagnosis

The key clinical elements to diagnosing SCI-induced osteoporosis include recognizing the time since the original SCI injury, establishing a baseline BMD value via a DXA scan, and following these patients closely to monitor the progression of bone loss. A relevant differential diagnosis pattern would entail initially categorizing a patient based on the bone loss spectrum via the established WHO criteria[19]:

- Normal BMD = t-score of -1.0 or greater (i.e., within 1 standard deviation below normal, healthy control group reference values)
- Osteopenia = t-score between -1.0 and -2.5
- Osteoporosis = t-score below -2.5

Also relevant in the differential diagnosis is considering underlying pre-existing medical conditions and medication use which may have already predisposed the patient to compromised BMD levels. Finally, always keep a heightened clinical suspicion for spontaneous fragility fractures, especially in the most compromised patients with SCI.

Prognosis

- Overall, the prognosis and decremental trend in BMD levels is worse compared to the general at-risk osteoporosis population
- By 1 year after the index SCI, over 50% of these patients will have osteoporosis
- Over 80% of chronic SCI patients develop osteoporosis

- Clinical efficacy and response to anti-osteoporosis treatment in these patients is less predictable compared to post-menopausal ambulatory women

Also, note the following timeline for prognostic implications.

- Two weeks following SCI: the patient at risk for rapid decreases in BMD levels
- Sublesion level bone loss: approximately 4% per month reduction in BMD can be expected
- Trabecular BMD bone loss: approximately 40% by 2 years after SCI injury
- Beyond 2 to 5 years post-injury: Controversy remains in the literature concerning ongoing decremental BMD rates into perpetuity. Some reports suggest that bone loss plateaus after 3 to 5 years, while others demonstrate chronic decreases in BMD.[3],[8],[22]

Complications

- The major complication of SCI-induced osteoporosis is the fragility fracture.[3],[10]
- The majority of fragility fractures occur at the sublesion levels, especially long bones.[10]
- Many fragility fractures in patients with SCI occur spontaneously and can be missed or delayed in diagnosis.[10]

Consultations

Patients with SCI should be immediately referred to a bone metabolic center, clinic, or establish early and regular care with an experienced physician capable of treating osteoporosis. Historically, follow-up rates for osteoporosis patients are notoriously low given the lack of a standardized care pathway. Treating physicians can include but are not limited to general practitioners, internists, endocrinologists, and/or some orthopedic surgeons.[2],[15]

Deterrence and Patient Education

Patients with SCI should be educated about their acute and chronic risk of decremental BMD levels and the potential for low-impact fractures. Particularly, emphasis should focus on the initial and most vulnerable clinical window acutely following the SCI. The core treatment options for osteoporotic patients involve early education on how to achieve and maintain healthy bone mass levels and extensive education and counseling on the relevant social, environmental, and lifestyle risk factors that compromise bone health.[2]

Enhancing Healthcare Team Outcomes

Osteoporosis secondary to spinal cord injury (SCI) presents a unique clinical subset of patients in the treatment of osteoporosis and at-risk patient populations. The care of these patients is optimized when a multifaceted and multi-phase approach is considered that involves nurses, pharmacists, and clinicians.

- **Acute SCI:** Initial presentation of the injured patient warrants diagnostic and treatment collaboration between the trauma team, spine surgeons (orthopedic surgery or neurosurgery), medical specialists, and intensive care physicians and nurses. The initial treatment phase should be given the utmost priority and will vary in terms of its complexity depending on the exact nature of the SCI.
- **Bone mineral density rapid progression phase:** During the initial 2 weeks following the acute SCI onset, physicians across all specialties must remain cognizant of the vulnerable period of rapid BMD loss. While knowledge of BMD losses over time in SCI-induced osteoporosis patients remains controversial, this acute phase would be a reasonable time to consult or refer the patient to a BMD-specialized clinic. Ideally, the clinic is experienced in initiating, managing, and following these patients over the long-term to combat the early onset of osteoporosis. The latter is especially imperative in younger patient populations.

- **Rehabilitation phases:** As these patients recover and rehabilitate over the long-term, equal attention should be given to the rehabilitation of the patient's overall mobility in addition to his or her overall bone health. This requires physical medicine and rehabilitation (PMR) clinicians, all physiotherapist-related personnel, and nurses caring for these patients to maintain a heightened clinical suspicion to avoid missed or delayed diagnosis of subtle fragility fractures. These fractures can occur without apparent mechanism (i.e., simple transfer of a patient from bed-to-chair). In the event that anti-osteoporosis medication has not been implemented or at least considered for these patients, the appropriate referrals should be made to the appropriate physician or clinic. [Level II]

Questions

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