A cross-sectional study of bone health in multiple sclerosis

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ABSTRACT

Background: Osteoporosis is an important risk factor for fragility fractures. Although osteoporosis is considered common in multiple sclerosis (MS), few previous studies focused on fractures in MS.

Objective: Using the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry, we investigated the frequency of osteoporosis, fractures, and clinical risk factors for fracture in MS.

Methods: In 2007, 9,346 NARCOMS participants reported fractures and clinical risk factors for fractures including history of osteoporosis or osteopenia (low bone mass), sedentary level of physical activity, falls in the last year, current smoking status, family history of osteoporosis, and impaired mobility.

Results: Among responders, 2,501 (27.2%) reported low bone mass. More than 15% of responders reported a history of fracture after age 13 years ($n = 1,482$). Among those reporting fractures, 685 (46.2%) reported multiple fractures, while 522 (35.2%) reported a wrist fracture, 165 (11.1%) reported a vertebral fracture, and 100 (7.4%) reported a hip fracture. Excluding age, 1,413 (15.1%) participants had 1 clinical risk factor for fracture, 2,341 (25.0%) had 2, and 5,393 (57.7%) had 3 or more. Among participants with a history of fracture, 746 (55%) reported taking calcium supplements, 858 (68.8%) reported taking vitamin D supplements or a multivitamin with vitamin D, and 334 (22.5%) reported taking a bisphosphonate.

Conclusion: Patients with multiple sclerosis (MS) often have multiple risk factors for osteoporotic fractures. Many patients with MS with low bone mass or previous fractures are not taking supplemental calcium or vitamin D, suggesting a potential area of improvement in care.

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GLOSSARY

MS = multiple sclerosis; **NARCOMS** = North American Research Committee on Multiple Sclerosis; **PDDS** = Patient Determined Disease Steps; **SES** = socioeconomic status.

Osteoporosis is regarded as more common in multiple sclerosis (MS) than in the general population, but osteoporosis is important chiefly as a risk factor for fragility fractures, which are associated with increased morbidity and mortality.¹ Using the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry, we evaluated the frequency of fractures, osteoporosis, and other risk factors for fractures, and osteoporosis screening.

METHODS The NARCOMS Registry is a voluntary self-report registry wherein participants provide demographic and clinical information about their MS.² In October 2007, participants reported fractures of the wrist, hip, or vertebrae occurring after the age of 13 years, and the age at which the most recent fracture had occurred. We examined the most frequently cited risk factors for fragility fractures,¹ using published questions where possible.³ Risk factors included osteoporosis or osteopenia (low bone mass), sedentary level of physical activity, falls in the last 12 months, smoking status, family history of osteoporosis, menopause, impaired mobility, and the use of anticonvulsants (primidone, phenobarbital, phenytoin, carbamazepine, and valproate) associated with low bone mass.¹ Based on descriptions we provided, participants reported their level of activity as inactive, light, moderate, and heavy.⁴ We assessed mobility impairment using Patient Determined Disease Steps (PDDS), a validated self-report measure of disability,⁵ classifying persons with a score of ≥ 3 as impaired. We assessed current smoking status using Behavioral Risk Factor Surveillance Survey (BRFSS)

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Table 1 Adjusted odds ratios (OR) and 95% confidence intervals (CI) showing the association between self-reported osteoporosis and demographic and clinical characteristics among North American Research Committee on Multiple Sclerosis participants

Characteristic	OR	95% CI
Sex		
Male	1.0	
Female	3.60	3.04, 4.28
Age, y		
≤44	1.0	
>44 to ≤51	2.60	1.91, 3.54
>50 to ≤56	4.62	3.44, 6.20
>55 to ≤62	7.31	5.48, 9.75
>62	10.2	7.67, 13.7
Region		
West	1.0	
Midwest	1.04	0.87, 1.24
South	1.28	1.07, 1.52
East	1.39	1.16, 1.65
Disability		
Mild	1.0	
Moderate	1.64	1.36, 1.98
Severe	2.92	2.47, 3.45

n = 9,021; c = 0.76; Hosmer Lemeshow goodness of fit $\chi^2 = 9.5$, $p = 0.30$.

questions.³ We asked participants about use of bisphosphonates, calcitonin, multivitamins with vitamin D, and calcium or vitamin D supplements.

We limited the analysis to US participants to minimize heterogeneity due to differences in access to care (n = 15,529), and to participants with a reported age at MS symptom onset be-

tween 10 and 60 years (n = 14,397), because these extremes of onset groups may be atypical.

We evaluated demographic and clinical predictors of osteoporosis, bone density testing, and osteoporosis treatment using χ^2 tests for categorical variables, t tests for normally distributed continuous variables, and multivariable logistic regression. Multivariable models considered the variables described above and age; sex; race; socioeconomic status (SES) as measured by education, income, and health insurance status; and region of residence as previously described.² All statistical analyses were conducted using SAS V9.1.3.

Standard protocol approvals, registrations, and patient consents. The NARCOMS Registry is approved by the Western Institutional Review Board. Participants give permission for their information to be used for research purposes.

RESULTS Of 14,397 eligible participants, 9,346 (64.9%) responded. Most responders were white (93.9%), were women (76.1%), had moderate disability (median PDDS 3, IQR [1–5]), and had mean (SD) age of 53.6 (10.3) years and mean (SD) disease duration of 23.0 (11.5) years. As compared to nonresponders, responders were more likely to be white, with higher levels of education and income (all $p < 0.0001$).

Among responders, 1,386/9,029 (15.4%) reported osteoporosis, while 1,507/8,820 (17.1%) reported osteopenia. Collectively, 2,501 (27.2%) responders reported low bone mass. The odds of osteoporosis were higher in women than men, and increased steadily with increasing age and higher levels of disability (table 1). Smoking, race, SES, and use of anticonvulsants were not associated with osteoporosis.

Sixteen percent of responders reported a fracture after age 13 years (n = 1,482), of whom 522 (35.2%) reported a wrist fracture, 165 (11.1%) reported a vertebral fracture, 100 (7.4%) reported a

Table 2 Frequency (%) of clinical risk factors for fracture among North American Research Committee on Multiple Sclerosis participants, stratified by age and sex

Risk factor	Men, n (%)		Women, n (%)		Overall n (%)
	Age ≤50 y	Age >50 y	Age ≤50 y	Age >50 y	
Impaired mobility	344 (64.2)	1,403 (82.5)	1,267 (46.3)	3,152 (72.2)	9,337 (66.0)
Falls in previous 12 mo	266 (51.2)	968 (58.3)	1,318 (49.6)	2,478 (58.1)	5,030 (55.2)
Family history of osteoporosis	111 (26.2)	292 (22.3)	1,026 (45.8)	1,638 (48.0)	3,067 (41.5)
Sedentary lifestyle	116 (26.7)	627 (44.0)	487 (21.5)	1,311 (34.8)	2,541 (32.2)
Low bone mass	44 (8.3)	225 (13.5)	358 (13.2)	1,871 (43.7)	2,498 (27.2)
Osteopenia, not osteoporosis	19 (3.6)	64 (3.7)	209 (7.7)	821 (18.5)	1,299 (9.7)
Osteoporosis	25 (4.7)	161 (9.8)	149 (5.5)	1,050 (25.2)	1,199 (17.5)
Any fracture after age 13 y	85 (16.4)	330 (20.2)	296 (11.0)	771 (18.2)	1,482 (16.4)
Previous fracture over age 50 y	—	90 (5.5)	—	405 (9.6)	495 (8.5)
Currently smoking	111 (20.8)	253 (14.9)	542 (19.8)	576 (13.2)	1,482 (15.9)
Steroid use	41 (7.7)	90 (5.3)	161 (5.9)	227 (5.2)	519 (5.6)
Menopause	—	—	672 (27.9)	3,972 (95.5)	—

Table 3 Adjusted odds ratios (OR) and 95% confidence intervals (CI) showing clinical and demographic characteristics associated with reporting bone densitometry testing in North American Research Committee on Multiple Sclerosis participants

Characteristic	Men*		Women*	
	OR	95% CI	OR	95% CI
Race				
White	—		1.0	
African American	—		0.53	0.33, 0.85
Other	—		0.91	0.60, 1.37
Age, y				
≤44	—		1.0	
>44 to ≤51	—		2.29	1.85, 2.84
>50 to ≤56	—		7.21	5.72, 9.10
>55 to ≤62	—		10.9	8.53, 14.0
>62	—		12.9	9.89, 16.7
Education				
<12 y	—		1.0	
High school diploma	—		1.25	0.69, 2.29
Associate's degree/technical degree	—		1.59	0.86, 2.95
Bachelor's degree	—		1.75	0.95, 3.23
Postgraduate degree	—		2.03	1.09, 3.78
Annual income				
<\$15,000	—		1.0	
\$15,001–\$30,000	—		1.33	1.01, 1.75
\$30,001–\$50,000	—		1.18	0.89, 1.55
\$50,001–\$100,000	—		1.35	1.02, 1.78
>\$100,000	—		1.42	1.03, 1.94
Health insurance				
Public	1.0		1.0	
None	0.35	0.08, 1.50	0.46	0.24, 0.88
Private	1.30	2.39, 4.85	1.13	0.93, 1.39
Region				
West	—		1.0	
Midwest	—		1.06	0.87, 1.30
South	—		1.31	1.07, 1.62
East	—		1.58	1.28, 1.95
Disability				
Mild	1.0		1.0	
Moderate	1.97	1.32, 2.94	1.37	1.04, 1.82
Severe	3.41	2.39, 4.86	1.31	1.07, 1.61
Fall in last 12 mo	—		1.42	1.23, 1.65
Fracture after age 13 y	2.16	1.66, 2.81	1.37	1.11, 1.70

*n = 1,795; c statistic = 0.65; Hosmer Lemeshow goodness of fit χ^2 3.8, p = 0.87.

*n = 3,926; c statistic = 0.77; Hosmer Lemeshow goodness of fit χ^2 10.8, p = 0.21.

hip fracture, and 685 (46.2%) reported multiple fractures.

Because age over 50 years is a strong fracture risk factor in the general population, we stratified other risk factors by age and sex (table 2). Risk factors for

fracture were common, with impaired mobility affecting 66% of responders. More than half of responders reported a fall in the last 12 months, and 60% of participants with osteopenia or osteoporosis fell in the last year. Twenty-four percent of participants reporting low bone mass reported a fracture vs 13.1% of participants reporting normal bone mass (p < 0.0001). Twenty-nine percent of participants who reported both a fall in the last year and low bone mass reported a prior fracture vs 10.2% of participants with normal bone mass and no history of falls (p < 0.0001). Excluding age but including fractures over age 50 years, 1,413 (15.1%) participants had 1 risk factor for fracture, 2,341 (25.0%) had 2, and 5,393 (57.7%) had 3 or more. The probability of reporting a prior fracture increased with the number of risk factors reported (test for linear trend, p < 0.0001).

Slightly more than half of participants (n = 4,675) had bone density testing. Women (60.5%) were more likely than men (21.9%) to report testing (p < 0.0001). Several factors were independently associated with increased odds of having bone density testing and these differed between men and women as shown in table 3. We noted racial and socioeconomic disparities; among men, participants with private health insurance were more likely to report testing than those with public insurance. Among women, the odds of bone density testing were higher among whites and those with higher levels of income and education.

Overall, 4,329 (49.8%) participants used calcium supplements, 5,341 (66.3%) used vitamin D supplements or a multivitamin with vitamin D, 1,337 (14.3%) used a bisphosphonate, and 61 (0.76%) used calcitonin. Eighty-two percent of participants with osteoporosis used supplemental vitamin D or a multivitamin, while 563 (54.4%) used a bisphosphonate. Among participants with a prior fracture, 746 (55%) used calcium supplements, 858 (68.8%) used vitamin D supplements or a multivitamin with vitamin D, 334 (22.5%) used a bisphosphonate, and 50 (2.4%) used calcitonin.

DISCUSSION More than 25% of participants reported osteopenia or osteoporosis. In MS, osteoporosis risk may reflect impaired mobility, lack of weight-bearing physical activity, low vitamin D levels, or other factors.⁶ Osteoporosis is a risk factor for fragility fractures.¹ More than 15% of our cohort reported fractures, consistent with earlier studies.⁷ Given these findings, fracture prevention is an important issue. Osteoporotic fractures are associated with substantial morbidity and mortality.¹

Often, NARCOMS participants had multiple clinical risk factors for fracture, including potentially modifiable factors such as low bone mass and

falls. Regular physical activity, adequate calcium and vitamin D intake, maintaining a healthy weight, falls prevention, and avoiding smoking and heavy alcohol consumption are important for bone health.¹ In one study, only 48% of Americans met recommendations for supplemental calcium intake.⁸ Our cohort reported a similar frequency of supplemental calcium intake, which was slightly higher in those with a prior history of fracture but still lower than recommended.¹

Fifty-one percent of participants reported having bone density testing and this varied with SES. This is consistent with a study of low income minorities with MS, in which one-third had inadequate preventive care for osteoporosis.⁹ Previously we reported socioeconomic and racial disparities in the management of bladder symptoms in MS.²

Several study limitations should be noted. The response rate was 65%, nonresponders differed from responders, and participants were volunteers; thus our findings may not generalize to all patients with MS. Our data were self-reported, possibly causing misclassification, but the literature supports the accuracy of self-reported osteoporosis and fracture history.¹⁰ We did not evaluate the impact of lifetime corticosteroid use, nor examine specific doses of vitamin D. Falls or fractures may lead to knowledge of having osteoporosis or osteopenia, thus potentially leading to a diagnosis bias in those without fractures or falls.

Patients with MS frequently have multiple risk factors for fractures. Many patients with MS with low bone mass and previous fractures are not taking supplemental calcium or vitamin D, suggesting a potential area of improvement in care. A focused research agenda leading to clinical practice guidelines to optimize bone health in patients with MS is needed.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Ruth Ann Marrie.

DISCLOSURE

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Institute of Neurological Diseases and Stroke, National Marrow Donor Program, Consortium of Multiple Sclerosis Centers; serves as a consultant to Peptimmune Inc., Aegis Creative Marketing, Novartis, National Industrial Sand Association, Bayer Pharmaceuticals, and Teva Pharmaceuticals Industries Ltd.; has served on independent data and safety monitoring committees for Antisense Therapeutics Limited, Sanofi-Aventis, Bayhill Pharmaceuticals, BioMS Medical Corp, Daiichi-Sankyo Co. Inc., Glaxo-SmithKline, Genmab, Medivation Inc., PTC Therapeutics Inc., Teva Pharmaceutical Industries Ltd., Vivus Inc., NHLBI, NINDS, NMSS; has received research support from ApopLogic Pharmaceuticals, LLC; receives research support from the NIH [NINDS 5U01NS042685-02 (PI), NINDS U01 NS45719-01A1 (PI, Coord Center), NIAID Contract No HHSN266200400068C [Co-I], NHLBI 5R01 HL06991-02 [PI, Coord Center], NIAID N01AI30025 [Director, Coord Center], NIDR 3R01DE016684-03S109 [Co-I], NHLBI 5P50HL084923-030001 [Director, Coord Center], NIDDK 1R01DK078826 [Co-I], NIAID P30AI27767 [Co-Director, Biostat Core], NIDDK 1P30DK079337 [Director, Biostat Core] and from the Consortium of Multiple Sclerosis Centers [Director NARCOMS Data Center] and the National Multiple Sclerosis Society; and serves as President of Pythagoras, Inc. Dr. Tyry has served as a consultant for EMD Serono, Inc. Dr. Vollmer has served on scientific advisory boards for Teva Pharmaceuticals Industries Ltd., Novartis, GlaxoSmithKline, EMD Serono, Inc., Biogen Idec, Abbott, Accord Therapeutics, Bayhill Therapeutics, Metabolic Solutions Development Co., and Genentech, Inc.; has received speaker honoraria from EMD Serono, Inc., Teva Pharmaceuticals Industries Ltd., Biogen Idec, and the National Multiple Sclerosis Society; has served on speakers' bureaus for Biogen Idec, Teva Pharmaceuticals Industries Ltd., and Athena Diagnostics, Inc.; has received research support from Teva Pharmaceuticals Industries Ltd., Daiichi Sankyo, Genzyme Corporation, Ono Pharmaceutical Co., Ltd., Eli Lilly and Company, Sanofi-Aventis, BioMS Medical, Novartis, PDL BioPharma, Inc., Pfizer Inc., Merck Serono S.A., Accord Therapeutics, Genentech, Inc., the NIH [NIAID/ITN NO1-AL015416/CFDA 93ZZZ (Co-I) and NINDS 1U01NS45719-02 A1 (Co-I)] and from the Barrow Neurological Foundation, Translational Genomics Research Institute, the Rocky Mountain Multiple Sclerosis Society, and the National Multiple Sclerosis Society; and gave expert testimony in a trial re: Genentech, Inc. vs Biogen Idec.

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Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

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A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

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