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PERSPECTIVE

Osteoporosis prophylaxis in acute SCI

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Abstract

Osteoporosis is a serious complication of spinal cord injury that is associated with increased fracture rates. Diagnosis and management of osteoporosis is limited by the lack of rigorous, well powered clinical trials with fracture as a primary outcome. Due to a lack of evidence-based guidelines, clinical practice varies greatly. This Point-counterpoint series address prophylaxis of osteoporosis in acute SCI.

There is little controversy regarding the clinical consequences of osteoporotic fracture after SCI. Because of the severity of potential fracture sequelae, including non-union, mal-union, amputation, and increased mortality [1], there is a strong clinical inclination to prevent bone loss from occurring during the acute phase of SCI. While this is an important therapeutic goal, there is limited evidence that any treatment, pharmacological or exercise-based, effectively prevents bone loss after SCI. Moreover, fracture is not a primary outcome in any of the clinical trials reported to date [2–13]. Therefore, there is no information on any intervention and fracture risk, either in acute or chronic SCI. Part of this limitation is due to the lack of multi-center studies of sufficient numbers to adequately assess fracture rates. A definitive answer regarding efficacy of various interventions to reduce fracture rates cannot be achieved using surrogate primary outcome measures, including change in bone density, bone volume, or bone geometry. Similarly, there is still not consensus on DXA scanning protocols at the distal femur or proximal tibia, the two skeletal sites most frequently fractured after SCI. These two skeletal sites are not included in clinical DXA scanning protocols and the software to analyze bone density at the knee is still considered research software by the manufacturers with limited distribution to clinicians.

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In their perspective, Anderson et al. advocate for osteoporosis screening in acute SCI to identify those individuals with premorbid osteoporosis based on the World Health Organization criteria. Once a diagnosis of osteoporosis is made, regardless of the etiology (age related, post-menopausal, or secondary osteoporosis due to immobility), best practices for therapeutic intervention are not clear in either acute or chronic SCI. Due to the lack of clinical trials with fracture as a primary outcome, there is no evidence that any approach will reduce fracture rates. Anderson et al. also suggest that therapeutic exercise may have a much more desirable risk to benefit ratio than pharmacological agents. This is a reasonable assumption only if adverse events are being appropriately reported in the weight-bearing literature. To date, there are few reports of fractures or other adverse events with weight-bearing therapies, and these have occurred mostly in the calcaneus and ankle [14, 15]. However, based on anecdotal reports and personal communications, it is entirely possible that fracture events are dramatically underreported in individuals with low bone density and SCI undergoing weight-bearing therapies. It is therefore unclear if therapeutic exercise is without risk from a musculoskeletal standpoint in either acute or chronic SCI. It is critical to the field that all adverse events be promptly reported so that safety profiles for various therapies can be assessed. Furthermore, it is difficult to develop practice guidelines for bone density-based contra-indications to weight-bearing therapies in SCI without this information.

Drugs used to treat osteoporosis, both anti-resorptive and osteoanabolic, are generally well-tolerated in SCI. Bisphosphonates have several well-known but relatively rare side-effects. With adequate education regarding invasive dental procedures, the risk of osteonecrosis of the jaw is mitigated. Osteomalacia remains a potential risk if treatment is

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initiated in the context of vitamin D deficiency. This risk is also reduced with adequate treatment of vitamin D deficiency when detected. GI intolerance is a frequent concern with oral bisphosphonates. This can be avoided with zoledronic acid infusion, which can instead cause acute phase reaction and, rarely, atrial fibrillation in women. Over suppression of bone metabolism is the leading concern with bisphosphonate use. This is associated with atypical femur fractures in the general population. For this reason, it is recommended that fracture risk be reassessed after 3 years of bisphosphonate therapy with consideration given to either a drug holiday or switching to an osteoanabolic agent. Unfortunately, oversuppression of bone metabolism has not been addressed in the SCI literature and the prevalence of this phenomenon in this population is completely unknown. The safety profile of denosumab is also poorly studied in SCI. The target of this drug, receptor activator of nuclear factor kappa-B ligand (RANKL), is not exclusive to the bone microenvironment. RANKL is also expressed on activated T and B lymphocytes and denosumab treatment is associated with an increased risk of serious infection in the general population [16]. While the incidence of serious infection was low in a study of postmenopausal women receiving denosumab compared to placebo, there is no information on serious infection risk and denosumab treatment in SCI, a condition associated with high rates of infection.

While Anderson et al. conclude there is insufficient evidence for osteoporosis prophylaxis in SCI, Dionyssiotis concludes that antiresorptive therapy may be efficacious for ambulatory individuals with acute SCI. This is based on a study of 13 participants within 6 weeks of injury that reported an interaction between bisphosphonate treatment and ambulatory status. Despite being a small study, the findings suggest that antiresorptive therapy is more effective in acute SCI when combined with mechanical loading of the lower extremity. Additional work focusing on this interaction is needed to confirm this.

The lack of rigorous clinical trials addressing safety and efficacy of bone health treatments in either acute or chronic SCI has created a therapeutic void that is filled clinically with opinion rather than evidence-based best practice. There are no treatment guidelines indicating when to screen for osteoporosis, what to prescribe if it is detected, or how to monitor response to therapy. There is less guidance for osteoporosis prophylaxis, though weight-bearing exercises are routinely recommended with the hope of mitigating bone loss, even if clinical trial data supporting this practice are absent. It is evident that the field would benefit greatly from focused efforts to design and implement multi-center clinical trials that are powered for fracture as a primary outcome. Consensus must be achieved regarding the adoption of a single protocol for bone density assessment at the knee. These are essential steps toward development of evidence-based clinical guidelines for osteoporosis diagnosis and management in SCI.

Compliance with ethical standards

Conflict of interest The author declares that she has no conflict of interest.

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