ARTICLE

Effects of drugs on bone metabolism in a cohort of individuals with traumatic spinal cord injury

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Abstract

Study Design: This study is a retrospective review examining the prevalence of drugs commonly used in the management of spinal cord injury (SCI) which may influence bone health.

Objective: The aim of our study was to examine the role commonly prescribed medications play in post-SCI bone health.

Setting: We included all males 21 years of age and older who were evaluated over a 10-year period at an SCI-specialized center for a trauma-induced SCI.

Method: We compared characteristics of individuals with normal bone mass to those with low bone mass according to their dual-energy X-ray absorptiometry (DXA) scan. Medication lists were reviewed for the presence of drugs considered to either positively or negatively affect bone metabolism.

Results: Comparing individuals with normal bone mass ($n = 68$) to those with low bone mass ($n = 211$), only “Time after Injury” and “Level of Injury” were found to influence the likelihood of having low bone mass. Multivariate analysis failed to demonstrate significant associations between bone mass and the sum of drugs which either positively or negatively affect bone metabolism. When medications were reviewed individually, only bisphosphonates and anticonvulsants were found to be significantly associated with bone mass.

Conclusions: Although 76% of our cohort was found to have low bone mass, the only major risk factors were “Time after Injury” and “Level of Injury”. Anticonvulsant use was more common in individuals with low bone mass compared to those with normal bone mass. Given the retrospective methodology of this work, our findings underline associations that warrant further investigation.

Keywords: Spinal cord injury · Bone health · Low bone mass · Medication use · Anticonvulsants

Introduction

The majority of spinal cord injuries (SCIs) are caused by physical trauma such as motor vehicle accidents, gunshots, falls, and sports injuries, and are consequently described as traumatic spinal cord injuries (tSCI). The prevalence of

tSCIs in the United States is estimated to be between 245,000 and 353,000, with an annual incidence of 54 cases/million population or approximately 17,500 new tSCI cases each year [1]. Life expectancy appears to be near normal for individuals with paralysis, especially for those with less severe injuries [1]. Nevertheless, living with chronic paralysis exposes individuals to several complications throughout their lifetime [2]. Bone loss is a well-recognized complication of SCI; it tends to begin immediately after injury, particularly at the sub-lesional level, and continues at a rate of 1% per week in areas of dominant trabecular bone for the first year after injury [3, 4]. Although the rate of bone loss tends to slow down after the first year, bone loss continues to occur long afterwards [5].

The rate of bone loss is substantially greater after acute SCI compared to other conditions associated with immobilization. Several mechanisms specific to SCI are likely responsible for this phenomenon; the severity of the

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Table 1 List of medications and their mechanism of impacting bone metabolism

Positive drugs	Negative drugs
<p>Calcium: Increasing calcium intake has been shown to increase bone mineral density (BMD) by 1–2% over 1–2 years [20]</p> <p>Vitamin D: Vitamin D supplementation has been shown to result in both an increase in BMD as well as a decrease in bone turnover. In a meta-analysis including 11 randomized control studies, combining vitamin D and calcium supplementation was shown to reduce the risk for total fracture as compared to placebo (relative risk = 0.88) [26]</p> <p>Bisphosphonates: Bisphosphonates are potent inhibitors of bone resorption and inhibit the activity of osteoclasts. Alendronate has been shown to increase BMD while reducing the incidence of fractures by 30–50% in women with established osteoporosis [7]</p> <p>Testosterone: Aging in men is associated with a gradual decline in serum testosterone levels and a concomitant increase in fracture risk. Treatment with testosterone for 1 year has been shown to increase BMD by 1.4% and 3.2% at the femoral neck and lumbar spine, respectively [27]</p> <p>Statin: In a meta-analysis of statin treatment for osteoporosis, statin use was associated with increased BMD at the hip and lumbar spine and was also shown to decrease the risk of overall fractures, particularly at the hip. Of note, compared to male subgroups, the effect on female subgroups was only slightly positive or of no statistical significance [29]</p>	<p>Antidepressants (SSRIs, SNRIs, and TCAs): SSRI use has been associated with a 4% lower total hip BMD and a 6% lower lumbar spine BMD [21], with an overall two-fold increased risk of clinical fragility fractures [22]. SNRI use has been shown to result in increased bone resorption [23], having a comparable fracture risk to SSRI use [24]. Lastly, according to a meta-analysis, the relative risk of fracture was increased by 45% in TCA users compared to that in non-TCA users [25]</p> <p>Anticonvulsants: A meta-analysis looking at anticonvulsants' effect on bone metabolism reported that use of this class of medication was associated with an 86% increase in fracture risk at any site by affecting both BMD and fall risk. Patients undergoing polytherapy with anticonvulsants had an increased risk of fracture compared to patients on monotherapy [8]</p> <p>Opioids: Opioids increase fall risk while also reducing BMD by directly inhibiting osteoblasts and causing drug-induced hypogonadism. Their use has been associated with increased fracture risk; in fact, higher opioid use (≥ 50 mg/day morphine equivalent dose (MED)) has been associated with a 9.95% annual fracture rate and a twofold increase in fracture risk compared to individuals not taking opioids [9]</p> <p>Proton pump inhibitors (PPIs): PPIs are known to decrease BMD by decreasing calcium absorption. Treatment with PPIs has resulted in an 18% increased risk of any fracture, a 45% increase for hip fracture, and a 60% increase for spine fracture after chronic use [28]</p> <p>Anticoagulants: In two prospective cohort studies, low-molecular-weight heparin treatment for 3–24 months was shown to decrease mean BMD by 2.8–4.8% compared to mean BMD decreases of 1.2–2.5% with oral vitamin K antagonists, such as warfarin [30]</p> <p>Steroids: Steroid exposure results in an increased fracture risk by as much as 75% within the first 3 months after initiation of therapy. Steroids ultimately decrease bone mass by decreasing the production of new osteoblast precursors while also causing premature apoptosis of both mature osteoblasts and osteoclasts [31]</p> <p>SSRI selective serotonin reuptake inhibitors, SNRI Serotonin and norepinephrine reuptake inhibitors, TCA tricyclic antidepressants</p>

immobilization, the loss of positive central and peripheral neural influences to the sub-lesional bone, the loss of essential anabolic factors, the administration of catabolic factors at the time of injury, and the subsequent use of commonly prescribed pharmacologic agents may all play a role [6].

A number of commonly prescribed medications have been shown to either positively or negatively affect bone mass, bone density, and consequently, fracture risk in the general population (Table 1). For example, bisphosphonates, the most commonly prescribed drug class to treat osteoporosis, are potent inhibitors of bone resorption and inhibit the activity of osteoclasts. Alendronate has been shown to increase bone mineral density (BMD) while reducing the incidence of fractures by 30–50% in women with established osteoporosis [7]. In contrast, a meta-analysis looking at anticonvulsants' effect on bone metabolism reported that use of this medication class was associated with an 86% increase in fracture risk at any site by affecting both BMD and fall risk. Patients undergoing polytherapy with anticonvulsants had an increased risk of fracture compared to patients on monotherapy [8]. Opioids also negatively affect bone metabolism; they increase fall risk while also reducing BMD by directly inhibiting osteoblasts and causing drug-induced hypogonadism. Their use has been associated with increased fracture risk. In fact, a high daily opioid dose (≥ 50 mg/day morphine equivalent dose (MED)) has been associated with a 9.95% annual fracture rate and a twofold increase in fracture risk compared to individuals not taking opioids [9].

The aim of our study was to retrospectively examine the role commonly prescribed pharmacologic agents play in post-tSCI bone metabolism. We hypothesized that the use of these drugs which are known to either positively or negatively affect bone metabolism in the general population is associated with changes in bone mass in individuals with tSCI-related paralysis, independent of time after injury.

Methods

Data utilized in this analysis were obtained from an ongoing Institutional Review Board-approved clinical outcomes database maintained since 2005 in a tertiary care center caring for individuals with SCI. Persons of all ages with SCI-related paralysis are entered in this database upon initial evaluation at the center. The database stores demographic, injury, therapy, and clinical outcome measurements that are recorded routinely during medical and therapeutic interventions occurring at the center.

For this analysis, we included all males 21 years of age and older with traumatic complete or incomplete (American Spinal Injury Association Impairment Scale (AIS) A to D)

SCI who were evaluated at the center over a 10-year period, between June 2005 and June 2015. Women were excluded from this analysis to avoid menopause as a potential confounder. This study was approved by the Institutional Review Board of the institution where the clinical database is housed.

In addition, each individual included in our cohort had undergone at least one bone mass assessment utilizing a dual-energy X-ray absorptiometry (DXA) scan. As defined by the National Osteoporosis Foundation, bone mass was considered “low” if the Z-score was less than -2.0 for individuals under the age of 50, or the T-score was less than -1.0 (osteopenia or osteoporosis) for individuals 50 years and older [10].

The medications lists for these individuals from all outpatient visits to the center prior to their first DXA scan were thoroughly reviewed for the presence of pharmacologic agents considered to either positively or negatively affect bone metabolism (Table 1). For the purpose of this study, we operationally defined use of a medication as continuous use for one year or more prior to DXA scan occurrence (Table 2).

All analyses were performed by comparing demographic and study characteristics between individuals with low bone mass and those with normal bone mass based on their Z or T scores. Characteristics included Race (Caucasian vs African American vs Other), Degree of Motor Completeness (Complete vs Incomplete), History of Pathologic Fracture (Yes vs No), Community Ambulatory Status (Yes vs No), and Functional Electrical Stimulation (FES) usage (Yes vs No), defined as at least 10 min/week for at least 1 month. Classic tests of hypotheses were used including *t*-tests, χ^2 , and Fisher's exact tests as applicable to compare the characteristics of the groups.

A logistic regression model was created to understand the contribution of demographic and injury characteristics,

Table 2 Medication use in a tSCI cohort ($n = 279$) prior to DXA scan

Medication	Number of individuals taking each medication for 1 year or more ($n = 279$)
Vitamin D	135
Calcium	102
Bisphosphonates	27
Testosterone	22
Statins	17
AntiDepressants	81
Anticonvulsants	122
Opioids	91
Proton pump inhibitors	43
Steroids	18
Anticoagulants	36

Table 3 Demographic, injury, and treatment characteristics in a cohort of males with traumatic spinal cord injury, $n = 279$

Factor	Normal bone mass ($n = 68$)	Low bone mass ^a ($n = 211$)	<i>P</i> -value
Race condensed, n (%)			0.52
Caucasian/White	38 (55.9)	133 (63)	
African American/Black	14 (20.6)	40 (19)	
Other (Hispanic, Asian, and Other)	16 (23.5)	38 (18)	
Motor, n (%)			0.31
Complete	31 (45.6)	111 (52.6)	
Incomplete	37 (54.4)	100 (47.4)	
Level, n (%)			0.04
Tetraplegia	33 (48.5)	132 (62.6)	
Paraplegia	35 (51.5)	79 (37.4)	
History of pathologic fracture	19 (27.9)	73 (34.6)	0.31
Functional electrical stimulation user, n (%)	43 (63.2)	134 (63.5)	0.97
Community ambulator, n (%)	10 (14.7)	26 (12.3)	0.61
Time after injury, n (%)			0.02
< 1 year from injury	45 (66.2)	105 (49.8)	
> 1 year from injury	23 (33.8)	106 (50.2)	

^aLow bone mass defined as a Z-score less than -2.0 for individuals under the age of 50 or a T-score less than -1.0 for individuals 50 years and older

Bold values are of significant value, with p values < .05

including age, race, and time after injury to the loss of bone mass. To determine the role of various drugs on bone metabolism in our cohort, the use of each medication was added to the regression model one at a time. A variable grouping the aforementioned drugs into two groups, one combining those drugs with a positive effect on bone mass (“positive drugs”) and the other combining the drugs with a negative effect on bone mass (“negative drugs”), was also created but failed to demonstrate any difference by group (Supplemental Data). Analyses were performed using Stata IC, 11, StataCorp LP, College Station, TX.

Results

Of the 279 men with tSCI, 211 (76%) met our criteria for low bone mass. As seen in Table 3, upon comparing the individuals in our cohort with normal bone mass ($n = 68$) to those with low bone mass ($n = 211$), we found no significant difference in Race ($p = 0.52$), Degree of Motor Completeness ($p = 0.31$), History of Pathologic Fracture ($p = 0.31$), Community Ambulatory Status ($p = 0.61$), or FES usage ($p = 0.97$) between the two groups. There were, however, two factors that were significantly different between the two groups: “Time after Injury”, with those individuals with injuries <1-year-old having a significantly

lower incidence of low bone mass compared to those with more chronic injuries ($p = 0.02$), and “Level of Injury”, with individuals with paraplegia having a significantly lower incidence of low bone mass compared to individuals with tetraplegia ($p = 0.04$).

Overall, a total of 92 individuals (33%) in our cohort had a history of low-impact, pathologic bone fracture, similar to previously reported figures in the SCI population [11]: 50 individuals had one pathologic fracture, 21 had two fractures, 19 had three fractures, and 2 had a total of four fractures each. Interestingly, in our cohort, having low bone mass was not associated with suffering a low-impact, pathologic fracture ($p = 0.31$).

Of the 279 men, 157 (56.3%) had taken at least one drug known to have a positive effect on bone metabolism, while 191 (68.5%) had taken at least one drug known to negatively affect bone metabolism. When grouped, there was no significant difference in the use of “positive drugs” ($p = 0.52$) or “negative drugs” ($p = 0.18$) between individuals in our cohort who had normal bone mass and those who had low bone mass.

Multivariate analysis using a logistic regression model did not demonstrate increased odds of developing low bone mass for demographic characteristics typically associated with lower bone mass in the general population such as age and race. In contrast, “Time after Injury”, namely >1 year, was a strong predictor of low bone mass in our cohort (Table 4).

Evaluation of each medication in the context of the aforementioned model failed to demonstrate significant associations when the “positive drugs” and the “negative drugs” were grouped. However, when each medication class was added independently, the use of bisphosphonates and anticonvulsants was found to be significantly associated with bone mass status (Table 4).

Discussion

This study is a retrospective analysis examining the prevalence of drugs commonly used in the management of tSCI which may be contributing to altered bone metabolism. Given that SCI patients who survive their first year post-injury are expected to live between 8 and 53 years after paralysis onset depending on their age and level of injury, they are likely to be exposed to several medications throughout their lifetime [1].

While age and race are known to influence bone mass in the general population, our analysis of tSCI males did not, surprisingly, show the same associations. Additionally, our results demonstrated that neither FES usage nor community ambulatory status was associated with increased bone mass, in contrast to several previous reports [12–14]. Although there are no studies specifically looking at the effects of

Table 4 Logistic regression models of low bone mass in a traumatic spinal cord injury cohort, $n = 279$

Variable	Model 1 OR/ <i>p</i> - value	Model 2 OR/ <i>p</i> - value	Model 3 OR/ <i>p</i> - value	Model 4 OR/ <i>p</i> - value	Model 5 OR/ <i>p</i> - value	Model 6 OR/ <i>p</i> - value	Model 7 OR/ <i>p</i> - value	Model 8 OR/ <i>p</i> - value	Model 9 OR/ <i>p</i> - value	Model 10 OR/ <i>p</i> - value	Model 11 OR/ <i>p</i> - value	Model 12 OR/ <i>p</i> - value
Age (at test time)	0.99/0.15											
Race												
African American	0.73/0.4											
Other	0.81/0.56											
Time since injury (less than 1 year comparator)	1.66/ 0.03											
Positive drugs												
Vitamin D		1.33/0.33										
Calcium			1.57/0.15									
Bisphosphonate				4.22/ 0.05								
Testosterone					1.0/1.0							
Statin						0.5/0.21						
Negative drugs												
Antidepressants							0.8/0.48					
Anticonvulsants								0.56/ 0.04				
Opioid									0.77/0.38			
Proton pump inhibitors										0.99/0.99		
Steroids											1.27/0.7	
Anticoagulants												0.7/0.36

OR odds ratio, *p* *p*-value

Model 1: logistic pathologic bone mass/race/age at DXA/time from injury

Model 2: Model 1 + Vitamin D

Model 3: Model 1 + Calcium

Model 4: Model 1 + Bisphosphonates

Model 5: Model 1 + Testosterone

Model 6: Model 1 + Statin

Model 7: Model 1 + Antidepressants

Model 8: Model 1 + Anticonvulsants

Model 9: Model 1 + Opioid

Model 10: Model 1 + Proton pump inhibitors

Model 11: Model 1 + Steroids

Model 12: Model 1 + Anticoagulants

Bold values are of significant value, with *p* values < .05

ambulation on bone health in tSCI individuals, one cross-sectional comparative study ($n = 31$) found that individuals with paraplegia who used standing frames had significantly higher bone mass than those who did not use standing frames as measured by quantitative computed tomography [15]. In contrast, our findings suggest that maintaining the ability to ambulate does not ensure preservation of bone mass in individuals with paralysis. This finding supports the hypothesis that the mechanism of bone loss in tSCI is multi-factorial and is not solely due to the loss of weight loading on bones.

Although 76% of our tSCI cohort was found to have low bone mass, the only major risk factors for low bone mass were “Time after Injury”, with longer time (>1 year) from injury being a strong predictor of low bone mass, and “Level of Injury”, with individuals with tetraplegia having significantly lower bone mass than individuals with paraplegia. Furthermore, having low bone mass in our study was not associated with sustaining a low-impact, pathologic fracture, in contrast to previous findings [16]. The lack of association between low bone mass and factors known to predispose to low bone mass in the general population such as age, race, and history of previous fracture is also likely due to the multi-factorial etiology of bone loss in our tSCI population.

We also did not find a significant association between bone mass and the sum of drugs which either positively or negatively affect bone metabolism. When looking at each drug class individually, bisphosphonates were the only “positive drug” class significantly associated with bone mass. In fact, bisphosphonates were more commonly encountered in individuals with low bone mass compared to individuals with normal bone mass ($OR = 4.22$). The likely explanation is that bisphosphonates had been started to treat the low bone mass state. Among the “negative drugs”, only anticonvulsants were found to have a significantly different prevalence in the two populations. Anticonvulsants were found to be more commonly used by individuals with low bone mass compared to those with normal bone mass ($OR = 0.56$). Carbone et al. [17] have similarly shown that the use of anticonvulsants in SCI patients is associated with an increased risk of fractures.

Limitations to this study include grouping medications into classes such as bisphosphonates and not further subdividing these classes into individual medications (i.e. oral medications such as etidronate versus injectables like zoledronic acid, an IV infusion). In the largest systematic review of randomized control trials (RCTs) looking at bone mass after tSCI, moderate-quality evidence was found for the effectiveness of zoledronic acid in preventing bone loss in acute SCI. In contrast, there was only very low-quality evidence for etidronate use, suggesting that different medications in the same class may have varying effects on bone mass in the tSCI population [18].

Due to low usage, we ultimately excluded denosumab, a human monoclonal antibody to RANKL and a novel immunological/pharmacological FDA-approved approach for the treatment of osteoporosis, from our analysis. Analyses of bone density and bone turnover rate have demonstrated the effects of denosumab on bone remodeling to be more effective than those of bisphosphonates [6].

This study also could not tease out the intensity and duration of some of the physical interventions assumed to help bone mass preservation and/or deposition (i.e. community ambulatory status and usage of FES ergometry). Bauman et al. [6] have shown that FES using cyclical muscle contraction appears to be beneficial to bone mass when initiated at the time of injury; however, the effect is more nebulous when FES is performed in individuals with chronic SCI. Similarly, the only RCT looking at the effects of non-pharmacologic modalities in chronic SCI did not show any benefit to low-intensity FES but did show modest benefit on bone health with higher-intensity FES [19]. At this time, there is no published data exploring the effectiveness of simultaneous administration of pharmacologic therapy with non-pharmacologic intervention on bone health in SCI.

Given the retrospective methodology of this work, our findings underline associations that warrant further investigation. Ultimately, it is important to prospectively assess the role of different pharmacologic agents on bone mass in the tSCI population, as low bone mass is a common comorbidity associated with paralysis with both economic and quality of life implications.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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