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Review Article

The impact of rehabilitation in bone loss management of patients with spinal cord injury: A systematic review

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Abstract.
BACKGROUND: Spinal cord injury (SCI) is a disabling condition characterized by multilevel skeletal muscle impairment and rapid cortical and trabecular bone loss. Rehabilitation is a cornerstone of the long-term management of patients with SCI; however, the optimal rehabilitation strategy for improving bone health has not been fully characterized.
OBJECTIVE: To characterize the current evidence supporting different rehabilitation interventions improving bone health in patients with SCI.
METHODS: On November 17th, 2022, five databases (PubMed, Scopus, Web of Science, Cochrane, and PEDro) were systematically searched for randomized controlled trials (RCTs) assessing SCI patients undergoing rehabilitation interventions. The primary outcomes were bone macroscopical effects. Secondary outcomes were changes in bone metabolisms and functional outcomes.
RESULTS: Out of 499 records, 11 RCTs met the eligibility criteria and were included. Electrical stimulation combined with physical exercise was assessed by 5 studies, standing intervention was assessed by 3 studies, vibration was assessed by 1 study, ultrasound therapy was assessed by 1 study, and electroacupuncture combined with a pulsed magnetic field was assessed by 1 study. The rehabilitation intervention was administered combined with pharmacological treatment (3 studies) or alone (8 studies). Positive effects in terms of BMD were reported by 3 studies. The quality assessment revealed some concerns in 9 out of 11 studies, in accordance with the Cochrane Risk of Bias assessment – version 2.
CONCLUSION: Our data suggest that multicomponent interventions including rehabilitation might be considered a suitable option to improve bone health management in SCI patients. Further studies are mandatory to characterize the optimal combination of non-pharmacological interventions reducing bone loss and improving the risk of fractures in patients with SCI.

Keywords: Osteoporosis, spinal cord injury, rehabilitation, bone health, physiotherapy

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1. Introduction

Spinal cord injury (SCI) is a disabling neurological condition characterized by the loss of both motor and sensory function and visceral dysfunction [1–4]. The prevalence of SCI is highly heterogeneous among different countries, ranging from 13.0 per million to 163.4 per million people, with a significant proportion of traumatic spinal cord injuries affecting young adults [5–7]. Regrettably, SCI is related to extremely high healthcare and assistance costs, while social and personal costs cannot be quantified [5–7].

After spinal cord injury, bone loss is a common complication related to skeletal muscle system disuse and impaired mechanical stimuli [3,8]. More in detail, osteoporosis generally affects the skeletal system caudal to the spinal cord damage, with bone loss occurring most rapidly and significantly in the distal femur and proximal tibia [9,10]. Within two to three years of SCI, individuals show a 50–100% trabecular bone mineral density (BMD) reduction, and 40–80% lower cortical bone mass [11–13]. As a result, SCI patients have a 20- to 100-fold higher fracture risk compared to the general population [14]. Therefore, it has been proposed that the comprehensive management of bone loss should be performed in patients with SCI, including both pharmacological and non-pharmacological approaches [15].

In this context, growing evidence highlighted the crucial role of a comprehensive rehabilitation program targeting both physical and psychosocial impairment of SCI patients [8,16–20]. To date, several studies reported positive effects of physical exercise and physical activity on bone health in several disabling conditions [21]. On the other hand, rehabilitation might effectively target not only bone health but also balance and the risk of falls [22].

Despite these considerations, the optimal rehabilitation strategies to prevent bone loss in people with SCI have yet to be fully characterized [23–26]. Furthermore, to our knowledge, no previous systematic review including only randomized controlled trials (RCTs) assessed the effects of specific rehabilitation protocols on bone health of SCI patients.

Therefore, the objective of this systematic review was to provide evidence supporting different rehabilitation strategies for improving bone health in patients with SCI. Moreover, we aimed at characterizing the effects of specific rehabilitation prescriptions in bone health in order to pave the way to an evidence-based approach preventing bone loss in people with SCI.

2. Methods

2.1. Registration

This systematic review of RCTs follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [27]. A preliminary search has been performed in the international prospective register of systematic reviews (PROSPERO) for comparable review protocols in progress, without finding similar studies. The systematic review was then submitted to PROSPERO and accepted on 27th November 2022 with registration number CRD42022376430 (available at https://www.crd.york.ac.uk/prospero).

2.2. Search strategy

The literature search has been performed from onset up to November 17th, 2022. Five databases (PubMed/Medline, PEDro, Web of Science, Cochrane Central Register of Controlled Trials - CENTRAL, and Scopus) were systematically searched independently by two investigators. The keywords “Spinal cord injury”, “Bone Loss”, “Osteoporosis”, “Management”, “Bone mineral density” were used, in addition the MeSH terms available on PubMed and the Boolean operators AND and OR were used. Supplementary Table 1 reports the full search strategy for each database.

2.3. Selection criteria

In accordance with the PICO model [28], we considered eligible all randomized controlled trials (RCT) satisfying the following criteria:

- P) Participants: adult (aged more than 18 years) male or female patients with spinal cord injury, without restriction in terms of time of injury.
- I) Intervention: all rehabilitation interventions administered as exclusive or integrated therapeutic intervention.
- C) Comparator: any comparator.
- O) Outcome: the primary outcomes were bone macroscopical effects, assessed by: i. Bone Mineral Density (BMD); ii. Bone Mineral Content (BMC); iii. Trabecular Bone Thickness (TBTh) and Trabecular Bone Separation (TBSp); iv. bone strength indices [Compressive Strength Index (CSI), Cortical Thickness Index (CTI), Cortical Bone Volume (CBV), Buckling Ratio (BR), and Torsional Strength Index (TSI)]; v. quantitative bone ultrasound (qUS) parameters; vi. Cross-

Sectional Area (CSA) of red and yellow bone marrow and cortical and trabecular bone. The secondary outcomes were: i. changes in body composition; ii. change in bone biomarkers; iii. hormonal and metabolic changes; iv. changes in physical functioning and physical performance.

Only RCTs published in peer-reviewed International Journal were included. No publication date restriction was applied.

The exclusion criteria were: i. participants with pregnancy, clinical instability (defined as hemodynamic alterations, respiratory events, abnormal laboratory values, reduced level of consciousness or temperature alterations), or palliation; ii. studies involving animals; iii. doctorate theses, conference proceedings, and reviews of the literature; iv. not RCT studies; v. language other than English.

Firstly, the articles resulting from the database-specific search strings were examined for duplication removal. Subsequently, the titles and abstracts were screened by two investigators that independently excluded records that did not meet the inclusion criteria. Lastly, the selected articles were examined in full text, and the articles included in the review were thus extracted. Any conflicting record along this chain was discussed between the two investigators, and in case of unresolved disagreement, a third reviewer was involved to reach consensus.

2.4. Data extraction and synthesis

All data were extracted by two independent reviewers through Excel database. Any difference was solved by discussion between the two reviewers or by consulting a third reviewer.

The data extracted were: i. authors, journal, publication year, and nationality; ii. study design; iii. sample characteristics [number of participants, mean age and age range, gender, time of injury, lesion level and grade, baseline body mass index (BMI) and osteoporosis grade]; iv. comparator characteristics; v. intervention characteristics [type, duration, frequency, and intensity of treatment in the experimental group and in the control group(s)]; vi. primary and secondary outcomes; vii. duration of the study (with possible follow-up); viii study results.

Data were independently synthesized by two reviewers. A qualitative analysis of the evidence was performed, given that the heterogeneity of the study samples, the type of intervention and the outcome measures did not allow a quantitative analysis of the data.

A subgroup analysis was performed based on participant characteristics, time from SCI, type of intervention, and outcome assessed.

2.5. Quality assessment and risk of bias

The qualitative analysis of the studies included in the review was carried out using the PEDro scale [29], which consists of 11 items. In particular, the first item assesses the external validity (or applicability) of the study although is not considered for the purposes of the total score; items 2–9 evaluate the internal validity of the study, while items 10–11 evaluate the interpretability of the results based on the statistical information. Each criterion has "yes" and "no" response options, 1 point for each item whose answer is "yes", 0 points for items whose answer is "no". The maximum score obtainable is 10/10. Scores from 9 to 10 were considered "excellent", 6 to 8 were considered "good", 4 to 5 were considered "fair", and < 4 were considered "poor" [29].

The risk of bias assessment of the studies included in the review was performed following the Cochrane Risk of Bias assessment – version 2 (RoB 2) [30], a validated tool for assessing the risk of bias in RCTs. It includes five different domains, each subdivided in criteria that are judged individually (low, high, unclear risk of bias). The overall judgment of a domain derives from the overall judgment of the various criteria. Studies were considered with low risk of bias if all domains evaluated had low risk of bias. Studies in which at least one domain presented unclear risk, were considered studies with some critical issues. Lastly, studies were considered with high risk of bias if at least one domain had a high risk of bias [30].

3. Results

3.1. Study characteristics

Overall, a total of 499 records resulted from the 5 databases assessed, while no other records were identified from other sources. After duplication removal, a total of 363 studies were assessed for eligibility and screened for title and abstract. As a result, 319 records were excluded, and 44 studies were sought for retrieval and then screened in full text. Lastly, 11 studies [31–38,38,40,41] were included in the present systematic review. Figure 1 shows the PRISMA flow diagram, reporting further details about the article selection process. Supplementary Table 2 summarizes the rea-

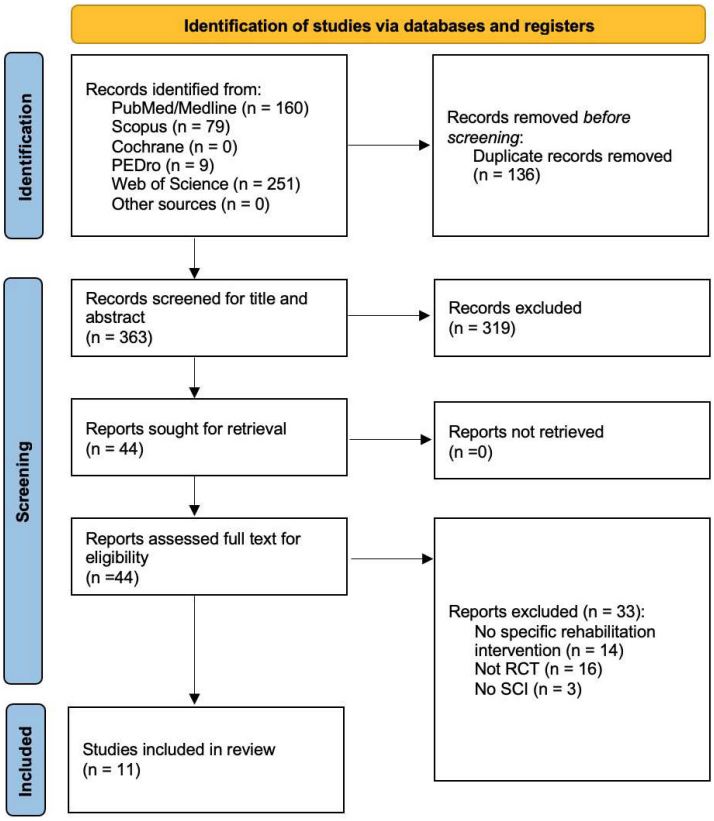

Fig. 1. PRISMA 2020 flow diagram.

son for exclusion of the remaining 33 studies assessed full-text for eligibility.

The following studies were included in the present systematic review: Afshari et al. [31], Arija-Blázquez et al. [32], Ben et al. [33], Chen et al. [34], Edwards et al. [35], Groah et al. [36], Holman et al. [37], Morse et al. [38], Shackleton et al. [39], Warden et al. [40], Xu et al. [41].

The studies included were published between 2001 [40] and 2022 [31,39] and were conducted in America (USA $n = 3$ [31,36–38]; collaboration between USA and Canada $n = 1$ [35]), Europe (Spain $n = 1$ [32]), Africa (South Africa $n = 1$ [39]) and Asia (China $n = 2$ [34,41], Australia $n = 2$ [33,40]).

The present review included a total of 301 patients (250 males, and 51 females). The patients were characterized by a mean age ranging between 23.9 $\pm$ 7.3 years [40] and 47.6 $\pm$ 16.3 years [35]. BMI was reported only by four studies [31,32,37,38], and ranged between 23.94 $\pm$ 3.62 kg/m2 [31] and 26.5 $\pm$ 4.9 kg/m2 [32]. Both post-acute and chronic SCI were assessed, with time since injury varied between 35.9 $\pm$ 16.9 days [36] and 21.1 $\pm$ 13.4 years [35]. More in detail, post-acute subjects were enrolled in five studies: Arija-Blázquez et al. [32], Ben et al. [33], Groah et al. [36], Warden et al. [40], and Xu et al. [41]. Chronic subjects were assessed in six studies: Afshari et al. [31], Chen et al. [34], Edwards et al. [35], Holman et al. [37], Morse et al. [38], and Shackleton et al. [39].

Patients with cervical SCI were assessed in five studies [31,35,37,39,40]; patients with thoracic SCI were evaluated in eight studies [31,32,34,35,37,39–41], and patients with lumbar SCI was assessed in two studies [35,41]. Two studies did not clarify the level of injury [33,38]. Asia Impairment Scale (AIS) was the most used tool used to characterize the functional impairment of SCI ($n = 6$ [31,35–37,39,40]).

Table 1 summarizes in detail the sample characteristics of both intervention groups and comparator groups of each study included in the present review.

3.2. *Intervention and control characteristics*

Heterogeneous rehabilitation modalities were assessed by the RCTs included. In particular, rehabilitation interventions currently proposed were:

Table 1
Literature search strategy on different databases

PubMed:
("spinal cord injury" [MeSH Terms] OR "spinal cord trauma" [All Fields] OR "spinal cord injuries" [All Fields] OR "spinal cord transection" [All Fields] OR "spinal cord laceration" [All Fields]) AND ("osteoporosis" [MeSH Terms] OR "osteoporosis" [All Fields] OR "bone loss" [All Fields]) AND ("management" [All Fields] OR "treatment" [All Fields] OR "therapy" [All Fields] OR "therapies" [All Fields] OR "treatments" [All Fields] OR "prevention" [All Fields]) AND ("bone density" [MeSH Terms] OR "bone mineral density" [All Fields] OR "bone mineral content" [All Fields] OR "risk of fracture" [All Fields] OR "risk of fractures" [All Fields]).
Physiotherapy Evidence Database (PEDro):
spinal cord injur* osteoporosis
Web of Science:
(spinal cord injury) AND (osteoporosis OR bone loss) AND (management OR treatment OR prevention) AND (bone mineral density OR risk of fracture)
Cochrane Central Register of Controlled Trials (CENTRAL) Advanced Search:
ID Search
#1 MeSH descriptor: [Spinal Cord Injuries] explode all trees
#2 MeSH descriptor: [Osteoporosis] explode all trees
#3 MeSH descriptor: [Therapeutics] explode all trees
#4 MeSH descriptor: [Bone Density] explode all trees
#5 #1 AND (#2 AND #3) AND #4
Scopus:
TITLE-ABS-KEY: spinal cord injury AND ((osteoporosis OR osteoporosis) AND (treatment OR management OR therapy OR prevention)) AND (bone mineral density OR bmd OR risk of fracture)

- Functional Electrical Stimulation (FES) combined with physical exercise was assessed in five studies [31,32,36–38]. Afshari et al. [31] positioned electrodes on the quadriceps and hamstrings muscles and delivered a stimulus to produce full knee flexion-extension during arms rowing training. The group compared this intervention against conventional physical rehabilitation arm and rowing training arm [31]. Similarly, Morse et al. [38] assessed the effects of FES and rowing training combined with Zoledronic acid 5 mg/100mL [38]. Arija-Blázquez et al. [32] performed bilateral FES, placing three electrodes on quadriceps muscle to produce contraction, comparing it to sham FES [32]. Groah et al. [36] performed FES bilaterally on the quadriceps muscle combined with non-specified individualized inpatient rehabilitation program, comparing it to the same rehabilitation program without FES [36]. Holman et al. [37] used FES to perform open kinetic chain neuromuscular electrical stimulation-evoked resistance training, with electrodes applied on distal and proximal thigh. The intervention group (IG) was also treated with transdermal testosterone patches, compared with transdermal testosterone patches alone [37].
- Standing modalities were studied in three RCTs [33,34,39]. More in detail, Ben et al. [33] tested weight-bearing and stretch achieved through a block under the experimental foot combined with a tilt table standing. The control was the opposite foot, without weight-bearing [33]. Chen et al. [34] assessed an intelligent standing mobile robot (XZ-Droid Home) with which the patient performed squatting and standing up, and tested it against a regular standing frame. Both IG and control group (CG) underwent rehabilitation, comprising management of pain and spasticity, preventing injury progression, managing secondary complications, guiding strength training, mat mobility and transfer, and personalized rehabilitation education [34]. Lastly, Shackleton et al. [39] used robotic locomotor training to achieve exoskeleton walking in IG. This training modality was compared to activity-based training, which focused on prehabilitation, muscle recruitment, posture and joint stability, resistance and endurance training, pregait, and gait training [39].
- Vibration therapy was studied by Edwards et al. [35]. The group used a vibration platform over which the patient placed both feet flat while remaining seated. This IG was compared to the administration of teriparatide 20 μg/day and sham vibration, and a group with both pharmacological and non-pharmacological interventions [35].
- Ultrasound (US) therapy was assessed by Warden et al. [40]. The authors applied active coupled US-heads on medial and lateral surfaces of the calcaneus, comparing it with sham treatment on contralateral calcaneus [40].
- Electroacupuncture combined with a pulsed magnetic field was assessed by Xu et al. [41]. More in detail, electroacupuncture was performed by treating points GB 34 and GB 39 on both sides. This treatment was combined with XT-20 0 0B Os-

teoporosis Treatment Apparatus (pulsed magnetic field below the level of spinal cord injury), Reneed tablet, and rehabilitation treatment (standing, limb air pressure, limb function training) [41].

Rehabilitation was combined with pharmacological and nutritional intervention as it follows. Morse et al. [38] treated IG patients with a one-time infusion of Zoledronic acid 5 mg/100mL solution [38]. Holman et al. [37] used transdermal testosterone patches in both IG and CG. In the study by Edwards et al. [35], control groups received teriparatide 20 μg/day [35]. Moreover, all subjects received 1000 mg/day of calcium carbonate and 1000 IU/day of cholecalciferol. Lastly, in the study by Xu et al. [41] SCI patients received Reneed tablet 500 mg daily in both IG and CG [41]. All interventions and control protocols characteristics are shown in detail in Table 1.

3.3. Primary outcomes

BMD was evaluated in eight studies [31–36,39,41]. Afshari et al. [31] assessed leg, pelvis and total BMD, and reported a significantly lower decrease in pelvis BMD ($p = 0.028$), a positive effect that was reported also after the CGs crossover (BMD Pelvis, $p < 0.05$). Moreover, the group reported a significant effect in preventing total BMD decrease ($p = 0.039$) [31]. Arija-Blázquez et al. [32] assessed leg, femoral neck, trochanteric, intertrochanteric, ward's triangle, whole hip and lumbar area BMD, without reporting any differences between IG and CG ($p =$ NS) [32]. Ben et al. [33] evaluated total proximal femur BMD (IG vs CG: 0.857 ± 0.131 vs 0.848 ± 0.142 g/cm2, $p =$ NR) and reported that the effect of the intervention was reducing the bone loss by 0.5% (-1.8% to 2.9%) ($p =$ NR) compared to the control group [33]. Edwards et al. [35] evaluated areal BMD at spine, hip, femoral neck, proximal and distal femur, and proximal tibia, and reported a significant difference in spine BMD in the CGs (treated with teriparatide, $p = 0.09$). Assessing volumetric BMD (vBMD) for trabecular bone of femur and tibia epiphyseal, metaphyseal, and diaphyseal regions, the authors reported significant differences over time in the IG at the trabecular vBMD femoral metaphysis ($p = 0.005$). Moreover, significant differences were underlined in CGs at the trabecular vBMD femoral epiphysis and metaphysis ($p = 0.08$ and 0.005, respectively) [35]. Chen et al. [34] evaluated BMD and assessed T score and Z score, which demonstrated a significant difference between IG and CG ($p = 0.04$ and $p = 0.03$, respectively). Groah et al. [36] assessed lumbar, hip, femoral and tibial BMD at 6 weeks and at 3 months after intervention without reporting any significant difference in intragroup and between group analysis ($p =$ NS) [36]. Shackleton et al. [39] reported a significant decrease in CG at the level of hip and femoral neck BMD ($p < 0.05$) [39]. Lastly, Xu et al. [41] did not find any significant differences in the intragroup and intergroup analysis in femoral neck, greater trochanter and Ward's triangle BMD ($p =$ NS) [41].

BMC was assessed in three studies [31,35,40]. Afshari et al. [31] did not find significant differences in leg, pelvis, and total BMC ($p =$ NS). Edwards et al. [35] evaluated BMC for cortical bone of femur and tibia at epiphyseal, metaphyseal, and diaphyseal regions, and found significant differences over time in the IG at the cortical BMC femoral metaphysis and diaphysis ($p =$ 0.001 and 0.054 respectively). Moreover, significant differences over time were found in the CGs at the cortical BMC femoral metaphysis and diaphysis ($p = 0.001$ and 0.054 respectively) [35]. Warden et al. [40] found a significant worsening over time ($p < 0.001$); however, no significant differences were found in between groups analysis ($p =$ NS) [40].

Trabecular bone thickness and trabecular bone separation parameters were assessed by Holman et al. [37] for distal femur and proximal tibia, though the authors did not perform statistical inference and multiple comparisons of the results [37].

Bone strength indices were assessed in two studies [35,38]. Edwards et al. [35] computed CSI and TSI for epiphyseal, metaphyseal, and diaphyseal regions of femur and tibia, without reporting significant differences ($p =$ NS). The authors also assessed BV for cortical bone of femur and tibia at epiphyseal, metaphyseal, and diaphyseal regions, without reporting any differences [35]. Morse et al. [38] assessed CBV, CTI and BR at the proximal tibia and distal femur level and reported significant differences between IG and CG (all $p < 0.05$) in all but distal femur CBV ($p = 0.05$) [38].

Bone ultrasound attenuation (BUA) and speed of sound (SOS) were evaluated in one study [40]. Although these parameters had a significant worsening over time ($p < 0.001$), no significant differences were found in the between-groups analysis ($p =$ NS) [40].

Holman et al. [37] assessed the yellow and red bone marrow CSA and cortical bone CSA at proximal, middle, and distal femoral levels, though the authors did not perform statistical inference and multiple comparisons of the results [37]. Further details are shown in Table 2.

Table 2
Main characteristics of the studies included in the systematic review

Authors Journal Year Nationality	Type of Study	Baseline Sample Characteristics				Intervention	Comparator	Outcomes
		Sample size	*Age (years)*	*BMI (kg/m²)*	*Time of SCI, Level of injury and Functional impairment*			
Afshari et al. *Plos One* 2022 USA	RCT +CG crossover	N (M/F) = 31 (28/3) IG (M/F): 18 (15/3) CG1 (M/F): 6 (6/0) CG2 (M/F): 7 (7/0)	IG: 29.06±5.40 CG1: 26.00±6.69 CG2: 27.57±7.09	IG: 24.10±4.29 CG1: 25.45±2.81 CG2: 23.94±3.62	*Mean time since injury (months):* 11.1±5.2 *Level of injury:* *Cervical* IG: 14 (73%) CG1:4 (66%) CG2: 4 (57%) *Thoracic* IG: 5 (26%) CG1:2 (33%) CG2: 3 (43%) *AIS A* IG: 9 (50%) CG1:4 (66.7%) CG2: 5 (71.4%) *AIS B* IG: 5 (27.8%) CG1: 1 (16.15%) CG2: 0 *AIS B/C* IG: 2 (11.1%) CG1:0 CG2: 1 (14.3%) *AIS D* IG: 2 (11.1%) CG1: 1 (16.15%) CG2: 1 (14.3%)	*Type of intervention:* FES combined with row training *Intervention modality:* stimulus intensity to produce full knee flexion-extension was provided by electrodes over motor points of the quadriceps and hamstrings *Protocol duration:* 26 weeks *Frequency:* 3x/week *Volume (session):* 30/40 min *Intensity:* Initially, 6 sets of FES combined with row training for 5 min at 60% of VO2peak with a work-to-rest ratio of 2:1 and progressed to continuous exercise. The goal was to achieve an intensity of 70–85% of VO2peak	*CG1: Wait list* *Type of intervention:* regular physical rehabilitation *Intervention modality:* NR *Protocol duration:* 26 weeks *Frequency:* NR *Volume (session):* NR *Intensity:* NR *CG2* *Type of intervention:* row training *Intervention modality:* Arms only rowing training *Protocol duration:* 26 weeks *Frequency:* 3x/week *Volume (session):* 30/40 min *Intensity:* Initially, 6 sets of rowing for 5 min at 60% of VO2peak with a work-to-rest ratio of 2:1 and progressed to continuous exercise. The goal was to achieve an intensity of 70–85% of VO2peak *Cross over* Participants in CG1 and CG2 were asked to perform row training combined with FES	*Primary outcomes* Leg, pelvis, total BMD; leg, pelvis, total BMC *Secondary outcomes* Exercise capacity (measured by VO2max, VO2, VCO2, RER, VE, expired O2 and CO2 gas fractions)
Arija-Blázquez et al. *The Journal of Spinal Cord Medicine* 2014 Spain	RCT	N (M/F) = 8 (8/0) IG (M/F): 5 (5/0) CG (M/F): 3 (3/0)	IG: 41.7± 12 CG: 36 ±13.6	IG: 24.3±2.7 CG: 26.5±4.9	*Mean time since injury (weeks):* IG: 5.5 ±1.1 CG: 5.8 ±1.7 *Level of injury:* Between T4–T12 *Complete motor:* 8 (100%)	*Type of intervention:* FES *Intervention modality:* Bilateral FES; one electrode on rectus femoris, one on vastus medialis, and one on vastus lateralis. The last two electrodes were connected to the first one. *Protocol duration:* 14 weeks *Frequency:* 5 days/week *Volume (session):* 47 min, set of 10 contractions with 1 min rest, for a total of 80 contractions. Every two sets, knee angle was changed. *Intensity:* 200-µs pulse duration at 30 Hz and maximum current amplitude of 140 mA.	*Type of intervention:* Sham FES *Intervention modality:* Bilateral sham FES; one electrode on rectus femoris, one on vastus medialis, and one on vastus lateralis. The last two electrodes were connected to the first one. *Protocol duration:* 14 weeks *Frequency:* 5 days/week *Volume (session):* 47 min. Every two sets, knee angle was changed. *Intensity:* 0 mA.	*Primary outcomes* Leg, femoral neck, trochanteric, intertrochanteric, ward's triangle, whole hip, lumbar area BMD *Secondary outcomes* Osteocalcin, CTX, ratio Osteocalcin/CTX
Ben et al. *Australian Journal of Physiotherapy* 2005 Australia	Within-subject RCT	N (M/F) = 20 (16/4)	34±15	NR	*Mean time since injury (months):* 4±2 Tetraplegia (N): 12 Paraplegia (N): 8	*Type of intervention:* Tilt table standing *Intervention modality:* Weight-bearing leg and stretch: a wedge inclined 15 degrees + high block under the experimental foot, ensuring a dorsiflexion torque *Protocol duration:* 12 weeks *Frequency:* 3 times/week *Volume (session):* 30 minutes *Intensity:* NR.	*Type of intervention:* Tilt table standing *Intervention modality:* Non-weight-bearing leg *Protocol duration:* 12 weeks *Frequency:* 3 times/week *Volume (session):* 30 minutes *Intensity:* NR	*Primary outcomes* Total proximal femur BMD *Secondary outcomes* *NR*
Chen et al. *Medicine in Novel Technology and Devices* 2020 China	RCT	N (M/F) = 24 (20/4) IG (M/F) = 12 (11/1) CG (M/F) = 12 (9/3)	IG: 37.17±10.47 CG: 42.92±8.89	NR	*Mean time since injury (months):* IG: 13.08±7.80 CG: 8.75±4.22 *Level of injury:* IG: T5-T12 CG: T5–T12 T5 (IG/CG): 1/1 T6 (IG/CG): 0/2 T7 (IG/CG): 3/2 T8 (IG/CG): 0/1 T10 (IG/CG): 3/2 T11 (IG/CG): 3/1 T12 (IG/CG): 2/3 *Complete:* 100% *Mean time since injury (years):* N = 19.0±13.8 IG: 15.4±13.4 CG1: 20.5±14.6 CG2: 21.1±13.4 *Level of injury:* *Cervical* N = 21 (34%) IG: 6 (30%) CG1:5 (25%) CG2: 10 (48%) *Thoracic* N = 38 (62%) IG: 14 (70%) CG1: 13 (65%) CG2: 11 (52%) *Lumbar:* N = 2 (3%) IG: 0 (0%) CG1: 2 (10%) CG2: 0 (0%) *AIS A* N = 43 (70%) IG: 14 (70%) CG1: 15 (71%) CG2: 14 (70%) *AIS B* N = 8 (13%) IG: 2 (10%) CG1: 3 (15%) CG2: 3 (14%) *AIS C* N =8 (13%) IG: 4 (20%)	*Type of intervention:* Rehabilitation + standing *Intervention modality:* Regular rehabilitation (management pain and spasticity, preventing injury progression, managing secondary complications, guiding strength training, mat mobility and transfer, and personalized rehabilitation education) + intelligent standing mobile robot XZ-Droid Home (squatting and standing up + standing) *Protocol duration:* 4 weeks *Frequency:* daily *Volume (session):* 30 + 30 min / 2x day *Intensity:* Squatting and standing up: 15 times within 3 min/ 30 min/ 2x day; standing: 30 min/ 2x day	*Type of intervention:* Rehabilitation + standing *Intervention modality:* Regular rehabilitation (management pain and spasticity, preventing injury progression, managing secondary complications, guiding strength training, mat mobility and transfer, and personalized rehabilitation education) + standing frame *Protocol duration:* 4 weeks *Frequency:* daily *Volume (session):* 30 min / 2x day *Intensity:* Standing: 30 min/ 2x day	*Primary outcomes* BMD (T value, Z value) *Secondary outcomes* NR
Edwards et al. *Journal of Bone and Mineral Research* 2018 Canada, USA	RCT	N (M/F) = 61 (47/14) IG (M/F): 20 (14/6) CG1 (M/F): 20 (17/3) CG2 (M/F): 21 (16/5)	N = 45.4±16.3 IG: 40.9±16.4 CG1: 47.6±16.3 CG2: 46.6±15.4	NR		*Type of intervention:* Vibration + placebo *Intervention modality:* Vibration platform (placing both feet flat on the platform, while remaining seated) + placebo *Protocol duration:* 1 year *Frequency:* daily *Volume (session):* 10 min *Intensity:* 30 Hz All subjects: 1000 mg/day calcium carbonate, and 1000 IU/day cholecalciferol	*CG1* *Type of intervention:* Teriparatide 20 µg/day plus sham vibration *Intervention modality:* Vibration platform (placing both feet flat on the platform, while remaining seated) + active drug *Protocol duration:* 1 year *Frequency:* daily *Volume (session):* 10 min *Intensity:* 0 Hz *CG2* *Type of intervention:* Vibration + Teriparatide 20 µg/day *Intervention modality:* Vibration platform (placing both feet flat on the platform, while remaining seated) + active drug *Protocol duration:* 1 year *Frequency:* daily *Volume (session):* 10 min *Intensity:* 30 Hz All subjects: 1000 mg/day calcium carbonate, and 1000 IU/day cholecalciferol.	*Primary outcomes* aBMD at spine, hip, femoral neck, proximal and distal femur, and proximal tibia; vBMD for trabecular bone of femur and tibia epiphyseal, metaphyseal, and diaphyseal regions; BMC for cortical bone of femur and tibia at epiphyseal, metaphyseal, and diaphyseal regions; CSI and TSI for epiphyseal, metaphyseal, and diaphyseal region of femur and tibia; BV for cortical bone of femur and tibia at epiphyseal, metaphyseal, and diaphyseal regions *Secondary outcomes* CTX, P1NP, BSAP

Table 2, continued

Groah et al. *American Academy of Physical Medicine and Rehabilitation* 2010 USA	RCT	N (M/F) = 26 (22/4) IG (M/F) = 16 (15/1) CG (M/F) = 10 (7/3)	IG: 26.2±12.8 CG: 31.1±12.2	NR	CG1: 2 (10%) CG2: 2 (10%) *AIS D* N −2 (3%) IG: 0 (0%) CG1: 1 (5%) CG2: 1 (5%) *Mean time since injury (days):* IG: 35.9±16.9 CG: 35.9±23.3 *AIS A (N):* 23 IG: 15 CG: 1 *AIS B (N):* 3 IG: 8 CG: 2 *Tetraplegia (N):* 12 IG: 9 CG: 3 *Paraplegia (N):* 14 IG: 7 CG: 7	*Type of intervention:* Individualized inpatient rehabilitation program + FES *Intervention modality:* FES (on quadriceps muscle bilaterally: the proximal dual-lead positive electrode was placed over the motor point of the quadriceps muscle. The 2 distal negative electrodes were placed over the vastus lateralis and vastus medialis motor points) *Protocol duration:* 6 weeks *Frequency:* 5 days/week *Volume (session):* 60 min (or until fatigue) *Intensity:* Pulse duration 300 microseconds, pulse frequency 25 Hz, amplitude 0 to 125 mA, and on:off time set at 5 seconds:5 seconds	*Type of intervention:* Individualized inpatient rehabilitation program *Intervention modality:* NR *Protocol duration:* 6 weeks *Frequency:* 5 days/week *Volume (session):* NR *Intensity:* NR	*Primary outcomes* Lumbar, hip, femur, tibia BMD *Secondary outcomes* Osteocalcin, urinary N-TX
Holman et al. *Osteoporosis International* 2020 USA	RCT	N (M/F) = 20 (20/0) IG (M/F) = 10 (10/0) CG (M/F) = 10 (10/0)	IG: 36±12 CG: 36±8	IG: 25.5±4.7 CG: 24.0±3.4	*Mean time since injury (years):* IG: 10±10 CG:7±6 *Level of injury (range:)* IG: C5–T11 CG: C6–T11 *AIS A (N)* IG: 7 CG: 7 *AIS B (N)* IG: 3 CG: 3 *Paraplegia (N)* IG: 8 CG: 5 *Tetraplegia (N)* IG: 2 CG: 5	*Type of intervention:* Resistance training + Transdermal testosterone patches *Intervention modality:* open kinetic chain FES-evoked resistance training (bilateral knee extension (progressive resistance), with activation facilitated through neuromuscular electrical stimulation (electrodes applied medially on the distal thigh and laterally on the proximal thigh) *Protocol duration:* 16 weeks *Frequency:* 2 days/week *Volume (session):* NR *Intensity:* biphasic waveform, 30 Hz, 450-μs pulse width, current intensity was adjusted enough to elicit full knee extension with ramp times of ~ 3–4 s and contraction/relaxation times of ~ 5 s on/off	*Type of intervention:* Transdermal testosterone patches *Intervention modality:* NR *Protocol duration:* 16 weeks *Frequency:* NR *Volume (session):* NR *Intensity:* NR	*Primary outcomes* Non-trabecular measures: yellow and red marrow CSA and cortical bone CSA for proximal, middle and distal femur Trabecular measures: TBTh and TBSp for proximal tibia and distal femur *Secondary outcomes* NR
Morse et al. *JBMR Plus* 2019 USA	RCT	N (M/F) = 20 (18/2) IG (M/F) = 10 (9/1) CG (M/F) = 10 (9/1)	N = 38.2±12.4 IG: 38.2±11.8 CG: 38.3±13.6	N = 25.3±5.0 IG: 24.6±5.0 CG: 26.0±5.1	*Mean time since injury (years):* N= 11.6±12.7 IG: 14.4±14.1 CG: 8.8±11.1 *Motor-complete:* 75% *Motor-incomplete:* 25%	*Type of intervention:* FES combined with rowing training and Zoledronic acid 5 mg/100mL solution infused over 15 min *Intervention modality:* Electrodes over motor points of the quadriceps (rectus femoris, vastus medialis, vastus lateralis), and hamstrings (biceps femoris and semitendinosus) attached to the 4-channel stimulator provided alternating contractions of the quadriceps and hamstrings (6 s per contraction) for full-knee extension and hamstrings isometric contraction; no ramp, pulse width = 450ms, frequency = 40 Hz *Protocol duration: 1 year* *Frequency:* 3 days/week *Volume (session):* up to 30 min *Intensity:* 75% to 85% of peak heart rate	*Type of intervention:* FES combined with rowing training *Intervention modality:* Electrodes over motor points of the quadriceps (rectus femoris, vastus medialis, vastus lateralis), and hamstrings (biceps femoris and semitendinosus) attached to the 4-channel stimulator provided alternating contractions of the quadriceps and hamstrings (6 s per contraction) for full-knee extension and hamstrings isometric contraction; no ramp, pulse width = 450ms, frequency = 40 Hz *Protocol duration: 1 year* *Frequency:* 3 days/week *Volume (session):* up to 30 min *Intensity:* 75% to 85% of peak heart rate	*Primary outcomes* Proximal tibia and distal femur CBV, CTI and BR *Secondary outcomes* NR
Shackleton et al. *American Academy of Physical Medicine and Rehabilitation* 2022 South Africa	RCT	N (M/F) = 16 (15/1) IG (M/F) = 8 (8/0) CG (M/F) = 8 (7/1)	N: 38.4±14.3 IG: 40.5±11.2 CG: 38.4±14.3	NR	*Mean time since injury (years):* IG: 13.8±8.2 CG: 7.3±6.4 *Level of injury (range):* IG: C4–C7 CG: C4–C7 *AIS C* IG: 4 CG: 5 *AIS D* IG: 4 CG: 3	*Type of intervention:* Robotic locomotor training *Intervention modality:* walking in exoskeleton *Protocol duration:* 24 weeks *Frequency:* 3 times/week *Volume (session):* 60 min *Intensity:* from standing and walking time of 10–50 mins, between 50 and 1800 steps taken	*Type of intervention:* Activity based training *Intervention modality:* prehabilitation, muscle recruitment, posture and joint stability, resistance and endurance training, pregait, and gait training *Protocol duration:* 24 weeks *Frequency:* 3 times/week *Volume (session):* 60 min *Intensity:* warm-up and mobility (5 mins), resistance training (20–30 mins), and cardiovascular training (20–30 mins)	*Primary outcomes* Spinal, hip and femoral neck BMD *Secondary outcomes* NR
Warden et al. Bone 2001 Australia	Within-subject RCT	N (M/F) = 15 (15/0)	23.9±7.3	NR	*Mean time since injury (days):* 110.3±34.5 *Level of injury:* *Cervical (N):* 9 *Thoracic (N):* 6 *AIS A (N):* 14 *AIS B (N):* 1 *Tetraplegia (N):* 9 *Paraplegia (N):* 6 *Complete (N):* 11 *Incomplete (N):* 4	*Type of intervention:* US *Intervention modality:* Two active US-treatment heads coupled to the medial and lateral surfaces of one calcaneus using US gel pads *Protocol duration:* 6 weeks *Frequency:* 5 days/week *Volume (session):* 20 min *Intensity:* Pulsed-wave US with a 10 μsec burst of 1.0 MHz sine waves at 3.3 kHz. Spatial-averaged temporal-averaged intensity: 30 mW/cm^2	*Type of intervention:* Sham US *Intervention modality:* Two inactive US-treatment heads similarly coupled to the contralateral calcaneus. *Protocol duration:* 6 weeks *Frequency:* 5 days/week *Volume (session):* 20 min *Intensity:* /	*Primary outcomes* BMC, BUA, SOS *Secondary outcomes* NR
Xu et al. *World Journal of Acupuncture – Moxibustion* 2020 China	RCT	N (M/F) = 60 (41/19) IG (M/F) = 30 (19/11) CG (M/F) = 30 (22/8)	IG: 42.53 ±10.03 CG: 44.07±7.59	NR	*Mean time since injury (days):* IG: 68.10±5.94 CG: 72.10±10.54 *Level of injury:* *Thoracic (N)* IG: 18 CG: 15 *Lumbar (N)* IG: 12 CG: 15 *Complete (N)* IG: 9 CG: 11 *Incomplete (N)* IG: 21 CG: 19	*Type of intervention:* conventional treatment (drug treatment and conventional rehabilitation treatment) + XT-20 0 0B Osteoporosis Treatment Apparatus + electroacupuncture *Intervention modality:* standing, limb air pressure, limb function training + pulsed magnetic field below the level of spinal cord injury *Protocol duration:* 8 weeks *Frequency:* 5 times/week *Volume (session):* conventional rehabilitation time + 30 min *Intensity:* 2mT, 15 Hz *Intervention modality:* Electroacupuncture on points GB 34 GB 39 of both sides; GB 34 positive pole and GB 39 negative pole *Protocol duration:* 8 weeks *Frequency:* 5 times/week *Volume (session):* 30 min *Intensity:* Intermittent wave, 15 HZ, intensity up to make the muscles slightly contract and to the patient's endurance	*Type of intervention:* conventional treatment (drug treatment and conventional rehabilitation treatment) + XT-20 0 0B Osteoporosis Treatment Apparatus *Intervention modality:* standing, limb air pressure, limb function training + pulsed magnetic field below the level of spinal cord injury *Protocol duration:* 8 weeks *Frequency:* 5 times/week *Volume (session):* conventional rehabilitation time + 30 min *Intensity:* 2mT, 15 Hz	*Primary outcomes* Femoral neck, greater trochanter, ward's triangle BMD *Secondary outcomes* BGP, ALP, PICP

Abbreviations aBMD: areal BMD; ALP: serum alkaline phosphatase; AIS: American Spinal Injury Association Impairment Scale; BGP: bone gla-containing protein; BMC: Bone Mineral Content; BMD: Bone Mineral Density; BR: Buckling ratio; BUA: bone ultrasound attenuation; CBV: cortical bone volume; CG: Control Group; CSA: cross-sectional area; F: female; IG: Intervention Group; M: males; min: minutes; N: absolute number; NR: not reported; NS: not significant; P1NP: serum type 1 procollagen N-terminal propeptide; PICP: procollagen type I C-peptide; RER: respiratory exchange ratio; SCI: spinal cord injury; SOS: speed of sound; TBTh: trabecular bone thickness; TBSp: trabecular bone spacing; VCO_2: CO_2 production; VO_2: O_2 consumption; US: ultrasound; vBMD: volumetric BMD; VO_2max: maximal aerobic power; wk: week.

3.4. Secondary outcomes

Changes in bone biomarkers were assessed in four studies [32,35,36,41].

- Serum alkaline phosphatase (ALP) was analyzed in the study by Xu et al. [41], reporting a significant difference in the intragroup analysis in both groups and in the intergroup analysis ($p < 0.05$) [41].
- Procollagen type I C-peptide (PICP) was analysed in one study [41]. Xu et al. reported a significant difference in the intragroup analysis in both groups ($p < 0.05$) [41].
- Bone gamma-carboxyglutamic acid containing protein (BGP) was analyzed in one study [41], reporting a significant difference in the intragroup analysis and in the intergroup analysis ($p < 0.05$) [41].
- Osteocalcin was evaluated in two studies [32,36], without reporting significant results ($p =$ NS) [32, 36].
- Urinary N-terminal telopeptide (N-TX) was evaluated in one study [36], at 6 weeks and at 3 months after intervention without reporting significant differences in intragroup and between group analysis ($p =$ NS) [36].
- Collagen type 1 cross-linked C-telopeptide (CTX) was analyzed in two studies [32,35], which did not report significant changes following intervention [32,35].
- The ratio Osteocancin/CTX was calculated in one study [32], that did not report significant changes [32].
- Type 1 procollagen amino-terminal propeptide (P1NP) was analyzed in one study [35], which did not report significant changes following intervention [35].
- Bone-specific alkaline phosphatase (BSAP) was analyzed in one study [35], which did not report significant changes following intervention [35].

Lastly, changes in physical functioning and physical performance were assessed by Afshari et al. [31], reporting significant improvement in the IG ($p < 0.001$) in terms of exercise capacity, without reporting significant effects in CGs [31]. See Table 2 for further details.

3.5. Quality assessment

In accordance with the PEDro scale [29], two studies resulted in poor quality [31,38], three studies were characterized as fair [36,39,41], while the remaining six studies resulted in good quality scores [32–35,37,40]. Table 3 shows in detail the results of the PEDro scale for each item.

The risk of bias assessment was performed according to the Cochrane Risk of Bias assessment – version 2 (RoB 2) [30]. Some concerns emerged from this analysis in domain 2, specifically "Deviations from the intended interventions", due to lack of an appropriate analysis estimating the effect of assignment to intervention. This resulted in total outcome of "some concerns" for 9 studies out of 11 [31,32,34–36,38–41]. Further details about the risk of bias assessment of each study are shown in Fig. 2.

4. Discussion

Rehabilitation is currently considered a cornerstone in the complex framework of care of SCI patients, with growing research suggesting several therapeutic strategies to improve bone health in these patients [3,8,16]. However, bone loss still remains a major issue in SCI patients and the optimal rehabilitation approach to prevent this burdensome condition has not been standardized yet.

Thus, this systematic review of RCTs aimed at summarizing the current evidence supporting the different therapeutic strategies to improve bone health in SCI patients trying to characterize the specific biological effects of a comprehensive rehabilitation approach to these patients.

Interestingly, our findings identified several therapeutic interventions to improve bone health in SCI patients, including FES, physical exercise, vibration therapy, standing, ultrasound, and electroacupuncture combined with pulsed magnetic field. Taken together, the results of the present systematic review underlined that several instrumental therapies were assessed to improve bone health of SCI patients, but with conflicting results and only 3 studies suggested positive effects in terms of BMD improvement at lower limb level [31,33,34].

While the effects of physical therapies on bone health are still controversial in the current literature [42–44], physical exercise is considered a non-pharmacological intervention supported by several guidelines in both osteoporosis prevention and management, due to its multitarget effects on the whole musculoskeletal system, improving both BMD and reducing the risk of falls [45–47]. Despite these considerations, few studies [31,32,36–38] assessed the effects of physical exer-

Fig. 2. Cochrane Risk of Bias assessment – version 2 (RoB 2).

cise on SCI patients. However, people with SCI could be affected by detrimental musculoskeletal impairment, with crucial implications in biological responses to physical exercise [48,49]. Indeed, as part of normal bone metabolism in adult individuals, bone tissue undergoes a continuous process of resorption and formation; when this turnover is at equilibrium, it results in unchanged bone mass, while when there is unbalance, it results in bone changes (growth, aging) and pathology. More in detail, osteoclasts initiate bone resorption, osteoblasts are responsible for bone formation, while osteocytes are the cells dedicated at maintaining bone tissue [50]. On the other hand, as early as 1892, it was determined that mechanical loads in live beings can influence bone architecture. This concept is known as Wolff's law, which was further explored till defining that loading on load-bearing bones determines the majority of their strength in adult life [51]. In this context, voluntary load bearing is lacking in SCI patients' life. In this context, it has been suggested that spasticity might have a protective role in bone tissue in patients with neurological disability [52,53], highlighting the close link between bone and muscle tissues due to their cross-regulation promoted by mechanical forces, in accordance with the mechanostat theory theorized by Frost [54]. On the other hand, it has been proposed that FES treatment might have positive effects on patients affected by spasticity [55]. Despite these considerations, our review underlined that no studies assessed spasticity combined with rehabilitation interventions to manage bone health in SCI patients and more in general the impact of spasticity on bone in these patients is far from being fully characterized.

On the other hand, muscle contraction has been targeted by different rehabilitative programs, including FES and vibration therapy, aiming at increasing mechanical stimuli on the bone and optimizing the pro-

Table 3
Main findings of the studies included in the systematic review

Authors Journal Year Country	Results			Study Duration
	Intragroup Analysis - IG	***Intragroup Analysis - CG***	***Intergroups Analysis***	
Afshari et al. *Plos One* 2022 USA	Primary Outcomes NR Secondary Outcomes *Exercise capacity (measured by VO_2max, VO_2, VCO_2, RER, VE, expired O_2 and CO_2 gas fractions):* significantly increased exercise capacity (NR, p<0.001)	Primary Outcomes NR Secondary Outcomes *Exercise capacity (measured by VO2max, VO2, VCO2, RER, VE, expired O2 and CO2 gas fractions):* no change (CG1: NR, p = 0.5; CG2: NR, p = 0.35)	Primary Outcomes BMD Leg: NR, p = NS Pelvis: NR, p = 0.028 Total: NR Significant effect preventing a decrease in total BMD: p = 0.039 BMC Leg, pelvis, total: NR, p = NS *Crossover* BMD Pelvis: p < 0.05 Secondary Outcomes NR	6 months + 6 months cross over
Arija-Blázquez et al. *The Journal of Spinal Cord Medicine* 2014 Spain	Primary Outcomes *BMD mean change* Leg: -2.92% (±5.14%), p = NS Femoral neck: -7.56% (±7.24%), p = NS Trochanteric: -9.94% (±6.86%), p = NS Intertrochanteric: -5.86% (±5.01%), p = NS Ward's triangle: -6.47% (±13.68%), p = NS Whole hip: -6.99% (±5.19%), p = NS Lumbar area: 3.47% (±5.54%), p = NS Secondary Outcomes Osteocalcin mean change %: 51.5±50.5, p = NS CTX mean change %: -26.4± 38, p = NS Ratio Osteocancin/CTX mean change %: 122.5±53.1, p = NS	Primary Outcomes *BMD mean change* Leg: - -3.34% (±8.58), p = NS Femoral neck: -8.34% (±2.48%), p = NS Trochanteric: -8.12% (±7.75%), p = NS Intertrochanteric: -0.95% (±8.28%), p = NS Ward's triangle: -7.74% (±1.01%), p = NS Whole hip: -0.42% (±6.23%), p = NS Lumbar area: 2.08% (±3.79%), p = NS Secondary Outcomes Osteocalcin mean change %: 27.7 ±57, p = NS CTX mean change %: -28.1± 26, p = NS Ratio Osteocancin/CTX mean change %: 84.6 ±92.1, p = NS	Primary Outcomes *BMD mean change* Leg: -2.92% (±5.14%) vs -3.34% (±8.58), p = NS Femoral neck: -7.56% (±7.24%) vs -8.34% (±2.48%), p = NS Trochanteric: -9.94% (±6.86%) vs -8.12% (±7.75%), p = NS Intertrochanteric: -5.86% (±5.01%) vs -0.95% (±8.28%), p = NS Ward's triangle: -6.47% (±13.68%) vs -7.74% (±1.01%), p = NS Whole hip: -6.99% (±5.19%) vs -0.42% (±6.23%), p = NS Lumbar area: 3.47% (±5.54%) vs 2.08% (±3.79%), p = NS Secondary Outcomes Osteocalcin mean change %: 51.5±50.5 vs 27.7 ±57, p = NS CTX mean change %: -26.4± 38 vs -28.1± 26, p = NS Ratio Osteocancin/CTX mean change %: 122.5±53.1 vs 84.6 ±92.1, p = NS	14 weeks
Ben et al. *Australian Journal of Physiotherapy* 2005 Australia	Primary Outcomes Total proximal femur BMD (g/cm²): 0.913 (±0.140) vs 0.857 (±0.131), p = NR Secondary Outcomes NR	Primary Outcomes Total proximal femur BMD (g/cm²): 0.909 (±0.158) vs 0.848 (±0.142), p = NR Secondary Outcomes NR	Primary Outcomes Total proximal femur BMD (g/cm²): 0.857 (±0.131) vs 0.848 (±0.142), p = NR Effect of standing: reduce bone loss by 0.5% (-1.8% to 2.9%), p = NR Secondary Outcomes NR	12 weeks
Chen et al. *Medicine in Novel Technology and Devices* 2020 China	Primary Outcomes T score: -0.03±0.21, p = NR Z value: -0.07±0.16, p = NR Secondary Outcomes NR	Primary Outcomes T score: -0.18±0.11, p = NR Z value: -0.20±0.11, p = NR Secondary Outcomes NR	Primary Outcomes T score: -0.03±0.21 vs -0.18±0.11, p = 0.04 Z value: -0.07±0.16 vs -0.20±0.11, p = 0.03 Secondary Outcomes NR	4 weeks
Edwards et al. *Journal of Bone and Mineral Research* 2018 Canada, USA	Primary Outcomes aBMD [mean percent difference (±95% Confidence Intervals)] Spine 1.67 (-0.83 to 4.16), p = NS Hip 0.55 (-1.95 to 3.05), p = NS Femoral neck -0.08 (-3.36 to 3.20), p = NS Proximal femur (knee) 2.80 (-0.95 to 6.56), p = NS Distal femur (knee) -0.24 (-4.06 to 3.58), p = NS Proximal tibia (knee) 2.65 (-2.10 to 7.40), p = NS Trabecular vBMD femoral epiphysis 10.3, 95 (−21.1 to 41.7), p = NS Trabecular vBMD femoral metaphysis CG1: -16.9 (-43.7 to 9.9), p = 0.005 Cortical BMC femoral metaphysis 4.0 (1.7 to 6.2), p = 0.001 Cortical BMC femoral diaphysis 2.0 (0.5 to 3.5), p = 0.054 Femur [epiphysis (cortical BMC, and cortical BV) metaphysis (cortical BV) and diaphysis (cortical BV)]: p = NS Tibia [epiphysis (trabecular vBMD, cortical BMC, and cortical BV) metaphysis (trabecular vBMD, cortical BMC, and cortical BV) and diaphysis (cortical BMC, and cortical BV)]: p = NS Finite Elements-predicted stiffness and strength at the proximal tibia: p = NS Secondary Outcomes CTX: -3.42 (-51.6 to 44.8), p = NS P1NP: -21.3 (-70.8 to 28.2), p = NS BSAP: -5.53 (-32.9 to 21.8), p = NS	Primary Outcomes aBMD [mean percent difference (±95% Confidence Intervals)] Spine CG1: 5.52 (3.19 to 7.85), p = 0.09 CG2: 4.83 (2.34 to 7.32), p = 0.09 Hip CG1: 0.90 (-1.76 to 3.56), p = NS CG2: 0.44 (-2.22 to 3.1), p = NS Femoral neck CG1: -0.59 (-4.08 to 2.91), p = NS CG2: 1.70 (-1.68 to 5.09), p = NS Proximal femur (knee) CG1: 2.84 (-1.03 to 6.71), p = NS CG2: -0.48 (-4.48 to 3.52), p = NS Distal femur (knee) CG1: 0.48 (-3.46 to 4.42), p = NS CG2: -0.61 (-4.68 to 3.46), p = NS Proximal tibia (knee) CG1: 4.81 (-0.08 to 9.71), p = NS CG2: -0.38 (-5.44 to 4.68), p = NS Trabecular vBMD femoral epiphysis CG1: -24.2 (-57.5 to 9.08), p = 0.08 CG2: -14.4 (-47.7 to 18.8), p = 0.08 Trabecular vBMD femoral metaphysis CG1: -16.9 (-43.7 to 9.9), p = 0.005 CG2: -16.9 (-43.7 to 9.9), p = 0.005 Cortical BMC femoral metaphysis CG1: 4.0 (1.7 to 6.2), p = 0.001 CG2: 4.0 (1.7 to 6.2), p = 0.001 Cortical BMC femoral diaphysis CG1: 2.0 (0.5 to 3.5), p = 0.054 CG2: 2.0 (0.5 to 3.5), p = 0.054 Femur [epiphysis (cortical BMC, and cortical BV) metaphysis (cortical BV) and diaphysis (cortical BV)]: p = NS Tibia [epiphysis (trabecular vBMD, cortical BMC, and cortical BV) metaphysis (trabecular vBMD, cortical BMC, and cortical BV) and diaphysis (cortical BMC, and cortical BV)]: p = NS Finite Elements-predicted stiffness and strength at the proximal tibia: p = NS Secondary Outcomes CTX CG1: 98.7 (47.4 to 150), p = NR CG2: 27.8 (-21.9 to 77.5), p = NS P1NP CG1: 126 (73.1 to 179), p = 0.044 CG2: 22.1 (-29.0 to 73.1), p = NS BSAP CG1: 56.7 (27.5 to 85.8), p = 0.005 CG2: 21.9 (-6.30 to 50.1), p = NS	Primary Outcomes NR Secondary Outcomes NR	1 year

Table 3, continued

Groah et al. *American Academy of Physical Medicine and Rehabilitation* 2010 USA	*(Baseline vs 6 weeks vs follow up)* *BMD* Lumbar (g/cm²): 1.315 vs 1.331 vs 1.298 (% change: 1.20% and -2.50%), p = NS Hip (g/cm²): 1.185 vs 1.168 vs 1.018 (% change: -1.85% and -12.84%), p = NS Femur (g/cm²): 1.107 vs 1.063 vs 1.025 (% change: -3.97% and -3.57%), p = NS Tibia (g/cm²): 1.035 vs 1.026 vs 0.916 (% change: -0.87% and -10.72%), p = NS Secondary Outcomes *(Baseline vs 6 weeks vs follow up)* Serum Osteocalcin (µg/L): 13.89 vs 11.86 vs 14.80 (% change: -14.61% and 24.79%), p = NS Urinary N-TX (IU/L): 160.56 vs 216.71 vs 154.67 (% change: 34.97% and -28.63%), p = NS	*(Baseline vs 6 weeks vs follow up)* *BMD* Lumbar (g/cm²): 1.274 vs 1.182 (% change: -7.22%), p = NS Hip (g/cm²): 1.192 vs 1.043 (% change: -12.50%), p = NS Femur (g/cm²): 0.964 vs 0.930 (% change: -3.50%), p = NS Tibia (g/cm²): 0.855 vs 0.844 (% change: -4.60%), p = NS Secondary Outcomes *(Baseline vs 6 weeks vs follow up)* Serum Osteocalcin (µg/L): 12.90 vs 24.00 vs 6.40 (% change: 86.05% and -73.33%), p = NS Urinary N-TX (IU/L): 115.00 vs 154.86 vs 171.33 (% change: 34.66% and 10.64%), p = NS	*(6 weeks)* BMD Lumbar (g/cm²): 1.331 vs 1.182, p = NS Hip (g/cm²): 1.168 vs 1.043, p = NS Femur (g/cm²): 1.063 vs 0.930, p = NS Tibia (g/cm²): 1.026 vs 0.844, p = NS *(Follow up)* BMD Lumbar (g/cm²): 1.298 vs 1.25, p = NS Hip (g/cm²): 1.018 vs 1.046, p = NS Femur (g/cm²): 1.025 vs 0.818, p = NS Tibia (g/cm²): 0.916 vs 0.731, p = NS Secondary Outcomes *(6 weeks)* Serum Osteocalcin (µg/L): 11.86 vs 24.00, p = NS Urinary N-Tx (IU/L): 154.86 vs 216.71, p = NS *(Follow up)* Serum Osteocalcin (µg/L): 14.80 vs 6.40, p = NS Urinary N-TX (IU/L): 154.67 vs 171.33, p = NS	6 weeks + follow up at 3 months
Holman et al. *Osteoporosis International* 2020 USA	Primary Outcomes Non-trabecular measures: Proximal femur Yellow marrow CSA (cm²): 1.60±1.08 vs 1.63±1.06, p = NR Red marrow CSA (cm²): 0.76±0.49 vs 0.82±0.43, p = NR Cortical bone CSA (cm²): 4.06±0.95 vs 4.03±0.92, p = NR Middle femur Yellow marrow CSA (cm²): 1.96±1.19 vs 1.94±1.12, p = NR Red marrow CSA (cm²): 0.65±0.4 vs 0.70±0.31, p = NR Cortical bone CSA (cm²): 3.87±0.86 vs 3.86±0.93, p = NR Distal femur Yellow marrow CSA (cm²): 3.44±1.95 vs 3.28±1.58, p = NR Red marrow CSA (cm²): 0.81±0.24 vs 0.84±0.23, p = NR Cortical bone CSA (cm²): 3.07±0.77 vs 3.14±0.67, p = NR Trabecular measures: Distal femur TBTh (mm): 0.33±0.03 vs 0.33±0.03, p = NR TBTh SD (mm): 0.16±0.04 vs 0.14±0.02, p = NR TBSp (mm): 0.88±0.50 vs 0.67±0.14, p = NR TBSp SD (mm): 0.65±0.35 vs 0.46±0.16, p = NR Proximal tibia TBTh (mm): 0.34±0.02 vs 0.36±0.04, p = NR TBTh SD (mm): 0.17±0.03 vs 0.18±0.06, p = NR TBSp (mm): 0.90±0.56 vs 0.65±0.11, p = NR TBSp SD (mm): 0.57±0.41 vs 0.39±0.12, p = NR Secondary Outcomes NR	Primary Outcomes Non-trabecular measures: Proximal femur Yellow marrow CSA (cm²): 2.12±0.90 vs -0.04±0.06 -0.16, p = NR Red marrow CSA (cm²): 0.98±0.41 vs 0.88±0.27, p = NR Cortical bone CSA (cm²): 3.51±0.96 vs 3.49±1.09, p = NR Middle femur Yellow marrow CSA (cm²): 2.40±0.95 vs 2.44±1.00, p = NR Red marrow CSA (cm²): 0.76±0.31 vs 0.72±0.25, p = NR Cortical bone CSA (cm²): 3.30±0.94 vs 3.30±0.99, p = NR Distal femur Yellow marrow CSA (cm²): 3.79±1.38 vs 3.85±1.40, p = NR Red marrow CSA (cm²): 0.84±0.18 vs 0.83±0.16, p = NR Cortical bone CSA (cm²): 2.69±0.75 vs 2.68±0.76, p = NR Trabecular measures: NR Secondary Outcomes NR	Primary Outcomes Non-trabecular measures: Mean difference of difference (± SE) Proximal femur Yellow marrow CSA (cm²): -0.04±0.06, p = NR Red marrow CSA (cm²): 0.08±0.04, p = NR Cortical bone CSA (cm²): -0.01±0.04, p = NR Middle femur Yellow marrow CSA (cm²): -0.03±0.04, p = NR Red marrow CSA (cm²): 0.04±0.03, p = NR Cortical bone CSA (cm²): -0.003±0.032, p = NR Distal femur Yellow marrow CSA (cm²): -0.11±0.09, p = NR Red marrow CSA (cm²): 0.02±0.03, p = NR Cortical bone CSA (cm²): 0.04±0.04, p = NR Trabecular measures: NR Secondary Outcomes NR	16 weeks
Morse et al. *JBMR Plus* 2019 USA	Primary Outcomes NR Secondary Outcomes NR	Primary Outcomes NR Secondary Outcomes NR	Primary Outcomes CBV (mm³) Proximal tibia (β±SE): 345 (109), p = 0.006 Distal femur (β±SE): 471 (225), p = 0.05 CTI (mm) Proximal tibia (β±SE): 0.012 (0.004), p = 0.013 Distal femur (β±SE): 0.016 (0.006), p = 0.009 BR Proximal tibia (β±SE): 4.51 (1.73), p = 0.019 Distal femur (β±SE): 5.47 (2.04), p = 0.015 Secondary Outcomes NR	1 year
Shackleton et al. *American Academy of Physical Medicine and Rehabilitation* 2022 South Africa	Primary Outcomes BMD [mean change(95%CI), g/cm²] Spinal: 0.00 (-0.09 to 0.09), p = NS Hip: 0.01 (-0.08 to 0.06), p = NS Femoral neck: 0.02 (-0.16 to 0.12), p = NS Secondary Outcomes NR	Primary Outcomes BMD [mean change(95%CI), g/cm²] Spinal: 0.00 (-0.14 to 0.14), p = NS Hip: 0.03 (-0.29 to 0.23), p = 0.04 Femoral neck: 0.06 (-0.34 to 0.22), p = 0.04 Secondary Outcomes NR	Primary Outcomes BMD [mean change(95%CI), g/cm²] Spinal: 0.00 (-0.09 to 0.09) vs 0.00 (-0.14 to 0.14), p = 0.96 Hip: 0.01 (-0.08 to 0.06) vs 0.03 (-0.29 to 0.23), p = 0.13 Femoral neck: 0.02 (-0.16 to 0.12) vs 0.06 (-0.34 to 0.22), p = 0.16 Secondary Outcomes NR	24 weeks
Warden et al. Bone 2001 Australia	Primary Outcomes BMC (g): 1.76±0.26 vs 1.62±0.26, p < 0.001 BUA (dB/MHz): 80.4±23.6 vs 73.2±20.2, p < 0.001 SOS (m/sec): 1626.7±39.1 vs 1605.9±47.6, p < 0.001 Secondary Outcomes NR	Primary Outcomes BMC (g): 1.74±0.22 vs 1.61±0.21, p < 0.001 BUA (dB/MHz): 83.5±19.5 vs 75.9±17.2, p < 0.001 SOS (m/sec): 1638.2±44.6 vs 1612.9±41.7, p < 0.001 Secondary Outcomes NR	Primary Outcomes BMC (g): 1.62±0.26 vs 1.61±0.21, p = 0.693 BUA (dB/MHz): 73.2±20.2 vs 75.9±17.2, p = 0.315 SOS (m/sec): 1605.9±47.6 vs 1612.9±41.7, p = 0.129 Secondary Outcomes NR	6 weeks
Xu et al. *World Journal of Acupuncture – Moxibustion* 2020 China	Primary Outcomes BMD (g/cm²) Femoral neck: 0.693±0.058 vs 0.694±0.056, p = NS Greater trochanter: 0.697±0.044 vs 0.700±0.046, p = NS Ward's triangle: 0.671±0.063 vs 0.673±0.061, p = NS Secondary Outcomes BGP (µg/L): 5.74±0.84 vs 7.03±0.82, p < 0.05 ALP (µ/L): 58.47±11.25 vs 67.93±7.33, p < 0.05 PICP (µg/L): 67.00±16.93 vs 73.40±12.66, p < 0.05	Primary Outcomes BMD (g/cm²) Femoral neck: 0.672±0.045 vs 0.673±0.044, p = NS Greater trochanter: 0.678±0.036 vs 0.680±0.034, p = NS Ward's triangle: 0.667±0.050 vs 0.669±0.048, p = NS Secondary Outcomes BGP (µg/L): 5.57±0.92 vs 6.60±0.81, p < 0.05 ALP (µ/L): 53.50±9.35 vs 63.47±7.98, p < 0.05 PICP (µg/L): 61.40±13.79 vs 71.07±11.87, p < 0.05	Primary Outcomes BMD (g/cm²) Femoral neck: 0.694±0.056vs 0.673±0.044, p = NS Greater trochanter: 0.700±0.046 vs 0.680±0.034, p = NS Ward's triangle: 0.673±0.061 vs 0.669±0.048, p = NS Secondary Outcomes BGP (µg/L): 7.03±0.82 vs 6.60±0.81, p < 0.05 ALP (µ/L): 67.93±7.33 vs 63.47±7.98, p < 0.05 PICP (µg/L): 73.40±12.66 vs 71.07±11.87, p = NS	8 weeks

Abbreviations ALP: serum alkaline phosphatase; BGP: bone gla-containing protein; BMC: Bone Mineral Content; BMD: Bone Mineral Density; BR: Buckling ratio; BUA: bone ultrasound attenuation; CBV: cortical bone volume; CG: Control Group; CSA: cross-sectional area; IG: Intervention Group; N: absolute number; NR: not reported; NS: not significant; NTX: crosslinked N-telopeptides of type I collagen; P1NP: serum type 1 procollagen N-terminal propeptide; PICP: procollagen type I C-peptide; RER: respiratory exchange ratio; SD: standard deviation; SE: standard error; SOS: speed of sound; TBTh: trabecular bone thickness; TBSp: trabecular bone spacing; VCO_2: CO_2 production; VO_2: O_2 consumption; US: ultrasound; VO_2max: maximal aerobic power; VE: ventilation.

Table 4
Qualitative assessment of the studies included using the PEDro scale

	1. Eligibility criteria	2. Random allocation	3. Concealed allocation	4. Baseline comparability	5. Blind subjects	6. Blind therapists	7. Blind assessors	8. Adequate follow-up	9. Intention-to-treat analysis	10. Between-group comparisons	11. Point estimates and variability	Total
Afshari et al. 2022	1	1	0	0	0	0	0	0	0	1	1	3
Arija-Blázquez et al. 2014	1	1	0	1	1	0	0	1	0	1	1	6
Ben et al. 2005	1	1	1	1	0	0	1	1	1	1	1	8
Chen et al. 2020	1	1	0	1	0	0	1	1	0	1	1	6
Edwards et al. 2018	1	1	1	1	1	1	0	1	0	1	1	8
Groah et al. 2010	0	1	0	1	0	0	1	0	0	1	1	5
Holman et al. 2020	1	1	0	1	0	0	0	1	1	1	1	6
Morse et al. 2019	1	1	0	0	1	0	0	0	0	1	0	3
Shackleton et al. 2022	0	1	0	1	0	0	0	1	0	1	1	5
Warden et al. 2001	1	1	0	1	1	0	1	0	0	1	1	6
Xu et al. 2020	1	1	0	1	0	0	0	1	0	1	1	5

Note: Eligibility criteria item does not contribute to total score. 0 = NO, 1 = YES. Scores from 9 to 10 are considered “excellent”, 6 to 8 are considered “good”, 4 to 5 are considered “fair”, and < 4 are considered “poor”.

tective role of muscle contraction on bone loss in these patients [31,32,35–38].

In accordance with the International Osteoporosis Foundation, non-pharmacological intervention should be considered the first-line therapy in osteoporosis management [56]. However, in patients with a higher risk of fracture, a pharmacological approach is necessary to increase BMD and reduce the risk of fractures [57,58]. In line with these findings, several studies included in the present review assessed the role of rehabilitation combined with both antiresorptive drugs (zoledronate [38]) and anabolic therapies (teriparatide [35] and testosterone [37]). The recent study by Dionyssiotis et al. [15] reported that level 1 supports intravenous zoledronic acid for preventing sublesional decline, while few studies are currently available about the effects of anabolic treatments for osteoporosis management in this specific population [15].

Lastly, a specific nutritional approach should be part of a comprehensive rehabilitation intervention, given the large consensus about the role of micronutrients in the management of bone health [57]. Despite this evidence, it was surprising to notice that just one study [35] assessed the effects of a combined intervention including rehabilitation and vitamin D + calcium supplementation in SCI patients. However, the most recent guidelines suggested a vitamin D supplementation targeting $>$ 40 ng/ml vitamin D serum levels in patients with SCI in order to optimize extraskeletal effects [15]. Therefore, further studies are needed to characterize the positive effects of rehabilitation combined with specific nutritional intervention in these patients, aiming at optimizing the synergic effects of non-pharmacological approaches targeting the multimodal bone metabolism modifications induced by SCI [4,8].

Interestingly, when consulting existing literature, previous reviews assessed the effects of rehabilitation interventions on bone health management of SCI patients. In particular, the review by Sutor et al. [10] assessed the effects of physical exercise and physical activity, providing interesting perspectives about the pathophysiology and molecular mechanisms underpinning physical activity positive effects on bone health of SCI patients. However, several studies with heterogenous designs were included and the authors did not apply a systematic approach. Similarly, the review by Chandrasekaran et al. [59] assessed the effects of FES in patients with SCI. Remarkably, the study highlighted the positive impact of FES in terms of muscle weight, muscle cross-sectional area, and physical functioning. However, the authors did not focus only on bone tissue modifications and the literature was assessed without a systematic approach.

Therefore, to the best of our knowledge, the present study is the first systematic review of RCTs assessing the effectiveness of different rehabilitation strategies to manage bone loss in SCI patients. Altogether, our data highlighted a large gap of knowledge about the potential role of rehabilitation interventions on bone health of SCI patients. On the other hand, a multitarget approach might further implement the synergisms between non-pharmacological and pharmacological interventions, with positive effects not only on bone health but also on functional outcomes of patients with SCI.

Despite these considerations, we are aware that this study has several limitations. In particular, the high heterogeneity of the study interventions limits to draw a quantitative synthesis of the study results. However, this is the first study addressing in a systematic way the effects of rehabilitation interventions on bone health management of SCI patients. In addition, this is the first systematic review assessing the effects of different rehabilitation modalities in this field, despite currently available literature does not allow to compare the effectiveness of different approaches. On the other hand, it should be noted that most of the studies included in the present systematic review showed some concerns in risk of bias assessment, highlighting the need for good quality studies assessing rehabilitation intervention in preventing bone loss of SCI patients.

Lastly, the etiology of SCI lesion, its level, and completeness might severely affect the rehabilitation outcomes, with potential sought of bias in the data synthesis. Therefore, further stratification might improve knowledge about the optimal therapeutic treatment tailored to patient's characteristics.

5. Conclusions

Altogether, findings of this systematic review underlined that several rehabilitation interventions have been studied to improve bone health in patients with SCI, with promising results reported for physical exercise combined with FES and vibrations. However, several questions are still open about the synergisms of different rehabilitation strategies and the role of a specific rehabilitation approach combined with pharmacological management should still be characterized. Further good-quality studies are needed to improve knowledge about the optimal rehabilitation approach in SCI, improving not only functional outcomes but also bone health of these frail patients.

Ethical approval

Not applicable.

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Informed consent

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

Conceptualization, L.L., A.d.S., and M.I.; methodology, L.L., A.d.S., and M.I.; investigation, L.L., A.F., and A.T.; writing – original draft preparation, L.L. and A.F.; writing – review and editing, A.d.S, and M.I.; figures, S.M.; visualization, C.C., S.M, and A.A.; supervision, A.d.S. and M.I. All authors have read and agreed to the published version of the manuscript.

Supplementary data

The supplementary files are available to download from http://dx.doi.org/10.3233//BMR-230006.

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