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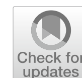
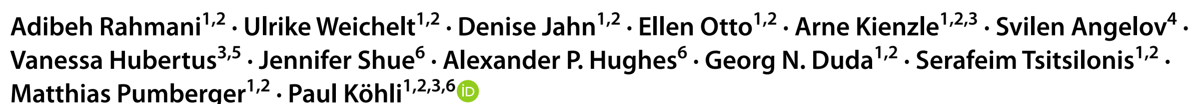
REVIEW



Beyond the initial impact: a systematic review of post-traumatic bone loss and its mechanisms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Abstract

Summary Post-traumatic bone loss occurs after major injuries like traumatic brain injury (TBI), spinal cord injury (SCI), burns, and fractures, yet its systemic effects remain underexplored. This review summarizes clinical and preclinical evidence, highlighting key mechanisms and their impact on fracture risk.

Introduction Traumatic injuries can lead to systemic bone loss. While spinal cord injury (SCI)–related bone loss is well studied, the effects of TBI, burns, and fractures on bone metabolism remain less clear. This review examines post-traumatic bone loss across different injuries to guide future research, preventive, and treatment strategies.

Methods We conducted a systematic review according to PRISMA guidelines. PubMed, Web of Science, Scopus, and Science Direct were searched up to January 2025 using MeSH terms and keyword combinations related to traumatic injuries and bone loss. Studies were screened based on pre-defined inclusion and exclusion criteria, and relevant clinical and preclinical data were extracted and synthesized.

Results The review included a total of 165 studies, including 5 clinical and 9 preclinical TBI studies, 73 clinical and 39 preclinical SCI studies, 16 clinical and 6 preclinical burn studies, and 10 clinical and 45 preclinical fracture studies. SCI can cause up to 50% BMD reduction within weeks, while burns lead to up to 8% BMD loss within two months, with osteoporosis affecting 10 to 50% of patients. TBI is linked to increased osteopenia and osteoporosis, and fractures result in BMD changes of 5 to 28% in the injured limb, along with a higher risk of subsequent fractures on either side. Preclinical studies confirmed impaired bone quality, increased resorption, and decreased formation across injury types. The potential mechanisms

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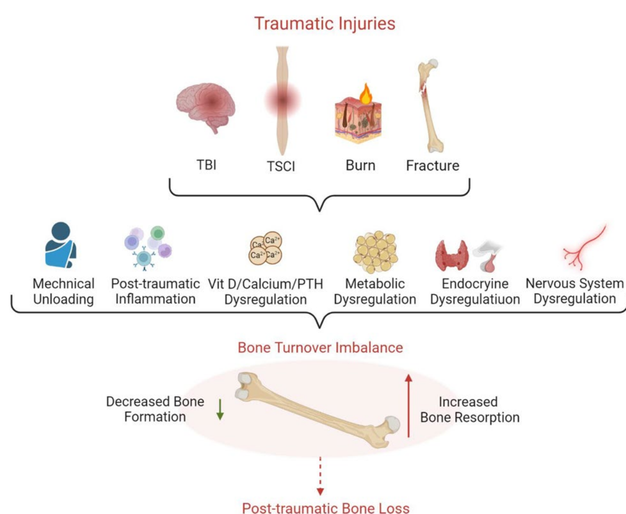
contributing to post-traumatic bone loss include mechanical unloading with increased sclerostin signaling, systemic inflammation driving osteoclastogenesis, nervous system dysregulation changing neuroosteogenic interaction, nutritional and metabolic imbalances, and hormonal disturbances involving parathyroid hormone, growth hormone, and cortisol.
Conclusion Post-traumatic bone loss presents a distinct etiology, resulting from an interaction of mechanical, inflammatory, neural, nutritional, and hormonal factors. Recognizing these mechanisms is essential for developing targeted interventions to prevent bone deterioration, reduce fracture risk, and improve long-term patient outcomes after trauma.

Graphical Abstract
Overview of mechanisms of post-traumatic bone loss. Mechanisms driving bone turnover imbalance following traumatic injuries, including TBI, TSCI, burns, and fractures. Contributing factors such as mechanical unloading, post-traumatic inflammation, disruptions in vitamin D, calcium, and PTH regulation, along with metabolic, endocrine, and nervous system dysregulation, result in reduced bone formation and increased bone resorption. These changes lead to bone loss, hindering recovery and compromising overall bone health. Created with BioRender (BioRender.com). https://BioRender.com/l4



Keywords Burn injury · Central nervous system (CNS) · Fracture · Thermal injuries · Post-traumatic osteoporosis · Bone loss · Spinal cord injury · Traumatic brain injury

Introduction

Although osteoporosis represents a well-established risk factor for fractures, evidence suggests traumatic injuries also cause bone loss that can lead to post-traumatic new-onset osteopenia and osteoporosis [1–3]. Traumatic injuries induce a series of whole-body pathophysiological changes, including immobilization and unloading, inflammatory responses, and metabolic changes, as well as endocrine and nervous system disturbances [4]. Because bone undergoes constant remodeling through formation and resorption under local and systemic control [5, 6], traumatic systemic changes can critically impact bone metabolism on multiple levels.

Post-traumatic reduced mobility or unloading with subsequent changes in mechanosensing-controlled local bone turnover, systemic inflammation stimulated osteoclast activity, poor nutrition, and deficiencies in calcium and vitamin D could impair post-traumatic bone health. Additionally, central nervous system (CNS) injuries have the potential to disrupt endocrine and neural pathways, thus potentially reducing bone quality [6–9]. These disturbances can lower bone quality and increase the risk of subsequent fractures, which can not only substantially set back the rehabilitation process but are also associated with relevant mortality and high morbidity [10].

Post-traumatic bone loss has been studied the most in the context of SCI, where there is a lot of clinical and preclinical data, as previously reviewed [2, 11, 12]. However, the impact of other traumatic injuries such as TBI, burn, or long bone fractures on bone metabolism is less known. While fractures are unique in that they involve primarily localized bone healing and remodeling, they can also contribute to systemic bone loss over time. Given that traumatic injuries are the most common cause of death and disability in young people worldwide [13] and that post-traumatically impaired bone quality significantly influences recovery,

hinders rehabilitation, and sets these vulnerable patients at risk of secondary fractures, a deeper understanding of post-traumatic bone loss is needed.

In this article, we systematically review the current clinical and preclinical scientific literature on post-traumatic bone loss, focusing on clinical and preclinical studies that explore the occurrence and pathophysiological mechanisms in major traumatic injuries, including TBI, SCI, burns, or fractures. Including both clinical and preclinical studies allows us to combine both mechanistic insights with clinical relevance to identify gaps in the pathophysiological understanding and translation of preclinical findings. The insights gained will guide future research, with the aim of developing strategies that improve patient outcomes by reducing post-traumatic bone loss, mitigating the risk of subsequent fractures, and ultimately enhancing long-term health-related quality of life.

Methods

A systematic review was conducted following the PRISMA guidelines [14]. The databases PubMed, Science Direct, Web of Science, and Scopus were searched for relevant literature from the earliest records available up to January 2025. The keywords were selected from the Medical Subject Headings (MeSH) database. The search strategy included the terms osteoporosis, osteopenia, prevalence, cross-sectional, post-traumatic, traumatic brain injury, TBI, traumatic spinal cord injury, SCI, burn injury, fracture, thermal injuries, and all the possible combinations of these terms by two researchers.

The following search strategy was applied in all databases: ((osteoporosis [Title/Abstract]) OR (Bone metabolism [Title/Abstract]) OR (Bone Loss [Title/Abstract]) OR (Bone Density [Title/Abstract]) OR (Bone Turnover [Title/Abstract])) AND (Post-Traumatic OR TBI OR Brain injury OR Spinal cord injury OR SCI OR Burn injury OR Fracture).

All identified articles were imported and managed in EndNote, where duplicates were removed. Two independent reviewers screened titles and abstracts for relevance, followed by full-text assessment based on the eligibility criteria. Disagreements were resolved by discussion until an agreement was achieved. In addition, the lists of references for the included articles were manually reviewed. The systematic review process, including screening and data extraction, was supported using the SyRF (Systematic Review Facility) platform.

Inclusion criteria:

1. Studies that examined the status of bone after traumatic injuries such as TBI, SCI, burn, and fracture.
2. Observational (cross-sectional) studies or experimental studies (including animal models)
3. Studies with full-text availability

Exclusion criteria:

1. Review article, editorials, and conference abstracts
2. Non-English language articles
3. Case reports and articles not providing original research data

This approach ensured a comprehensive review of relevant literature, enabling the identification of studies that give insights into bone health following traumatic injuries such as TBI, SCI, burns, and fractures.

A standardized data extraction form was developed in Microsoft Excel to collect key information, including study design, injury type, species (if applicable), bone related outcomes, time points, and key findings. All extracted data were cross-checked by a second reviewer to ensure accuracy. Studies were grouped by injury type and categorized into clinical or animal research. Main results were summarized in structured tables to allow direct comparison among trauma categories.

Due to the broad scope of this review, which includes both clinical and preclinical studies with diverse designs, outcome measures, and endpoints, we did not perform a formal risk of bias assessment using standard tools. Common tools such as SYRCLE, ROBINS-I, or Cochrane RoB are not applicable across this heterogeneous dataset. Instead, we focused on transparent reporting of study characteristics and limitations, and we address the implications of study quality in the Discussion.

Results

During the systematic search, 8,925 manuscripts were identified and listed. After removing 3,565 duplicates, 5,360 records remained for screening. During title and abstract screening, 2,630 records were excluded based on predefined exclusion criteria (e.g., non-English language, reviews, editorials, conference abstracts, or not reporting original research). A total of 2,321 studies remained for full assessment. Of these, 1,644 were excluded for not addressing the specific research question or not reporting bone-related outcomes. After applying inclusion criteria, the remaining 677 eligible studies resulted in a final selection of 164 studies that were included in the review. One additional study was identified through manual reference screening, resulting in a total of 165 included studies (Fig. 1). These encompassed 5 clinical investigations and 10 animal studies addressing bone status post-TBI, 73 clinical investigations and 39

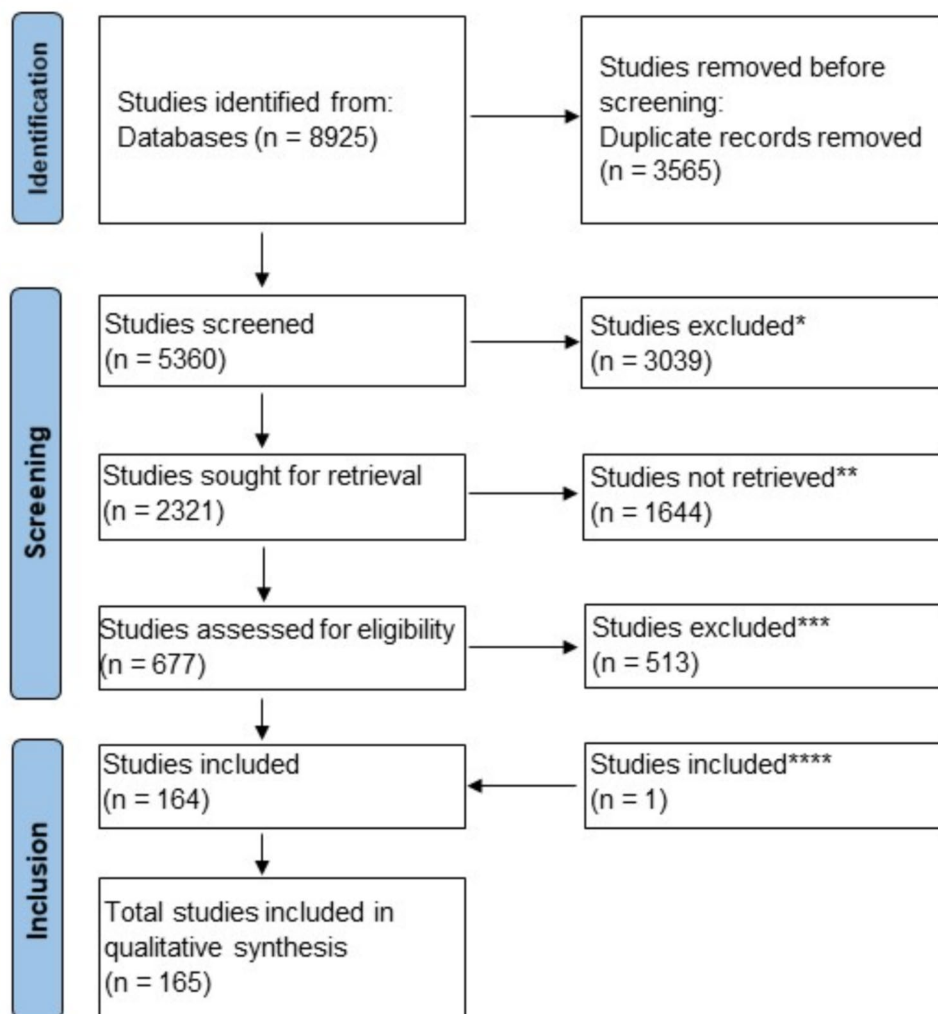


Fig. 1 PRISMA Flowchart of the systematic review process * = excluded: not a primary research article, non-English. ** = not retrieved: not addressing the specific research question. *** = not included based on inclusion criteria. **** = identified through manual reference screening

animal studies on bone status post-SCI, 10 clinical investigations and 5 animal studies exploring bone metabolism post-fracture, and 16 clinical investigations and 7 animal models examining bone status post-burn.

Evidence on post-traumatic bone loss

TBI

The profound impact of acute and chronic TBI on disability and systemic pathophysiology raises the question of how it affects post-traumatic bone metabolism.

Clinical evidence The systematic literature search identified five clinical studies investigating bone status after TBI [15–19] (Online Resource 1 (Table 3.1)). Research by Banham et al. on 51 TBI patients (age range 20 to 60 years) at a neurorehabilitation unit—at a mean of 13 years post-injury—showed a high prevalence of osteopenia (35%) and osteoporosis (16%) in the tibia, with Z-scores different from the population-based normal BMD for their age [16]. Similarly, Smith et al. noted that 40% of disabled individuals (including TBI) had osteopenia, 22% had osteoporosis (based on T-scores), and 20% had fractures, with only 53% of patients having a Z score within the normal range for their age [17]. Out of the 112 participants in their study, 29 suffered a TBI. Unfortunately, this study did not provide a comparison between different disability groups (TBI vs. others).

Al et al. assessed BMD and frailty fractures among various neurological conditions, including SCI, neuromuscular disorders, TBI, or post-polio syndrome in a cross-sectional investigation involving 435 patients [18]. The dual-energy absorptiometry (DXA) scans of the distal femur and proximal tibia in 288 individuals (66/2% of the total population) revealed that 47.9% had osteoporosis. Additionally, 18.8% of younger participants (under 50 years) had a BMD lower than expected in this age group, highlighting that bone health impairment can affect younger individuals as well. Fractures were reported in 21.8% of the total cohort, with the highest prevalence in patients with post-polio syndrome (42.6%),

followed by those with TBI (31.8%), combined TBI and SCI (30%), and neuromuscular disorders (24.5%). According to multivariable analysis, fragility fracture remained independently associated with distal femur and proximal tibial BMD. Karr et al. investigated veterans with or without probable TBI. 25.4% of the whole population had probable TBI, and they were 1.51 times more likely to have osteoporosis or osteopenia compared to those without TBI [19].

Trentz et al. examined serum markers of bone turnover in a cohort of 80 patients across three groups: isolated TBI, TBI combined with fractures, and fractures only. They observed decreased osteocalcin levels in patients with isolated TBI or TBI plus fractures compared to fracture-only patients, suggesting impaired bone formation [15].

Together, these findings suggest that TBI is linked to clinically significant reductions in bone density and increased risk of fractures, although direct comparisons are limited by the heterogeneity of study populations' methodologies.

Preclinical evidence Ten animal studies were identified, all demonstrating negative impacts of TBI on bone metabolism and structure, leading to both local and systemic effects on bone health (Online Resource 1 (Table 3.2)) [20–29]. In a rat model, TBI caused a 6.2% decrease in lumbar BMD within one week and up to 6% loss in the distal femur by three weeks [20]. Another study revealed that the BMD of the distal metaphysis of the femur was decreased by 6% at 1 week after the injury, with significant reductions in cortical thickness and content beginning at 1 week and persisting at 12 weeks (up to 11% loss) [24]. A long-term study (12 weeks) showed a considerable loss of trabecular bone in addition to a decrease in femoral cortical thickness and content [25].

In a mouse model of repetitive mild TBI, a 5–15% reduction in BMD, bone mineral content (BMC), and bone area was observed in both femur and tibia, along with cortical thinning, trabecular architecture deterioration (up to 44% loss in trabecular bone volume fraction (BV/TV)), and reduced bone strength by one month post-injury [22]. Similarly, micro-CT analysis of the tibial mid-diaphysis showed a significant 6.9% decrease in bone volume and a 7% reduction in density, indicating compromised cortical bone strength [21]. Separately, another study found that mild TBI alone led to a 22% reduction in tibial BV/TV, which was further exacerbated to 75% under conditions of skeletal unloading [27].

Similarly, up to 12 weeks after TBI, trabecular BV/TV was reduced by 10–26% in the tibia and 5–11% in the lumbar vertebrae, primarily as a result of decreased trabecular thickness, with cortical bone remaining largely unaffected [26]. In terms of mechanical properties, TBI also reduced femoral torsional strength and stiffness at 3 weeks, though these changes normalized by 4 weeks [23]. Regarding mechanistical studies, reduced osteoblast activity and bone formation [22] as well as increased osteoclast-mediated resorption [28, 29] were observed after TBI alongside a downregulation of osteogenic markers (BP2, RUNX2, osteocalcin), increased inflammatory cytokines, and increased osteoclast number [28, 29].

Taken together, the clinical and preclinical evidence suggests the occurrence of post-traumatic bone loss after TBI.

SCI

SCI has long been studied in relation to post-traumatic bone loss, as acute hypercalcemia and skeletal complications have driven research interest [2]; in this context, 112 clinical and preclinical studies addressing bone loss after SCI were identified.

Clinical evidence The systematic review identified 73 studies investigating bone status after traumatic SCI (Online Resource 1 (Table 3.3)). Bone loss after SCI shows inter-individual and site-specific differences, with the prevalence of osteoporosis ranging from 10 to 80% post-injury in different bone regions [30–102].

Bone mineral density and fracture risk Early studies of patients with complete SCI (C7–L1 levels) showed reduced density in the trabecular but not the cortical bone of forearms (radius and ulna) [30] as well as rapid BMD loss in the femur (25%) and tibia (> 50%) but not in the spine [31, 32] with no significant difference in the complete vs. partial paralysis [33]. However, Saltzstein et al. demonstrated that complete SCI injuries lead to lower BMD [34]. Wilmet et al. observed rapid and lasting bone loss of 4%/month in trabecular bone and 2%/month in cortical bone in paralyzed legs [35].

The rate of bone loss varies from a rapid onset within 2 weeks after injury, with 67% loss in the trabecular part of the distal tibia at 1 year, which was associated with a higher risk of fracture [85] and long-term bone loss [52, 95], to patients with small BMD losses in the same time (around 1% in the distal tibia trabecular BMD) [95]. Zehnder et al. directly linked this trabecular bone loss to increased fracture incidence, noting that fractures in SCI patients, primarily in the lower extremities such as the tibia, are preceded by trabecular bone loss [58]. Rodrigo et al. similarly observed substantially reduced cortical and trabecular vBMD in the tibia of SCI patients, but no change in the radius [100]. Maïmoun et al. compared people with tetraplegia and paraplegia with healthy controls and noted significant bone loss in both trabecular and cortical bone in the sub-lesional bones of SCI patients, with greater femoral bone loss in patients with tetraplegia [96].

Furthermore, smoking and activity level impact BMD, as shown by significantly lower BMD and BMC in the forearms of active smoking men with SCI [93]. A large cohort study, among 775 SCI patients, revealed that only 168 (21.7%) had normal BMD, while 607 (78.3%) had low bone density (LBD), including 451 (58.2%) with osteopenia and 156 (20.1%) with osteoporosis [102]. Mun et al. investigated temporal changes of BMD in 427 patients and observed a higher lumbar spine BMD and T-scores in the "< 1 year" post-injury group compared to later groups, while femoral neck and total hip BMD and T-scores were significantly lower, showing a progressive decline over time [101]. Additional studies confirmed that hip and femur BMD declines after SCI while spine BMD remains unaffected [66, 67, 73, 99]. De Bruin et al. confirmed this progressive deterioration of the tibia, reporting decreased BMD, strength, and stiffness during chronic SCI [45, 62].

Comparing two diagnostic criteria, Lim et al. demonstrated a high prevalence of osteoporosis in different bone regions (lumbar spine, femoral neck, and total hip) among SCI patients, with notable discrepancies between the criteria [98]. Regional BMD loss is also influenced by body composition and gender. For instance, women experienced greater trabecular bone loss than men [97], and Jiang et al. found that lumbar spine BMD correlated with gender and weight, while hip BMD correlated with gender, height, weight, and time since injury [99].

Most studies report reduced BMD after SCI, especially in the lower limbs (femur, tibia), with rapid trabecular bone loss and increased fracture risk. Bone loss varies by injury completeness, sex, and time. Spine BMD is often preserved. Factors like smoking, inactivity, and body composition influence regional BMD. Osteoporosis is common post-SCI, particularly in chronic cases.

Bone turnover markers Serum levels of bone resorption markers (osteocalcin, C telopeptide, N-telopeptide, deoxypyridinoline) surge up to tenfold and peak approximately four months after injury, while bone formation markers remain low/suppressed [40, 67, 90]. Longitudinal studies suggest that bone resorption is initially high but declines over time [66, 67]. Lee et al. observed that sclerostin, a bone formation inhibitor secreted by osteocytes upon loss of mechanical stimulation, was elevated early after SCI in men with paraplegia. Their study found that factors such as age, bone density, and bone resorption activity influenced sclerostin levels, which corresponded to increasing fracture incidence over time post-injury [94].

Zheng et al. observed early bone loss in the tibia, followed by bone loss in the femoral neck in SCI patients within 12 months post-injury compared to controls, highlighting the importance of monitoring tibial and femoral BMD along with bone metabolism markers [92].

In summary, SCI-related bone loss is consistently observed in the femur, tibia, and hip, with variations linked to injury characteristics, time since injury, and patient-specific factors such as sex, activity level, and smoking.

Preclinical evidence Thirty-nine animal models studied bone metabolism after SCI, all showing evidence of bone loss following SCI [103–141] (Online Resource 1 (Table 3.4)): Sugawara et al. reported decreased bone strength (femur and tibia) in rats suffering from an SCI, with mechanical testing at 24 weeks showing only 50–63% of the values observed in controls [103], while Jiang et al. confirmed significant bone health deterioration within 3 weeks, including reductions in proximal tibia parameters by ~ 60–80% in SCI rats compared to sham. Significant decreases in trabecular parameters in the fourth lumbar vertebrae were reported, and in the femur, bone strength (load to failure) was reduced by 51% at 24 weeks[104, 105]. Liu et al. highlighted reduced trabecular bone structure and density in the tibia following SCI and hemi-cord injury [106]. In mice and rat models of SCI, significant decreases (34%) in BMD were observed in the distal femoral metaphysis [107] and in cancellous bone volume (22.4%) and trabecular bone thickness (10.65%) within 10 days of injury [108]. Using Raman microscopy to assess bone mineralization, bone from SCI rats showed a lower mineral-to-matrix ratio compared to healthy controls, indicating less mineralization [109].

Different studies found that severe SCI led to ongoing bone loss (up to 83% lower cancellous bone volume), decreased strength (16–25%), and significant deterioration in both trabecular and cortical bone structure [111–113, 115, 117, 118, 120–123, 125–129, 132, 135, 140]. Regarding bone regions, Metzger et al. showed that SCI rats had significantly lower total BMC ($p = 0.017$) and cancellous BMD ($p = 0.03$) in the proximal tibia, along with a 55% reduction in bone volume fraction (BV/TV), but not in the distal femur ($p = 0.078$) [124]. Further investigation by them revealed that SCI resulted in bone loss in both male and female rats, regardless of age (young and middle-aged). This bone loss was more pronounced in younger animals at earlier time points (30 days) and persisted to longer time points after recovery of weight-supported locomotor activity (180 days) [136].

In a recent study, they revealed that the temporal changes of bone turnover and microarchitecture were assessed above the injury level in young and adult male and female rats after SCI. At the proximal humerus, bone formation decreased and osteoclast activity increased at 30 days in all groups, but only males showed sustained reduced bone formation at 180 days, while females recovered [141]. McManus et al. observed a 12% bone density decrease in the tibia within 10 days after SCI, which continued to 15% by 40 days [110]. Similarly, 8-week post-SCI rats showed BMD

loss of − 10.6% ($p < 0.01$) in the distal femur and − 8.8% ($p < 0.01$) in the proximal tibia [138].

Regarding mechanistical studies, Zhong et al. employed micro-CT, RT-PCR, western blot, and three-point bending tests to assess bone status in an SCI mouse model, observing significant bone loss in the femur and vertebrae, characterized by reduced BMD, impaired bone formation, increased osteoclast markers, and disrupted cellular signaling pathways [139].

Using a cervical hemi-contusion SCI model in monkeys, Wu et al. reported BMD reduction in the ipsilateral distal radius (33.3%) and proximal humerus (40.8%) compared to the contralateral side [130]. Micro-FE showed loss of trabecular bone and deterioration of bone structure significantly reducing stiffness (by 28.9% and 36.6%) and failure load (by 27.2% and 40.2%) in the humerus and radius on the injured side compared to the uninjured side. Despite partial behavioral recovery (standing by grasping cage bars), ipsilateral forelimb functions remain limited, such as severely impaired movement below the elbow.

Taken together, these animal studies offer strong evidence that SCI causes a rapid, region-specific, and permanent loss of bone strength and structure, confirmed by disturbed bone remodeling processes, highlighting the critical need to address post-injury osteoporosis in both clinical and research settings.

Bone Fracture

While localized demineralization at the fracture site is well recognized, fractures may also contribute to systemic bone loss.

Clinical evidence Our systematic review identified ten studies investigating the metabolic bone status after bone fracture [142–151] (Online Resource 1 (Table 3.5)).

The local BMD decrease can be substantial, ranging from 5 to 28% depending on the bone and the time passed since the fracture occurred [151]. For example, in patients with wrist fractures, the BMD of the uninjured forearm remained stable, while the injured forearm experienced a decrease of up to 18% in BMD within a few months, with sustained BMD reduction for years [142, 144, 148].

Lower extremity fractures including femur [146], hip, and tibia [145, 150] fractures were also linked to lower BMD in the injured leg compared to the uninjured one. This difference lasts for many years, especially in the femoral condyle [145, 149]. Most studies focus on bone loss of the affected side (3–31% relative to baseline values, which are measured shortly after the fracture occurred) and demonstrate increased fracture risk after fracture [148, 150, 151].

Interestingly, Clement et al. observed a 12.5% bone loss on the fractured side and 1.5% on the contralateral side after 1 year, supporting evidence for a reduction in systemic bone quality after fracture [149].

These studies showed localized reduction in BMD, particularly in the injured limb after fracture, but little evidence exists on changes in systemic BMD.

Preclinical evidence Historically, research on fracture healing has concentrated merely on the fractured bone itself. However, recent studies have explored potential systemic effects. Five animal studies have investigated the time course and mechanisms of systemic bone loss and recovery in mice following femur fracture or osteotomy and provide evidence for this greater impact [152–156] (Online Resource 1 (Table 3.6)).

Kirkeby et al. showed that after femoral osteotomy in rats, the strength of the ipsilateral tibia was around 83% after 4 weeks and 88% after 9 weeks compared to the contralateral side, with stiffness decreasing after 4 weeks [155].

Two studies addressed calcium malabsorption [153] and deficiency [152]. In a murine model of hypochlorhydria-induced calcium malabsorption with femoral osteotomy and external fixation, Haffner-Luntzer et al. observed unaltered fracture healing but systemic bone loss after fracture [153]. Fischer studied the effects of nutritional calcium and vitamin D deficiency (Ca/Vitamin D deficiency) on bone health in ovariectomized mice with and without femoral osteotomy and observed systemic bone loss after fracture only in the calcium-deficient group, possibly due to increased PTH levels [152].

Emami et al. observed systemic bone loss in whole-body after femoral fracture in both young and middle-aged mice at 2-week post-injury (− 2.45% in young, − 1.95% in middle-aged) as measured by micro-CT analysis [154]. Osipov et al. reported that whole-body BMD and BMC declined in mice 2 weeks after fracture, independent of gender. BMD dropped by − 8.1% in fracture males ($p = 0.02$) compared to − 3.6% in females ($p = 0.78$) at 2 weeks. BMC decreased by − 24% in fracture males and − 17% in fracture females (both $p < 0.001$). At the lumbar spine, only fracture males showed reduced BMD by week 2 (− 8%, $p = 0.07$), while no significant changes were seen in fracture females [156].

Taken together, the preclinical evidence shows localized but also systemic post-traumatic bone loss after fracture beyond the injured limb.

Burn

The management of burn patients has long prompted investigation into post-traumatic bone loss, as early reports of metabolic disturbances, including acute hypercalcemia

and skeletal complications, drew attention to the impact of severe burns on the skeletal system.

Clinical evidence The systematic review found 16 studies investigating bone status after burn injuries [157–173] (Online Resource 1 (Table 3.7)). Klein et al. found decreased bone formation in burn patients, with lower osteoid area, osteoblast surface area, and initial osteocalcin levels. Despite normal bone structure, children showed lower bone density post-burn, indicative of increased fracture risk. They suggested that the magnitude of BMD loss was correlated with the severity and extent of the burn injury [157, 159]. Przkora et al. found similar results, noting that extensive burns led to marked reductions in BMD at the lumbar spine and femur, which persisted for up to 2 years post-injury [162].

Studies observed a significant BMD decrease in severely burned patients in various bones (distal forearm, proximal femur, lumbar spine) after 4.5 months and higher deoxypyridinoline levels, a marker for bone resorption [160, 163, 173]. Duke et al. found a higher risk for fractures in burn patients, especially women, children, and those over 20, persisting for at least 5 years post-burn [164, 167]. Kaewboonchoo et al. confirmed a 1.35 times higher osteoporosis incidence in patients with burns involving 20–49% of total body surface area and burns confined to the lower/upper limbs [170].

Studies noted increased bone resorption markers [165, 171] and decreased albumin, vitamin D, and calcium levels in severe burn patients [165]. Muschitz et al. did a follow-up study in severely burned men after 1 year and confirmed decreased radius bone density and elevated bone turnover markers [168]. Roshanzamir et al. observed lower BMD, particularly in the lower spine, in electrical burn patients, with osteopenia being more common than osteoporosis [166, 169]. Edelman et al. highlighted significant BMD decreases (Z-scores decrease by an average of 0.85 units from baseline), especially 131 days post-burn, in 79.3% of patients [160]. Overall, these results suggest that burn injuries can cause chronic disruptions in bone remodeling, which include decreased formation, increased resorption, and an increased fracture risk.

Preclinical evidence Of the seven identified experimental studies analyzing bone metabolism after burn, all showed reduced bone quality. (Online Resource 1 (Table 3.8)) [174–180].

Miller et al. observed a decline in bone formation and an increase in bone resorption markers, highlighting a disrupted metabolic balance. Bone growth rates in the trabecular tibia bone were significantly slower in burned mice [174]. This is further supported by Baer et al., who investigated how burn injuries and disuse (hindlimb immobilization) affect bone health in rats. Larger burn areas (> 40% total body surface area (TBSA)) and post-burn inactivity significantly impact bone health [175]. Halloron et al. demonstrated that even minor burns (< 15% TBSA) can lead to bone loss [177].

Riniken et al. on the other hand found that burn injury combined with tenotomy did not worsen bone health compared to tenotomy alone. However, burn injury alone led to decreased bone volume and mineral content at early time points compared to control mice. Tenotomy alone also caused some bone loss at early time points. Overall, the study suggests that burn injuries and tenotomy can both negatively impact muscle health, but their effects on bone are less well investigated [178].

Hoscheit et al. found that burn injury significantly decreased BMD in both the tibia and lumbar vertebrae at later time points (21 and 42 days). Burn injury increased the expression of genes that promote bone resorption and decreased the expression of genes that promote bone formation in the tibia and lumbar vertebrae [179]. El Ayadi et al. also observed a decrease in bone formation markers in serum as early as 3 days after a burn, suggesting an early onset of bone loss [180].

The experimental evidence consistently demonstrates that burn injuries lead to abnormal bone metabolism, characterized by reduced bone quality, increased bone resorption, and decreased bone formation.

As systematically reviewed, the evidence indicates that traumatic injuries such as TBI, SCI, fractures, and burns markedly impair bone health, increasing the risk of osteopenia, osteoporosis, and fractures. While SCI and burns are well studied, data on bone metabolism after TBI or long bone fractures remain limited. Clinical and preclinical studies consistently show that these injuries disrupt bone remodeling, leading to significant bone loss and reduced strength.

These findings underscore the need to elucidate underlying mechanisms and develop targeted strategies to preserve bone health in affected patients.

Pathophysiology of post-traumatic bone loss

Systemic post-traumatic bone loss after traumatic injuries may be caused by various factors such as mechanical unloading, systemic inflammation, vitamin D (Cholecalciferol)/Calcium/parathyroid hormone (PTH) disturbances, metabolic and nutritional deficiencies, complex hormonal changes, and nervous system dysregulation, all of which are induced by the injuries and contribute to bone metabolism disturbances (Fig. 2). Recognizing the clinical sequelae of bone loss after traumatic injuries and understanding the underlying mechanisms are important in the development of targeted therapeutic interventions.

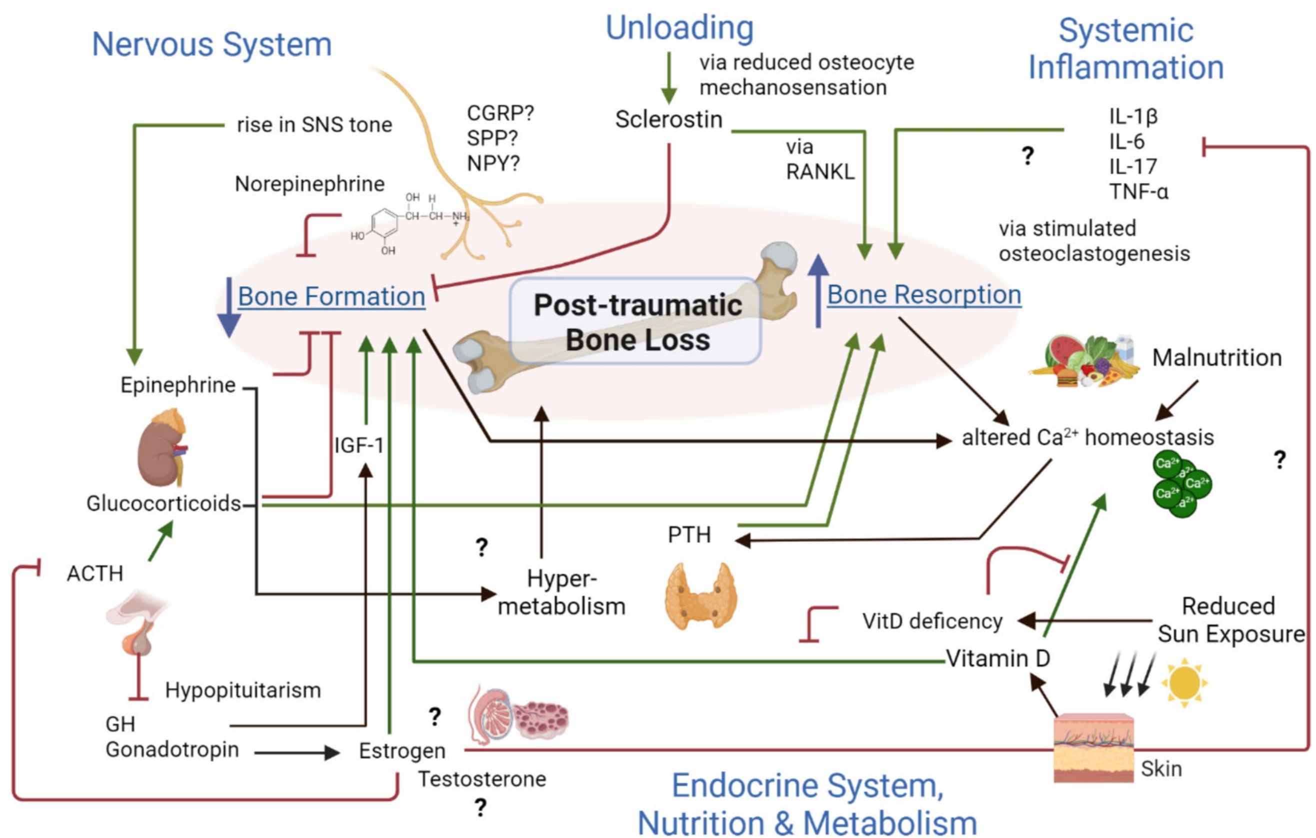


Fig. 2 Overview of pathways of post-traumatic bone loss. There is compelling evidence for the involvement of multiple mechanisms in post-traumatic bone loss. These include unloading after spinal cord injury (SCI) and fracture, as well as the inhibition of bone formation via the sympathetic nervous system after traumatic brain injury (TBI) and potentially SCI. Nevertheless, direct mechanistic proof is lacking for other potential pathways, including systemic inflammation, nociceptive peptides such as CGRP and SPP, hypermetabolism, and calcium pull due to callus mineralization during fracture healing. Despite this, mediators involved in these pathways are known to be altered after trauma and are relevant to bone metabolism (green arrow: stimulation, red line: inhibition, black arrow: influencing/contributing). Pathways involved in bone metabolism, potentially mediating post-traumatic bone loss based on observed alterations but lacking mechanistic proof, are marked with question marks. SNS = sympathetic nervous system, CGRP = calcitonin gene-related peptide, SPP = substance P, NPY = neuropeptide Y, ACTH = adrenocorticotropic hormone, GH = growth hormone, IGF-1 = insulin-like growth factor 1, PTH = parathyroid hormone, RANKL = receptor activator of nuclear factor kappa-B ligand, IL-1β = interleukin-1 beta, IL-6 = interleukin-6, IL-17 = interleukin-17, and TNF-α = tumor necrosis factor alpha. The figure was created using BioRender (BioRender.com) https://BioRender.com/p85j848

Mechanical unloading

Evidence and molecular pathways

Unloading leads to bone loss, as demonstrated in multiple clinical and preclinical studies [47, 94, 146, 168]. In this systematic review, we identified 13 clinical and 10 preclinical studies investigating immobilization or unloading and its effects on post-traumatic bone turnover in these injuries (Online Resource 1 (Table 3.9) and (Table 3.10)).

To date, there are no clinical studies on how TBI may induce unloading and subsequently affect bones. However, one TBI animal model, using neuromotor assessment, demonstrated that decreased bone formation and increased bone resorption caused by TBI are not due to unloading [26].

SCI causes unloading and restricted movement of the paralyzed upper and/or lower limbs and joints for longer periods, which could induce osteoporosis [92]. Significant muscle atrophy and an increased risk of osteoporosis have been reported in these patients [65, 75, 133]. Further clinical studies confirmed that BMC value is decreased more in cervical SCI patients than in thoracic SCI [31, 43]. A comparison of patients with tetraplegia and paraplegia revealed that the level of injury affects the injury-induced bone loss, which is more dominant in unloaded bones below the SCI level [39, 44].

Animal studies confirmed that after unloading the hind limbs, osteoblasts start decreasing in numbers and activity, while osteoclasts become more active over time [113, 120, 126, 128]. On the other hand, Metzger could show in

rats with a moderate low thoracic SCI (level T12, controlled direct impact with 1.5 N for 1 s) that despite some weight-bearing recovery by day nine, rats still had lower bone mass, decreased bone formation, and increased bone resorption compared to controls at 30 days post-injury, underlining the importance of factors other than mechanical unloading [124]. In a more recent rat model of SCI (male and female) with weight-supported hindlimb stepping recovery by day 15 post-injury, significant alterations in bone turnover were observed at the supralesional humerus within 30 days [141].

Regarding burn injuries, Muschitz et al. assessed changes in BTMs as well as regulators of bone signaling pathways involved in skeletal health in 32 male burn patients (TBSA > 20%) over a period of 24 months. Regardless of weight-bearing and non-weight-bearing anatomical sites, volumetric BMD declined continuously, being pronounced at the radius. A continuous decline in the number and thickness of trabeculae resulted in a reduced trabecular bone volume. The cortical thickness decreased but was more pronounced and in line with trabecular parameters at the radius [168]. Furthermore, Leblebici et al. confirmed a BMD reduction at different bones (L1–L4 vertebrae, left proximal femur, left distal forearm) during the first month following burn injury, which was not correlated to functional status [163].

On the other hand, Klein et al. demonstrated that in burn patients, partial immobilization was associated with reduced rates of bone formation and mineral apposition, as well as a decreased number of osteoclasts without a significant reduction in resorptive surface, based on histomorphometry analysis[157]. Similar observations were made in adults and children confined to bed rest following injury and during the process of early wound excision and grafting [158]. Baer investigated how burn injuries and disuse (hindlimb immobilization) affect bone health in rats. They observed that larger burn areas (> 40% body surface area) and post-burn inactivity decreased trabecular and cortical bone volume, the latter being more prominent [175].

Open field analysis in one experimental study revealed a reduction in activity parameters (total distance traveled, vertical sensor breaks, and ambulatory time) in both fractured and sham mice 4 days post-fracture, with no significant differences at later time points [154].

Regarding molecular pathways, increased levels of sclerostin, a protein produced by osteocytes in response to unloading conditions, have been observed in acute, but not chronic, SCI, and the levels in the acute phase were not correlated with lower extremity motor scores [94]. Studies have found that sclerostin levels in SCI patients are inversely proportional to bone mass [64, 107, 116, 120], with mechanical loading shown to reduce sclerostin production by osteocytes. Maïmoun et al. showed that despite the higher osteoprotegerin/receptor activator of nuclear factor kappa-B ligand (OPG/RANKL) ratio—usually a sign of reduced bone resorption—SCI patients still experience bone loss, indicating dysregulation of the RANKL/RANK/OPG pathway after SCI [64]. Similarly, in burn patients, Muschitz et al. reported that sclerostin, and to a lesser extent Dkk-1, showed a pattern of spiking after injury [3, 164, 168, 174].

Post-traumatic inflammation

The systematic review found one clinical and five experimental studies investigating the association between post-traumatic inflammatory markers and post-traumatic bone metabolism (Online Resource 1 (Table 3.11)).

In a murine model simulating moderate TBI by controlled cortical impact (CCI), inflammatory stress on bone and bone marrow (BM) following TBI was shown to activate nuclear factor kappa-B (NFκB), inducing osteoclastogenesis and bone resorption [28].

Regarding SCI and in clinical settings, Valderrábano et al. investigated the association between c-reactive protein (CRP)—a marker of sustained inflammation—on bone metabolism in chronic SCI patients and observed an unexpected positive association with trabecular bone parameters at the tibia, suggesting a potential role of inflammation in local bone adaptation [100]. However, the overall bone microarchitecture remained severely impaired in SCI individuals. This condition could contribute to secondary organ complications and highlights the detrimental effects of chronic inflammation on bone health, as highlighted by Metzger et al. in a rodent model of SCI [124]. Compared to healthy controls, SCI rats had higher levels of inflammatory markers (tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-17 (IL-17), regulators of bone resorption (RANKL), and bone formation inhibition (sclerostin)).

Burn injuries quickly trigger a rise in proinflammatory cytokines, notably interleukin-1β (IL-1β) and IL-6, within 24 h, leading to increased osteoclastogenesis and bone resorption [159]. Muschitz also noted prolonged elevated CRP levels that negatively influence calcium, PTH homeostasis, and bone metabolism [168].

Although the inflammatory response is essential for fracture healing, evidence for inflammation-induced bone loss post-fracture is limited; studies in mice have shown increased IL-6 levels and bone resorption after fractures [154].

Vitamin D/calcium/PTH homeostasis

The systematic review identified 19 clinical studies and four preclinical investigations on the effects of post-traumatic Vitamin D/PTH and calcium homeostasis on bone metabolism in these injuries (Online Resource 1 (Table 3.12) and (Table 3.13)).

While many clinical studies measured calcium, PTH, and vitamin D levels as biochemical markers for bone metabolism after SCI, TBI, burn, and fracture [58, 92, 148, 150], not all of them reported a direct link between these measurements and bone status.

Regarding TBI, Trentz observed that calcium and inorganic phosphorus levels in TBI patients were within the physiological range [15]. Smith reported that 27.7% of participants with various types of acquired brain injuries, including TBI, had a vitamin D deficiency that was associated with decreased lumbar BMD ($r = -0.269$, $p = 0.005$) at an average follow-up of 7.5 months [17].

In a study investigating the course of calcium homeostasis and its endocrine control during the first 24 weeks after SCI, there was a rise in bone resorption markers that peaked 3 months after injury, with elevated calcium levels and suppression of PTH [40]. Similar results were found in paraplegic men < 1 year after SCI, but not observed > 1 year after SCI [58]. Hyperparathyroidism was observed in SCI patients with positive correlations between PTH levels and bone resorption markers 3–9 months [53, 79, 85] and 1–9 years [42] after SCI. Moreover, urinary calcium excretion was significantly elevated in SCI patients during the acute phase of injury [44, 64]. Animal studies showed that BMD is negatively correlated with age and calcium levels after SCI [117]. Zhong et al. showed that calcium supplementation in combination with Resveratrol (RSV) enhances the protective effect of calcium on bone by regulating the SIRT1/FOXO3a pathway in SCI mice [139]. Thakkar et al. reported that most (n = 16/30) SCI patients had suboptimal vitamin D levels (< 20 ng/mL) within one month of injury and subsequently received oral vitamin D supplementation [90]. Zheng et al. identified age and 25OHD as significant factors influencing distal femur (DF) BMD, and age and gender as key factors for proximal tibia (PT) BMD [92]. Wu et al. measured the serological levels of calcium, phosphorous, and vitamin D in monkey models of SCI, 6–12 months after injury, and no significant differences were found between sham and SCI groups, as well as no association was observed between vitamin D and bone turnover markers.

Burn patients are at an increased risk of vitamin D deficiency due to impaired ability to synthesize the vitamin because of skin loss, potential pre-existing deficiencies already prior to injury, and impaired calcium uptake [164, 173]. Muschitz highlighted that hypocalcemia frequently occurs in the early phase after burn injury and contributes to the challenge of determining nutrient requirements in this pathologic state. Burn injuries give rise to calcium wasting, failure of bone to take up excessive calcium, and vitamin D insufficiency to deficiency [168].

Fischer et al. studied the effect of fracture on post-traumatic bone loss in mice with different amounts of dietary calcium [152]. Three weeks after osteotomy, lumbar vertebrae trabecular bone volume fraction (BV/TV) decreased, and osteoclast activity increased in fractured mice compared to controls. They showed that early calcium/vitamin D supplementation post-fracture reduced bone resorption and prevented bone loss.

In summary, trauma such as TBI, SCI, burns, and fractures can disrupt bone health by causing imbalances in vitamin D, calcium, and PTH homeostasis.

Metabolism/nutrition

The systematic review identified four clinical studies investigating the effects of nutrition and metabolism on bone status in the context of traumatic injury (Online Resource 1 (Table 3.14)).

Researchers investigated the effects of neurological injury on BMC and body composition among patients with paraplegia with similar durations of paralysis, showing that BMC and lean mass were significantly reduced in paraplegic individuals compared to healthy controls, while fat mass remained unchanged [71]. Additionally, a notable correlation was observed between the duration of paralysis and fat mass in high-level paraplegics.

Sabour investigated the link between dietary protein and BMD in patients with SCI and showed that higher protein intake was associated with lower BMD in the lumbar vertebrae after SCI. High total protein and amino acids, except for alanine, arginine, glutamic acid, and aspartic acid, have been associated with lower BMD in the lumbar vertebrae of individuals with SCI [82]. Intake of certain amino acids (tryptophan, isoleucine, lysine, cysteine, tyrosine, threonine, leucine, methionine, phenylalanine, valine, and histidine) was also linked to lower BMD in the lumbar spine [82].

Establishing a cohort of 43,532 patients, Kaewboonchoo showed that the incidence of osteoporosis in burn victims was 6.40 per 1000 person-years, but this risk heightened to 22.7 per 1000 person-years for those also living with diabetes [170]. Furthermore, Muschitz confirmed unfavorable metabolic changes with higher levels of myostatin in burn patients [168]. No clinical and preclinical study investigating dysregulated energy expenditure and metabolic disturbance to bone health after fracture or TBI was identified by the systematic review.

Endocrine dysregulation

The systematic review identified five clinical and three preclinical studies investigating the effects of endocrine dysregulation on bone health after traumatic injuries (Online Resource 1 (Table 3.15)).

Valderrábano demonstrated a significant association between Estradiol levels and trabecular thickness at the radius of SCI patients [100]. Studies confirm an association

between gender and bone loss after SCI, with some suggesting men experience bone loss four times more [99], while others identify women as a higher-risk group [101], regardless of time post-injury.

Adiponectin, a hormone produced by fat tissue and known to promote bone formation, shows no clear association with BMD in SCI patients [81]. In contrast, Tan et al. observed a link between high serum adiponectin levels and lower BMD in paralyzed men after SCI [80]. Leptin is another fat-derived hormone, and studies have reported conflicting results between leptin levels and bone density [81].

In burn patients, elevated stress levels and consequent cortisol release can result in increased bone resorption and reduced bone formation [3, 161, 166] with evidence showing reductions in osteoblasts and biomarkers of osteoblast differentiation, and a reverse relationship between type-I collagen mRNA and free cortisol excretion in urine [161, 165]. Animal studies investigating endocrine dysregulations in a rat model of SCI [125] and mice models of TBI [21, 26] demonstrated lower testosterone and leptin levels in SCI than in sham, and significantly reduced IGF-1 in TBI mice, which was shown to be correlated with trabecular bone volume [26]. No clinical study about endocrine dysregulation-induced bone loss after TBI or fracture was identified by the systematic review.

Nervous system

The systematic review identified 3 clinical and 4 preclinical studies investigating the effects of post-traumatic dysregulated innervation on bone status (Online Resource 1 (Table 3.16) and (Table 3.17)).

Regarding TBI, our group observed that increased beta-2 adrenergic signaling after TBI has an inhibitory effect on bone formation [29].

Two clinical [43, 71] studies focused on SCI patients: Dionyssiotis compared patients with tetraplegia/paraplegia and observed more pronounced bone loss with a higher level of injury [71]. Tsuzuku reported differences in BMD between tetraplegic and paraplegic patients [43]. Three animal studies [106, 118, 130] investigated the correlation between the nervous system and bone health. Liu et al. observed sustained increases in substance P immunoreactivity and reductions in NF200-positive nerve fibers in the proximal tibiae of SCI rats [106] and highlighted the role of nerve damage and further supported the crucial role of both sensory and sympathetic innervation in regulating bone remodeling through communication with bone cells [106]. Liu et al. used carvedilol, a non-selective beta blocker, in a rat weight-drop model (30 g, 5 cm) of thoracic SCI and observed reduced bone loss, suggesting beta-adrenergic signaling plays a role in SCI-induced osteoporosis [118].

In burn victims, the autonomous dysregulation measured by sympathetic skin response (SSR) in the first 2–5 weeks after trauma was predictive of bone loss 9–12 months after [172], proposing a correlation between the sympathetic nervous system and bone loss after burn.

No clinical or preclinical evidence on dysregulated neural control of bone metabolism after fracture was identified.

Discussion

Occurrence of post-traumatic bone loss in different trauma settings

While the available evidence suggests that traumatic injuries such as TBI, SCI, fractures, and burns negatively affect bone health, the extent, pattern, and mechanisms of bone loss vary substantially between them. SCI shows the most severe and consistent post-traumatic bone loss, particularly in sub-lesional areas of the lower limbs (e.g., distal femur, proximal tibia), often exceeding 50% trabecular bone loss within weeks post-injury [181]. Osteoporosis prevalence in SCI patients varies widely—from 10 up to 80%—depending on the bone site and individual factors. This is primarily attributed to mechanical unloading, loss of neural input, and chronic neurohormonal dysregulation, including heightened sympathetic tone and suppressed anabolic signaling [118, 182].

The degree of bone loss associated with TBI varies depending on some factors, including systemic inflammatory and neuroendocrine response, heterogeneous injury severity, and partial mobility preservation. Patients with TBI may have a variety of neurological and physical impairments that result in a less predictable pattern of bone remodeling than those with SCI, which frequently causes uniform unloading and total paralysis. This emphasizes the necessity of tailored monitoring and treatment strategies for TBI-associated osteoporosis.

Fractures, while often considered a local event, also contribute to bone loss both at the injured site and systemically. Despite the relatively larger volume of data on SCI and TBI, evidence for post-traumatic bone loss in fracture patients is rather limited. Both clinical and preclinical research show that BMD declines in both the fractured limb and other skeletal locations, sometimes for years after injury [183]. Several studies observed a 2–10 times increased risk for subsequent fractures at any skeletal site or long-term imbalance in serum markers of bone turnover [183]. The well-established increased risk of subsequent fracture is probably caused by this systemic bone loss following fracture, indicating that fracture healing initiates broader skeletal remodeling beyond the immediate injury. Although this risk gradually decreases over time, it remains elevated long term compared

to individuals without a history of fractures [184]. While the exact reason for this elevated fracture risk is not fully understood, underlying risk factors such as bone loss after fracture and changes in mechanical load, inflammatory signaling, and metabolic alterations may also be involved.

Burn injuries, on the other hand, elicit a systemic inflammatory and hypermetabolic response that accelerates bone resorption and impairs formation, leading to diffuse osteopenia, particularly in pediatric populations [3]. Clinical studies show significant and persistent BMD reduction at multiple skeletal sites, including lumbar spine, femur, and forearm, with severity correlated to burn extent and lasting for several years after injury [157–170, 172, 173]. This underscores the necessity for future studies to establish clear guidelines and improve bone health management in trauma patients, considering injury severity, polytrauma, and mobility limitations to reduce the risk of secondary fractures.

Mechanisms/pathophysiology of post-traumatic bone loss

This systematic review identified evidence for the several mechanisms contributing to post-traumatic bone loss, which are summarized in Fig. 2.

Unloading

Bones respond dynamically to mechanical stress, and without it, they lose their biomechanical stability and deteriorate [185]. While mechanical unloading is a known contributor to bone loss, particularly in SCI patients, where paralysis results in severe disuse of sub-lesional limbs, it is not the sole contributor to post-traumatic bone loss. The catabolic effects of disuse on the skeleton have long been recognized in contexts such as bed rest, immobilization, and space flight [183], but mechanistic evidence supporting disuse as a driver of systemic bone loss at sites remote from the injured limb remains limited [185]. Mechanical unloading increases osteoclast activity while suppressing bone formation, thus accelerating bone resorption and compromising skeletal integrity. However, the extent of bone loss is more severe and faster than in sole unloading conditions such as bed-rest or spaceflight [186], so the speed and severity of bone loss after SCI cannot be fully explained by unloading alone. Additional systemic changes such as neurohormonal changes, post-traumatic inflammation, and disrupted sympathetic signaling likely act synergistically.

This is further supported by experimental models. In rodents, mechanical unloading via tail suspension simulates disuse, but it is unable to reproduce the full extent of bone loss seen in SCI [187]. Notably, tail suspension models, which only involve unloading and do not cause neurological damage, did not show a visible increase in osteoclast numbers. In contrast, SCI significantly enhances osteoclast-mediated resorption, suggesting that mechanical unloading alone does not increase the osteoclastogenic capacity of bone marrow cells [39, 188]. Therefore, the pathophysiology of post-traumatic osteoporosis depends on factors essential to SCI, not just the absence of mechanical stimuli.

Mechanistic studies have identified piezo1 receptor, a key component of bone mechanosensation, becomes inactivated during mechanical unloading and has been shown to increase fracture risk and induce osteoporosis in animal models [189]. Similarly, sclerostin, a glycoprotein produced by osteocytes in response to unloading conditions, inhibits bone formation by binding to LRP5/6 receptors, thus antagonizing the Wnt signaling pathway [190]. Its upregulation following trauma has been reported not only in SCI but also in TBI, fracture, and burn injury patients, often correlating with immobilization levels [119, 191–194]. Sclerostin upregulation stimulates RANKL expression in osteoblasts and enhances osteoclast activity. While these are central mechanisms, other factors influencing osteoblast activity, such as increased levels of Dickkopf-related protein 1 (Dkk-1), another antagonist of the Wnt signaling pathway, might further contribute to impaired bone formation in SCI patients [195]. However, the upstream regulators of increased Dkk-1 secretion is unclear, while it has been shown to be a phenomena observed also in other cases of damage to neural tissues such as in Alzheimer's disease [196]

Comparatively, bone loss occurs in TBI patients, albeit in a more variable pattern, even though mechanical unloading may be partial or temporary. Here, alterations in neuroendocrine signaling (e.g., growth hormone, IGF-1, and leptin) [26, 27] and increased sympathetic tone [29] may play dominant roles, with unloading as a contributing secondary factor. Fractures cause immobilization, often on a local scale; however, systemic bone loss has been observed, particularly in the contralateral limb and axial skeleton, suggesting systemic contributors. In burn injury, patients are frequently immobilized during acute care, yet bone loss is primarily driven by systemic inflammation, hypermetabolism, and hormonal dysregulation, with unloading acting as an aggravating rather than initiating factor.

Even though unloading is a common feature among these trauma types, its impact varies depending on the situation and is frequently linked to more extensive systemic changes. The necessity of early rehabilitation and injury-specific mobilization techniques is highlighted by this multifactorial understanding. Additionally, molecular targets such as sclerostin and Piezo1 as possible therapeutics for maintaining bone mass in patients who are paralyzed or neurologically impaired are suggested [116, 197].

Inflammation

Inflammation plays a crucial yet complex role after traumatic injuries [198–201]. The trauma-triggered immune system response leads to the release of pro-inflammatory cytokines that can adversely affect bone metabolic homeostasis, leading to pathological bone diseases [202]. Clinical research on the effect of inflammation after SCI and TBI on bone health is limited and mostly focused on fracture healing [203, 204]. Nevertheless, trauma-induced inflammation elevates pro-inflammatory cytokines in all injury types, which has been shown to stimulate RANKL production and osteoclastogenesis [168, 205, 206], thereby exacerbating bone resorption and decreasing skeletal integrity.

Prior studies showed significant inflammation post-SCI, with approximately 47% of patients diagnosed with acute systemic inflammatory response syndrome (SIRS) upon hospital admission [207]. In TBI and SCI, chronic inflammation, disruption of the blood–brain barrier, and systemic inflammatory responses could further disrupt bone remodeling and contribute to increased bone loss [8, 208–210]. Fractures also trigger an inflammatory response essential for healing [211], though the systemic effects of this acute inflammation remain less well understood. While the effect of chronic inflammation is well-established to contribute to bone loss in diseases like rheumatoid arthritis [212], the effect of short-term inflammation specifically caused by fractures on bone health is less clear [206]. Additionally, Dkk-1 could serve as a potential target in trauma-related bone loss, as proinflammatory cytokines like TNF-α—elevated after injury—induce Dkk-1 expression, which impairs osteoblast differentiation and bone formation [213]. Overall, targeting inflammatory pathways for therapeutic interventions could potentially mitigate bone complications, but additional research is required.

Vitamin D, calcium, PTH

Vitamin D and PTH are essential in regulating bone metabolism to maintain stable serum calcium levels and skeletal health. Activated vitamin D enhances calcium absorption in the intestines, retention in the kidneys, and deposition in the bones, while PTH stimulates bone resorption to release calcium [214]. Traumatic injuries such as SCI, TBI, and burns often disrupt this delicate hormonal balance. As vitamin D synthesis is dependent on sun exposure [215], prolonged hospital stays with limited sun exposure could contribute to vitamin D deficiency. Studies confirm a high prevalence of vitamin D deficiency after these injuries, ranging from 46.5% in TBI, up to 93% in SCI, and 76% in burns [216–218]. In burn patients, the high prevalence of vitamin D deficiency (up to 76%) can be attributed not only to reduced sun exposure during hospitalization but also to direct damage to the skin, which impairs the skin's capacity to synthesize vitamin D.

In addition to a post-traumatic vitamin D deficiency, vitamin D–PTH axis dysregulation has been observed, particularly in SCI and TBI patients, which may exacerbate bone resorption and BMD loss [7, 219]. However, the exact mechanisms need further studies. In murine studies, a systemic "calcium pull" toward the healing bone site after a fracture can reduce systemic BMD, a phenomenon that may be further worsened by insufficient vitamin D levels [152].

Altogether, these findings underscore the importance of early screening, monitoring, and supplementation of vitamin D and calcium in patients with traumatic injuries, not only to support fracture healing but also to prevent long-term skeletal deterioration.

Metabolism/nutrition

Trauma triggers a hypermetabolic state characterized by increased caloric expenditure to support tissue repair. This can lead to increased protein breakdown and potential muscle wasting, indirectly and possibly directly impacting bone health as muscles provide support and contribute to bone formation [226].

SCI and TBI are known to cause metabolic dysregulation and alterations in energy expenditure and protein metabolism [227, 228]; however, there are only a few clinical studies that investigate the relationship between these changes and disturbed post-traumatic bone turnover. Their findings suggest that the neurological level of injury influences not only bone health but also body composition, highlighting the importance of monitoring metabolic parameters in this population. The inverse relationship between protein and amino acid intake and lumbar BMD in SCI patients challenges the traditional view that protein intake supports bone health. These results underline the importance of considering both the quantity and type of protein consumed in managing bone health after neurological injuries.

The increased risk of osteoporosis in burn victims, especially those with diabetes, and the detection of higher myostatin levels show systemic metabolic disruptions with skeletal consequences. Together, these findings emphasize a critical gap in mechanistic and translational studies linking energy metabolism and post-traumatic sarcopenia to bone turnover in the context of traumatic injuries, particularly TBI and fracture.

In addition, pre- and post-traumatic nutritional status significantly impacts bone health. Obesity, malnutrition, and deficiencies in micronutrients like vitamin C could negatively affect bone formation. Trauma-induced hypermetabolism and malnutrition compounded by post-discharge challenges such as pain, fatigue, and difficulty maintaining

adequate nutrient intake further complicate bone healing [220–225].

Altogether, post-traumatic nutritional and metabolic dysregulations are an important—because potentially modifiable—potential cause of post-traumatic bone loss. Mechanistic and preclinical data are still lacking, especially for fracture and TBI, despite some clinical findings emphasizing the effects of altered protein metabolism, energy expenditure, and nutrient deficiencies, particularly in patients with SCI, TBI, and burns. In order to prevent post-traumatic bone loss, future studies are needed for the development of targeted nutritional and metabolic interventions and to attempt to elucidate the relationship between post-traumatic malnutrition, post-traumatic sarcopenia, and bone metabolism.

Endocrine dysregulation

Traumatic injuries such as TBI, SCI, and burns can lead to significant endocrine dysregulation—including imbalances in cortisol, thyroid hormones, growth hormones (GH), sex steroids, and leptin—all of which are known to impair bone formation and contribute to bone loss [6, 8, 229–236]. These dysregulations are often compounded by disruptions in sleep and circadian rhythms [251, 252], as well as dysfunctions of the hypothalamic–pituitary–adrenal (HPA) axis [253, 254], all of which further compromise bone health.

TBI and SCI are reported to disrupt the normal functioning of the HPA and thyroid-stimulating hormone (TSH) axes, which in turn can affect various hormones that play a crucial role in bone metabolism [237, 238]. Pituitary dysfunctions post-TBI are common and occur in 25–70% of patients, depending on injury severity [238]. The most common manifestations of hypopituitarism are GH, gonadotrophin, and TSH deficiencies [239]. Functional GH deficiency with low serum levels of insulin-like growth factor-I (IGF-I), which may result from increased glucocorticoid production and short-term increased circulating levels of IGF-binding proteins, could reduce bone formation [157], thus contributing to post-traumatic bone loss.

In a series by Huang et al., approximately 80% of female patients with complete SCI (levels C6 to L1) were found to have at least one axis abnormality of either the hypothalamus–pituitary–ovary or hypothalamus–pituitary–thyroid axes [240].

Additionally, reduced sex steroid (estrogens and androgens) might negatively affect bone health in SCI due to the prevalence of hypogonadism in this population [239]. Leptin has been shown to inhibit bone formation [241] by stimulating sympathetic nervous system activity. However, leptin's effects on bone are complex and sometimes contradictory; some studies suggest it may also have bone-protective roles through direct peripheral actions or modulation of other hormonal pathways [242]. For example, Garland et al. showed that the secondary effects of the overall metabolic disturbances might play a more important role in bone loss than hormonal changes [33]. These conflicting results underline the need for further research on the role of endocrine disturbances and to clarify leptin's precise impact on post-traumatic bone metabolism.

Innervation/neuropeptides

The nervous system plays a crucial role in maintaining bone health through neural pathways and the release of neurotransmitters (e.g., norepinephrine) and neuropeptides (e.g., calcitonin gene-related peptide, substance P, neuropeptide Y) [6, 243]. Trabecular and cortical bone, as well as bone marrow, are innervated by sympathetic nerve fibers. Functional receptors for norepinephrine and several neuropeptides have been identified in bone cells, suggesting a biological relevance of post-traumatic changes in innervation to bone metabolism [182, 244].

Among the neural regulators, the sympathetic nervous system (SNS) plays a crucial role by modulating bone formation and resorption via affecting osteoblast and osteoclast activity [9, 26, 29, 244, 245]. Recent studies suggest that the SNS directly influences fracture healing by promoting callus neovascularization and altering the local inflammation in the fracture, while inhibiting bone formation in intact bones, thus inducing post-traumatic bone loss after TBI [29, 246]. At the same time, nociceptive neurotransmitters like CGRP and substance P may play a role in these processes, as recently reviewed [247–249].

Patients with SCI, especially with lesions above T6, are at risk for a condition called autonomic dysreflexia that involves severe disruptions in automatic body functions. This includes significant **SNS dysfunction**, which has been proposed as a key contributor to the rapid and extensive bone loss observed in these patients [71]. Supporting this, experimental studies demonstrated sympathetic denervation in animal models causes reduced bone deposition and mineralization, alongside increased bone resorption, suggesting a direct effect of neural loss on bone function [206, 212].

Similarly, in burn patients, autonomic dysregulation measured by sympathetic skin response (SSR) within the first 2–5 weeks post-injury was predictive of significant bone loss 9–12 months later [172]. This suggests a strong correlation between SNS dysfunction and subsequent osteoporosis following burn trauma, further highlighting the role of the sympathetic nervous system in systemic bone health across different injury types.

Conversely, Tam et al. observed increased bone formation two days after traumatic brain injury (TBI), which was linked to endocannabinoid-mediated inhibition of SNS activity [211], illustrating the complex and sometimes opposing influences of neural pathways on bone.

Overall, these findings highlight the critical and multifaceted role of the nervous system, especially the sympathetic nervous system, in regulating bone metabolism after trauma, emphasizing the need for further research to unravel the complex neural mechanisms.

The pathophysiology of post-traumatic bone loss leading to osteoporotic bone shares some similarities with other forms of osteoporosis, such as post-menopausal and glucocorticoid-induced osteoporosis [250, 251]. Many of the mechanisms we discussed—endocrine disruptions, sympathetic nervous system dysregulation, metabolic imbalances, and inflammatory changes—also play pivotal roles in these well-characterized osteoporosis types. Like post-menopausal osteoporosis, post-traumatic osteoporosis often involves hormonal imbalances that lead to reduced bone density and increased fracture risk. Similarly, both post-traumatic and glucocorticoid-induced osteoporosis feature increased bone resorption and decreased bone formation, contributing to overall bone loss. However, a distinctive aspect of post-traumatic osteoporosis is the acute disruption of bone homeostasis due to injury-related inflammation, immobilization, and nervous system dysregulation, which are not typically present in the other forms of osteoporosis. These differences underscore the need for tailored treatment strategies that address the specific mechanisms involved in post-traumatic bone loss.

Diagnostic challenges regarding post-traumatic bone loss

Diagnosing post-traumatic bone loss presents significant challenges due to variability in clinical presentations and limitations of currently available diagnostic tools [252]. DXA, the standard tool for measuring BMD, has several technical challenges post-trauma [151]. Many disabled patients are physically unable to undergo a DXA due to mobility issues or the inability to maintain the necessary positions during the scan. Moreover, measuring BMD in standardized regions affected or unaffected by trauma may not accurately reflect overall bone loss. Advanced imaging techniques, such as high-resolution peripheral quantitative computed tomography (HR-pQCT), provide detailed assessments of bone microarchitecture but are not widely available due to high costs and the need for specialized user training [253]. Both DXA and HR-pQCT may not be accessible in emergency settings.

Biochemical markers of bone turnover can offer valuable insights into bone resorption and formation rates [254], but in the context of post-traumatic bone loss after fracture, they were not correlated with BMD changes during the first postoperative year after fracture, despite observing changes in bone markers and bone density [255]. However, their use remains limited due to the need for standardized assays and specific laboratory capabilities, which are not widely available.

The often asymptomatic nature of early-stage post-traumatic bone loss further complicates timely diagnosis [256]. Following hospital discharge, there is usually a significant attrition rate in patient follow-up that can result in a significant amount of undiagnosed or untreated cases. Moreover, the complex interplay of factors such as immobilization, systemic inflammation, endocrine dysregulation, and nutritional deficiencies can obscure the clinical picture, making it challenging to pinpoint the precise etiology of bone loss [257]. Addressing these diagnostic challenges requires a multimodal approach that integrates advanced imaging, biochemical markers, and comprehensive clinical risk assessments. Currently, aside from SCI, no clinical guidelines exist for defining specific treatment thresholds in post-traumatic bone loss, which may need to be addressed earlier during the osteopenic phase to prevent osteoporosis. There is a pressing need to develop standardized diagnostic criteria and more accessible diagnostic technologies to facilitate early and accurate detection of post-traumatic bone loss in diverse clinical environments.

Clinical implications and future research needs

The pathophysiological mechanisms of post-traumatic osteoporosis, especially the role of the nervous system, compared to other forms of osteoporosis, are unique and may facilitate the development of both established and personalized treatment strategies.

While weightbearing alone has shown limited effects, early mobilization combined with strategies like functional electrical stimulation or vibration may help mitigate bone loss, highlighting the importance of both mechanical and systemic mechanisms in posttraumatic bone loss.

[258, 259]. Nutritional optimization, including providing energy and protein requirements as well as ensuring sufficient calcium and vitamin D supplementation after initial hypercalcemia, may further improve the declination of bone density. Established anti-osteoporotic medications, including antiresorptive (such as bisphosphonates and Denosumab) and osteoanabolic (such as Teriparatide and Abaloparatide) agents, could be beneficial either to prevent or to treat post-traumatic bone loss. Bisphosphonate treatment, fracture risk, and guidelines for osteoporosis management in SCI care have been recently reviewed [2, 181, 260, 261]. Although these treatments are shown to reduce bone loss, they do not always decrease the increased risk of fractures. However, a comprehensive overview of the available and possible treatment options for post-traumatic bone loss, as well as their comparative effectiveness in treating other condition-induced osteoporosis, requires further research.

In cases of SCI or severe TBI with immobilization, the preventive use of antiresorptive therapies or anti-sclerostin antibodies might address the dual problem of initial hypercalcemia and long-term bone loss. In contrast, osteoanabolic therapies might be superior in cases with high secondary fracture risk, delayed treatment initiation beyond the mid-term post-injury, or in patients with fractures, as they can stimulate bone healing [262, 263].

Future research on the differential and shared molecular mechanisms of trauma-induced bone loss and other forms of osteoporosis is required to develop optimized targeted treatment strategies. Current mechanistic studies primarily address bone loss in SCI [264, 265], leaving significant gaps in our understanding of how TBI and fractures contribute to systemic bone loss. Areas requiring further study include the chronic (neuro-)inflammation post-TBI, disuse-induced sclerostin upregulation in non-fractured bones, systemic inflammatory responses post-fracture, trauma-induced disruptions in vitamin D, calcium, and PTH, and the sympathetic nervous system in bone health post-trauma. This is especially interesting, as pharmacologic agents modulating the sympathetic nervous system are widely used in other disciplines of medicine and may contribute or be employed to modulate post-traumatic bone loss. Addressing these gaps through targeted research will help develop better interventions and improve clinical guidelines for managing bone health in trauma patients.

Limitations

While this study focused on traumatic injuries to the central nervous system, burns, and fractures, other traumatic injuries were not systematically reviewed, limiting this study's validity for injuries such as thoracic trauma and liver ruptures, or additional effects in polytrauma.

Variability in study quality and possible bias are major limitations in the current literature on post-traumatic bone loss that need to be carefully considered when interpreting the results. The use of animal models with varying trauma severity, species, and time points in preclinical studies may restrict their applicability to human patients. Given the heterogeneous study designs and preclinical models, a formal bias analysis was not performed. Small sample sizes, diverse potential populations, and inconsistent diagnostic standards for bone loss are common problems in clinical research, which raise the possibility of measurement and selection bias.

Conclusion

In conclusion, this systematic review highlights the relevance of post-traumatic bone loss associated with traumatic injuries such as TBI, SCI, burn injuries, and fractures. While progress has been made in understanding the impact of immobilization, VitD/calcium homeostasis or hormonal imbalances, this review highlights the growing importance of neural signaling—particularly the sympathetic nervous system—in causing bone loss after trauma. To refine diagnostics, optimize preventive strategies, and develop personalized treatment regimens to reduce subsequent fracture risk and improve mobilization after severe injuries, understanding the differential pathophysiology of post-traumatic bone loss is crucial. Nevertheless, supportive strategies for bone health such as early mobilization, sufficient nutrition, and vitamin D supplementation could already be employed to mitigate post-traumatic bone loss.

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Data Availability The systematic review summary results are available in the eletronic supplement of this article. Further data underlying this article is available from the corresponding author upon reasonable request.

Declarations

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Statement on medical device(s)/drug(s) The manuscript submitted does not contain information about medical device(s)/drug(s).

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