Osteoporos Int (2011) 22:2935–2949
DOI 10.1007/s00198-011-1644-8

REVIEW

Bone health in multiple sclerosis

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Received: 3 January 2011 / Accepted: 14 April 2011 / Published online: 21 May 2011

Abstract People who are disabled with multiple sclerosis (MS) may be at increased risk of osteoporosis. This review discusses issues relevant to bone health in MS and makes practical recommendations regarding prevention and screening for osteoporosis and fracture risk in MS. A search of the literature up until 5 April 2011 was performed using key search terms, and articles pertinent to bone health in MS were analysed. Bone mineral density (BMD) is reduced at the lumbar spine, hip and total body in MS, with the degree of reduction being greatest at the hip. A strong relationship exists between the disability level, measured by the Expanded Disability Status Score, and BMD at the lumbar spine and femoral neck, particularly the latter. The rate of loss of BMD also correlates with the level of disability. Pulsed corticosteroids for acute episodes of MS, even with a high cumulative steroid dose, do not significantly affect BMD, but an effect on fracture risk is yet to be elucidated. There appears to be no correlation between vitamin D levels and BMD, and the relationship between disability and vitamin D levels remains unclear. Falls and fractures are more common than in healthy controls, and the risk rises with increasing levels of disability. The principal factor resulting in low BMD and increased fracture risk in MS is immobility. Antiresorptive therapy with bisphosphonates and optimising vitamin D levels are likely to be effective interventions although there are no randomised studies of this therapy.

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Keywords Bone mineral density · Corticosteroids · Falls · Fractures · Multiple sclerosis · Vitamin D

Introduction

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system in which lymphocytic infiltration leads to damage of myelin and axons. Although initially the inflammation is transient and remyelination occurs, over time the pathological changes become dominated by widespread microglial activation associated with extensive and chronic neurodegeneration [1]. Three main patterns of disease seen in MS are relapsing/remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS). Approximately 65% of people enter the secondary progressive phase, whereas in 20%, the illness is progressive from the outset [1]. Between 3 and 7 people per 100,000 population are diagnosed with MS each year and about 100 to 120 people per 100,000 population have MS [2].

Before the 1990s, there was little to offer patients by way of disease modification and the mainstay of medical treatment was pulsed corticosteroids for acute episodes along with measures to control symptoms such as pain, spasticity and bladder dysfunction. However, the last 20 years has seen a surge of interest in disease-modifying therapies. In contrast, an awareness of bone health issues in MS has lagged behind. Until recently, only a few studies with small patient numbers have been published and none of these have included randomised controlled trials of therapies. This is surprising considering the impact a fracture may have on someone who is already disabled, as well as the number of potential risk factors for osteoporosis and fractures in people with MS, such as immobility, repeated courses of corticosteroids, possible vitamin D deficiency, muscle weakness and falls.

There has been an increasing publication rate in the field of bone health in MS in the last 10 years, as well as a large

number of studies exploring the possible role of vitamin D in the aetiology of the condition.

The aim of this report was to review the evidence regarding bone health in MS. A search of the databases AMED, CINAHL, Embase, Medline and PsychInfo was performed up to 5 April 2011 using relevant search terms (see Fig. 1). Scientific papers pertinent to bone health in MS were analysed and included in the evidence base, as well as additional papers identified from reference lists. We excluded commentary papers and letters to editors, but included case reports and studies published only in abstract form. Only one randomised control trial was identified [3].

We discuss bone mineral density (BMD), fractures and falls in MS and their relationship to disability levels and corticosteroid administration, as well as the effects of corticosteroids on bone turnover and fracture risk. We also attempt to elucidate the role of vitamin D in relation to BMD and immobility in MS. We use the available data to make practical recommendations regarding prevention and screening for osteoporosis and fracture risk in MS and suggest treatment guidelines.

Bone health in MS

Bone mineral density

Information on BMD in MS is available from 20 published papers comprising 1,331 patients and 428 controls. One study is unpublished [4], three are published in abstract form [5–7] and six are case–control studies [8–13]. Five of the case–control studies show that BMD is reduced in people with MS at the lumbar spine [8–10, 13], femoral neck [8, 9, 13] and total body [11]. In the case–control studies where average bone density results are reported, BMD is reduced by between 3% and 28% at the hip in MS patients, whilst at the spine, the results vary from a 6% increase to a 23% reduction in BMD in comparison to controls [8–10, 12]. Only Zorzon et al. found no reduction in BMD at the lumbar spine or hip, although this was a group of patients with low levels of disability with a mean Expanded Disability Status Score (EDSS) score <3 (see Table 1) [12]. In the non-controlled studies, which compare BMD in people with MS to age- and sex-matched normal

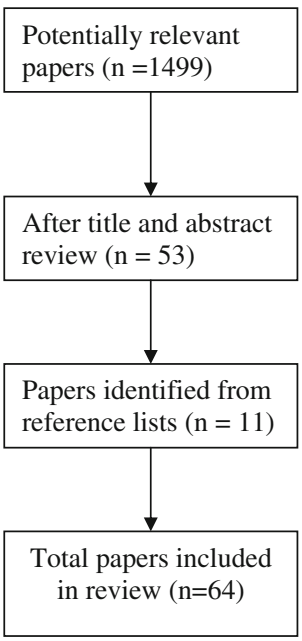

Fig. 1 Flowchart showing selection of papers

Table 1 Kurtzke expanded disability status scale

0.0	Normal neurological examination
1.0	No disability, minimal signs in one functional system (FS)
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 h/day despite relatively severe disability; able to walk without aid or rest some 500 m
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterised by relatively severe disability; able to walk without aid or rest some 300 m
5.0	Ambulatory without aid or rest for about 200 m; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 m; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 m with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 m without resting
7.0	Unable to walk beyond approximately 5 m even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 h/day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorised wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self-care functions
9.0	Confined to bed; can still communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

reference data—reported as Z-scores—the overall picture is of reduced BMD at the lumbar spine and hip [4, 14–19] (see Table 2). The two studies which reported positive Z-scores included patients with low disability levels (mean EDSS <3.1) [17, 18]. In general, the degree of reduction in BMD in people with MS is greater at the hip than the lumbar spine [4, 8, 14–16, 19].

A consistent finding is a strong negative correlation between disability level, measured by EDSS, and total body bone mineral content (TBBMC) [11], lumbar spine BMD [13, 16] and femoral neck BMD [6, 10, 12, 13, 16, 20], the correlation being strongest at the femoral neck. Terzi et al. found a significant negative correlation between MS disease duration and BMD at both lumbar spine and femoral neck [13]. A meta-analysis of studies using Z-scores, from papers where data are presented in a suitable form, shows a mean femoral neck Z-score −0.85 (95% confidence interval [CI] −1.32 to −0.38) (see Fig. 2) and mean lumbar spine Z-score −0.38 (95% CI −0.8 to 0.04) (see Fig. 3).

Body composition seems to have an important influence on BMD. In non-MS populations, there is a strong relationship between physical activity levels and muscle mass, as well as between muscle mass and BMD [21]. There have been similar findings in MS where case–control studies have shown no difference in muscle mass between ambulatory MS patients and healthy controls [11, 22], but there is a significant reduction in muscle mass in non-ambulatory patients [11]. Muscle mass showed a strong negative correlation with EDSS [11] and was an independent predictor of BMD [11, 17].

The annual rates of bone loss at the femoral neck in men and women with MS were threefold to sixfold higher than losses in control subjects, and there was a significant association between EDSS at baseline and annual rate of loss of bone over a 2-year period [8]. In the lumbar spine, the annual rate of bone loss in women, although not in men, was higher than controls [8]. In physically active people with MS on continuous low-dose steroids, EDSS correlated with C-terminal collagen cross-links (CTX). C-terminal telopeptide of type I collagen, and this bone resorption marker was significantly elevated only in patients with EDSS >5.5 [23].

The finding of a reduced BMD in MS is similar to that seen in other disabling diseases such as spinal cord injury (SCI) [24–26] and stroke [27–29] where there is also a correlation between BMD and the degree of immobility. In SCI, BMD is significantly lower in complete compared to incomplete lesions [24], and after stroke, BMD falls more rapidly at the proximal femur of the paretic side in "non-ambulatory patients than in those who are ambulatory [26, 28, 29]. The pattern of bone loss seen in MS—greater at the femoral neck than the lumbar spine—is comparable to SCI [26] and the reduction in physiological loading of the hip may be an explanation for this. The spine, however, is subject to relatively greater forces in the sitting position and over time accumulates degenerative changes, thereby elevating BMD when measured by dual-energy X-ray absorptiometry (DXA).

Fractures

Many of the fractures recorded in people with MS are due to low trauma such as stumbles and falls from standing height or less [8, 30, 31]. Some are virtually atraumatic, for example, a rib fracture due to turning in bed at night, a vertebral fracture due to lifting [32] and pelvic, hip or femoral fractures in wheelchair-dependent individuals with no obvious precipitating cause [33–35]. Fractures can be found incidentally [33] or present with pain and immobility [33, 34], leg swelling [35] or even shortness of breath (attributed to fat embolism) [35].

The incidence of fractures during the course of MS has been described in four studies (see Table 3) [16, 32, 36, 37]. Logan et al. used the Veterans Health Administration (VHA) National Spinal Cord Dysfunction Register to identify retrospectively inpatient and outpatient encounters for non-axial fractures in people with MS (n=1,700) and traumatic spinal cord injury (n=6,132). Over a 9-year period, the MS cohort experienced a total of 219 non-axial fractures, giving an annual fracture incidence of 1.43% [36]. A prospective case–control study by Sibley et al. followed up 170 people with MS with an average EDSS of 6.5 at monthly intervals for an average of 5.2 years. This study was conducted primarily to investigate the effect of trauma (including fractures) on disease activity in MS. During the study period, a total of 55 fractures were recorded, giving an annual fracture incidence of 6.2% [37]. Troiano et al. interviewed and reviewed the records of a series of 103 corticosteroid-treated MS patients. The number of fractures occurring during the years of corticosteroid treatment (mean average of 7.1 years) was recorded. Overall, 26 of the 103 patients had a total of 30 fractures, yielding an annual fracture incidence of 3.2% [32]. Weinstock-Guttman et al. assessed 40 consecutive male patients attending their MS centre with a mean age of MS symptom onset of 34 years, a mean MS disease duration of 17 years and a mean EDSS of 5.8. Eight patients had nine fracture events subsequent to their MS diagnosis, equating to an annual fracture incidence of 1.3% [16].

There were several limitations to these studies. The VHA population study by Logan et al. [36] may not be generalisable to a non-veteran population in which there is likely to be a higher percentage of females with MS. Since it relied on a broad variety of health professionals to perform ICD-9 coding, fracture rates may have been inconsistent. In addition, there was no record of axial

Table 2 Studies addressing BMD and disability

Author	Subgroups	MS subjects															
		No.	Age	Percent female	EDSS	LS BMD (g/cm^2)	LS Z-score	LS T-score	Osteoporosis LS	Osteopenia LS	TBBMC (kg)	Total body Z-score	FN BMD (g/cm^2)	FN Z-score	FN T-score	Osteoporosis FN	Osteopenia FN	TH BMD (g/cm^2)
Cosman et al. [8]	Whole group	54	46	67			−1 (estimated by author)						−1.0 to 1.6 (estimated by author)					
	Premenopausal female	22	40	100	6.5	0.99 SEM 0.04							0.75 SEM 0.03					
	Postmenopausal	14	55	100	6.3	0.87 SEM 0.05							0.60 SEM 0.03					
	Men	18	46	0	7	0.95 SEM 0.04							0.72 SEM 0.03					
Dovio et al. [14]		13	32	84	1.9 SEM 0.3	0.998 SEM =0.036	−0.42 SEM 0.36	−0.51 SEM 0.35										0.873 SEM 0.044
El-Ghoneimy et al. [20]	Whole group	30	29	63					20%	50%								
	RRMS	15				1.08±0.14			13%	48%								0.93±0.16
	PPMS	6				1.02±0.2			17%	50%								0.87±0.22
	SPMS	9				0.95±0.13			33%	56%								0.74±0.13
Formica et al. [11]		71	46	100							2.4±0.1	0.3±0.1						
Gallagher et al. [7]		93	35	100														
Francis et al. [4]		171	51	66			−0.2 CI +0.05 to −0.45	−0.9 CI −0.67 to −1.13	12%	37%				−0.69 CI −0.5 to −0.88	−1.52 CI −1.31 to −1.73	21%	46%	
Havrdova et al. [5]		299	43	80														
Herndon et al. [93]		11	58	27	6.9±1.8			−3.5±1.6	73%	7%								
Mojtahedi et al. [17]		29	45	100	2.9±1.2	1.04±0.1	0.51±1.01	−0.06±0.94		24%	2.29±0.28	0.85± 0.89	0.79±0.13					0.93±0.14
Nieves et al. [15]		80	45	100		0.905± 0.191	−0.979± 1.27				2.36±0.49		0.676± 0.157	−1.72±1.31				
Ozgocmen et al. [10]		31	38	61	3.13±2.0	1.08±0.13	−0.98±1.0						0.93±0.16	−0.37±1.0				
Schwid et al. [19]		30	44	70	5.18±1.26		0.07±1.51							−0.87±1.35				
Shuhaibar et al. [18]		37	39	65	3.1±1.9	0.99±0.19	0.53±1.17											0.99±0.12
Steffensen et al. [53]	Whole group	80		69														
	Women	55	41	100	2.5													
	Men	25	42	0	2													
Stepan et al. [23]		70	41	67	4.4±1.9			−1.46±1.3							−1.78±1.34			
Terzi et al. [13]		52	36	100	2.2±1.8	0.89±0.33	−0.92±0.86	−1.29±1.0					0.83±0.12	−0.2±0.91	−0.55±0.98			0.85±0.1
Tuzun et al. [9]	Whole group	65		71														
	Women	46	34	100	3.6±2.3	0.953± 0.143							0.758±0.139					0.844± 0.146
	Men	19	35	0	3.5±1.9	0.881± 0.108							0.804±0.114					0.868± 0.129
Varoglu et al. [71]	Whole group	32																
	Interferon-treated	17	36	59	2.64±0.7	0.9±0.13			18%	47%						29%	41%	0.76±0.13
	Non-interferon-	15	34	53	2.8±1.2	0.96±0.12			7%	40%						13%	60%	0.73±0.2

	treated																
Weinstock-Guttman et al. [16]		40	51	0	5.8±1.9	1.1±0.16	−1.01±1.39	−1.06±1.35				0.88±0.18	−1.28±1.2	−1.64±1.34			
Zorzon et al. [12]	Whole group	43															
	Regular pulsed steroids	25	43	72	1.6±1.3	1±0.1						0.808±0.22					
	Pulsed steroids for relapses	18	42	61	2.8±2.1	1.023±0.11						0.790±0.12					

Author	MS subjects					Control subjects											
	TH Z-score	TH T-score	Osteoporosis TH	Osteopenia TH	BMD comments	No.	Age	Percent female	LS BMD (g/cm^2)	LS Z-score	LS T-score	TBBMC (kg)	Total body Z-score	FN BMD (g/cm^2)	FN Z-score	FN T-score	TH BMD (g/cm^2)	BMD comment
Cosman et al. [8]						49												
							42	100	1.19 SEM 0.03					0.92 SEM 0.03				
							55	100	1.03 SEM 0.07					0.83 SEM 0.04				
							48	0	1.08 SEM 0.04					0.85 SEM 0.05				
Dovio et al. [14]	−0.52 SEM 0.38	−0.6 SEM 0.37																
El-Ghoneimy et al. [20]			23%	40%														
			7%	47%														
			33%	17%														
			44%	44%														
Formica et al. [11]						71						2.5±0.1						
Gallagher et al. [7]					‘82% had bone loss’	104	52	100										‘45% had bone loss’
Francis et al. [4]																		
Havrdova et al. [5]					25% osteoporosis, 45% osteopenia													
Herndon et al. [93]																		
Mojtahedi et al. [17]	0.32±1.13	−0.09±1.13		10%														
Nieves et al. [15]																		
Ozgocmen et al. [10]						30	36	67	1.18±0.14	−0.06±0.1				0.98±0.13	−0.18±0.9			
Schwid et al. [19]																		
Shuhaibar et al. [18]	0.72±0.88																	
Steffensen et al. [53]					Z-score ≤−2 in 24%													
					Z-score ≤−2 in 20%													
					Z-score ≤−2 in 32%													
Stepan et al. [23]		−1.41±1.3			34% osteoporosis, 46% osteopenia													
Terzi et al. [13]					10% osteoporosis, 38% osteopenia	41	36	100	1.1±0.12	0.56±1.1	0.23± 1.22			0.95±0.12	0.8±1.01	0.42± 0.93	0.98±0.1	0% osteoporosis, 27% osteopenia
Tuzun						72		58										

Table 2 (continued)

Author	MS subjects				Control subjects										
	TH Z-score	TH T-score	Osteoporosis TH	Osteopenia TH	BMD comments	No.	Age	Percent female	LS BMD (g/cm^2)	LS Z-score	LS T-score	TBBMC (kg)	Total body Z-score	FN BMD (g/cm^2)	FN Z-score	FN T-score	TH BMD (g/cm^2)	BMD comment
et al. [9]						42	33	100	1.083± 0.133					0.89±0.108			0.95±0.087	
						30	32	0	1.147± 0.114					1.018±0.125			1.035± 0.144	
Varoglu et al. [71]																		
Weinstock-Guttman et al. [16]					38% osteoporosis, 43% osteopenia													
Zorzon et al. [12]					5% osteoporosis, 58% osteopenia	61	42	67	0.965±0.02					0.811±0.04				7%osteoporosis, 34% osteopenia

Values are quoted as mean ± standard deviation where available from study data unless otherwise stated

SEM standard error of mean, *CI* confidence interval

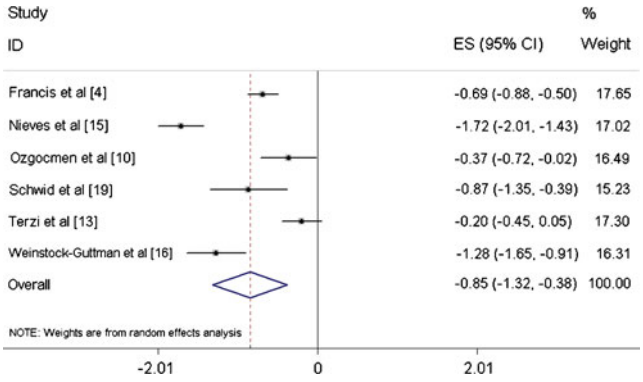

Fig. 2 Forrest plot of femoral neck Z-scores

fractures or any fracture care outside of the VHA [36]. A limitation of two studies [16, 32] was the reliance or part reliance on self-reporting of fractures by people with MS who can experience cognitive deficits. These considerations may partly explain why, with one exception [37], fracture rates were not increased compared to the general population annual fracture incidence, which has been estimated at 3.6% [38]. Furthermore, there is currently no evidence of an increase in lifetime prevalence of fractures in people with MS: in a cross-sectional survey of 9,346 people registered on the North American Research Committee on MS (NARCOMS), with a mean age of 53.6 years, only 15% gave a history of fracture occurring after 13 years of age [39]. Although there is no directly comparable control cohort, this figure is low compared to, for example, a self-reported survey of a nationally representative general population sample of 45,293 individuals in England in which lifetime fracture prevalence was more than 50% in middle-aged men and 40% in

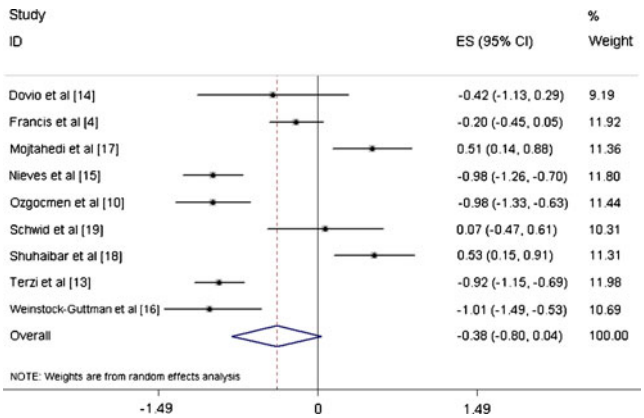

Fig. 3 Forrest plot of lumbar spine Z-scores

Table 3 Papers addressing fractures in MS

Author	Year	Paper type	MS patient numbers	Percent female patients	Mean age	Hip/pelvis/femur fractures	Vertebral fractures	Upper limb fractures	Other/not specified	Annual fracture incidence (%)	Time frame for fractures
Aggarwal [34]	2004	Case report	1	100	43	3					Presentation
Bazelier [40]	2010	Cohort study (abstract)	5,565						394		
Cocksedge [35]	1984	Case report	2	100	50	3					Presentation
Cosman [8]	1998	Case control	54	67	46	1	1		10		After age of 35 years
Edlich [94]	2010	Case report	1			1					Presentation
Francis [4]	Unpublished	Cross-sectional	171	66	51	4	2	14	12		Since MS diagnosis
Hemdon [93]	2000	Case series	11	27	58				3		
Logan [36]	2008	Cross-sectional	1,700	9	54	77		38	104	1.43	9 years retrospectively
Marrie [39]	2009	Cross-sectional	9,346	76	54	100	165	522	685		Since 13 years of age
Peterson [31]	2008	Cross-sectional	354	67	67	12		17	51		
Sibley [37]	1991	Case–control	170	62	43				55	6.2	5.2 years prospectively
Stenager [30]	1991	Cross-sectional	299	63		13		3	10		22 years retrospectively
Troiano [32]	1992	Case series	103	66	38				30	3.2	7.1 years retrospectively
Weinstock [16]	2004	Case series	40	0	51				9	1.43	Since MS diagnosis
Williams [33]	1984	Case report	2	100	64	2					Presentation

women over the age of 75 years [38]. Lifestyle differences between the MS and control cohorts resulting in a lower exposure to trauma, the inclusion of childhood fractures in the English study [38] and possibly underreporting of fractures by some cognitively impaired MS patients may have contributed to the lower fracture prevalence in the MS study [39].

Case–control studies do, however, suggest an increased rate of fracture in people with MS. Whilst the study by Sibley et al. presented no numerical data for the control group, a graph showed approximately half the fracture incidence in the control group compared to the MS group [37]. Another case–control study documented a self-reported fracture rate in the absence of major trauma occurring above the age of 35 years in 22% of 54 patients with MS with a mean EDSS of 6.2 compared with only 2% of 49 healthy controls [8]. A recent longitudinal population-based cohort study, using the UK General Practice Research Database (GPRD), compared fracture numbers in 5,565 people with MS with healthy controls. It reported that people with MS have a 1.2-fold increase risk of any fracture (adjusted hazard ratio [HR], 1.2). The HR of hip fractures was 2.8. The study is in abstract form only and the precise duration of follow-up for the people with MS was unclear [40].

The cross-sectional postal survey reported by Marrie et al. established a link between increasing levels of disability and fractures in people with MS [39]. In that population, the prevalence of hip, wrist or vertebral fractures after age 13 was 11.2% in participants with mild disability (approximate EDSS $\leq$3), increasing to 17.1% in those with moderate disability (approximate EDSS 4 to 5.5) and 20.3% in those with severe disability (approximate EDSS $\geq$6) [39].

Case–control studies, therefore, suggest an increase in annual fracture incidence in people with MS, and cross-sectional data have shown an increase in fracture rate with increasing levels of disability. There is currently a lack of evidence from large population-based studies to confirm an increase in lifetime fracture prevalence in people with MS.

Fracture risk in MS

Falls

Falls are common in people with MS. Six non-controlled studies have commented on falls frequency in MS [31, 39, 41–44], one of these looking specifically at tips from wheelchairs [43]. Fall frequency in these studies ranged from 34% of people with MS reporting at least two falls in the past 2 months [45] to 64% reporting

at least two falls in 1 year [31]. Of 66 non-institutionalised wheelchair users with MS, 32 (53%) had experienced a complete tip or fall from their wheelchair at some time [43]. These figures are high when compared to fall frequency in the elderly of whom approximately 30% fall annually [46–48]. People with MS who are more disabled fall more often; in the study by Marrie et al., 41.6% of participants with mild disability, 66.4% of those with moderate disability and 62.1% of those with severe disability reported at least one fall in the past 12 months [39].

One recent study used data from the VHA Consumer Health Information and Performance Set to estimate the relative risk of an injurious fall requiring medical attention in veterans with MS compared with veterans without MS [49]. The veteran cohort consisted of 195,417 people, of whom 721 had a diagnosis of MS. During 1 year (October 1, 2007–September 31, 2008), 20 (2.8%) people with MS reported an injurious fall requiring medical attention compared to 2,846 (1.5%) people without MS. The adjusted odds ratio (OR) of an injurious fall was three times higher in females with MS than females without MS (OR=3.0, 95% CI=1.6–5.5), and whilst the adjusted OR of an injurious fall was higher in males with MS compared to males without MS, this difference was not statistically significant (OR=1.2, 95% CI=0.8–2.1).

Corticosteroids

The corticosteroid regimens used in the studies reviewed here were more intensive than the standard 1 g intravenous methylprednisolone (IVMP) daily for 3 days, which is the recommended treatment for acute episodes in the UK. Five studies have looked at the effect of a single course of corticosteroids [8, 14, 19, 50, 51], with dosing schedules ranging from daily IVMP for 3 to 14 days, followed by oral prednisolone 60 to 80 mg daily, tapered over 3–4 weeks [8, 19, 51]. Three studies examined the effect of regular monthly or four monthly pulsed steroids [12, 16, 23].

IVMP profoundly suppresses bone formation as well as increases bone resorption. There are effects on bone and kidney within hours of administration, seen as a rapid decrease in osteocalcin [14, 50, 51], P1NP [14] and serum phosphate [50, 51] with a nadir at about 3 days. The phosphate effects suggest an acute change in the renal tubular re-absorption thresholds. A rising CTX [14], as well as urinary calcium [14, 50, 51]—both peaking at around 10 days—reflect an increase in bone resorption. The mechanism for this increase in bone resorption following intravenous steroids is unknown but may be due to a direct effect of steroids on osteoclasts or osteoclast signals from osteoblasts [14] or perhaps secondary to the parathyroid hormone (PTH) rise [51]. Ninety days after an initial 10-day course of IVMP, all bone turnover markers are raised, suggesting that a high bone turnover state exists which results in reparative bone synthesis [14].

It seems likely, therefore, that intermittent corticosteroid administration will have less effect on bone than continuous therapy. Two prospective studies in which MS patients received repeated pulses of IVMP have demonstrated no evidence of bone loss over 6 months [14] or 12 months [52]. In a third study, Schwid et al. noted no overall loss of bone in a study of 17 patients followed up for 6 months, although non-ambulatory patients lost 1.6% BMD at the femoral neck, whereas ambulatory patients had a 2.9% gain in femoral neck BMD. It was noted that the pattern of bone loss seen was more typical of immobility than steroid use as spinal BMD increased in both groups [19]. In cross-sectional studies, which provide a snapshot of patient exposure to pulsed steroids over an average of approximately 11 years, there is no significant correlation between cumulative steroid dose and lumbar spine, femoral neck or total body BMD [6, 8, 9, 12, 13, 15–18, 20, 23, 53, 54]. Only two cross-sectional studies reported bone loss, which might be linked to corticosteroid use. Formica et al. found a deficit in TBBMC only in non-ambulatory patients, which could be accounted for by a reduction in fat-free mass (FFM). The duration of corticosteroid therapy was the major determinant of FFM reduction, although it could not be independently linked to TBBMC [11]. Ozgocmen et al. found that the estimated cumulative steroid dose (from patient interviews) was negatively correlated with the femoral trochanteric BMD, although there was no correlation with BMD at the femoral neck, Ward's triangle or lumbar spine [10].

The available studies, therefore, show that corticosteroid use in MS does not adversely affect the rate of bone loss, BMD or tibial speed of sound, although long-term prospective data are lacking. Nevertheless, the finding is consistent when looking at different treatment durations and regimens [6, 8, 9, 12–18, 20, 52–54], suggesting that the transient negative effect of pulsed steroids on bone metabolism may be counterbalanced by a beneficial effect in helping people with MS to remain more mobile.

Frediani et al. showed a similar lack of adverse effect of pulsed steroids on BMD in rheumatoid arthritis patients [55]. Pulsed methylprednisolone every 76 days for 12 months with a cumulative dose of 18.9 g had no significant bone loss, whereas those taking daily oral methylprednisolone

with a cumulative dose of 3.06 g experienced significant loss of BMD from the lumbar spine and hip. In the single study in which MS patients were treated with continuous low-dose prednisolone for a mean duration of 6.2 years (average dose of 7.3 mg/day), there was no correlation between bone loss and treatment duration, mean or total dose of corticosteroid. However, the study did not include a non-steroid-treated comparison group [23].

The lack of effect of corticosteroids on BMD does not necessarily imply a low fracture risk since studies in non-MS steroid users have shown that fractures occur at a higher BMD than non-steroid users, implying an effect on bone quality [56]. An elevated fracture risk might also be mediated through an increased risk of falls, which has been associated with long-term corticosteroid use [57]. The daily dose of prednisolone associated with an elevated fracture risk was found to be 2.5 mg/day or more in one study [58] and 10 mg/day in another, after adjustment for confounders [59], suggesting that the dose of 7.3 mg/day for MS patients in the study quoted above [23] may not be benign. The early onset of fracture risk following initiation of corticosteroids is dependent upon daily dose and is seen within 2–3 months with doses above 7.5 mg/day [59, 60]. Cessation of corticosteroids leads to a normalisation of fracture risk within 12 months [59, 61]. Cumulative corticosteroid dose is likely to be more useful when assessing the long-term impact of intermittent corticosteroids on fracture risk [60]. There is no doubt that the fracture risk of intermittent corticosteroid use is far less than with continuous steroids [61]. In a study involving patients with inflammatory bowel disease, chronic obstructive pulmonary disease and arthritis, intermittent high-dose corticosteroid use had little effect on fracture risk with low cumulative doses (<1 g), but the risks of osteoporotic fracture escalated with higher cumulative doses [61].

Concern about fracture risk in MS patients is supported by data from the GPRD recently presented in abstract form which shows an HR for fracture of 1.8 (95% CI, 1.4–2.4) in corticosteroid users [40]. There was a strong relationship to daily dose: HR 1.1 (<7.5 mg prednisolone equivalents) and 2.4 (>7.5 mg prednisolone equivalents). These results were not adjusted for level of disability, so further data are required before drawing any firm conclusions on this issue.

Vitamin D

The role of vitamin D in MS has been investigated both from the point of view of bone health and, more controversially, to explore a possible link to the aetiology of the condition and the occurrence of relapses. A recent report from the Institute of Medicine concluded that there is no proven link between vitamin D status and non-skeletal outcomes, including MS [62]. Reduced sunlight exposure, resulting in low serum 25-hydroxyvitamin D (25-OHD) concentrations, is likely to be a problem for disabled MS patients who are housebound. Heat intolerance is also a well-recognised feature of MS, worsening fatigue and increasing muscle weakness, which may in turn lead patients to protect themselves from sunlight exposure [63]. The effects of serum 25-OHD deficiency on bone and muscle may lead to osteoporosis, osteomalacia and falls.

Although the reported prevalence of serum 25-OHD insufficiency or deficiency in people with MS ranges from 17% to 86.7% [14–16, 20, 64–66], five of the nine case–control studies found no statistically significant difference in serum 25-OHD levels between people with MS and healthy controls [8, 64, 67–69]. Both Ozgocmen et al. and Terzi et al. found a significant reduction in serum 25-OHD levels in MS patients versus control subjects [10, 13], whilst Kragt et al. reported reduced levels in summer but not in winter in people with MS [70]. One controlled study recorded reduced levels in people with RRMS, but not PPMS [70]. People with MS appear to have reduced levels of serum 25-OHD during acute episodes [64, 70].

There seems to be no correlation between vitamin D levels and BMD in MS, although this may be due to the small numbers of patients included in the published studies and the different countries in which these studies were conducted [8–10, 53]. One Australian case–control study found a strong negative correlation between the degree of disability, measured by EDSS, and serum 25-OHD levels, which were mathematically adjusted for the season [66]. Conversely, a Dutch case–control study found no correlation between EDSS and serum 25-OHD levels in summer or winter [69].

Interferon β

The effect of interferon on bone health in MS is not entirely clear. Two small studies suggest that long-term therapy with interferon β has no significant effect on BMD at the spine or hip [18, 71]. However, if patients taking interferon experience fewer relapses, maintaining mobility levels could potentially impact on bone health indirectly.

Osteopontin

Osteopontin (OPN) is a protein component of the bone matrix produced by both osteoblasts and osteoclasts and

is thought to have actions on the cells of many tissues including those involved in immunoregulation [72]. OPN is important for bone resorption, and serum levels are positively correlated with serum CTX and negatively correlated with BMD [72]. A confusing picture has emerged in patients with MS with reports of higher [73, 74] or lower OPN levels [75] compared with controls. This could be due to the studies containing different numbers of people with currently relapsing MS as higher levels of OPN have been recorded during acute episodes [73, 74].

Assessment of bone health

Osteoporosis prevention and screening in people with MS currently lacks consistency. Relatively high rates of intervention were noted by Marrie et al. in the NARCOMS study in which 50% of the patients had undergone bone density testing, 50% were taking calcium supplements, 66% used vitamin D supplements and 14% were on bisphosphonates [39]. In another study of women with MS, only 15% had undergone bone density testing, 50% were taking calcium supplements and 29% took vitamin D [76]. It may be that some patients use vitamin D supplements primarily for their alleged disease-modifying effect rather than for bone health reasons. Women with MS feel that few healthcare providers proactively address the issue of osteoporosis [77, 78].

Assessment of bone health and fracture risk should be an integral component of the care plan for people with MS, particularly postmenopausal women, men over 50 years of age and those who are disabled. When carrying out an assessment, it is important to include immobility as a risk factor and it is suggested that a sustained EDSS of ≥6 (see Table 1) [79] should trigger BMD measurement by DXA. An EDSS of 6 is an appropriate cutoff as it is an established landmark in irreversible disability progression [80–82], fracture risk continues to rise with higher levels [39] and the use of a cane is itself a recognised risk factor for falls in MS [44, 45]. The presence of a prior fragility fracture is a particularly important risk factor and may prompt treatment initiation without BMD measurement if the latter is not readily available.

MS can be factored into the FRAX® tool under the 'secondary osteoporosis' category. In FRAX®, 'secondary osteoporosis' contributes to the fracture risk when the calculation is performed without BMD, but in the presence of a BMD value, 'secondary osteoporosis' has no additional effect on the calculated risk; FRAX®, therefore, assumes that any excess fracture risk attributable to poor mobility operates entirely through the reduction in BMD. This may underestimate the true fracture risk in people with MS who are also at increased risk of falls, which is not included in the FRAX® risk assessment.

Treatment

Treatment options for protecting the bones of people with MS include lifestyle measures such as stopping smoking, reducing alcohol intake, increasing physical activity and optimising vitamin D status, and for those at high risk of fracture, drug treatment to inhibit bone loss or encourage new bone formation.

Progressive resistance training can improve quality of life, fatigue and depression as well as reduce fear of falling in patients with MS [83–85]. Short-term exercise programmes lasting up to 3 months have demonstrated objective improvements in lower limb muscle strength, functional capacity and walking distance [84]. As yet, there have been no longer-term studies and no information is available on possible improvements in bone health. Nevertheless, exercise programmes in elderly populations can reduce risk of falling [86], and encouraging exercise in patients with MS would seem to be a positive step. A recent meta-analysis concluded that exercise training leads to a small improvement in walking mobility in individuals with MS [87].

Although vitamin D deficiency does not seem to be more prevalent in people with MS than control subjects, it makes sense to ensure adequate serum 25-OHD levels, and people with MS should be encouraged to have sufficient exposure to sunlight. We suggest that people with an EDSS ≥6 and those who are housebound should have serum 25-OHD status determined and, if necessary, treated with a target 25-OHD level of at least 50 nmol/L [62]. Although a target serum 25-OHD level of ≥75 nmol/L has been recommended by some authorities [88], a recent placebo-controlled study of high-dose vitamin D supplementation in ambulatory MS patients <50 years of age showed no reduction in bone loss at the hip or spine over 96 weeks. In the intervention group, 92% of the patients achieved a 25-OHD level >75 nmol/L compared with 30% of the placebo group [3]. It is not yet known if these results are applicable to a more disabled MS population. Whilst there may be some concern over the risk of urinary tract calcification in immobility, a recent case–control study comparing mobile with immobile elderly people did not find a significant difference in the two groups regarding urinary calcium secretion [89].

The principal pharmacological interventions for the treatment of osteoporosis are bisphosphonates, denosumab, PTH peptides, raloxifene and strontium ranelate

(see Box 1 and Fig. 4). Our recommendations for treatment are based on extrapolation from the general non-disabled population as there are no treatment studies of these agents in MS. There is, however, evidence for bone protection with bisphosphonate use in other disabling diseases such as hemiplegia [90] and Parkinson's disease [91].

Box 1 Pharmacological interventions for osteoporosis in MS

ANTIRESORPTIVE THERAPY

Bisphosphonates

DRUGS: Alendronate (oral), Risedronate (oral), Zoledronate (iv)
BENEFIT: Prevents vertebral, hip and non-vertebral fractures
ADVERSE EFFECTS: Upper gastrointestinal intolerance (oral), flu-like reaction (iv)
CONTRAINDICATIONS: Dysphagia (oral), eGFR < 35 ml/min

Selective Oestrogen Receptor Modulator

DRUG: Raloxifene
BENEFIT: Reduces vertebral fractures
ADVERSE EFFECTS: Hot flushes, thromboembolism
CONTRAINDICATIONS: liver disease, uterine bleeding

Monoclonal Antibody to RANK ligand

DRUG: Denosumab (6 monthly subcutaneous injection)
BENEFIT: Reduces vertebral, hip and non-vertebral fractures in post menopausal women
ADVERSE EFFECTS: cellulitis
CONTRAINDICATIONS: hypocalcaemia

ANABOLIC THERAPY

DRUGS: Parathyroid hormone (PTH) peptides (daily subcutaneous injection for 18-24 months):Teriparatide (PTH 1-34) and Preotact (intact PTH)
BENEFIT: Protects against vertebral and non-vertebral fractures.
ADVERSE EFFECTS: Dizziness, hypercalcaemia
CONTRAINDICATIONS: malignancy, metabolic bone disease

DUAL ACTION

DRUG: Strontium ranelate (oral)
BENEFIT: prevents vertebral, hip and non-vertebral fractures
ADVERSE EFFECTS: diarrhoea, rashes, thromboembolism
CONTRAINDICATIONS: eGFR<30ml/minute

A weekly oral aminobisphosphonate (BP) such as alendronate or risedronate is recommended as first-line treatment. Dysphagia, which occurs in nearly one third of people with progressive MS [92], is a major contraindication to oral BP therapy. Strontium ranelate, another oral therapy, may be useful in MS patients who suffer from dysphagia or who are intolerant of oral BP, although it should be used with caution in immobile MS patients because of its possible association with thrombosis. Raloxifene is a further treatment option for postmenopausal women who have predominantly vertebral osteoporosis. Although it is free from gastrointestinal adverse effects, the increased risk of thrombosis together with its lack of efficacy for hip fracture reduction makes it an unsuitable choice for disabled older women with MS. Parenteral antiresorptive therapy with subcutaneous denosumab or intravenous zoledronic acid is a good treatment option in MS patients with BP intolerance or contraindications to oral BP. Up to 2 years of anabolic therapy with subcutaneous PTH peptides may be effective in MS patients, but the drugs are expensive and generally reserved for those with severe osteoporosis. There are, however, no studies of PTH peptides in patients with immobility. Once the course of therapy is completed, an antiresorptive drug is started in order to maintain any gain in BMD.

Conclusions

In MS, decreasing mobility is strongly associated with an increasing degree of osteoporosis and muscle wasting, as well as more frequent falls and fractures. At vulnerable skeletal sites, such as the hip, elevated bone resorption owing to decreased mechanical forces progressively reduces the integrity of the bone, thus increasing fragility and fracture risk. A person disabled because of MS who has a simple fall may, therefore, suffer a major fracture leading to prolonged bed rest, with further loss of bone

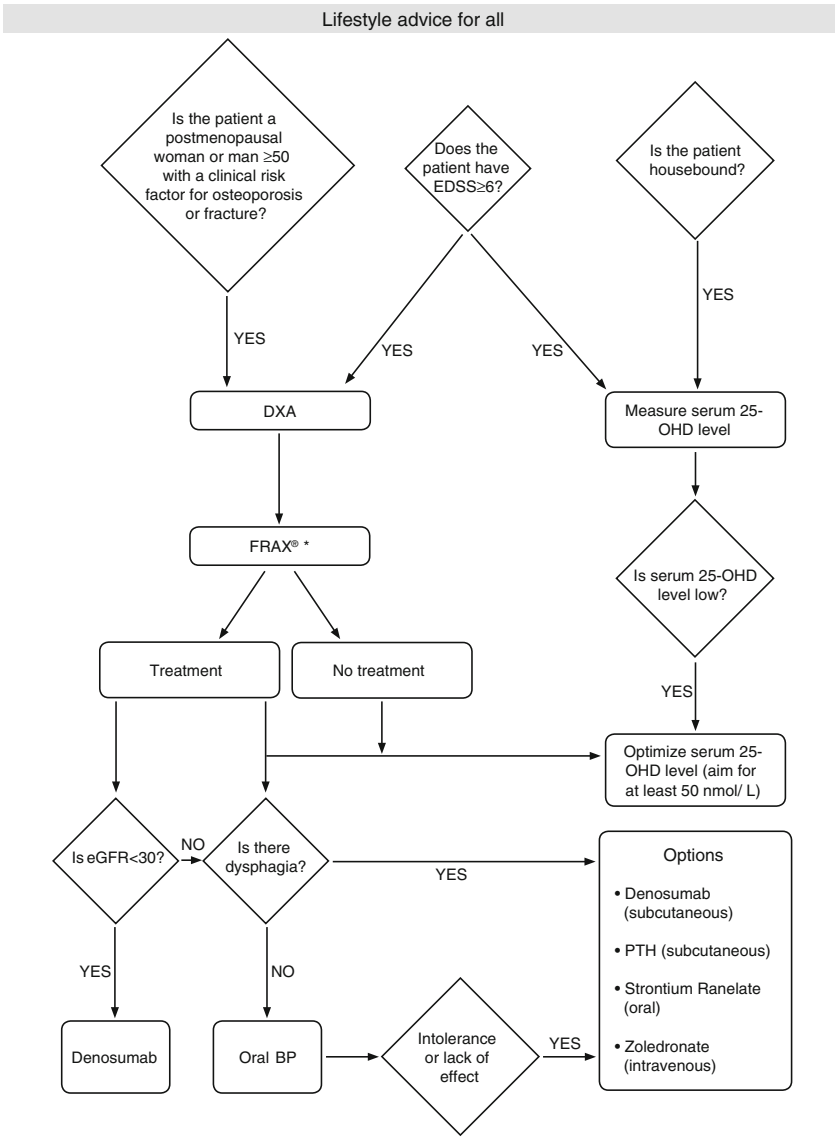

Fig. 4 Management flowchart for bone health in MS

and muscle, thus compounding their disability. In many cases, this situation can be avoided as treatments are currently available to attenuate bone loss and reduce fracture risk. It is, therefore, incumbent upon those caring for patients with MS to evaluate and manage their bone health appropriately.

Future research in this area should look at which patient groups to target with drug therapy and a particularly priority is to find a way to incorporate falls risk into the FRAX® algorithm. It is important to explore the role of physical activity in osteoporosis prevention and treatment including regular standing for those who are severely disabled. The possible interaction between immobility, physical activity and anabolic drug therapies should also be examined in order to maximise the benefit of expensive treatments. It is imperative that disability resulting from the neurological consequences of MS is not compounded by the effects of skeletal failure

Acknowledgments We wish to acknowledge Drs. James Francis and Ian Gaywood for their personal communications and provision of their unpublished data. We would also like to thank Apostolos Fakis for the statistical advice.

Conflicts of interest None.

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