Osteoporosis Development in Individuals with Multiple Sclerosis

Multiple Sclerosis (MS) is the second leading cause of neurologic disability in the world with over 2.5 million adults affected worldwide. Median longevity is 30 years from onset of MS and the course of disease is progressive, causing considerable health complications including osteoporosis. Osteoporosis alone is a major cause of morbidity and mortality in individuals, as reduced bone mineral density (BMD) is associated with increased risk of fracture. Hip and radial fractures are the most common osteoporotic fractures, with hip fractures being the largest cause of morbidity, involving long-term hospital stays, and secondary complications. While there is a lack of guidelines for screening, treating, and preventing osteoporosis in individuals with MS, there is a clear connection between having MS and developing secondary osteoporosis. Therefore, it is recommended that individuals with MS be screened for osteoporosis and prevention of falls should be a priority when treating MS patients.

Osteoporosis (OP)

Typical, healthy individuals experience peak bone mass around age 30, they then undergo an age-related decline in BMD after age 40.[1] Bone mass is developed through genetics and environmental factors such as calcium, vitamin D, exercise, alcohol and cigarette use, hormone levels, in addition to a variety of medications and chronic illnesses. Osteoporosis is characterized by low bone mass and weakened bone infrastructure that leaves bone susceptible to fractures and injury.[2] The World Health Organization (WHO) defines osteoporosis for individuals older than 50 years as a BMD 2.5 or more standard deviations (SD) below peak bone mass.[1] Individuals who are between -1 and -2.5 SD's are considered to have osteopenia.[1] In individuals younger than 50 years of age, low BMD is classified using age, sex, and ethnicity-matched z-scores of less than or equal to -2 at multiple sites.[1] In general, women are at an increased risk for

developing osteoporosis after menopause.[1] Additional risk factors for developing osteoporosis include age >50, female, BMI<20 kg/m^2, nutrition intake, physical activity, falls, immobilization, increased alcohol consumption, cigarette use, medications (steroids), and caffeinated drinks and dark sodas.[1]

Multiple Sclerosis (MS)

Multiple Sclerosis (MS) is a neurodegenerative disease classified by the gradual collection of focal demyelination in the brain and spinal cord causing damage to the central nervous system that results in the various symptoms individuals experience.[3] MS is an immune-mediated disease where the body mistakenly attacks myelin in the central nervous system, most experts believe MS is an autoimmune disease, though no specific antigens have been identified in relation to MS. The cause of MS is currently unknown but is believed to involve genetics, abnormalities in the immune system, and environmental factors that trigger the disease.[3] There are 4 types of MS: clinically isolated syndrome (CIS), relapsing remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS) (Figure 1). Relapsing-remitting MS is the most common disease course and is characterized by periods of symptom exacerbations and periods of partial or complete recovery (Figure 2).[3] Each MS type comes with its own set of impairments, progressions, and complications. Each have wide varieties of symptoms and effect individuals differently. The commonality between them is that mobility is greatly affected and can lead to a multitude of secondary complications.

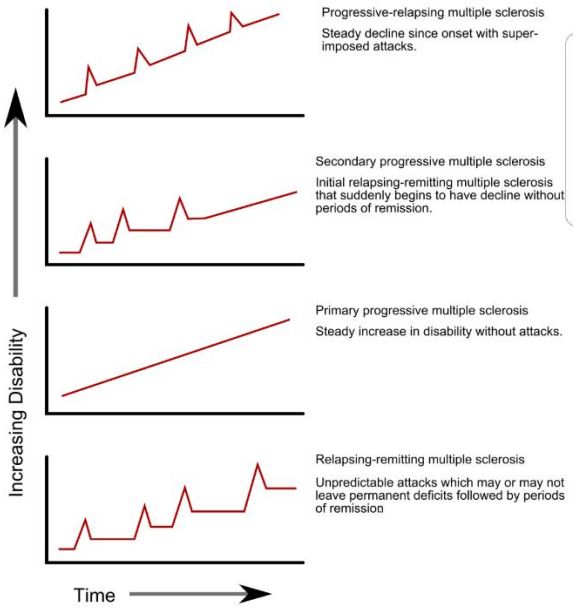
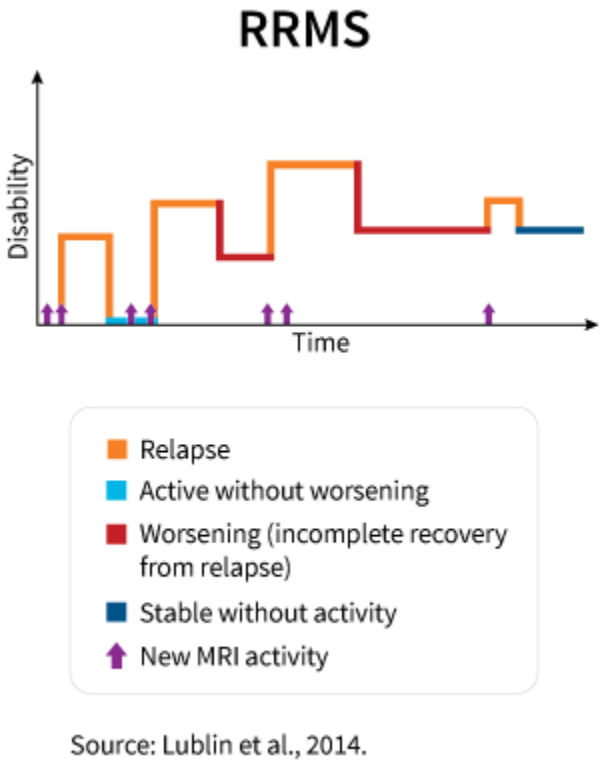


Figure 1. *The four types of Multiple Sclerosis and their projected disease and impairment progression.*



Source: Lublin et al., 2014.

Figure 2. *Disease course that can occur in individuals with RRMS, the most common MS type. Following a relapse, the symptoms may partially or fully disappear. New lesions on an MRI (arrows) often accompany a relapse.*[3]

Risk Factors for Osteoporosis Development

There is a high prevalence of osteoporosis (OP) in Multiple Sclerosis (MS) patients. Research has shown that changes in BMD occur at a younger age in individuals with MS compared to the general population. MS patients have been found to have lower bone mineral density (BMD) when compared to controls.[1] This relationship may be attributed to the disease-modifying drugs (DMD) MS patients are prescribed, and their reduced mobility due to their symptoms. Interferon (IFN) is a common MS medication that is a DMD, it has been shown to inhibit osteoclastogenisis which affects bone re-absorption.[4] Osteoclastogenisis is the formation of bone-resorbing cells (osteoclasts), osteoclasts are the cells that degrade bone to initiate normal bone remodeling and mediate the amount of bone loss.[5] Fatigue and reduced mobility are common impairments individuals with MS experience. Immobility is a common osteoporosis risk factor, therefore, the more immobile an individual with MS is, the more at risk they are for developing osteoporosis. Data has shown that 25% of ambulatory individuals with MS still had low BMD levels.[4] This shows that there is many factors related to MS and osteoporosis development.[4] Another potential cause of osteoporosis in individuals with MS is the impaired ANS system which affects bone mineral density. This alters the function of the neuronal, systemic, and local mediators of bone remodeling.[6] Another commonality typically found in individuals with MS is low vitamin D levels. Vitamin D is a moderator that helps with calcium absorption and can influence osteoblast and chondrocyte activity.[7] Low vitamin D levels can be a culprit to developing osteoporosis in persons with MS as well as in the general population.

Individuals with vitamin D levels below 50nm are considered to be insufficient in vitamin D.[1] Due to disability severity, individuals with MS may have limited outdoor activity, therefore limiting their exposure to the sun, which can contribute to the increased prevalence of vitamin D insufficiency in the MS population. Additionally, during MS exacerbations, steroids are typically prescribed to combat the increased symptoms. High-dose, short-term glucocorticoids cause an immediate and persistent decrease in bone formation and remodeling.[8] Prolonged glucocorticoid treatments decreases BMD and increases an individual's risk for fracture. Intermittent treatment of glucocorticoids increases the risk for developing osteoporosis.[7] Another factor in osteoporosis development includes smoking. The pro-inflammatory effects of smoking increases leukocytes and abnormal T-cell functions.[4] Smoking contributes to osteoporosis by decreasing vitamin D levels and damaging the body's ability to differentiate osteoblasts.[4] Smoking can result in increased disease progression in both MS and OP and smoking cessation programs should be utilized. Risk factors for osteoporosis can be summarized below in Table 1.

Table 1: Osteoporosis risk factors

Congenital Factors	**Acquired Factors**	**Lifestyle Factors**	**Iatrogenic Factors**
Age (65+ female, 75+male	Visual Impairment	Low CA2+ Intake	Glucocorticoids

Previous history of fracture	Recurrent Falls	Excessive Alcohol Consumption (>14 units/week)	Anticonvulsants
Chronic Disease	Dementia	Ca2+ Deficiency	Cyclosporine
Caucasian	Low Body Weight	Vitamin D Deficiency	Aromatase Inhibitors
Female	Early Menopause	Inactivity	Thyroxine
	Prolonged Premenstrual Amenorrhea	Current Smoker	GnRH Agonists
			Lithium

Table 1: *identified risk factors for osteoporosis.*[7]

Complications from Osteoporosis in Persons with MS

Individuals with MS are at an increased risk of falls and fractures due to common MS symptoms such as weakness, fatigue, impaired gait and balance, coordination, and sensory deficits (vision, sensation, etc.). Individuals with MS have an increased prevalence of falls with data showing more than 50% of people falling in the past 6-months. Previous research into fall consequences show that increased injury rates, fractures, and their adverse events are significant

predictors of morbidity.[9] Risk fracture is high in individuals with osteoporosis and individuals with MS individually, those who have both disorders are at further increased risk for fractures. Patients with higher levels of disability (higher EDSS scores) are at increased risk for falls and subsequent fractures. The Expanded Disability Status Scale (EDSS) is a scale used to classify disability in persons with MS and can be used to track disability over time. [10] The scale ranges from 0 to 10 in 0.5 increments with higher scores representing more severe disease progression.[10] EDSS scores 1.0-4.5 represent people with MS who are able to ambulate independently without any assistance. Scores 5.0-9.5 are defined by ambulation impairments.[10] (Figure 3) Research has shown that BMD at the femoral neck decreases with increasing MS-related disability (increasing EDSS score). Again, this is most likely due to the reduced ambulation and weight-bearing activities that correlate to increased disability. These activities are necessary for preservation of bone mass.[1] Data has shown that individuals with MS have up to a 1.2 times increased risk for fracture. The risk for fracture related to osteoporosis in individuals with MS is 1.4 higher. Compared to the general population, patients with MS have 3 times higher the risk for hip fractures.[1,11] Fractures can have a wide variety of consequences from the fall itself, the fracture sustained, and the subsequent surgery to fix it. Medical complications affect up to 20% of individuals who undergo surgery for their fracture.[12] Further impairments may be seen in cognitive, neurologic, and cardiovascular systems. Complications from hip fracture surgery are somewhat common and can vary in severity. The main problem of intracapsular fractures are biological with delayed or impaired fracture healing such as a non-union or avascular necrosis.[12] In extracapsular fractures, the main problem is usually mechanical in nature and relates to load-bearing as well as possible screw cut-out, femur fracture, and implant failure. 90% of hip fracture patients are aged 65 or older and have additional comorbidities. Hip fracture has an overall 1

year mortality rate between 14-36% in patients 65 years and older, and these individuals have a shorter life expectancy. [12] Mortality is influenced by preoperative cognitive status, other comorbidities, and mobility level. [12]

EDSS Score	Disability Stage/Description
0.0	Normal neurological exam
1.0	No disability, minimal signs on 1 FS
1.5	No disability, minimal signs on 2 of 7 FS
2.0	Minimal disability in 1 of 7 FS
2.5	Minimal disability in 2 FS
3.0	Moderate disability in 1 FS, or mild disability in 3–4 FS, although fully ambulatory
3.5	Fully ambulatory but with moderate disability in 1 FS and mild disability in 1 or 2 FS, moderate disability in 2 FS or mild disability in 5 FS
4.0	Fully ambulatory without aid, up and about 12 hours a day despite relatively severe disability; able to walk 500 metres without aid
4.5	Fully ambulatory without aid, up and about much of day, able to work a full day, may otherwise have some limitations of full activity or require minimal assistance; relatively severe disability; able to walk without aid for 300 metres
5.0	Ambulatory without aid for about 200 metres; disability impairs full daily activities
5.5	Ambulatory for 100 metres; disability precludes full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch or brace) required to walk 100 metres with or without resting
6.5	Constant bilateral support (cane, crutch or braces) required to walk 20 metres without resting
7.0	Unable to walk beyond 5 metres even with aid, essentially restricted to wheelchair, wheels self, transfers alone; active in wheelchair about 12 hours a day
7.5	Unable to take more than a few steps, restricted to wheelchair, may need aid to transfer; wheels self, but may require motorised chair for full day's activities
8.0	Essentially restricted to bed, chair, or wheelchair, but may be out of bed much of day; retains self-care functions, generally effective use of arms
8.5	Essentially restricted to bed much of day, some effective use of arms, retains some self-care functions
9.0	Helpless bed patient, can communicate and eat
9.5	Unable to communicate effectively or eat/swallow
10.0	Death due to MS

Levels of disability at each 0.5 increment in score. EDSS = Expanded Disability Status Scale; FS = functional systems (there are eight in EDSS); MS = multiple sclerosis.
Source: Kurtzke, 1983.[8]

Figure 3. *The Expanded Disability Status Scale used to classify the severity of disability in individuals with Multiple Sclerosis. A functional system (FS) represents a network of neurons in the brain that have a responsibility for a particular task. Each FS is scored on a scale of 0-6, with higher scores representing more severe disability.*

Importance of Screening for Osteoporosis for Individuals with MS

It's important to screen for osteoporosis in individuals with MS and intervene appropriately in order to provide comprehensive MS care. The current recommendations for measuring bone mineral density are for those who have disease or are receiving interventions that are likely to cause secondary osteoporosis as well as in patients with fragility fractures. Multiple Sclerosis is not yet on the list of causes of secondary osteoporosis, but many argue that it should be considered. The gold standard for measuring bone mineral density is using dual x-ray absorbance spectrometry (DEXA). This scan measures bone density per unit area, which allows a healthcare professional to normalize the results to age- and sex-matched controls. T-scores are used to diagnose osteoporosis or osteopenia, with t-scores of <-2.5 resulting in osteoporosis and t-scores of -1 to -2.5 correlating to an osteopenia diagnosis.[13] The World Health Organizations FRAX tool provides a validated 10-year fracture risk estimate for individuals but fails to consider vitamin D levels, and other factors found in individuals with MS (Table 3).[13] The FRAX tool can be very useful for physical therapists as the inputs required for this tool (which can be found online) does not necessarily need BMD measured via DEXA. It can help indicate if a person should get a DEXA scan as well. Currently, there is a lack of evidence surrounding screening for osteoporosis in individuals with MS and the subsequent treatment. From the available research, individuals with MS should get a DEXA scan to measure their bone mineral density within 2 years of being diagnosed with MS. They should get 'routine' DEXA scans every 3-5 years in individuals with normal bone density. Individuals with MS should be evaluated for fall risk and subsequent fall-prevention measures should be employed as appropriate (Table 4).[1] There are a multitude of evaluation measures and guidelines to use for individuals with MS, but screening these patients for osteoporosis is lacking. A multidisciplinary

team should be utilized to provide comprehensive care to individuals with MS, and education, screening, and treating osteoporosis should be included.

Table 1. Data included in the FRAX® score calculation and additional risk factors for osteoporotic fractures. Table adapted from references 9 and 48.

FRAX score determinants	Other risk factors for osteoporosis
Age	Ethnicity
Gender	Medication (including anticonvulsants, immunosuppressants, chemotherapy, heparin)
Body mass index	Vitamin D deficiency
Previous fracture (a previous fracture in adult life occurring spontaneously, or a fracture arising from trauma that, in a healthy individual, would not have resulted in a fracture)	
Parental hip fracture	
Current smoking	
Glucocorticoids (past or present exposure to prednisolone 5 mg/day or more (or equivalent) for more than three months)	
Rheumatoid arthritis	
Other medical disorder strongly associated with secondary osteoporosis (such as MS, diabetes, anorexia nervosa)	
>3 units alcohol/day	
Femoral neck bone mineral density (if known)	

Table 3. *Data included in the FRAX score calculation and additional risk factors for osteoporotic fractures.* [13]

Table 4. Suggestions for screening and treatment of osteoporosis in the MS population.

- Measure bone mineral density (BMD) within a couple of years after diagnosis of MS

- Treat osteoporosis using guidelines for the general population (refer patients below 50 years of age to osteoporosis specialist)
- Repeat BMD measurements after 3–5 years in patients with normal bone density
- Identify persons in whom proactive fall-prevention measures are indicated
- Recommend high-impact weight-bearing exercise with a special focus on balance
- Treat vitamin D insufficiency (serum 25(OH)D < 50 nM)
- Consider measures to optimize serum 25(OH)D (> 75 nM)
- Ensure daily intake of between 1000 and 1500 mg of elemental calcium
- Encourage 'healthy lifestyle': adequate nutrition, cigarette smoking cessation and alcohol consumption limited to a maximum of two units a day

Table 4. *A more proactive approach to screen patients with Multiple Sclerosis for osteoporosis is recommended.* [1]

Treatment Suggestions

Clearly, reduced BMD is a significant problem in the management of MS and the risk of falls and subsequent fractures are important considerations when treating these individuals.

Guidelines for treating osteoporosis for individuals with MS appears to follow general osteoporosis treatment interventions. A multifactorial approach is suggested including lifestyle changes like smoking cessation, reducing alcohol intake, increasing physical activity, and pharmaceutical interventions. [4] This includes vitamin D and calcium supplements, and biphosphates, currently the most effective medication for slowing the deterioration of BMD. The main pharmacological interventions for the treatment of osteoporosis are bisphosphonates, denosumab, parathyroid hormone, and raloxifene. The UK National Institute for Health and Care Excellence (NICE) suggests alendronate as the first-line treatment for osteoporosis. Estrogen or hormone replacement therapy drug are also options for treatment of menopause and postmenopausal osteoporosis. There are of course risks of these drugs such as cardiovascular problems, breast cancer, and stroke. It's important to note that the National Osteoporosis Foundation recommends that these therapies should not be taken forever, and a reexamination should be done every 3-5 years.[4] Recommendations for vitamin D in individuals with MS suggest year-round levels of 55-70mg/mL. [8] Newer research also suggests that taking a melatonin supplement may help normalize bone metabolites in persons with MS.[14] In addition to pharmaceutical interventions, data has shown that physical activity such as non-weight bearing high force exercise like resistance training for the LE can be effective for improving BMD in the neck of the femur.[15] Loading of the skeleton promotes increased bone mass, but needs to be safe and effective.[16] Resistance training with body weight or external weight needs to be completed for a longer period of time (over 1 year). Body weight should be used for exercises like squats, step-ups, and planks. Machines, free weights, and therbands are also viable options for exercise progression as long as the person is proper trained to use them. Extra attention should be paid to strengthening the gluteus muscles, trapezius, hamstrings, abdominals, erector spinae, and ankle

dorsiflexors for both MS and osteoporosis populations. A training frequency of 203x/week with an intensity of 8-15 reps is recommended. Individuals should begin with 1-3 sets of 8-10 reps and gradually progress this to 3-5 sets of 10-15 reps. For a global resistance training intervention, a variety of 5-10 exercises should be chosen with a focus on larger muscle groups and lower extremities. [21] Decreasing falls risk appears to be one of the most important factors to address in both the MS and osteoporosis populations. Balance and functional training have been shown to decrease an individual's fall risk, therefore potentially protecting against fractures. Screening for balance impairments should be routine in patients with MS. This can be done via the Berg Balance Scale, the Activities-specific Balance Confidence Scale (ABC Scale), or the mini-BESTest.[17]Ideas for balance exercises for patients with MS at risk for osteoporosis include ankle sway, tandem stance, single leg stance, reaches, multi-directional lunges, tandem walking, and Otago exercise programs. Fatigue is a common MS symptom that is also correlated to increased fall risk. Education about managing fatigue for individuals with MS should be routine. Gait impairments are also crucial factors that relate to fall risk and therefore should be evaluated and treated to prevent falls and consequent fractures. The Dynamic Gait Index (DGI), Functional Gait Assessment (FGA), Timed-Up and Go (TUG), 12-Item MS Walking Scale (MSWS-12), and 6-Minute Walk Test (6MWT) are all valid and reliable outcome measures used to evaluate gait and fall risk. Education about tripping hazards can also reduce fall risk. Things such as adding lighting, removing rugs and cords, and installing handrails and grab bars can be lifesaving measures. Interventions should be aimed at improving gait and use of appropriate assistive devices to maximize function and prevent fractures.[17] Stretching should be done in addition to aerobic and strength training. Muscles that are typically restricting include the hip flexors, pectoralis muscles, latissimus dorsi, iliotibial band, hamstrings, and gastroc-soleus muscles.

When prescribing exercise interventions aimed at MS symptoms and preventing osteoporosis, its important to keep ion mind that individuals with MS commonly experience heat sensitivity and should be educated on preventing overheating and safe exercise parameters. Each patient is unique, and therefore requires individualized, goal-oriented rehabilitation interventions. The goal of rehabilitation in general is to improve functional independence and prevention of secondary complications. At the core of these goals is patient education and self-management tools.[18] While high intensity or high impact exercise is recommended for osteoporosis treatment, individuals with MS may have increased difficulties performing these types of exercises. Modifications may be used to increase safety and effectiveness for the MS population. Education and interventions focused on "bone safe movements" should be included for these individuals. Bone safe movements include proper posture and core stability during exercises[19]. Improvements in trunk strength and balance should also be incorporated. Individuals with MS and those at risk for developing osteoporosis should be educated on avoiding trunk flexion and loaded trunk rotation.[19] Core strength is important and abdominal strengthening should be performed with a neutral spine position. TheraBand resistance in supine or standing positions are options for lower level strengthening.[19] Exercises that should be avoided include the rowing machine, overhead press, chest press, trunk extension machine, child's pose, and knees to chest stretches.[19] Some ideas for exercise prescription include "YTW" upper extremity exercises done in supine, standing, or prone, and/or with the use of bands.[19] Bridges, clamshells, hip abduction, hip extension, squats, and side steps are also potential exercises.[19] Aquatic therapy is also a viable option for patients with MS and/or osteoporosis. Water temperature should be a consideration as individuals with MS can experience heat sensitivity as previously mentioned. Current recommendations for exercise prescription for individuals with MS includes aerobic exercise 2-

5x/week separated by 24 hours from resistance training sessions. Starting intensity should be between 40-70% VO2max (60-80% HRmax or 11-13 on the Rating of Perceived Exertion Scale (RPE)).[20] Finding have shown that HR may not an accurate exercise intensity evaluation for those with MS due to the autonomic dysfunction commonly found in MS.[20,21] Interval training and/or circuit training may be the best option for exercise for persons with MS. Interval and circuit training allow for moderate-high intensity exercise followed by a lower-intensity exercise and/or rest break. This allows for the load-bearing exercises required for bone health while not fatiguing the individual too much and therefore promoting a safer, healthier physical activity environment. This style of interventions also permits a wider range of exercises that can be completed and impairments that can be addressed without overwhelming the person. Gradual progression of exercise parameters is paramount to avoid injuries and provide the best outcomes possible. Table 5 lists the special considerations to take when prescribing exercise interventions to individuals with MS.

Special considerations and precautions for exercise prescription in MS patients

Special considerations	Precautions
Fatigue	Schedule resistance training on non-endurance training days [13, 53, 54].
Spasticity	Consider foot and/or hand straps for ergometers. Use machines instead of free weights [53–55].
Heat intolerance and reduced sweating response	Encourage adequate hydration, keep room temperature between 20 and 22 ° C. Using of cooling fans and precooling before aerobic exercise might have positive effects on performance. It is better to plan exercise in the morning when body temperature is at the lowest [53, 54, 93].
Cognitive deficits	Provide written instructions, diagrams, frequent instructions, and verbal cues [53–55, 94]. Exercise tasks should be initially performed with minimal resistance. Individuals with cognitive impairments may require additional supervision during exercise to ensure their safety [18].
Lack of coordination in extremities	Consider using a synchronized upright or recumbent arm/leg ergometer to ensure balance and safety [53–55, 94].
Sensory loss and balance problems	Perform all exercises preferably in a seated position; use machines or elastic bands instead of free weights [53–55, 94].
Higher energy cost of walking (2–3 times greater than age-matched healthy persons)	Adjust workloads to maintain target heart rate and check heart rate regularly [13, 53–55, 94].
Daily variations in symptoms	Provide close exercise supervision and make daily modifications to exercise variables [13, 53–55, 94].
Urinary incontinence /urgency	Ensure adequate hydration, and schedule exercise in close proximity to restrooms [53–55, 94].
Symptom exacerbation	Discontinue exercises and refer the patient to a physician. Resume exercise program. Once symptoms are stable and the patient is medically ready to continue [13, 53–56, 94].

Table 5: *Special considerations to take when prescribing exercise interventions to those with Multiple Sclerosis.*[20]

Conclusion

As you can see, the risk for developing osteoporosis in individuals with MS is high. These individuals should be routinely screened for osteoporosis using DEXA scans, lab work, and a physical examination. Regardless of osteoporosis classification, individuals with MS are at an increased risk for falls and fractures and should see a physical therapist routinely to address deficits and disease progression impairments. As physical therapists, it's our duty to evaluate these impairments and consider the individuals risk for developing or having osteoporosis. Education and self-management interventions are paramount to improving patient's quality of life, and preventing secondary complications or adverse events. Future research and guidelines should be completed in regard to MS and the osteoporosis correlation. In the meantime, following the general osteoporosis guidelines with proper modifications is recommended.

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