Review

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Osteoporosis in multiple sclerosis

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Abstract

Fractures resulting from osteoporosis are a major cause of morbidity and mortality in the developed world. People with multiple sclerosis experience reduced mobility and are susceptible to falls. Glucocorticoid use and reduced mobility are known risk factors for osteoporosis. This paper is a review of osteoporosis in people with multiple sclerosis, looking at its prevalence, risk factors and possible mechanisms. We also review management guidelines for osteoporosis in the general population and use these to propose guidelines for osteoporosis management amongst multiple sclerosis patients. A number of studies have examined the incidence of reduced bone mineral density amongst people with multiple sclerosis; the majority provide convincing evidence that bone mineral density is significantly reduced in multiple sclerosis patients. The most significant risk factors appear to arise from the chronic disease process of multiple sclerosis and not from glucocorticoid use. There are currently no guidelines or consensus as how best to treat osteoporosis amongst multiple sclerosis patients despite their being at an increased risk. We propose an algorithm for the screening and treatment of osteoporosis in people with multiple sclerosis.

Keywords

multiple sclerosis, osteoporosis, clinical guideline

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Introduction

Multiple sclerosis (MS) is the second most significant cause of neurological disability in young adults in the developed world with 2.5 million affected people worldwide. The mean age of onset is in early adulthood and the disease has a lifelong course with limited influence on mortality but considerable impact upon disability.[1,2] Median time to death is 30 years from onset of the disease.[3] The long disease duration and the fact that survival in most patients lasts into late adulthood results in considerable consequences to health, including osteoporosis.

Osteoporosis is a reduction of bone strength due to a reduction of bone mineral density (BMD). It is predominantly a disease of ageing and occurs due to imbalance in the rates of bone resorption, mediated by osteoclasts, and bone formation, mediated by osteoblasts. This process tends to begin during the fourth and fifth decades and becomes exaggerated in women following the menopause.[4,5]

Osteoporosis is a major cause of morbidity and mortality. Reduced BMD gives a lower threshold for fracture. One sixth of White women will have a hip fracture during their lifetime. Hip fractures followed by vertebral and Colle's fracture of the distal radius are the most common osteoporotic fractures. The annual cost of these fractures within the European Union has been estimated at $30 billion. Hip fractures are the biggest cause of morbidity, involving long-term hospital admission, and also carry significant mortality with estimates of 10–20% within the first year.[5]

The standard for diagnosing osteoporosis is Dual X-ray Absorbance Spectrometry (DEXA). This measures bone density against bone area. Results are reported in terms of T and Z scores where T scores are the number of standard deviations (SD) the BMD is away from an equivalent population of young adults and Z scores the number of standard deviations from an age matched group. Osteoporosis is defined as being a T score of −2.5 standard deviations or lower, osteopenia as a T score of between −1 and −2.5.

Risk factors for osteoporosis in women are summarized in Table 1. In men, significant risk factors are: smoking, alcohol excess, previous fracture and low body mass index (BMI).[6] The widespread use of

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Table 1. Risk factors for osteoporosis (adapted from Sambrook and Cooper[5])

Congenital factors	Acquired factors	Lifestyle factors	Iatrogenic factors
Age	Visual impairment	Low calcium intake	Glucocorticoids
Previous and family history of fracture	Recurrent falls	Alcoholism	Anticonvulsants
Chronic disease	Dementia	Calcium deficiency	Cyclosporine
Caucasian	Low body weight	Vitamin D deficiency	Aromatase inhibitors
Female gender	Early menopause*	Inactivity	Thyroxine
	Prolonged premenstrual amenorrhea*	Smoker (current)	Aluminium
			GnRH agonists
			Lithium
			Bilateral oophrectomy*

*Factors that are direct causes of oestrogen deficiency.

glucocorticoids in people with MS (PwMS), along with their reduced mobility, decreased sunlight exposure and tendency to fall, as well as a predominance of female patients, suggest that PwMS may have a higher susceptibility to osteoporosis. This paper examines the evidence for this and evaluates the roles of the various risk factors involved. We suggest guidelines for the management of osteoporosis in PwMS, based on best available evidence.

Prevalence of osteoporosis in multiple sclerosis

A large retrospective study, analysing a registry of 9029 PwMS in the USA, found that 1386/9029 (15.4%) PwMS reported osteoporosis.[7] We have identified eight studies which have compared BMD in PwMS with age matched healthy controls. A further study has compared total body bone mineral (TBBM) content in PwMS with controls. These are summarized in Table 2. Six out of eight studies show statistically significantly lower BMD in PwMS than in controls. In one, 80% of male PwMS were osteopenic or osteoporotic.[8] A small study of 30 PwMS showed that baseline Z scores in PwMS were -0.87 ($p = 0.0002$).[9] Similarly in a study of 65 PwMS, bone mineral density was significantly reduced in L1-L4 and femoral sites compared with controls ($p < 0.0001$).[10] Lower TBBM is also reported in PwMS compared with controls ($p < 0.04$).[11]

In an early study[12] the BMD of 80 female patients was compared with reference ranges. Mean lumbar Z scores were -0.98 and -1.7 at the femoral neck. This translated to a 2–3.4-fold higher risk of fracture than in age matched members of the general population. Similarly another study found significantly higher femoral BMD loss in postmenopausal women and men and vertebral BMD loss in women. Fracture rates of 22% were found in PwMS compared with 2% in controls and a 3–6-fold higher rate of bone loss was observed in PwMS.[13]

Some uncertainty exists as to whether the femoral region or the vertebrae are more affected from loss of BMD in PwMS. As in Nieves et al.,[12] vertebral BMD was shown to be affected by MS to a lesser degree than femoral BMD. Z scores of around -1.0 SD were reported in the vertebrae whereas Z scores of up to -1.6 were reported in the hip.[13] However, in another small study contrasting 31 premenopausal female and male patients of a mean age of 38.2 with age matched controls, PwMS were found to have significantly lower BMD in their L2–L4 vertebrae and femoral trochanter but not in their neck of femur. Mean Z score in L2–L4 vertebrae was -0.98 (-2.9–1.3) compared with -0.06 (-1.8–2.5) for the control group ($p = 0.001$). Mean Z score in femoral trochanter was -0.67 (-2.5–1.5) compared with 0.2 (-1.4–3.1) for the control group ($p = 0.001$).[14]

Patients with progressive forms of MS appear to have more severe osteoporosis than those with relapsing–remitting MS (RRMS). One study showed that TBBM is lower in patients with primary progressive disease (PPMS) compared with secondary progressive (SPMS) and RRMS.[12] However, another group found lower BMD in patients with SPMS and PPMS compared with RRMS.[8] This may be a reflection of difference in disability rather than the type of MS.

There remains uncertainty as to whether all PwMS are more susceptible to osteoporosis. One group found no significant difference in BMD between patients and controls. Despite no significant increase in number of patients with osteoporosis amongst the MS group, there were significantly higher numbers of patients with osteopenia.[15] The lack of significance in this study may be because of the small sample size ($n = 43$). A larger study which used ultrasound to monitor cortical bone density in 256 PwMS and a control group found no significant difference in BMD between PwMS as a whole and the control group. Interestingly

the authors reported that 30.4% of female PwMS had a T score > 1.0 SD compared with only 7.4% of the controls ($p < 0.001$).[16] Both these studies had low mean Expanded Disability Status Scale (EDSS) scores compared with other studies, which may explain the lack of significant difference in BMD between patients and controls.

Potential pathogenic mechanisms

Glucocorticoids

Prolonged glucocorticoid treatment reduces BMD and results in increased fracture rates,[17] whilst pulsatile treatment of more than 15 mg/day increases risk of osteoporosis. This effect is small but rises with cumulative steroid use.[18] Given their frequent use to control MS relapses, it is reasonable to hypothesize that glucocorticoid use in PwMS may contribute to osteoporosis risk.

The evidence for glucocorticoids being primarily responsible for osteoporosis in PwMS is contentious. Markers of bone formation are acutely reduced following administration of glucocorticoids in PwMS[19] and two of the studies reviewed above report correlation between steroid dose and specific BMD in the femoral trochanter ($r = -0.38$, $p = 0.03$[14] and $r = -0.34$, $p = 0.039$[8]). However, another found no statistical significance in the relationship.[13] A further two of the studies found that BMD was higher amongst patients treated with steroids.[9,12] In one of these, this relationship was abolished when a multivariate analysis with age included was conducted.[12] In the second, when patients were separated into those with EDSS scores of 5.5 and higher and those with EDSS scores of lower than 5.5, the less disabled group showed a mean gain of BMD of 2.9% whilst the more disabled group lost 1.6%, $p = 0.04$.[9] Therefore these studies indicate that it is age and disability that are significant contributors to osteoporosis in PwMS and not glucocorticoid use.

In a further study comparing patients treated with regular high-dose methylprednisolone with those treated with IVMP for relapses only, higher levels of osteopenia (although not osteoporosis) were present in patients treated with IVMP only for relapses compared with those on regular pulses.[15] The authors suggested that this may indicate a more significant role for decreased mobility than corticosteroid treatment. However, this effect was maintained when the patient population was restricted to those with an EDSS score lower than 5.0. The authors suggested this also implicates the inflammatory process of MS in the aetiology of osteoporosis amongst this cohort.[15] Therefore amongst PwMS the driving factors influencing osteoporosis appear to result from chronic disease. The next subsections analyse the evidence for the roles of disability and the inflammatory process in this.

Disability

Reduced bone loading results in induction of osteoclast activity and suppression of osteoblast activity. This causes bone loss with a reduction of BMD, a process called immobilization or disuse osteoporosis.[20] Aetiologies include reduced mobility[21] and maintained mobility with muscle atrophy.[20,22,23]

Spinal cord injury (SCI) patients lose BMD[24] preferentially at femoral sites with the vertebrae being largely spared in a similar pattern to that described in PwMS.[25] The most implicated aetiology is disuse osteoporosis.[26] Patients with hemiparesis have lower BMD in their paralysed limbs.[26,27] In stroke patients the duration of immobility and severity of paresis are the major determinants of BMD loss.[28]

The degree of disability appears to be a major contributor to the pathogenesis of osteoporosis in PwMS. In a retrospective study of self-reported data from a 9029-patient MS registry in the USA, the degree of disability reported conferred the greatest odds of also reporting osteoporosis, following increasing age.[7] From Table 2 it can be seen that every study looking at BMD in PwMS has found a statistically significant negative correlation between at least one measure of physical impairment and BMD. Further, in the two studies that found little or no evidence of PwMS being at increased risk of osteoporosis subjects had low mean EDSS scores.[15,16] Impairment as measured by the Kurtzke EDSS score correlated with bone mineral density for PwMS.[13] EDSS scores correlated with BMD in the proximal portions of the femur but not in the lumbar vertebrae.[14] Higher TBBM is reported in ambulatory patients (EDSS score ≤ 6.5) compared with non-ambulatory patients (EDSS score ≥ 7.0), $p < 0.02$,[11,12] and non-ambulatory patients have been found to show a higher prevalence of osteoporosis.[29] A particularly strong correlation exists between use of a walking aid and the likelihood of osteoporosis.[8] Absolute fracture risk will thus be confounded by an increased risk of falls conferred by use of walking aids.[30,31]

Degree of motor impairment has been reported to affect fracture rate. In a four-point scale ranging from little to severe motor impairment, highest fracture rates were found in PwMS in the middle two bands, reporting some or moderate motor impairment. Patients with most severe impairment are less likely to fall and therefore have lower fracture rates.[32]

A significant correlation between disease duration and hip BMD has been established.[10] It is difficult to attribute this definitively to immobility. MS is a progressive disease and thus the longer the disease duration

Table 2. Summary of the studies that have investigated BMD in MS patients. FIM = Functional Independence Measure, EDSS = Expanded Disability Status Scale, TBBM = Total Body Bone Mineral Content

Study author	Study date	Number of MS patients recruited to the study	Mean age	Mean EDSS score	Evidence of increased risk of MS	Risk factors
Tuzun et al.[10]	2003	65	Female patients: 33.5 ± 5.3 Male patients: 35.1 ± 5.5	3.6 ± 2.3 3.5 ± 1.9	BMD lower at femoral and lumbar sites ($p < 0.0001$) in MS patients compared with controls	Correlation between FIM and BMD ($r = 0.507$, $p = 0.001$) Correlation between disease duration and BMD ($r = -0.504$, $p = 0.001$)
Nieves et al.[12]	1994	80	44.24 ± 7.97	5.15 ± 1.22	Mean Z score of −0.98 at lumbar sites and −1.7 at femoral neck reporting representing a 2–3.4-fold increased risk	Higher total body bone mineral levels found in patients who were ambulatory compared with non ambulatory patients ($p < 0.02$)
Schwid et al.[9]	1996	30	45 ± 10	Mean EDSS score not calculated	Mean Z score of −0.87 at the femoral neck ($p = 0.002$)	Patients with EDSS score of ≤5 gained 2.9% BMD at 6 months following pulse of steroid treatment. Patients with EDSS score of ≥5.5 lost 1.6% BMD. $p = 0.04$
Cosman et al.[13]	1998	54	Premenopausal women: 40 ± 1.4 (26–50) Postmenopausal women: 55 ± 1.4 (44–64) Men: 46 ± 2.9 (25–70)	6.5 6.3 7.0	BMD in MS patients 1 SD below that found in age matched controls at the lumbar spine and 1–1.6 SD below in the femoral neck Fracture rates in MS patients: 22% fracture rates in age matched controls: 2% $p < 0.002$ Rate of bone loss 3–6 times higher in MS patients $p < 0.01$	Higher rates of bone loss in patients with insufficient 25-0H D Levels $p < 0.001$ Correlation found between EDSS score and rate of bone loss in the lumbar vertebra and hip (spine: $r = -0.40$, $p = 0.008$; hip: $r = -0.38$, $p = 0.01$)
Ozgocmen et al.[14]	2005	31	38.2 ± 10.1 (20–54)	3.13 ± 2.03 (1.0–8.0)	Mean Z score in MS patients L2-L4 vertebrae was −0.98 (−2.9–1.3) compared with −0.06 (−1.8–2.5) for the control group ($p = 0.001$). Mean Z score in femoral trochanter was −0.67 (−2.5–1.5) compared with 0.2 (−1.4–3.1) for the control group	Significantly lower levels of 25 OH D in MS patients compared with controls ($p = 0.001$) but not correlating with BMD Correlation found between steroid dose and BMD for the femoral trochanter ($r = -0.38$, $p = 0.03$) Correlation between pain thresholds and BMD ($r = 0.35$, $p = 0.05$) EDSS scores correlated with BMD in the proximal portions of the femur ($r = -0.66$, $p < 0.001$) but not in the lumbar vertebrae

(continued)

Table 2. Continued

Study author	Study date	Number of MS patients recruited to the study	Mean age	Mean EDSS score	Evidence of increased risk of MS	Risk factors
Weinstock-Guttman et al.[8]	2004	40 (male)	51.2 ± 8.7	5.8 ± 1.9	80% of patients had reduced bone mass, 42.5% osteopenic and 37.5% osteoporotic	Multiple linear regression modelling retains EDSS ($p = 0.0018$) as significant variable Multiple linear regression modelling retains BMI ($p = 0.004$) as significant variable Correlation found between EDSS and femoral BMD ($r = -0.53$, $p = 0.001$) Correlation found between disease duration and femoral BMD ($r = -034$, $p = 0.0035$) Correlation found between BMI and femoral BMD ($r = 0.44$, $p = 0.005$) Correlation found between number of cycles of steroid treatment and femoral BMD ($r = -0.34$, $p = 0.039$)
Zorzon et al.[15]	2005	43	Patients treated with continuous steroids: 43.3 ± 10.3 (26–63) Patients treated with steroids during relapses only: 41.7 ± 10.3 (27–62)	Patients treated with continuous steroids: 1.6 ± 1.3 (1.0–6.0) Patients treated with steroids during relapses only: 2.8 ± 2.1 (1.0–6.0)	Increased probability of MS patients being osteopenic compared with age matched controls (Odds Ratio = 2.6, $p = 0.016$). However, no overall difference in BMD between patients and controls No significant difference between BMD of patients and controls in male patients	Correlation found between EDSS and femoral BMD ($r = -0.31$, $p < 0.05$)
Achiron et al.[16]	2004	256	44.3 ± 11.4 (18–69)	3.7 ± 2.5 (0–8.5)	Significantly higher proportion of female MS patients with a T score >1 than in control group ($p = 0.001$)	
Formica et al.[11]	1997	71	45.6 ± 1.1	Ambulatory patients' mean EDSS = 5.8 ± 0.2 $n = 39$ Non-ambulatory patients' mean EDSS = 7.8 ± 0.2 $n = 32$	Significantly lower TBBM when expressed as a Z score compared with control group ($p < 0.04$)	Lower total body bone mineral in MS patients with EDSS >6.5 than in MS patients with EDSS <6.5 (2.3 ± 0.1 *vs.* 2.5 ± 0.1 kg, $p < 0.05$) EDSS scores correlated with total body bone mineral content ($r = 0.33$, $p < 0.01$)

the greater the impairment. However, if osteoporosis was a result of the disease process of MS itself, this would also be observed. Finally, age may also have a confounding effect; however, none of the studies has looked for a correlation between age and BMD.

Some of the most interesting evidence about the role of disability in the pathogenesis of MS osteoporosis comes from a study which found no significant overall difference between BMD in patients and the control group.[16] The variables that correlated with BMD were EDSS (positive correlation), pyramidal function (positive correlation) and cerebellar function (negative correlation). Most significantly the mean EDSS in the study was relatively low at 3.79 (median score was 3.0) with only 5.5% of patients wheelchair dependent with an EDSS score of > 7.0.[16]

The impact of motor disability is confounded by other factors. A correlation between BMD in the lumbar vertebrae and patient pain thresholds has been found.[14] In male patients, a positive correlation has been observed between BMD and both BMI (correlation with femoral BMD only) and EDSS score (correlation with femoral and vertebral BMD). It was also shown that EDSS score and BMI two years prior to the study could be used as future indicators of low BMD.[8]

Overall, degree of disability appears to be an important risk factor for osteoporosis amongst PwMS.

The chronic inflammatory process of multiple sclerosis

The inflammatory process of MS may also contribute to the reduction in BMD. Osteoclast differentiation is driven by a paracrine factor called receptor activator of nuclear factor kappaB ligand (RANKL), which is in turn inactivated by its decoy receptor, osteoprotegrin.[17] The pathogenesis of osteoporosis following oestrogen withdrawal is thought to be mediated by changes to cytokine levels with RANKL being the most important. It is also thought that changes in RANKL levels are responsible for the increased bone loss observed in chronic conditions such as myeloma and rheumatoid arthritis.[33] Serum RANKL and osteoprotegrin (OPG) levels have been compared between PwMS (mean age 31.2 ± 6.7 years) and age matched controls. Significantly higher levels of RANKL ($p < 0.01$) and OPG ($p < 0.05$) were found in the PwMS.[34] Interestingly, patients had a low mean EDSS of 2.38 ± 2.45.[34] The fact that levels have risen in patients with such low levels of disability implies that they are not doing so in a response to reduced bone stress but are due to the inflammatory disease process of MS itself, which may be more severe in the early disease phases.

A further factor, osteopontin (OPN), has been implicated in the shared pathogenesis of MS and osteoporosis. Knockout studies in mice have revealed that OPN has an important role in control of bone mineralization. OPN $-/-$ mice have hyper-mineralized but more fragile bones.[35] A study compared OPN levels and BMD in 50 PwMS (33 RRMS, 12 SPMS and 5 PPMS) and 30 demographically matched controls. Mean OPN levels in controls were $154.4 +/-81.8$ ng/ml compared with levels of only $15.9 +/-3.62$ ng/ml ($p < 0.001$) in PwMS. Although no significant difference was found in BMD between the two groups, PwMS had a three-fold higher incidence of osteoporosis (34% compared with 10.3%, $p = 0.017$). OPN levels were also found to correlate with femoral neck BMD ($r = 0.85$, $p = 0.010$). There was no correlation with OPN levels and cumulative steroid dose.[36] It is difficult to ascertain the significance of these results in the context of osteoporosis without further studies. However, other studies have found that OPN levels are raised in PwMS[37] and that the OPN is capable of modulating the T-helper 1 response to induce relapses in RRMS patients whilst its absence has been shown to provoke remission in murine knockout studies.[38,39] Clearly there is an interesting role in the shared pathogenesis of osteoporosis and MS which remains to be fully elucidated.

Vitamin D, multiple sclerosis and osteoporosis

The role of vitamin D in bone homeostasis is well understood. This is mostly mediated by acting on gut epithelium to increase calcium absorption but more recently it has been shown to have a secondary role in controlling epiphyseal plate growth by acting directly on osteoblasts and chondrocytes.[40]

PwMS are susceptible to vitamin D deficiency. Eighty per cent of PwMS have low intake and 40% limited sunlight exposure.[12] Mean 25(OH)D levels of PwMS are lower than in age matched controls[13,14] with mean 25(OH)D levels below the acceptable level of 20 ng/ml.[13]

A significant correlation between 25(OH)D levels and BMD has been reported ($r = 0.292$, $p = 0.047$); however, multivariate analysis correcting for age reduced the correlation.[12] In other studies there were no[14] or only statistically insignificant correlations.[13] Thus while PwMS are susceptible to low 25(OH)D levels the evidence implicating linking levels to reduced BMD in PwMS is unclear. Few studies have investigated this link.

Other Iatrogenic aetiologies in multiple sclerosis

Anti-epileptic drug treatment can lead to osteoporosis. All classes of anti-epileptic have been implicated.[41–46] Meta-analysis has shown that barbiturate class anti-epileptic drugs confer a two-fold relative risk of osteoporotic fracture compared with control groups (relative risk, RR = 2.17; 95% confidence interval,

Table 3. Pharmacological therapies for management of osteoporosis. Summarized from Sambrook and Cooper[5] and Miller[51]

Drug mechanism	Examples	Efficacy	Indications
Antiresorptive agents	Calcium	Little efficacy when used alone. Synergistic effect when used with vitamin D	All patients at risk of deficiency should have dietary calcium supplementation
	Vitamin D	Shown to be effective at reducing fracture rates in at risk patients	All patients at risk of deficiency should have dietary vitamin D supplementation
	Hormone Replacement Therapy – oestrogen or combined oestrogen and progesterone	Shown to reduce osteoporotic factors around the menopause	Due to adverse events (increased cardiovascular events and increased breast cancer) hormonal therapy is only used as a short-term measure to treat peri-menopausal symptoms
	Bisphosphonates e.g. alendronate, etidronate, residronate, ibandronate, zoledronic acid	Gold standard for osteoporosis treatment and prophylaxis. Shown to reduce vertebral fractures by up to 50% and non-vertebral fracture by 20-40%	See Table 4A–C
	Selective Oestrogen Receptor Modulators (SERMs) e.g. raloxifene, bazedoxifene	Reduced efficacy compared with bisphosphonates. Little evidence of efficacy at non-vertebral sites. Beneficial reduction in rates of breast cancer	Restricted to use in postmenopausal women with mild osteoporosis. Avoid in women at risk of venous thrombosis.
	Calcitonin	Evidence for efficacy unclear	May have a role in treatment of patients with osteoporosis who cannot comply with dosing instructions of bisphosphonates
	Tibolone	Reduces incidence of vertebral compression factors and better effects on BMD at non-vertebral sites compared with SERMs	Use limited by increase in cerebrovascular events observed in patients taking tibolone
	RankL monoclonal antibodies e.g. denosumab	Early trials show excellent short-term effects on BMD with short duration of action	Phase II clinical trials ongoing
Anabolic agents	Parathyroid hormone e.g. teriparatide	Good acute reduction in fracture rates but effects reduced upon withdrawal of treatment	Use limited to 24 months
Other agents	Strontium ranolate	Comparable efficacy to bisphosphonates at vertebral sites and reasonable efficacy at vertebral sites	Useful alternative to bisphosphonates – see Table 4A–C

CI 1.35, 3.50). Non-barbiturate anti-epileptics have a lower but still clinically significant effect (RR = 1.54; 95% CI 1.24, 1.93).[47] Given the widespread use of these drugs in the treatment of MS, they may also have a role although this has yet to be investigated. Indeed, other drugs may also be important. Meta-analysis has revealed that antidepressant antipsychotic and benzodiazepine treatment also increases a patient's risk of osteoporosis.[47]

Interferon beta (IFN-β) treatment may also exacerbate patients' risk of osteoporosis. IFN-β acutely increases OPG and RANKL levels as well as decreasing osteoclast differentiation.[48] This is backed up by in vitro data showing that IFN-β can decrease osteoclast maturation when used at similar levels to those used in vivo.[48]

Formulation of an approach to management of osteoporosis in multiple sclerosis patients

Reduced BMD is clearly a significant problem in the management of MS and falls remain an important and common symptom. Despite this, the UK National

Institute for Health and Clinical Excellence (NICE) guidelines for MS make no reference to osteoporosis.[49] Osteoporosis as a co-morbidity is a significant predictive variable that a fall will result in seeking medical treatment.[50] PwMS are at a higher risk of falls resulting in fracture, albeit at almost half the risk of spinal cord injury patients.[32] Therefore there is a need for management guidelines.

Guidelines for the management of osteoporosis in the general population

The mainstays of osteoporosis therapy and prevention are vitamin D, calcium supplements and bisphosphonates, the most effective drugs currently available for slowing decline in BMD.[4,5] Pharmacological management of osteoporosis is reviewed by Sambrook and Cooper[5] and Miller;[51] these are summarized in Table 3.

Algorithms have been produced to guide the treatment of osteoporosis in some but not all patient populations. NICE has published guidelines for the primary prevention of osteoporosis in postmenopausal women[52] and the secondary prevention of osteoporosis in postmenopausal women who have already suffered an osteoporosis fragility fracture.[53] These guidelines are not necessarily applicable to patients on long-term glucocorticoid therapy. In both cases one should first ensure that patients have adequate intakes of calcium and vitamin D. If it is suspected that they are deficient then supplements should be given. NICE has not published guidelines for treatment of men or postmenopausal women; however, guidelines are being developed for assessment of fracture risk and the prevention of osteoporotic fractures in all at-risk individuals.[54]

For primary prevention in those with established osteoporosis, NICE recommends alendronate as first-line treatment for osteoporosis. Risedronate or etidronate are recommended second-line treatments with strontium ranelate providing a third-line option. Raloxifene is not recommended as primary prophylaxis in postmenopausal women.[52] The criteria that must be met to receive these treatments are shown in Table 4, A–C.

Guidelines for the treatment in men, premenopausal women and patients on long-term glucocorticoid therapy are less clear. Patients are detected either once they have developed an osteoporosis fragility fracture or by clinicians identifying risk factors and choosing to assess their BMD by DEXA. The World Health Organization's FRAX® tool[55] is an algorithm which determines the 10 year probability of osteoporotic fractures for the UK and other populations.[56] The inputs required to calculate a risk are shown in Table 5. It works with or without input of BMD measured by DEXA. It can be combined with guidance from the National Osteoporosis Guidance Group (NOGG) to plot whether a patient is within the intervention threshold. If BMD is not available then it also indicates the need for a DEXA scan in those patients whose requirement for treatment cannot be determined by summation of risk factors.[56] The Royal College of Physicians recommends that men over 50 years with osteoporosis risk factors use the 10 year risk factors computed by FRAX® using BMI to guide treatment.[56] The fracture

Table 4. Bone mineral density cut-offs for primary prevention of osteoporosis for alendronate (A), residronate or etidronate (B) and strontium renilate (C). Independent risk factors for fragility fracture are: parental history of hip fracture, alcohol intake greater than 4 units per day and rheumatoid arthritis. Indicators of low bone mineral density are: BMI $<22\,kg/m^2$, ankylosing spondilitis, Crohn's disease, conditions resulting in prolonged immobility and untreated premature menopause

A

Age	Requirements for treatment
≥75	At least 2 independent risk factors for fracture or indicators of low BMD OR T score ≤2.5
70–74	Independent risk factors for fracture or indicators of low BMD AND T score ≤2.5
65–69	Independent risk factors for fracture AND T score ≤2.5
<65	Independent risk factors for fracture AND indicators of low BMD AND T score ≤2.5

B

Age	Maximum T score for treatment		
	Number of risk factors for fragility fracture		
	0	*1*	*2*
≥75	−3.0	−3.0	−2.5*
70–74	−3.5	−3.0	−2.5
65–69	–	−3.5	−3.0

C

Age	Maximum T score for treatment		
	Number of risk factors for fragility fracture		
	0	*1*	*2*
≥75	−4.0	−4.0	−3.0
70–74	−4.5	−4.0	−3.5
65–69	–	−4.5	−4.0

*A DEXA scan may not be required for treatment to be commenced in these patients. Adapted from NICE.[52]

Table 5. Inputs for the FRAX® algorithm

FRAX® algorithm input	Notes
Age	Accepted between ages of 40 and 90
Sex	
Weight	in kg
Height	in cm
Previous fracture: Yes/No	
Parental history of hip fracture: Yes/No	
Current smoker: Yes/No	
Glucocorticoid treatment >3 months: Yes/No	Dose must equal or exceed 5 mg/day prednisolone or equivalent
Rheumatoid arthritis: Yes/No	Arthritis must be confirmed as rheumatoid arthritis, as osteoarthritis is protective
Secondary osteoporosis: Yes/No	Disorders strongly associated with osteoporosis: type I diabetes untreated long-standing hyperthyroidism osteogenesis imperfecta in adults hypogonadism/premature menopause (<45 years) malabsorption chronic malnutrition chronic liver disease
Alcohol intake >3 units per day: Yes/No	
Bone mineral density	

risk in men rises as BMD decreases and is comparable to that of women of the same age and BMD. Best evidence shows that bisphosphonates are equally effective at reducing fracture risk and increasing BMD in men as they are in women (reviewed by Brown and Guise[57]).

The Royal College of Physicians of London has published guidelines on the management of glucocorticoid-induced osteoporosis.[58] These recommended that high-risk patients starting glucocorticoids or patients who are to take glucocorticoids for at least three months be considered for bone-protective therapy. These guidelines are due for review and do not provide a succinct management algorithm. They recommend that because fragility fractures tend to occur at higher T scores in glucocorticoid-induced osteoporosis, T scores of −1.5 SD or even −1.0 SD should be considered appropriate points for treatment though age should also be taken into account. The report recognizes the inadequacy of a situation which cannot adjust T score cut-offs to appropriate fracture risk with age.[58] The FRAX® algorithm treats long-term glucocorticoid therapy as a separate risk factor when calculating 10 year fracture risk. It therefore represents a useful tool for determining treatment screening and treatment in these patients.

Proposed screening and treatment algorithm

The relative lack of attention MS osteoporosis has received in the literature means that it is difficult to establish guidelines as to which patients should receive screening in the form of DEXA scans or prophylactic treatment. Nonetheless, the excess risk in this population suggests that thresholds for prophylactic treatment should be different amongst PwMS than in the general population. Evidence reviewed here indicates that it is the degree of disability, specifically mobility, which is the most significant risk factor to be considered in devising a treatment algorithm, although other risk factors are likely to be important.

We propose the approach based on the algorithm shown in Figure 1. MS patients who are felt to be at risk from deficiency should have their calcium and vitamin D status checked. Supplements should be prescribed to those with deficiency. Vitamin D supplementation of 800 IU daily is recommended in the form of 20 μg of ergocalciferol.[59] Patients with calcium and vitamin D supplementation require regular monitoring of serum calcium levels, initially weekly. Symptoms of nausea and vomiting are also indications for urgent monitoring. Breast feeding in these patients can lead to hypercalcaemia in the infant. In these patients specialist advice should be sought.[59]

Postmenopausal women should be routinely scanned and then treated with bisphosphonates as per the NICE guidelines. MS fits the criterion of 'condition resulting in reduced mobility' and thus qualifies as an 'Indicator of low BMD'. In all other patients EDSS scores should be used as an indicator for screening. The loss of

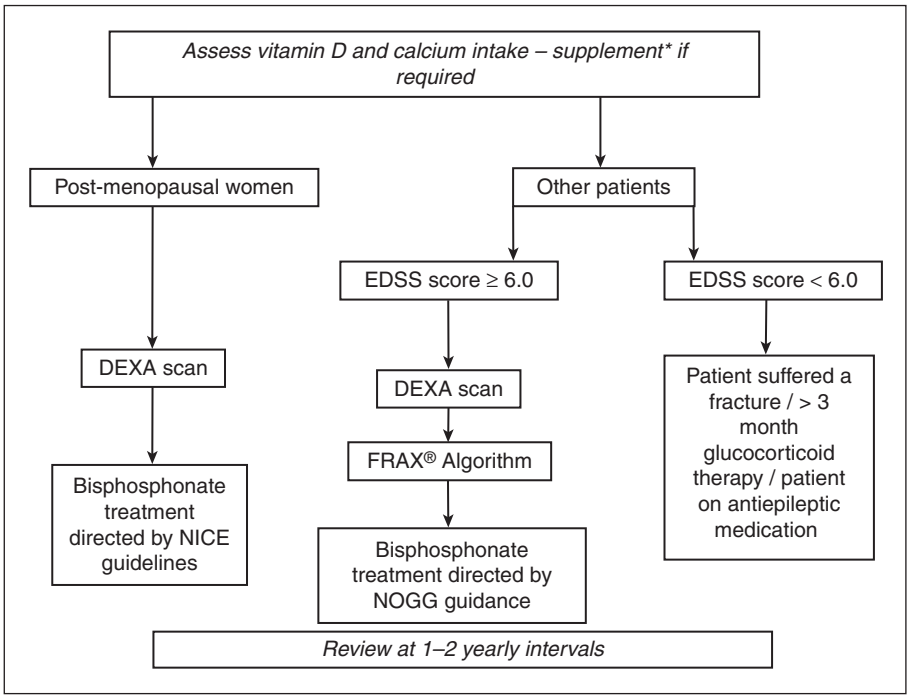

Figure 1. Proposed algorithm for management of osteoporosis in MS patients. *Vitamin D should be given at a dose of 800 IU daily. Patients given calcium supplements must have serum calcium levels regularly monitored, initially weekly.

independent ambulation (EDSS scores of 7 or greater) has been found to correlate well with reduced BMD.[8,12] We propose an EDSS score greater than or equal to 6.0 be used as a threshold at which all patients should routinely receive a DEXA scan. In patients with an EDSS score of less than 6.0 who are not postmenopausal women, fractures should be treated with a high index of suspicion and result in a DEXA scan. Similarly patients on courses of steroids lasting greater than 3 months should receive a DEXA scan as per The Royal College of Physicians guidelines.[58] It has also been shown that anti-epileptics, which are commonly used in the treatment of MS, reduce BMD.[45,46] We recommend patients on any anti-epileptic be routinely scanned. Methotrexate is also used in the management of MS and has been implicated in osteoporosis when used in high chemotherapeutic doses but not at low doses used in MS.[60] Therefore methotrexate should not be considered a risk factor.

DEXA scan results should then be used in the FRAX® algorithm with NOGG guidelines being used to determine patients requiring treatment with bisphosphonates. No consensus exists as to how frequently patients at risk of osteoporosis should have follow-up scans. Rate of bone loss in the general population is reported to be 1.6% of the Z score per year.[57] This data was replicated in a large 15-year follow-up study of 955 women. Mean bone loss at the femoral neck over this period was found to be 1.67%[58] Precision error of a DEXA scan is between 0.85% and 1% depending upon length of scan.[59] Therefore in the general population yearly scans would be excessive. In PwMS and other high risk populations one- to two-yearly scans represents a reasonable approach in the absence of a solid evidence base.

Further research

In order to establish evidence-based guidelines, a large-scale prospective audit of PwMS needs to be conducted with the aim of quantifying the effect of MS on BMD, qualifying exactly which risk factors are leading to a drop in BMD and then applying this to create a management algorithm. Specific issues which will need to be addressed include:

- The role of disability. It is clear that this an important risk factor but not yet clear at what stage it becomes significant. Patients with low EDSS scores have normal or even raised BMD.[16] Loss of ambulation and dependence upon walking aids have been shown to correlate well with reduced BMD.[8,12] EDSS scores could provide a useful indicator as to when DEXA scanning should be performed or prophylaxis commenced. Further elucidation as to the relative risk inferred by differing EDSS scores is required before this can be performed to a good evidence base.

- The role of the inflammatory disease process. It is unclear as of yet what degree of impact the disease process itself has upon osteoporosis. This will become gradually clearer as more is understood about the pathophysiology of MS itself. However, clinical studies could be conducted to better establish the effects of disease duration and severity on BMD.
- The role of interferon-β treatment. Weinstock-Guttman et al. have shown interferon-β treatment may have a protective effect against osteoporosis.[48] Clinical studies are required to establish whether this occurs in vivo.
- Men. The role of osteoporosis in male PwMS needs to be better understood.

We believe our proposed management algorithm will provide clinicians with a useful framework, based on best current evidence, to manage osteoporosis in PwMS until guidelines built on better evidence are in place.

Conclusions

This paper demonstrates that convincing evidence exists showing PwMS are at increased risk of osteoporosis and consequently fragility fractures. As in all populations menopausal status is the most significant risk factor. The most significant reported aetiology in PwMS compared with control populations appears to be the level of disability within individual patients. The roles of inflammation, glucocorticoid use, vitamin D and other potential risk factor levels remain unclear and call for large-scale prospective studies to better determine their influences. These prospective studies are also required to create screening and management guidelines built from a solid evidence base. Until this is achieved we have proposed a simple algorithm for the management of osteoporosis in MS patients.

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