MSBEST

MULTIPLE SCLEROSIS BEST EVIDENCE-BASED STRATEGIES AND TREATMENT/THERAPIES FOR REHABILITATION

Bone Health

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Key Points

- Fingolimod may prevent declines in bone mass in persons with MS.
- It is unclear if interferon beta improves bone mineral density in persons with MS, but it may induce changes in proteins related to bone homeostasis.
- A physical activity behavioural intervention may result in improved bone mineral density and bone mineral content in persons with MS.
- Vitamin D deficiency or insufficiency are common in the MS population. Supplementation with vitamin D3 increases serum levels of vitamin D; however, the effects of vitamin D supplementation on fracture risk are not known.
- Evidence for bone strengthening treatments specifically for the MS population is unavailable. Cautious extrapolation from other clinical populations is currently standard practice in most MS clinical care settings.

Patsakos EM, Mirkowski M, Bruno T, Craven BC, on behalf of the MSBEST Team. (2019). Bone Health. *Multiple Sclerosis Best Evidence-Based Strategies and Treatment/Therapies for Rehabilitation*. Version 1.0: p 1-16.

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Abbreviations

25(OH)D	25-hydroxyvitamin-D
BAP	Bone-Specific Alkaline Phosphatase
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BTM	Bone Turnover Markers
CTX1	C-Terminal Cross-Linking Telopeptide of Type 1 Collagen
DXA	Dual-Energy X-Ray Absorptiometry
EDSS	Expanded Disability Status Scale
FRAX	Fracture Risk Assessment Tool
HDE	High Dose Ergocalciferol
IFN-α	Interferon Alpha
IFN-β	Interferon Beta
IMT	Immunomodulatory Therapy
LDC	Low Dose Cholecalciferol
MS	Multiple Sclerosis
N-TX	Type 1 Collagen Cross-Linked N-telopeptide
NICE	National Institute for Health and Care Excellence
OPG	Osteoprotegerin
P1NP	Procollagen Type 1 Amino-Terminal Propeptide
PDDS	Patient Determined Disease Steps
PEDro	Physiotherapy Database Evidence
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
PTH	Parathyroid Hormone
PwMS	Persons with Multiple Sclerosis
RANK	Receptor Activator of Nuclear Factor-kB
RANKL	Receptor Activator of Nuclear Factor-kB Ligand
RCT	Randomized Controlled Trial
RRMS	Relapsing-Remitting Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
TRACP	Tartrate-Resistant Acid Phosphatase
UVB	Ultraviolet B
VDR	Vitamin D Receptor

Bone Health

1.0 Introduction

Osteoporosis is more common in persons with multiple sclerosis (PwMS) than in healthy controls and is a known risk factor for fragility fracture and increased mortality (Herndon & Mohandas, 2000). Osteoporosis is typically diagnosed as a lumbar spine or hip region T-score less than -2.5 in postmenopausal women or men over the age of 50 years. Low bone mass is a term used to describe a Z-score of less than -2.0 in premenopausal women and men under age 50 years. The onset of multiple sclerosis (MS) typically occurs in premenopausal women and men aged 29 to 45 years (Imitola, 2019). PwMS typically have weakness and lack of coordination which contributes to falls and fracture risk in this population (Herndon & Mohandas, 2000). Several factors contribute to low bone mass among PwMS including decreased physical activity, increased risk of falls leading to fear of walking, adverse effects of corticosteroids and antiepileptic medications (carbamazepine, phenobarbital), and suboptimal nutrition including vitamin D deficiency (Oleson, 2017).

A fragility fracture, as defined by the World Health Organization, is a "fracture caused by injury that would be insufficient to fracture normal bone: the result of reduced compressive and/or torsional strength of bone" (World Health Organization, 1998). Further, clinically, a fragility fracture can be defined as a fracture that occurs "as a result of minimal trauma" (i.e., falling from standing height or less) (Brown, Josse, & Scientific Advisory Council of the Osteoporosis Society of Canada, 2002). Fragility fractures place additional burden on an individual with a disability, reduce an individual's quality of life, lead to functional limitations, and increase morbidity and mortality (Nuti et al., 2019). Additionally, fragility fractures and the associated pain may precipitate a pseudo-relapse. Fracture-related restrictions often lead to physical deconditioning and changes in functional mobility such that ambulation is no longer safe or feasible. If ambulation is possible, it may take several weeks or months of therapy for the individual to regain their premorbid physical capabilities (Herndon & Mohandas, 2000). Deconditioning following impairment-related immobility, such as a fragility fracture, will have a slower recovery than the same impairment in the general population. Many PwMS do not return to their pre-injury level of ambulation, need gait aids, or become non-ambulatory following a period of extended immobility (Herndon & Mohandas, 2000). Further, fragility fracture-related immobility may cause venous thromboembolism or pulmonary embolism especially in PwMS with lower extremity fractures. Specifically, after a hip fracture the expected mortality rate in PwMS increases from 6.3% to 36.7% (Miller & Bonnick, 1997). Additionally, serious iatrogenic complications of fracture in PwMS include ileus (obstruction of the intestines among patients administered narcotics (Wiesel & Bell, 2004)) and aspiration pneumonia. In addition, among PwMS with a Kurztke Expanded Disability Status Scale (EDSS) score of 7 or higher, vital capacity is markedly decreased (Smeltzer, Utell, Rudick, & Herndon, 1988), often to one litre, and is accompanied with an impaired cough (low peak cough flow) leading to hospitalizations for respiratory complications (Tzelepis & McCool, 2015). Maintenance of bone mass is one strategy for augmenting bone health and reducing fracture risk.

Due to a combination of environmental and dietary factors, vitamin D deficiency and decreased bone mineral density (BMD) or low bone mass are frequently reported (Oleson, 2017). Currently, management of bone health in PwMS is challenging due to difficulties in identifying an individual's fracture risk as most PwMS are young premenopausal women or men under the age of 50 years for whom gold-standard fracture risk assessment tools may not apply (i.e., Fracture Risk Assessment Tool (FRAX)). There is a small body of literature suggesting an alternate tool for identifying fracture risk in PwMS (Dobson & Giovannoni,

2013; Murphy, Zandi, Lindenberg, Murphy, & Chataway, 2016). Once a person's fracture risk is identified as low, moderate, or high, therapeutic options may be explored. Some of the most frequent controversies for treatment of low bone mass in PwMS relate to receiving an adequate dietary calcium and vitamin D supplementation to maintain an adequate serum 25-hydroxyvitamin-D (25(OH)D) level.

Although vitamin D deficiency has been associated with the development of MS (Alharbi, 2015), vitamin D status remains an area of concern following MS diagnosis. Vitamin D has been used to prevent onset of disease in family members of PwMS, to modulate disease progression in PwMS, and to treat low bone mass in PwMS. A succinct review of some of these non-skeletal mechanisms is provided below, however, this module will focus on vitamin D for maintenance of bone mass or treatment of low bone mass or osteoporosis.

Heat intolerance in PwMS may result in limited sunlight exposure, an essential source of natural vitamin D, thereby reducing time outdoors for sufficient sunlight exposure and adequate absorption of vitamin D. Gastroesophageal reflux and neurogenic bowel issues may discourage milk product consumption, and many calcium supplements precipitate constipation. Subsequently, while vitamin D increases calcium absorption from the gastrointestinal tract, restricted dietary calcium intake is likely an independent risk factor for the development of osteoporosis in PwMS. Additionally, gene polymorphisms in vitamin D metabolism and regulation may affect vitamin D levels even with sufficient ultraviolet B (UVB) exposure in PwMS (Elkama & Karahalil, 2018). Secondary hyperparathyroidism may develop due to vitamin D insufficiency, leading to upregulated parathyroid hormone (PTH), elevated levels of PTH stimulating osteoclasts to resorb bone, and in turn increasing bone remodeling and decreasing bone mass (Zikan, 2011). Treatment of PwMS with glucocorticoids further complicates bone health as glucocorticoid use opposes vitamin D action by reducing calcium absorption from the gastrointestinal tract, further increasing the risk for calcium and vitamin D insufficiency and low bone mass (Zikan, 2011).

There is an association between low serum vitamin D levels and high rate of bone fracture in PwMS (Lambrinoudaki et al., 2013; Tajouri et al., 2005). However, it is unclear if vitamin D deficiency potentially increases the risk of MS "by putting the immune system in a more pro-inflammatory state" (Elkama & Karahalil, 2018). Vitamin D has been shown to have immunomodulatory protective effects on the brain (Shirazi, Rasouli, Ciric, Rostami, & Zhang, 2015) and direct immunomodulatory effects on T cells, leading to improved regulatory T-cell suppressive function in PwMS (Jagannath et al., 2018). Several case-control studies have noted that in PwMS, vitamin D levels are significantly lower than in controls (Elkama & Karahalil, 2018).

Falls are a serious health concern in PwMS and over 50% experience a fall within any six-month period (Gunn, Creanor, Haas, Marsden, & Freeman, 2013; Nilsagard, Lundholm, Denison, & Gunnarsson, 2009). Of these falls, 50% result in injury, 23% of which need medical care (Matsuda et al., 2011; Peterson, Cho, von Koch, & Finlayson, 2008). This may result in a detrimental effect on the ability to perform daily activities (Cattaneo et al., 2018). Given the impact of falls and fragility fractures on the health and longevity of PwMS, one can understand the importance of optimizing bone health. Prevention and treatment of low bone mass or osteoporosis is critical to prevent fragility fractures from occurring; these interventions have the potential to decrease the morbidity and mortality associated with fracture in PwMS. It is important to identify PwMS at risk for fragility fracture and osteoporosis and initiate appropriate treatment interventions.

This module provides an overview of the available evidence for pharmacological and non-pharmacological interventions for the prevention and treatment of low bone mass and high fragility fracture risk in PwMS.

For the purposes of this review, *prevention* refers to interventions initiated prior to meeting diagnostic criteria for osteoporosis or concurrent with the onset of low bone mass. *Treatment* refers to interventions intended to maintain or augment bone mass and reduce fracture risk among individuals with established low bone mass or high fracture risk.

2.0 Interventions for the Prevention and Treatment of Low Bone Mass

2.1 Pharmacological Interventions

Pharmacological interventions for the prevention and treatment of low bone mass in PwMS to date have focused on immunomodulatory therapies, including fingolimod and interferon beta (IFN-β). In contrast to the general osteoporosis population, there is limited research evaluating pharmacotherapy for the prevention of declining bone mass in PwMS. There are no prospective clinical trials investigating anabolic agents such as teriparatide (recombinant human PTH 1-34, brand name Forteo) or antiresorptive medications such as bisphosphonates or Denosumab in PwMS (Oleson, 2017). Gupta et al. (2014) noted that the guidelines for osteoporosis management developed by the UK National Institute for Health and Care Excellence (NICE) may also be used for PwMS as there are currently no guidelines developed for the treatment of osteoporosis in PwMS. NICE recommends alendronate as the first-line treatment, and risedronate and etidronate as a second-line treatment for osteoporosis (Gupta et al., 2014).

Although there are no studies evaluating the effect of anabolic or antiresorptive drugs on bone markers and BMD, treatments such as fingolimod and IFN-β have been investigated.

2.1.1 Disease Modifying Therapies

Table 1. Studies Examining Disease Modifying Therapies for the Prevention and Treatment of Low Bone Mass in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Miyazaki et al. 2016 *Fingolimod suppresses bone resorption in female patients with multiple sclerosis* Japan Cohort $N_{Initial}$=83, N_{Final}=83	**Population:** *Fingolimod group (n=29):* Mean age=37.4yr; Gender: males=9, females=20; Disease course: RRMS=24, SPMS=5; Mean EDSS=2.3; Mean disease duration=10.7yr. *Untreated group (UT; n=29):* Mean age=37.3yr; Gender: males=9, females=20; Disease course: RRMS=26, SPMS=3; Mean EDSS=2.1; Mean disease duration=7.7yr. *Healthy controls (HC; n=25)*: Mean age=36.8yr; Gender: males=8, females=17. **Intervention:** Participants received fingolimod or no treatment (UT). Fingolimod was administered at 0.5mg/d for a mean of 12.9mo. The UT group received no pharmacological agents or immunosuppressants that could modify MS symptoms for at least 3mo. HC were also used for comparison. Samples were collected	1. Serum concentrations for a resorption BTM (N-Tx) was significantly decreased in fingolimod compared to HC and UT ($p<0.05$). 2. The other bone resorption marker (TRACP5b) and two formation markers (BAP/P1NP) did not significantly differ between groups ($p>0.05$). 3. Females, but not males, taking fingolimod had lower N-Tx levels compared to females in UT ($p<0.01$). 4. The BTM N-Tx was significantly positively correlated with EDSS for ambulatory females in the UT (p=0.0264), but not fingolimod group (p=0.3198). 5. TRACP5b, BAP, AND P1NP did not differ between the different study groups

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	once in the morning on the day of testing. **Outcomes/Outcome Measures:** Bone turnover markers (BTM) in serum and urine samples; urinary type 1 collagen cross-linked N-telopeptide (N-Tx); tartrate-resistant acid phosphatase (TRACP) 5b in serum; bone-specific alkaline phosphatase (BAP) in serum; procollagen type 1 amino-terminal propeptide (P1NP); creatinine in serum; serum free thyroxine; 25(OH)D in serum.	(healthy control, untreated-MS, fingolimod-MS) ($p<0.01$). 6. In males that were fully ambulatory (EDSS ≤ 3.5), TRACP5b and P1NP had a significant negative correlation with EDSS in UT ($p=0.0458$; $p=0.0072$), but not fingolimod group ($p=0.7131$; $p=0.3956$). 7. Treatment duration was significantly positively correlated with level of BAP, a BTM, in females. No significant correlation existed with males.
Varoglu et al. 2010 *The effect of interferon beta 1B on bone mineral density in multiple sclerosis patients* Turkey Cohort $N_{Initial}=32$, $N_{Final}=32$	**Population:** *Interferon Beta (IFN-β) group (n=17)*: Mean age=36.2yr; Gender: males=5, females=12; Disease course: PPMS or SPMS; Mean EDSS=2.64; Mean disease duration=4.2yr. *Control group (CG; n=15)*: Mean age=34.1yr; Gender: males=7, females=8; Disease course: PPMS or SPMS; Mean EDSS=2.80; Mean disease duration=3.4yr. **Intervention:** Participants in the IFN-β group received IFN-β 1b treatment, while participants in the CG did not receive IFN-β. The IFN-β group received treatment for at least 1yr. **Outcomes/Outcome Measures:** Bone mineral density (BMD) of the lumbar spine (L1-L4, anteroposteriorly) and total left hip by DXA using Hologic QDR 4500.	1. Lumbar BMD in IFN-β group was 0.90 ± 0.13 g/cm^2. Lumbar BMD in CG was 0.96 ± 0.12 g/cm^2. 2. Left hip (total) BMD was 0.76 ± 0.13 g/cm^2. Left hip (total) BMD was 0.73 ± 0.20 g/cm^2. 3. After treatment there was no significant difference between IFN-β and CG groups in the femoral neck ($p=1$) or lumbar spine ($p=0.3$).
Shuhaibar et al. 2009 *Favorable effect of immunomodulatory therapy on bone mineral density in multiple sclerosis* Ireland Case Control $N_{Initial}=37$, $N_{Final}=37$	**Population:** Mean age=38.8yr; Gender: males=13, females=24; Disease course: Unspecified; Mean EDSS=3.1; Mean disease duration=5.8yr. **Intervention:** Individuals receiving immunomodulatory therapy (IMT) for an average of 3.1yr underwent bone mineral density (BMD) tests. BMD was measured at both the hip and lumbar spine. Outcomes were compared to age and sex-matched BMD scores. Types of IMT administered included: Interferon β-1a (70%), Interferon β-1b (27%), and Glatiramer (3%). Intravenous steroid treatment (methylprednisolone 500mg) was administered in 81% of individuals. **Outcomes/Outcome Measures:** Bone mineral density (BMD) was measured via DXA at the lumbar spine (L1-L4) and left total femur site using a Hologic QDR4000 Elite Densitometer.	1. BMD Z-scores at the spine ($p=0.0084$) and at femur ($p=0.0001$) were significantly greater than age and sex-matched BMD scores. 2. There was no difference between men and women in regards to BMD z-scores.
	Population: *MS participants (n=9)*: Mean age=46.5yr; Gender: males=3, females=6; Disease course: RRMS; Mean EDSS=2.44;	1. Significant changes from pre-treatment levels occurred at the 8 and 24hr time points in treated MS patients but not in

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Weinstock-Guttman et al. 2006 *Interferon-beta modulates bone-associated cytokines and osteoclast precursor activity in multiple sclerosis patients* USA Cohort $N_{Initial}$=18, N_{Final}=18	Mean disease duration: Unspecified. *Healthy Controls (n=9)*: Mean age=44.5yr; Gender: males=2, females=7. **Intervention:** All MS participants received an intramuscular injection of 30mg interferon-b (IFN-β-1a). Healthy controls did not receive any treatment. Outcomes were measured at 8hr, 24hr, and 6mo. **Outcomes/Outcome Measures:** Osteoprotegerin (OPG) plasma protein; free, uncomplexed RANKL protein in plasma; osteocalcin; plasma levels of C-telopeptides of type 1 collagen; osteocalcin.	controls; there was a significant decrease in OPG levels at 8hr post treatment (p<0.001), and a significant increase in OPG levels at 24hr post treatment (p=0.007). 2. The OPG levels at the six-month time point were not significantly different from baseline. 3. Levels of the bone formation marker osteocalcin were lower in MS participants compared to untreated healthy controls at baseline (p=0.007) and increased to 142 ± 17% of pre-treatment levels after one yr of IFN-β-1a treatment.

Discussion

Fingolimod, a sphingosine-1-phosphate receptor agonist, is used as a MS disease modifying drug that inhibits inflammatory activity in MS (Miyazaki et al., 2016). Studies in animal models have shown that fingolimod can suppress bone loss by reducing the number of mature osteoclasts on the bone surface and have also been shown to increase bone mass by enhancing the bone forming capacity of osteoblasts (Miyazaki et al., 2016). A cohort study by Miyazaki et al. (2016) described the effect of fingolimod on bone resorption in MS patients with mild disability (mean EDSS=2.3). Female fingolimod-treated participants had reduced levels of the N-telopeptide, a bone resorption marker, suggesting that fingolimod treatment alters bone resorption without adversely affecting bone formation by osteoblasts. Further studies are required to investigate whether suppression of bone resorption will lead to an increase in the BMD of PwMS.

IFN-β is a first-line immunomodulatory treatment for MS and is typically prescribed to patients with relapsing-remitting MS (RRMS). IFN-β plays an important role in disease modulation within the central nervous system and inhibits osteoclast formation. Receptor activator of nuclear factor-κB ligand (RANKL) mediates a negative feedback loop, which signals IFN-β production in osteoclastogenesis. In a pharmacodynamic study, Weinstock-Guttman et al. (2006) demonstrated that IFN-β treatments may have a protective effect against osteoporosis, as the levels of the bone formation marker osteocalcin increased after one year of treatment. Although the authors were able to demonstrate that IFN-β acutely increases RANKL and osteoprotegerin (OPG) levels while decreasing osteoclast differentiation in vitro, a well-designed clinical trial is required to establish whether these changes also occur in vivo. In a small case-control study investigating the effects of interferon alpha (IFN-α) and IFN-β, Shuhaibar et al. (2009) found that BMD z-scores at the hip and spine were significantly greater than controls. However, this study had a poor research design and provided limited data. Additionally, the authors did not provide actual BMD values, only stating that the mean Z-score values were greater than zero.

Moreover, a similar study conducted by Varoglu et al. (2010) examined the effect of IFN-β treatment on BMD in the lumbar spine and left femur. After one year of treatment, there were no significant differences in BMD scores between the treatment and control groups. Very limited data on the actual BMD scores at the hip and lumbar sites were provided and the authors did not provide data on T-score values that were noted to have been determined. Due to limitations of the available evidence to date, the formation of firm conclusions on the role of IFN-β treatment on BMD remains challenging.

Important limitations of the available data is the lack of stratification by serum 25(OH)D levels at baseline, and although bone density values and related T or Z scores are sometimes reported, the participants' fracture risk categories are not reported.

Conclusion

There is level 2 evidence (from one cohort study; Miyazaki et al. 2016) that fingolimod may prevent declines in bone mass compared to no treatment in persons with MS.

There is conflicting evidence (from one cohort study and one case control study; Varoglu et al. 2010; Shuhaibar et al. 2009) regarding whether or not interferon beta improves bone mineral density compared to no treatment in persons with MS.

There is level 2 evidence (from one cohort study; Weinstock-Guttman et al. 2006) that interferon beta treatment has in vivo effects on bone homeostasis-mediating markers, cells, and cytokines with the potential to modulate bone mineral density compared to healthy controls in persons with MS.

Fingolimod may prevent declines in bone mass in persons with MS.

It is unclear if interferon beta improves bone mineral density in persons with MS, but it may induce changes in proteins related to bone homeostasis.

2.2 Non-pharmacological Interventions

There is limited evidence to date regarding non-pharmacological interventions for the prevention and treatment of low bone mass in PwMS. Only one study has investigated an internet-delivered physical activity behavioural intervention.

2.2.1 Physical Activity

Table 2. Studies Examining Physical Activity for the Prevention and Treatment of Low Bone Mass in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Pilutti et al. 2014 *Internet-delivered lifestyle physical activity intervention improves body composition in multiple sclerosis: Preliminary evidence from a randomized controlled trial* USA RCT PEDro=6 $N_{Initial}$=82, N_{Final}=72	**Population:** *Physical activity group (n=41):* Mean age=48.4yr; Gender: males=11, females=30; Disease course: RRMS=31, PPMS=2, SPMS=8; Median PDDS=2.0; Mean disease duration=10.6yr. *Waitlist control group (n=41):* Mean age=49.5yr; Gender: males=9, females=32; Disease course: RRMS=34, PPMS=5, SPMS=2; Median PDDS=3.0; Mean disease duration=13.0yr. **Intervention:** Individuals were randomized to the intervention group or a waitlist control group. The intervention received online information on physical activity and a pedometer to increase physical activity, particularly walking. There were also video conferences with a behavioural coach based on principles of social cognitive theory. Outcomes were assessed at baseline and 6mo. **Outcomes/Outcome Measures:** Whole-body bone mineral content (BMC), bone mineral density (BMD), and soft tissue composition were assessed by DXA using a Hologic QDR 4500A bone densitometer (software version 11.2); body mass index; percent body fat; whole-body fat mass; whole-body lean soft tissue mass.	1. The physical activity group had significantly greater whole-body BMC (2269.9 ± 8.7 g, p=0.04) and BMD (1.111 ± 0.003 g/cm^2, p=0.01) compared to controls (2244.7 ± 8.5 g and 1.101 ± 0.003 g/cm^2, respectively) at 6mo. 2. There were no significant differences between the intervention and control groups at 6mo in terms of: a. whole-body fat mass (22,264.7± 483.9 g vs 27,611.7± 470.6 g, p=0.05), b. whole-body lean soft tissue mass (48,102.7 ± 248.1 g vs 48,484.5± 241.3 g, p=0.28), c. percent body fat (33.4 ± 0.36 vs 34.3 ± 0.35, p=0.09), and d. BMI (28.2± 0.24 g vs 28.2± 0.24 g, p=0.86).

Discussion

In a non-pharmacological treatment study conducted by Pilutti et al. (2014), an internet-delivered physical activity behavioural intervention was used to investigate the effects of physical activity on body mass and BMD in ambulatory men and women. The intervention group had a significantly greater whole-body bone mineral content (BMC) and BMD. However, the study was not powered to perform sub-group analysis by disease course: RRMS, primary progressive MS (PPMS), and secondary progressive MS (SPMS).

Conclusion

There is level 1b evidence (from one randomized controlled trial; Pilutti et al. 2014) that a physical activity behavioural intervention may improve whole body bone mineral density and bone mineral content compared to no intervention in persons with MS.

A physical activity behavioural intervention may result in improved bone mineral density and bone mineral content in persons with MS.

3.0 Interventions for the Treatment of Low Bone Mass

3.1 Complementary and Alternative Treatment

Interventions for the treatment of low bone mass in PwMS to date have focused on vitamin D supplementation. Vitamin D has been shown to have both direct and indirect effects on prevention of osteoporosis and fractures (Bikle, 2014). Vitamin D has been shown to have a direct effect on bone by increasing osteoblast activity and reducing osteoclast activity. The biological action of $1,25(OH)_2D$ is mediated by the vitamin D receptor (VDR), a member of the steroid receptor family. Normal levels of $1,25(OH)_2D$ act via the VDR in mature osteoblasts to decrease the ratio of RANKL/OPG, reduce osteoclastic bone resorption and increase bone formation rate which results in increased cortical and trabecular bone (Goltzman, 2018). RANKL is a key factor for osteoclastogenesis and binding to its receptor, receptor activator of nuclear factor-kB (RANK), favours the activation of osteoclasts and bone resorption. OPG reduces RANKL-RANK interaction and inhibits osteoclastogenesis. Therefore, RANKL/OPG ratio is important in regulating bone homeostasis (Remuzgo-Martinez et al., 2016). Additionally, vitamin D via its active form, $1,25(OH)_2D$, maintains calcium homeostasis by stimulating intestinal phosphorous and calcium absorption which can facilitate skeletal mineralization (Goltzman, 2018).

3.1.1 Vitamin D

Table 3. Studies Examining Vitamin D for the Treatment of Low Bone Mass in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Holmøy et al. 2017 (Secondary analysis of Kampman et al. 2012) *High dose vitamin D supplementation does not affect biochemical bone markers in MS* UK RCT PEDro=10 $N_{Initial}$=71, N_{Final}=68	**Population**: *Vitamin D group (n=35):* Mean age=40yr; Gender: males=11, females=24; Disease course: Unspecified; Median EDSS=2.5; Mean disease duration=11yr. *Placebo group (n=33):* Mean age=41yr; Gender: males=9, females=24; Disease course: Unspecified; Median EDSS=2.0; Mean disease duration=10yr. **Intervention**: Participants were randomized to receive vitamin D_3 (20,000IU/wk) or placebo for 96wks. Outcomes were at baseline, 48wks, and 96wks. **Outcomes/Outcome Measures**: 1. Mean C-terminal cross-linking telopeptide of type 1 collagen (CTX1), precollagen type 1 N propeptide (P1NP), parathyroid hormone (PTH) from	1. ¼ of patients had low BMD z-scores (below -2) at baseline. 2. In the vitamin D group, serum concentration of 25(OH)D increased from 55.6 ± 29.0 nmol/L to 123.2 ± 34.2 nmol/L. 3. In the placebo group, serum concentration of 25(OH)D increased from 57.3 ± 21.8 nmol/L to 61.8 ± 25.2 nmol/L. 4. Mean CTX1 levels were similar in the vitamin D and placebo groups at baseline (0.22µg/L vs 0.20µg/L, p=0.59), 48wks (0.21µg/L vs 0.22µg/L, p=0.79), and 96wks (0.23µg/L vs 0.23µg/L, p=0.98).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	baseline, at 48 and 96 wks within and between group changes. 2. Change in 25-hydroxyvitamin-D (25(OH)D) serum level from baseline (vitamin D and placebo group). 3. Describe proportion bone mass density (BMD) spine, hip and distal radius at baseline (% with low z-score at baseline).	5. Mean CTX1 reduction in the vitamin D group from baseline to 48wks (-6.68%, p=0.63) and to 96wks (-13.69%, p=0.09) was not significant when compared to placebo. 6. Mean P1NP levels were similar in the vitamin D and placebo groups at baseline (40.32µg/L vs 43.10µg/L, p=0.57), 48 wks (38.56µg/L vs 43.36µg/L, p=0.43), and 96wks (43.52µg/L vs 42.54µg/L, p=0.22). 7. Mean P1NP change in the vitamin D_3 group from baseline to 48 wks (-5.10%, p=0.043) and to 96 wks (+10.26%, p=0.12) was not significant when compared to placebo. 8. Mean PTH levels were similar in the vitamin D and placebo groups at baseline (4.68pmol/L vs 4.75pmol/L, p=0.66), but were significantly lower in the vitamin D group at 48wks (3.13pmol/L vs 3.68pmol/L, p=0.017) and 96wks (3.39pmol/L vs 3.96pmol/L, p=0.046). 9. Mean PTH reduction in the vitamin D group from baseline to 48wks (-13.69%, p=0.09) and to 96wks (-10.9%, p=0.17) was not significant when compared to placebo.
Steffensen et al. 2013 (Secondary analysis of Steffensen et al. 2011) *What is needed to keep persons with multiple sclerosis vitamin D-sufficient throughout the year?* Norway RCT PEDro=8 $N_{Initial}$=71, N_{Final}=68	**Population**: *Vitamin D_3 (n=35)*: Mean age=40.0yr; Gender: males=11, females=24; Disease course: RRMS; Median EDSS=2.5; Mean disease duration=11.0yr. *Placebo (n=33)*: Mean age=41.0yr; Gender: males=9, females=24; Disease course: RRMS; Median EDSS=2.0; Mean disease duration=10.0yr. **Intervention:** Participants were randomized to receive either vitamin D_3 (20,000 IU) or placebo capsules, administered once a wk for 96 wks. All participants received 500mg/d of calcium. Outcomes were assessed at baseline and 96wks. **Outcomes/Outcome Measures**: 1. Change in serum 25-hydroxyvitamin-D (25(OH)D) levels by mass spectroscopy. 2. Change in dietary vitamin D intake calculated from a food frequency questionnaire.	1. In the vitamin D_3 supplementation group, 25(OH)D improved significantly from baseline to 96wks (p<0.01), where 91% of participants had high levels >75nmol/L. 2. In the vitamin D_3 supplemention group, levels of 25(OH)D increased from 56 nmol/L to 123nmol/L (p<0.01), with a mean increase of 2.4nmol/L per 100IU vitamin D_3. 3. Mean 25(OH)D levels at baseline during winter was 58 nmol/l, and 87 nmol/l during the summer months (p<0.001). 4. From the food frequency questionnaire, predictors of serum 25(OH)D levels within all participants at baseline are: dietary and supplemental vitamin D, total vitamin D intake, and tanning beds and sun vacation in last 3mo (all p<0.01).
Steffensen et al. 2011	**Population:** *Vitamin D_3 (n=35)*: Mean age=39.7yr; Gender: males=11, females=24; Disease course: RRMS; Median EDSS=2.5;	1. After 96wks, there was no significant difference between participants who received vitamin D_3 and placebo in terms

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Can vitamin D3 supplementation prevent bone loss in persons with MS? A placebo-controlled trial Norway RCT PEDro=10 $N_{Initial}$=71, N_{Final}=68	Mean disease duration=10.9yr. *Placebo (n=33)*: Mean age=41.0yr; Gender: males=9, females=24; Disease course: RRMS; Median EDSS=2.0; Mean disease duration=10.0yr. **Intervention:** Participants were randomized to receive either vitamin D_3 (20,000 IU) or placebo capsules once a wk, in addition to 500mg calcium daily for 96 wks. **Outcomes/Outcome Measures:** Bone mineral density (BMD) at the hip (mean of left and right total hip), spine (anterior-posterior spine L1-L4) and ultradistal radius by DXA using a Lunar Prodigy advanced densitometer; serum 25-hydroxyvitamin-D (25(OH)D) by mass spectroscopy.	of % change in BMD in the hip (p=0.332), lumbar spine (p=0.793) or ultradistal radius (p=0.506). 2. BMD decreased at the hip by 1.4% in the placebo group (p=0.006) and by 0.7% in the vitamin D_3 group (p=0.118). 3. In the intervention group, 25(OH)D serum levels increased from 55.6± 29.0 nmol/L to 123.2± 34.2. 4. 32/35 (91%) of participants in the intervention group reached desired vitamin D levels of ≥75 nmol/L.
Hiremath et al. 2009 *Vitamin D status and effect of low-dose cholecalciferol and high-dose ergocalciferol supplementation in multiple sclerosis* UK Retrospective Cohort $N_{Initial}$=199, N_{Final}=49	**Population**: Mean age=42yr; Gender: males=43, female=156; Disease course: RRMS=115, PPMS=10, SPMS=16; Severity: Unspecified; Disease duration: Unspecified. MS participants=141. **Intervention**: Participants received low dose cholecalciferol (LDC (vitamin D_3), ≤800IU/d), high dose ergocalciferol (HDE (vitamin D_2), 50,000IU/d), or no supplement (NS, n=9) for >6mo. The supplemented participants were divided into groups based on those who just started taking LDC (NS-LDC, n=10) and HDE (NS-HDE, n=12), those who continued taking LDC (LDC-LDC, n=8), and those who switched from LDC to HDE (LDC-HDE, n=10). Outcomes were assessed before and after treatment. **Outcomes/Outcome Measures**: Change in 25-hydroxyvitamin-D (25(OH)D) serum level from baseline (vitamin D and placebo group).	1. 50 (26%) patients had 25(OH)D levels greater than 100 nmol/L at baseline. 2. 167 (84%) patients had insufficient levels of 25(OH)D and 61 (31%) patients were deficient. 3. Mean calcifediol increased in the NS group (73nmol/L to 87nmol/L), but the difference was not significant. 4. Mean serum calcifediol increased in the NS-LDC group (56nmol/L to 84nmol/L) and slightly decreased in the LDC-LDC group (97nmol/L to 92nmol/L), but neither difference was significant. 5. Mean calcifediol increased from baseline in the LDC-HDE group (64 ± 19 nmol/L to 108 ± 36 nmol/L, p=0.21) and the NS-HDE group (74 ± 26nmol/L to 116 ± 53 nmol/L, p=0.01), but only the latter difference was significant.

Discussion

In general, there is a paucity of literature addressing the treatment of osteoporosis in PwMS, and the current literature contains a significant risk of bias related to population sample and study design. Participants in the above studies had very low EDSS scores (< 2.5); an EDSS score of 2.5 indicates that an individual is ambulatory and has mild disability in one functional system or minimal disability in two functional systems. Prevailing myths that PwMS who remain ambulatory with minimal to no reduction in standing tolerance are unlikely to be at a high risk for fragility fracture and unlikely to have low bone density are incorrect (Moen et al., 2011; Sioka et al., 2011). As PwMS with high EDSS scores are underrepresented in the available literature, the effect of vitamin D as treatment for osteoporosis in PwMS who demonstrate limited to no ambulation is unknown. In addition, a majority of participants receiving treatment are premenopausal women, with postmenopausal women and men being underrepresented. A systematic review by Gaugris et al. (2005) reported that postmenopausal women

without MS receiving therapy for the prevention or treatment of osteoporosis have a high prevalence of vitamin D inadequacy, and similar findings have been reported by Holick et al. (2005).

To date, four studies have investigated the use of vitamin D_3 for correction of vitamin D deficiency in the MS population, with only two studies examining the impact of the intervention on bone density or fracture risk outcomes (Holmøy et al., 2017; Steffensen et al., 2011). Holmøy et al. (2017) examined the use of vitamin D_3 (20,000 IU weekly) for 96 weeks on biomarkers of bone turnover. This weekly high dose vitamin D supplementation protocol did not demonstrate an effect on bone formation or turnover. The results suggest that high dose weekly vitamin D supplementation alone is not beneficial for bone health in PwMS who are not vitamin D deficient. In a cohort study, Hiremath et al. (2009) evaluated the effects of low dose cholecalciferol (LDC) versus high dose ergocalciferol (HDE) on serum 25(OH)D levels in persons with RRMS. LDC supplementation was insufficient to increase serum levels to the optimal level (≥100 nmol/L), as defined by the authors. Additionally, although HDE supplementation raised 25(OH)D levels significantly, optimal levels were achieved in less than 40% of participants. However, the authors did not use any outcome measures to determine the effects of the intervention on markers of bone formation, bone turnover, or BMD. Additional studies are required to determine the appropriate dosing regimen to achieve optimal 25(OH)D levels. Steffensen et al. (2011) conducted a randomized controlled study of 71 ambulatory participants with RRMS to evaluate the efficacy of 20,000 IU of vitamin D3 at the hip, spine, and ultradistal radius. No significant differences in absolute BMD were observed between the experimental and control groups after 96 weeks of vitamin D_3 administration. Of note, this study was not adequately powered to determine whether weekly administration of 20,000 IU vitamin D_3 prevents bone loss in PwMS. Further, Steffensen et al. (2013) conducted a secondary analysis of the data from the previous study (Steffensen et al., 2011) and found that supplementation with 20,000 IU vitamin D increased 25(OH)D levels to optimal levels as defined by the Institute of Medicine and the Norwegian Directorate of Health (≥50 nmol/L). Similar to the cohort study by Hiremath et al. (2009) and Steffensen et al. (2013), the authors did not investigate changes in bone formation or bone turnover.

Overall, there is some evidence that vitamin D_3 supplementation for at least 96 weeks will correct vitamin D deficiency for a subset of premenopausal women with MS. Validation of the optimal serum level of 25(OH)D to maintain bone mass in the MS population is needed as the current threshold values are not well-defined, with discrepancies in the optimal 25(OH)D levels observed across all three studies. Optimal levels of vitamin D in PwMS has been the subject of debate. The Endocrine Society has stated that serum 25(OH)D levels of 100-150 nmol/L is “ideal” taking into account assay variability and serum levels up to 250 nmol/L can be considered “safe” (Sintzel, Rametta, & Reder, 2018). Additionally, the Society recommends screening and corrective action in persons at risk of vitamin D deficiency, including older adults with a history of falls or nontraumatic fractures, obese adults (BMI > 30 kg/m^2, and patients with musculoskeletal disease, hepatic failure, and malabsorption syndromes (Sintzel et al., 2018). The Endocrine Society has recommended Vitamin D supplementation at doses of 1500-2000 IU/day which is well tolerated (Sintzel et al., 2018). Moreover, supplementation vitamin D is available as ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Vitamin D_3 has been shown to be the more potent form of vitamin D in the general population with osteoporosis (Houghton & Vieth, 2006). To reach adequate levels of vitamin D, supplements can be administered daily, weekly, monthly, or every four months (Sintzel et al., 2018).

Further, vitamin D is generally regarded in preventing bone loss; however, there is increasing evidence that vitamin D may also contribute to immunomodulation in the progression of MS (Smolders, Damoiseaux, Menheere, & Hupperts, 2008). The level of circulating vitamin D that may be appropriate for bone health in PwMS (to prevent vitamin D deficiency or bone loss) may not reflect the levels of vitamin

D necessary for modulating immune function. There is no "one size fits all" approach to vitamin D supplementation in PwMS, however, correction of vitamin D insufficiency at recommended doses is a "sensible" clinical target and provides a "favorable risk-benefit profile for vitamin D for most patients with MS" (Sintzel et al., 2018) in the absence of contradictory evidence.

Conclusion

There is level 1a evidence (from two randomized controlled trials; Holmøy et al., 2017; Steffensen et al. 2011, 2013) that vitamin D supplementation may not improve bone health compared to placebo in a mixed MS population with an EDSS less than 2.5.

Vitamin D deficiency or insufficiency are common in the MS population. Supplementation with vitamin D3 increases serum levels of vitamin D; however, the effects of vitamin D supplementation on fracture risk are not known.

Evidence for bone strengthening treatments specifically for the MS population is unavailable. Cautious extrapolation from other clinical populations is currently standard practice in most MS clinical care settings.

4.0 Summary

Although there is limited evidence that high dose weekly vitamin D supplementation will correct vitamin D deficiency and increase serum 25(OH)D levels, vitamin D supplementation alone is not sufficient for bone health in ambulatory PwMS. Moreover, there is very limited research evaluating the effectiveness of pharmacological interventions for the prevention and/or treatment of osteoporosis. Given the paucity of literature, clinicians are advised to use their clinical judgement based on the needs of the patient. Oleson (2017) suggests that PwMS should perform weight-bearing activities even with assistive devices and recommends that clinicians ensure that therapeutic serum vitamin D and calcium levels are maintained by periodic lab testing. Additionally, Oleson (2017) recommends that bone density should be evaluated annually by dual-energy x-ray absorptiometry (DXA) screening if there is a consistent or rapid loss of motor function or ability to ambulate.

There is a need for the development of risk stratification tools for premenopausal women and men with MS that take into consideration their disease type (RRMS, SPMS, PPMS, and progressive relapsing MS (PRMS)), their functional impairments, and baseline 25(OH)D. Future studies should stratify results based on the individual's level of function as per the Kurtzke EDSS which describes levels of disability of PwMS regardless of disease course, predominately related to lower limb function. A score of 4.0 or above represents substantial disability with MS-related impairments significantly affecting an individual's daily functioning. By the time an individual reaches a score 6.5, they must use bilateral support for ambulation. By the time a person reaches 7.0, at least for some part of the day, they are reliant on wheeled mobility. Persons with a score of 6.5 have limited mobility and therefore are at risk for developing osteoporosis as there is infrequent mechanical loading in bone which attenuates osteoblast activity and stimulates osteoclast activity, leading to an excess of bone resorption relative to bone formation (Klein-Nulend,

Bacabac, & Bakker, 2012). Due to the heterogeneity observed among PwMS, stratification using EDSS and disease subtype (RRMS, SPMS, PPMS, and PRMS) will provide clinicians with the ability to identify patients with low bone mass and an elevated fracture risk for whom therapy is appropriate. Prospective studies should be completed using a representative sample of MS participants with the highest risk of fracture, with the intent of evaluating the effect of pharmacotherapies on outcomes of importance including changes in bone turnover, bone mass, and fracture risk reduction.

There is level 2 evidence (from one cohort study; Miyazaki et al. 2016) that fingolimod may prevent declines in bone mass compared to no treatment in persons with MS.

There is conflicting evidence (from one cohort study and one case control study; Varoglu et al. 2010; Shuhaibar et al. 2009) regarding whether or not interferon beta improves bone mineral density compared to no treatment in persons with MS.

There is level 2 evidence (from one cohort study; Weinstock-Guttman et al. 2006) that interferon beta treatment has in vivo effects on bone homeostasis-mediating markers, cells, and cytokines with the potential to modulate bone mineral density compared to healthy controls in persons with MS.

There is level 1b evidence (from one randomized controlled trial; Pilutti et al. 2014) that a physical activity behavioural intervention may improve whole body bone mineral density and bone mineral content compared to no intervention in persons with MS.

There is level 1a evidence (from two randomized controlled trials; Holmøy et al. 2017; Steffensen et al. 2011, 2013) that vitamin D supplementation may not improve bone health compared to placebo in a mixed MS population with an EDSS less than 2.5.

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