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REVIEW

Non-pharmacological treatment and prevention of bone loss after spinal cord injury: a systematic review

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Objective: Review the literature on non-pharmacological prevention and treatment of osteoporosis after spinal cord injury (SCI).

Methods: PubMed, EMBASE and the Cochrane Controlled Trials Register were searched. All identified papers were read by title, abstract and full-length article when relevant. Hand search of the articles' sources identified additional papers. For included studies, the level of evidence was determined.

Results: No studies conclusively showed an effective intervention. However, there are few randomized controlled trials (RCTs), and those that exist assess interventions and outcome measures that could be improved. Five studies on weight-bearing early post-injury are conflicting, but standing or walking may help retain bone mineral. In the chronic phase, there was no effect of weight bearing (12 studies). One study found that an early commencement of sports after SCI improved bone mineral, and the longer the period of athletic career, the higher the (leg) bone mineral. Early after SCI, there may be some effects of electrical stimulation (ES) (five studies). Chronic-phase ES studies vary (14 studies, including mixed periods after injury), but improvement is seen with longer period of training, or higher frequency or stimulus intensity. Improvements correspond to trabecular bone in the distal femur or proximal tibia. Impact vibration and pulsed electromagnetic fields may have some positive effects, whereas pulsed ultrasound does not. Six studies on the influence of spasticity show inconsistent results.

Conclusions: Bone mineral should be measured around the knee; the length and intensity of the treatment should be sufficiently long and high, respectively, and should commence early after SCI. If bone mineral is to remain, the stimulation has to be possibly continued for long term. In addition, RCTs are necessary.

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Introduction

Significant osteoporosis develops, in particular, in the long bones of the lower extremities in the first months and years after spinal cord injury (SCI),[1–3] and may well continue years after SCI, with trabecular bone after a log curve levelling off from 1 to 3 years after SCI, whereas the cortical bone sites appear to decrease progressively beyond 10 years after SCI.[4]

Factors leading to more bone loss include the level of injury (tetraplegics more than paraplegics), complete lesions and longer duration after injury. Aging may also be a contributing factor.[3–6]

The sublesional bone loss means an increased risk of fragility fractures, in particular in the distal femur and the proximal tibia.[7,8] Unfortunately, criteria for assessing fracture risk in the SCI population are lacking.[4,9]

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In contrast to the long bones in the lower extremities, there is no obvious loss of bone in the lumbar spine, which may be because of the weight-bearing function, although degenerative changes may influence the high values found.[3]

There have been recent reviews on bone loss and osteoporosis in individuals after SCI.[3,9–12] The present systematic review will concentrate on the evidence related to the treatment and prevention possibilities with non-pharmacological-related interventions.

Methods

For identification of articles for the review, PubMed and EMBASE were searched with no language restrictions using the following words: osteoporos*/osteopen*/bone mineral/bmc/bmd and spinal cord inj*/spinal cord lesion*/spinal cord dis*/parapleg*/tetrapleg*/quadripleg*. Searches were performed in the Cochrane Controlled Trials Register using osteoporosis/bone mineral and spinal. The PEDro database

was hand searched under the key words: Osteoporosis and Spinal Cord Injury.

All identified papers were initially read by title, and, if relevant, by abstract. When abstracts indicated results within the purpose of the review, the full-length articles were found and reviewed.

In addition, a hand search from the other articles' sources identified additional papers that could be included.

To determine the level of evidence, the studies were judged according to the five levels used in SCIRE (Spinal Cord Injury Rehabilitation Evidence)[13] (Box 1)

Two of the authors (FB-S and BH) independently evaluated all studies, and those that were judged differently were discussed for possible agreement. If the first two authors were still in conflict, a third author (BL) evaluated the same paper independently to adjudicate a final decision.

Box 1 Levels of evidence—SCIRE[13]

Level 1	Randomized controlled trial (RCT) (PEDro score >6) Includes within-subjects comparison
Level 2	RCT (PEDro score <6); prospective controlled trial (not randomized); Cohort (prospective longitudinal study using at least two similar groups with one exposed to a particular condition)
Level 3	Case control (retrospective study comparing conditions, including historical controls)
Level 4	Pre–post (prospective trial with a baseline measure, intervention and post-test using a single group of subjects); post-test (prospective with two or more groups, intervention and then post-test using a single group of subjects); case series (retrospective study collecting variables, for example, from chart review)
Level 5	Observational (cross-sectional analysis to interpret relations); clinical consensus; case report (involving one case)

Abbreviation: SCRIE, Spinal Cord Injury Rehabilitation Evidence.

Table 1 The effect of weight bearing by standing and walking on bone in individuals with SCI within the first year of injury

Author (year)	*Level of evidence*	*Population*	*Design*	*Intervention*	*Measurements*	*Results*
De Bruin (1999)[14]	2	13 males; 21–53 years; C4-T12; AIS A–D Weight bearing 1–4 weeks after injury	Controlled single-case, experimental, multiple baseline. Random allocation. Randomization method not described	Weight bearing by standing and treadmill walking, 1/2→ $\geqslant$1 h day^{-1} 5 $\times$/week for half year. Monitored over 25 weeks (1) Immobilization: 0–5 h/week loading exercises ($n=4$); (2) Standing exercises: $\geqslant$5 h/week ($n=5$); (3) Combined standing and walking exercises: $\geqslant$5 h/week ($n=4$)	BMD by pQCT of the tibia 5 and 25 weeks after injury Flexural wave propagation velocity with a biomechanical testing method	Decrease in trabecular bone with non-intervention, early mobilization gave no or insignificant loss of trabecular bone. No difference between Groups 2 and 3
Frey-Rindova (2000)[15]	4	24 males; 19–59 years; traumatic SCI C4-L1; Frankel A-C Weight bearing 1–4 weeks after injury	Prospective repeated measure	Standing/walking at least 30 min 3 times/week No intervention (because of motivational or health problems): 8. Intervention: 16	BMD by pQCT of the tibia 1, 6, 12 months after SCI	Standing/walking program did not significantly influence the BMD loss
Ben (2005)[16]	1	20 (4 females); 34 years (s.d. $=15$); 4 months (s.d. $=2$) after injury; $<2/5$ strength in the lower limbs (100 screened)	Assessor blinded within-subject contralateral limb randomized controlled trial	40 legs Weight bearing through one leg on a tilt table for 30 min 3 $\times$/week for 12 weeks	BMD by DXA of the proximal femur	No effect on femoral BMD
Giangregorio (2005)[17]	4	5 traumatic C3-C8, AIS B-C, within 2–6 months of injury	Prospective case series	48 sessions: twice weekly BWSTT for 6–8 months	BMD by DXA of the lumbar spine, proximal femora, proximal tibia	BWSTT did not prevent bone loss
Alekna (2008)[18]	2	54 (10 females, 44 males) traumatic AIS A-B; C2-L1; 21 tetraplegic, 33 paraplegic; female age 37.3 $\pm$ 10.0 years; male age 33.4 $\pm$ 12.0 years	Prospective matched pairs	27 gender, age and height matched in each group: Standing group (standing $\geqslant$1 h/day $\geqslant$5 days/week) Non-standing (not standing at all)	BMD by DXA of arms, legs, pelvis and L2-L4. 6–16 weeks, 12 and 24 months after injury	Standing group: significant higher BMD in legs ($P=0.0004$) and pelvis ($P=0.014$) after 2 years

Abbreviations: AIS, American Spinal Injury Association (ASIA) Impairment Scale; BMD, bone mineral density; BWSTT, body weight-supported treadmill training; DXA, dual-energy X-ray absorptiometry; pQCT, peripheral quantitative computed tomography; SCI, spinal cord injury.

Table 2 The effect of weight bearing by standing and walking on bone in individuals with SCI more than a year after injury

Author (year)	*Level of evidence*	*Population*	*Design*	*Intervention*	*Measurements*	*Results*
Biering-Sørensen (1988)[19]	5	16 with paralegia; 16 years and older at SCI; 2–25 years after SCI	Cross-sectional Descriptive	Long leg braces: minimum 1 h daily: 5; Not using long leg braces: 11	BMC by DPA of the lumbar spine, femoral neck and shaft, and proximal tibia	No effect of the use of long leg braces
Saltzstein (1992)[20]	5	20 complete SCI; ~20 years after injury; 7 incomplete SCI; ~10 years after injury; 15 able-bodied controls. All males; age 42 ± 13 years	Cross-sectional Descriptive	Mobility index from 1. Complete paralysis to 9. Able bodied—unlimited ambulation: (1) 7 incomplete SCI; (2) 20 complete SCI; and (3) 15 able-bodied controls	BMD by single-photon absorptiometry of distal tibia	BMD was positively correlated with mobility index scores ($P<0.01$). Difficult to understand (Figure 2[20]) and the correlation, as 20 should be mobility index 1, and 15 index score 9?
Kunkel (1993)[21]	4	6 C5-T12 males; 36–65 years; 4 SCI for 10–28 years, 2 multiple sclerosis	Pre–post trial	Standing frame: 10→30 min 3 × /day, changed to 45 min 2 × /day for 5 months	BMD by DPA of the lumbar spine and femoral neck	No effect
Ogilvie (1993)[22]	4	4 (2 females) paraplegic, 16–42 years. Wheelchair for at least 1 year	Pre–post trial	Reciprocating gait orthosis for 24–30 months	BMD by a quantitative CT of the lumbar spine and femoral neck	3 of 4 increased or maintained femoral neck BMD
Goemaere (1994)[23]	5	53 with complete traumatic paraplegia for at least 1 year	Cross-sectional Descriptive	None—15 did not and 38 did regularly perform passive weight bearing: long leg braces: 20; standing frame: 9; standing wheelchair: 9	BMD by DXA of the lumbar spine, hip and the femoral shaft	Femoral shaft higher BMD ($P=0.009$) in the standing group
Thoumie (1995)[24]	4	7 (1 female) T2-T10; 26–33 years; SCI 15–60 months	Pre–post trial	Gait rehabilitation program with reciprocating gait hybrid orthoses (RGO-II). Training program with 2 h sessions 3 × /week (14–18 months)	BMD by DPA of the lumbar spine and femoral neck	No gain in BMD
Needham-Shropshire (1997)[25]	4	16 (3 females), T4-T11 complete SCI. Mean age 28.8 years, mean 3.8 years after injury	Pre–post trial	32 sessions, approximately 12 weeks, using Parastep1 ambulation system	BMD by DPA of the femoral neck, head and Ward's triangle	No change in BMD using repeated measures analyses of variance
Frey-Rindova (2000)[15]	4	24 males, traumatic C4-L1, Frankel A-C; 19–59 years, weight bearing 1–4 weeks after injury	Prospective repeated measure	Standing/walking at least 30 min 3 times/ week: No (due to motivational or health problems): 8, Yes: 16	BMD by pQCT of tibia for 1, 6, 12 months after SCI	Standing/walking did not significantly influence the BMD loss
Dauty (2000)[26]	5	31 males; 22 AIS A, 4 AIS B, 3 AIS C, 2 AIS D; 36 ± 12.3 years (range 18–60); more than 1 year after injury	Cross-sectional Descriptive	Duration of daily verticalization: (1) <1 h/day; (2) 1 h/day; and (3) >1 h/day Long leg braces used by six individuals	BMD/BMC by DPA the of lumbar spine, femoral neck, distal femur and proximal tibia	No significant difference between groups No correlation between use of long leg braces and BMC of the lower limb
Sabo (2001)[27]	5	46 C4-T12 males; 24 cervical, 22 thoracic lesions; 33 Frankel A, 13 Frankel B, C, D; 32.0 ± 10.7 years (mean ± s.e.m.); 8 years after injury (1–26 years)	Cross-sectional Descriptive	7 in ambulatory group, that is, household or community walker 39 non-ambulatory group, that is, wheelchair or therapeutic standing only	BMD by DXA of the proximal femur, lumbar spine and distal forearm	Ambulatory status had no significant influence on BMD

Table 2 Continued

Author (year)	*Level of evidence*	*Population*	*Design*	*Intervention*	*Measurements*	*Results*
Eser (2005)[28]	5	54 (5 females) C5-L3 AIS A and B; 24–72 years; 5–48 years after injury; 6 acquired SCI before the age of 18 years	Cross-sectional Descriptive	Divided into: (1) no standing; (2) passive standing $\leqslant 2$ h/week; (3) passive standing >2 h/week; and (4) passive standing >1 h/day	BMD by pQCT of the radius, femur and tibia	No relation to bone status
Giangregorio (2006)[11]	4	13 (2 females) C4-T12 AIS B-C; age 20–53 years; 1.2–24 years after injury	Pre–post trial	12 months BWSTT: 3 times/week for 144 sessions	BMD by DXA of the spine, proximal and distal femur, and proximal tibia	No significant changes in BMD or bone geometry at any site. Whole-body BMD decreased
Goktepe (2008)[29]	5	71 (11 females); 64 traumatic, 7 non-traumatic; 56 paraplegia, 15 tetraplegia, AIS A-B. 18–46 years; at least 1 year after injury	Cross-sectional	(1) Standing $\geqslant 1$ h/day (2) Standing <1 h/day (3) Non-standing	BMD by DXA of L2-L4, hips, trochanters, Wards's triangles and femoral necks	No difference between groups on any site

Abbreviations: AIS, American Spinal Injury Association (ASIA) Impairment Scale; BMC, bone mineral content; BMD, bone mineral density; BWSTT, body weight-supported treadmill training; CT, computer tomography; DPA, dual-energy photon absorptiometry; DXA, dual-energy X-ray absorptiometry; pQCT, peripheral quantitative computed tomography; SCI, spinal cord injury.

Table 3 The effect of exercise on bone in individuals with SCI

Author (year)	*Level of evidence*	*Population*	*Design*	*Intervention*	*Measurements*	*Results*
Jones (2002)[30]	5	17 C4-L3 Frankel A-C males, 7–372 months after injury, 32 ± 8 years and 17, weight- and height-matched able-bodied males	Cross-sectional descriptive comparing active with SCI and able-bodied	SCI males: 442 ± 225 min/week physical activity Able-bodied: 367 ± 167 min/week physical activity	BMD, BMC by DXA of total body, hip and leg	BMD/BMC lower in the SCI group ($P=0.0001$). Lumbar and arm no difference
Goktepe (2004)[31]	5	34 AIS A-C males mean age 28.5 years, 6.2 years after injury	Cross-sectional descriptive comparing elite basketball players and sedentary persons with SCI	17 paraplegic basketball players 17 sedentary paraplegic persons	BMD by DXA of the distal radius of the dominant arm, lumbar, trochanters, Ward's triangle and femoral neck	No difference between groups except distal radial BMD higher in basketball players ($P=0.01$)
Miyahara (2008)[32]	5	28 paraplegic; 34.7 ± 9.3 years; 14.6 ± 8.4 years after injury	Cross-sectional descriptive	Wheelchair athletes	BMD by DXA of the entire body, both arms and legs, and body trunk	The earlier the athlete restarted sports after injury, the higher the BMD of legs ($P=0.019$), body trunk ($P=0.018$) and the entire body ($P=0.011$). The period of athletic career after restating was significantly related with leg BMD ($P=0.022$)

Abbreviations: AIS, American Spinal Injury Association (ASIA) Impairment Scale; BMC, bone mineral content; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; SCI, spinal cord injury.

Results and discussion

The Pedro Search identified nine articles for individual review (including review articles for bibliographic searching), whereas the EMBASE review revealed 415 references and the Medline revealed 349 references for abstract review. A total of 45 studies were explored in detail (Tables 1–7). Seventeen studies analyzed the effect of weight

Table 4 The effect of electrical stimulation on bone in individuals with SCI early after injury

Author (year)	*Level of evidence*	*Population*	*Design*	*Intervention*	*Measurements*	*Results*
Eser (2003)[33]	2	38—19 in each group comparable regarding age, and lesion level: C5-T12, AIS A-B; 2 females in each group; 20–60 years; 1–3 months after injury	Self-selection for intervention or control Pre–Post trial	Intervention: Up to 30 min FES cycling 3 days/week; +2 days/ week 30 min passive standing Control: 5 days/week 30 min passive standing For the period of their primary rehabilitation (mean 6 months)	BMD by CT of the right tibia diaphysis	No significant effect
Shields (2006)[34]	2	7 C5-T10 AIS A males; 21–43 years; within first 6 weeks of injury	Within-subject, contralateral limb control Pre–Post trial	Training 1.9–3.1 years with 83% compliance: unilateral tibial nerve electrical stimulation for plantar flexion. 4 bouts of 125 contractions/day, 5 days/week	BMD by pQCT of the distal tibia (only 4 males)	BMD was higher in the trained limb than in the untrained limb ($P<0.05$)
Shields (2006)[35]	2	6 C5-T10 AIS A; age at SCI 21–43 years; 0.16–0.35 years after injury	Repeated measures, within-subject contralateral limb control	Training 1.7–3 years with compliance 70.9–93.9%: Unilateral electrical stimulation of plantar flexor muscles. 4 bouts of 120 contractions/day, 5 days/week	BMD by DXA of the spine, hips and knees	Decline in tibia BMD in the trained less than in untrained ($P<0.05$)
Clark (2007)[36]	2	33 AIS A-D: FES group 23 C4-Th10; age 29 ± 9 years; 10 lost for 6 months follow-up. Controls 10 C5-Th12; 31 ± 11 years; 3 lost for 6 months follow-up	Controlled repeat measures study	Two weeks preconditioning. FES to quadriceps femoris and anterior tibial muscles $2 \times$ 15 min FES/leg, 5 days/week for 5 months	BMD by DXA of the total body, spine and hip within 3 weeks, 6 weeks 3 and 6 months after injury	Three months after injury, the FES group had higher total body BMD ($P<0.01$), but not thereafter and not for the hip or spine
Dudley-Javoroski (2008)[37]	5	One T4 AIS: A male 21 years, 7 weeks after injury	Single-case prospective, within-subject, contralateral limb control (randomized)	Unilateral soleus muscle electrical stimulation over 4.8 years home-based training 30 min/day, 5 days/week	BMD by pQCT of the distal tibia every 6 months	BMD of the untrained tibia declined ~14% per year, and 7% in the trained tibia. BMD preferentially preserved in the posterior half of the tibia with annual decline of 2.6%

Abbreviations: AIS, American Spinal Injury Association (ASIA) Impairment Scale; BMC, bone mineral content; BMD, bone mineral density; C, complete spinal cord lesion; DXA, dual-energy X-ray absorptiometry; FES, functional electrical stimulation; IC, incomplete spinal cord lesion; pQCT, peripheral computed tomography; SCI, spinal cord injury.

bearing by standing and walking, of which five included data from the first year after injury. Three studies looked at the effect of exercise, 19 studies analyzed electrical stimulation, 3 looked at other physical interventions and 6 studies made some reference to the effect of spasticity/spasms. Two studies only showed adequate randomization, allocation concealment and blinding (PEDro score $\geqslant 6$).[16,54] Both studies showed no effect, used a within-subjects study design and dual-energy X-ray absorptiometry but analyzed different outcome measures. Ben *et al*.[16] used bone mineral density (BMD) at the proximal femur and Warden *et al*.[54] used bone mineral content (BMC) at the heel. The intervention group for Ben *et al*.[16] (Table 1) was standing weight bearing on one leg on a tilt table for 30 min, thrice weekly for 12 weeks, whereas Warden *et al*.[54] (Table 6) carried out a low-intensity pulsed ultrasound on one heel for 20 min day^{-1}, 5 days/week over 6 weeks. None of these considered bone changes around the knee, where the majority of bone loss occurs after SCI.

The effect of weight bearing by standing and walking

The studies on weight bearing from the early period (within the first year) after SCI (Table 1) are conflicting. The single level 1 study by Ben *et al*.[16] showed that early-period weight bearing did not increase BMD; however, the therapy period was relatively short and only involved simple static weight bearing compared with the other two studies showing positive results within this group. In addition, BMD was

Table 5 The effect of electrical stimulation on bone in individuals with SCI longer time after injury or including mixed periods after injury

Author (year)	*Level of evidence*	*Population*	*Design*	*Intervention*	*Measurements*	*Results*
Pacy (1988)[38]	4	4 T4–6 males, 20–35 years, 1–8 years after injury	Pre–Post trial	Quadriceps muscle stimulated: (1) leg raising against graded load—5 × /week, 10 weeks; (2) cycling on modified bicycle ergometer—32 weeks	BMC by DPA of the lumbar spine and right femur	No changes in BMC or bone density
Kiratli (1990)[39]	4	6 SCI >2 years—25 years after injury	Pre–Post trial	FES to the quadriceps femoris muscle 50–60 min, 3 times/week for 8 months	BMD by DPA of the lumbar spine and proximal femur	No change
Leeds (1990)[40]	4	6 C4–6 males, 18–27 years, 2–9 years after injury. 2 paraplegic and 1 tetraplegic males, 24–31 years, trained for 3 years	Pre–Post trial	FES conditioning 1 month. Up to 30 mins FES cycle ergometry, 3 × /week for 6 months Extra three males exercised for 3 years	BMD by DPA of Ward's triangle, trochanter, femoral neck and proximal femur	No increase in BMD
Rodgers (1991)[41]	4	12 (3 females) C4-T10 SCI, 5 C and 7 IC; 19–63 years; 0.7–17 years after injury	Pre–Post trial	Quadriceps stimulation for knee extension progressive resistance exercise training up to 3 × /week for 36 sessions	BMD method or details not described	No significant change in BMD
Sloan (1994)[42]	4	C7, IC female, 40 years, 8 months after injury C6, IC male, 55 years, 4.5 years after injury	Pre–Post trial	Up to 30 min FES cycling 3 × /week. The female trained for 1 year, the male for 6 months	BMD by DXA of the lumbar spine, trochanter, Ward's triangle and femoral neck	No restoration of BMD
Hangartner (1994)[43]	4	15 C5-T10, 17–46 years, 0.3–15.4 years after injury	Pre–Post trial	Three did FES-induced knee extension resistance exercise only; 9 did FES cycling only; 3 did both. They did 1–5 exercise periods of 36 sessions, median of 14.5 weeks	BMD by special isotope-based CT of tibia	Rate of bone loss for the FES exercise group less than expected from the regression line
BeDell (1996)[44]	4	12 C5-T12, AIS A males, 23–46 years, 2–19 years after injury	Pre–Post trial	(1) Quadriceps strengthening, (2) up to 30 min FES cycling, (3a) FES cycling for 30 min, 68 ± 14 sessions; (3b) 8 continued combination of upper and lower extremity FES cycling for 37 ± 15 extra sessions	BMD by DXA of the lumbar spine, trochanters, Ward's triangle and femoral neck	No significant increase in femoral BMD
Bloomfield (1996)[45]	4	9 C5-T7 Frankel A-B, 21–39 years, 3–12 years after injury	Pre–Post trial	9 months FES cycling: 4 participants trained at ⩾18 W (Watts) for at least 3 months	BMD by DXA of the femoral neck, distal femur and proximal tibia	No significant change for the whole group. For those trained at ⩾18 weeks for at least 3 months increase in BMD at 18% in the distal femur
Mohr (1997)[46]	4	10 C6-T4 SCI, 27–45 years, 2–24 years after injury	Pre–Post trial	30 min FES cycling: (1) 3 × /week for 12 months; (2) 1 × /week for 6 months	BMD by DXA of the lumbar spine, femoral neck and proximal tiba	After 12 months, BMD in the proximal tibia increased 10% ($P<0.05$). After 18 months, returned to the original level

Table 5 Continued

Author (year)	*Level of evidence*	*Population*	*Design*	*Intervention*	*Measurements*	*Results*
Bélanger (2000)[47]	2	14 (3 females) C5-T5, Frankel A-C, 2 IC and 12 C; 23–42 years; 1.2–23 years after injury	Controlled within-subject, contralateral limb Pre–Post trial	1 h/day, 5 days/week, for 24 weeks: left quadriceps stimulated to contraction against isokinetic load (resisted) vs right quadriceps contracted against gravity (unresisted)	BMD by DXA of the distal femur, proximal tibia and mid-tibia	Distal femur and proximal tibia nearly 30% recovery of the lost bone ($P<0.05$). No difference between resisted or unresisted training
Chen (2005)[48]	4	15 C5-T8 complete motor SCI males, 23–37 years; 3–16 years after injury	Pre–Post trial	30 min FES cycling 5 times/day for 6 months, followed by 6 months without intervention	BMD by DXA of the lumbar spine, femoral neck, distal femur, proximal tibia and calcaneus	BMD of the distal femur, proximal tibia increased ($P<0.05$), but decreased significantly without intervention ($P<0.05$)
Cavalho (2006)[49]	2	21 C4–8 AIS A-B males; age 31.95 ± 8.01 years; 25–180 months after injury	Controlled pre–post trial	Gait group: 11 AIS A electrically stimulated treadmill gait with 30–50% body weight support for 20 min, 2 times/week for 6 months Control group: 10 AIS B no gait training	BMD by DXA of the lumbar spine, proximal femur and total femur	Differences between before and after or between groups not calculated, but is insignificant
Shields (2007)[50]	2	4 T1-T7 AIS A males; 37–68 years; 2–12 years post injury	Pre–Post trial, within subject, contralateral limb control	Trained soleus muscle using an isometric plantar flexion electrical stimulation 30 min/day, 5 days/week for 6–11 months. Untrained limb control	BMD by DXA of proximal tibia	BMD for proximal tibia did not differ before and after training
Frotzler (2008)[51]	4	11 (2 females) traumatic T3–9 AIS A; 41.9 ± 7.5 years; 11.0 ± 7.1 years after injury	Pre–Post trial	Preconditioning until FES cycling for 10 min without resistance. FES to gluteal, quadriceps and hamstring muscles. 3 months FES-cycling for upto 1 h/day. 9 months FES-cycling for 1 h/day	BMD by pQCT bilaterally in the femur and tibia before conditioning, after 6 and 12 months of FES cycling	After 12 months, trabecular and total BMD and cross sectional area in the distal femoral epiphysis increased significantly

Abbreviations: AIS, American Spinal Injury Association (ASIA) Impairment Scale; BMC, bone mineral content; BMD, bone mineral density; C, complete spinal cord lesion; CT, computer tomography; DXA, dual-energy X-ray absorptiometry; FES, functional electrical stimulation; IC, incomplete spinal cord lesion; pQCT, peripheral computed tomography; SCI, spinal cord injury.

measured at the proximal femur only. The study by De Bruin *et al*.[14] indicates that early mobilization led to no or insignificant loss of trabecular bone, whereas the immobilized individuals showed a marked decrease when monitored for 25 weeks. In addition, the recent prospective study by Alekna *et al*.[18] found that standing, particularly after 2 years, gave significantly higher BMD in legs, pelvis and the total body. The long follow-up carried out in this study is unique. The other studies in Table 1 were of shorter duration and/or less weight-bearing stimulation.

For the chronic phase (Table 2), the picture seems more uniform, with very little evidence for any gain in BMD when the first year after injury has passed. All these studies were of evidence levels 4 and 5.

The ineffectiveness of shorter term (<3 months), less-aggressive early intervention therapy and the overall ineffectiveness of the chronic-phase studies raise the hypothesis that if a weight-bearing intervention is to be considered, it should be more aggressive and should intervene in the early period after injury if a treatment effect is to be found.

The effect of exercise

The quality of evidence available for evaluation is poor. The most interesting study in this group with only three investigations of level 5 evidence (Table 3) is by Miyahara *et al*.[32] They found that the earlier the athlete started sports after injury, the higher the BMD of the legs, body trunk and the entire body. Further, a longer period of athletic career after restarting was significantly related to higher leg BMD. This result is encouraging, and supports the hypothesis of early intervention after injury (suggested in the weight-

Table 6 The effect of other physical interventions on bone in individuals with SCI

Author (year)	*Level of evidence*	*Population*	*Design*	*Intervention*	*Measurements*	*Results*
Petrofsky (1984)[52]	4	2 SCI individuals, no further description	Before and after trial. Case studies	Impact vibration (force of 3 Gz, frequency 15 Hz) 1 h for 3 days/week for 3 months	CT scans were used to quantify the density of leg bones	53.5% increase in BMD of the proximal tibia
Garland (1999)[53]	2	6 complete SCI males, 2 tetraplegic and 4 paraplegic; 20–39 years; 3–17 years after injury	Repeated-measures, within-subject contralateral limb control	On one knee stimulated with pulsed electromagnetic fields for minimum of 8 h/day for 6 months. The opposite knee control	BMD by DXA of the knees initial, after 3, 6 and 12 months	At 3 months, BMD increased in the stimulated knee ($P<0.05$) and declined in the control knee. By 6 months, BMD returned to near baseline values, and at 12 months, both knees had lost bone at similar rate. Larger effect closer to the stimulation
Warden (2001)[54]	1	15 C5-T10, AIS A-B, 17–40 years; 46–153 days post injury	Double–blinded, within-subject randomized controlled trial with contralateral limb placebo treated	Low-intensity pulsed ultrasound on one heel 20 min/day, 5 days/week over 6 weeks. The other heel placebo treated	Calcaneal BMC by DXA	No difference between active and inactive treatment

Abbreviations: AIS, American Spinal Injury Association (ASIA) Impairment Scale; BMC, bone mineral content; BMD, bone mineral density; CT, computer tomography; DXA, dual-energy X-ray absorptiometry; SCI, spinal cord injury.

Table 7 The influence of spasticity/spasms on bone in individuals with SCI

Author (year)	*Level of evidence*	*Population*	*Design*	*Spasticity*	*Measurements*	*Results*
Biering-Sørensen (1988)[19]	5	16 thoracic and lumbar SCI for 2–25 years, acquired at the age of $\geqslant$16 years	Cross-sectional Descriptive	6 with spasticity 10 without spasticity	BMC by DPA of the lumbar spine, femoral neck and shaft, and proximal tibia	No effect of spasticity
Wilmet (1995)[55]	4	31 (7 females) traumatic T2-L3; mean age 32.5 years (17.5–65.5); within 8 weeks of injury	Prospective	11 spastic; 12 flaccid	BMC by DXA of the regional and total body 10, 20, 30, 40 and 50 weeks after injury, with 26 of 2 measurements at each time point	BMC of the paralysed areas varies in a very similar way in the lower limbs of spastic and flaccid patients
Demirel (1998)[56]	5	41 (9 females) 5 C4-5, 6 T1-6, 20 T7-12, 10 L1-3; 19–49 years; 2–30 months after injury	Cross-sectional Descriptive	Spasticity assessed on the Ashworth Peterson scale (0–4); 35 were spastic: 13, grade 1; 14, grade 2; 4, grade 3; 4, grade 4; and 6, had no spasticity (numbers and percentages do not match)	BMD by DXA of the whole body using arms and legs	Those with spasticity had higher BMD when compared with flaccid individuals ($P<0.05$)
Frey-Rindova (2000)[15]	4	24 males, traumatic SCI C4-L1 Frankel A-C completed the study	Prospective repeated measures	Spasticity assessed on the Ashworth Peterson scale (0–4). 5: grade 1; 11: grade 2; 8: grade 3	BMD by pQCT of the tibia 1, 6, 12 months after SCI	Spasticity assessed by the Ashworth scale did not significantly influence the BMD loss

Table 7 Continued

Author (year)	*Level of evidence*	*Population*	*Design*	*Spasticity*	*Measurements*	*Results*
Eser (2005)[28]	5	54 (5 females) traumatic C5-L3 AIS A and B; 24–72 years; 5–48 years after injury; 6 acquired SCI before 18 years	Cross-sectional Descriptive	Spasticity assessed with the Ashworth scale for knee flexion/extension, hip abduction/ adduction/flexion/ extension summed for each leg. 48 spastic; 6 flaccid	BMD by pQCT of the radius, femur and tibia	Spasticity measurement vs pQCT of femur: total BMD ($P=0.008$), trabecular BMD of distal epiphysis ($P=0.014$), and the cortical thickness of shaft ($P=0.003$). Spasticity was not found to increase bone mass of the lower leg
Shojaei (2006)[57]	5	132 male veterans with complete paralysis; 12.9% cervical, 78% thoracic, 9.1% lumbar; 25–51 years; 5–23 years after injury	Cross-sectional Descriptive	37.1% severe spasticity 40.1% had mild-to-moderate spasticity 22.7% had no experience of spasticity Assessment method not specified	BMD by DXA of the L4 and neck of right femur	No statistically significant relation between BMD and spasticity

Abbreviations: AIS, American Spinal Injury Association (ASIA) Impairment Scale; BMC, bone mineral content; BMD, bone mineral density; DPA, dual-energy photon absorptiometry; DXA dual-energy X-ray absorptiometry; pQCT, peripheral computed tomography; SCI, spinal cord injury.

bearing analysis) if a treatment effect is to be found in future studies.

The effect of electrical stimulation

Of the four level 2 studies performed early after SCI (Table 4), three showed that there may be some effect of electrical stimulation with stimulation of 5 days/week. The single-case long-time prospective investigation by Dudley-Javoroski and Shields[37] additionally suggests the importance of where the muscles stress the bone. This further emphasizes the value of specific methods for BMD measurement, that is in most studies, the dual-energy X-ray absorptiometry[35,36,42,44–50] is used as it is considered to be the 'gold standard,' but peripheral quantitative computed tomography has the advantage of being able to differentiate the cortical from the trabecular bone, and assess both bone geometry and volumetric density.[14,15,37,51] A quantitative ultrasound has also been used, but probably is still not suitable to monitor the effect of intervention on BMD,[58] whereas magnetic resonance imaging also seems to have a potential in future studies in assessing bone geometry.[59]

For the chronic phase (Table 5), the studies are conflicting, but those investigations that show improvement seem to be those with a longer period of training, that is 12 months,[46] or higher frequency, that is 5 times/week[47,48] or stimulus intensity.[45] It is also evident that all these studies measured their improvement corresponding to the trabecular bone, in particular in the distal femur or the proximal tibia. The challenge may be to provide sufficient mechanical stimulus without increasing the risk of fracture.[12,60]

It is also observed that the positive effect of electrical stimulation on the bone mass only remains if the stimulation is continued and in sufficient amounts.[46,48] Therefore, the recommendation following the experience gained from the studies is that the electrical stimulation should be at least 2–3 times per week, and probably has to be continued for the long term if the bone mass is not to decline further.

The effect of other non-pharmacological interventions

Table 6 shows that the only randomized study by Warden *et al*.[54] did not indicate any benefit from low-intensity pulsed ultrasound. Potentially, both impact vibration[52] and pulsed electromagnetic fields[53] showed positive results, but the studies are of poor quality. These results could support the hypothesis that a more dynamic loading may be necessary to elicit a detectable treatment effect.

The influence of spasticity/spasms

The studies evaluating the possible influence of spasticity (Table 7) show inconsistent results. Demirel *et al*.[56] found that those with spasticity had higher BMD when compared with flaccid individuals, and Eser *et al*.[28] showed a significant correlation between the degree of spasticity measured with the modified Ashworth scale and BMD.

The available studies are generally of a low level of evidence, and do not support the hypothesis that spasticity maintains bone mineral in individuals with SCI.

Concluding remarks

The level of evidence is important and in this study area, there is no conclusive indication of any effective interven-

tion. This review illustrates that there are issues important in the design of future clinical trials in this area. This includes where the BMD is measured (which is most relevant to be performed around the knee), and the length and intensity of the non-pharmacological intervention carried out. It is important to be aware that the stimulation used has to be maintained if the positive effect on BMD is to remain.

It has to be acknowledged that longitudinal randomized controlled investigations over very long periods on osteoporosis in individuals with SCI are difficult to carry through because of the relatively small number of persons with SCI available for the studies and a potentially high drop out rate over a long follow-up period. At the same time, adequate matching by gender, age, level and completeness of lesion, and time after injury is a challenge to the potential number of individuals recruited.[4] Unfortunately, if the hypothesis regarding aggressive, high-intensity therapies is true, the ability to practically design and perform within patient evaluations to reduce sample size requirements as conducted by Ben *et al*.[16] and Warden *et al*.[54] becomes more challenging.

The detection of an effective clinical intervention in this study area will require rigorous minimization of bias through a randomized controlled clinical trial design and likely require the involvement of multiple centers. It will also be dependent on appropriate measurement, with adequate intensity and duration of the intervention to detect a treatment effect. Any prospective intervention is likely to benefit from early timing after acute SCI.

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