

Comorbidities Management and Lifestyle Modification in Patients With Multiple Sclerosis

Over the past several years, the treatment armamentarium for multiple sclerosis (MS) has grown rapidly, giving physicians and patients more opportunities to potentially optimize regimens and manage disease symptoms. In addition to the expanding landscape of disease-modifying therapies, the spectrum of MS treatment has grown to encompass the consideration of comorbidities and lifestyle management as part of a growing emphasis on the overall preservation of long-term brain health. This article reviews findings and implications related to comorbidities and lifestyle interventions in the management of MS.

Prevalence of Comorbidities in Multiple Sclerosis

Diseases that commonly present alongside MS, the comorbidities, include vascular and cerebrovascular disease, autoimmune diseases, chronic lung disease, gastrointestinal disease, renal disease, and visual disorders.¹ MS has also been associated with various psychiatric comorbidities, such as anxiety and depression. Results from a systematic review indicated that the most prevalent comorbid conditions were depression (23.7%), anxiety (21.9%), hypertension (18.6%), hyperlipidemia (10.9%), and chronic lung disease (10.0%).² Approximately 30% of patients with MS present with autoimmune comorbidities.³ According to results from a study using retrospective chart review and quantitative magnetic resonance imaging (MRI) data in 815 patients with MS, the most common autoimmune diseases were thyroid disease (11.9%), asthma (5.0%), type 2 diabetes mellitus (4.9%), psoriasis (4.0%), and rheumatoid arthritis (2.7%) (**Figure 1**).³

MS is more commonly diagnosed in women than men, but the prevalence of comorbidities varies significantly by sex.⁴ Results from a population-based study to determine the prevalence of comorbidities at the time of diagnosis in the MS population compared with the general population showed that 71.9% were female and the most prevalent comorbidity was depression, which presented in 19.1% of cases.⁴ Relative to the matched population, the prevalence of hypertension in patients with MS was 48% higher in men and 16% higher in women. Among all patients with MS, rates of depression and chronic lung disease were higher in women, while rates of heart disease and hyperlipidemia were higher in men (**Figure 2**).⁴

Comorbidities affect the disease course of MS. The pathogenesis of MS comorbidities has not been elucidated but may be attributable to a complex interplay of factors,

such as genetic predisposition, environment, inflammation, and the use of disease-modifying therapies.^{1,3,5,6} Notably, findings from a 2017 study revealed that patients with 3 or more comorbidities had a 45% increased relapse rate over 2 years compared with patients with no comorbidities.⁷ MS comorbidities are also associated with decreased whole-brain and cortical volumes.⁸ Psoriasis, thyroid disease, and type 2 diabetes were associated with more severe nonconventional outcomes.³

In addition to the clinical impact of comorbidities, the presence of comorbid conditions in patients with MS has been associated with diagnostic delays and increased hospitalizations,⁹ which has an influence on the cost of care. MS ranks second among all chronic conditions in direct all-cause medical costs, with approximately \$8528 to \$54,244 in spending per patient per year.^{10,11} Moreover, approximately 80% of Medicare spending is attributable to those with ≥ 4 chronic conditions.¹⁰

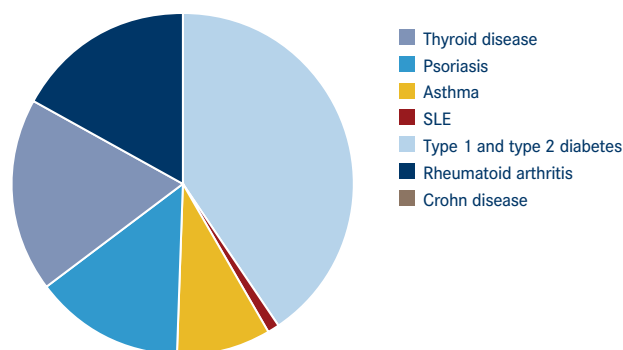
Comorbidity Burden and Impact

Cardiovascular risk factors are associated with clinical outcome changes in patients with MS. In a prospective study that enrolled 326 patients with relapsing-remitting MS and 163 patients with progressive MS, researchers investigated the frequency of cardiovascular risks in patients with MS and their association with MRI outcomes. The association between individual or multiple cardiovascular risks and MRI outcomes was examined and adjusted for age, sex, race, disease duration, and treatment status. The results showed that patients with MS who had 1 or more cardiovascular risk factors had an increased lesion burden and more advanced brain atrophy.¹²

Comorbidities also increase the likelihood of disability at diagnosis and subsequent progression of disease.^{2,9} A retrospective cohort study examined the relationship between physical comorbidities and disability progression, analyzing adults with MS that was diagnosed between 1990 and 2010. The outcome was the Expanded Disability Status Scale (EDSS) score. Among 3166 individuals with MS, physical comorbidity was associated with disability, and each additional comorbidity had a mean increase in the EDSS score of 0.18 (95% CI, 0.09-0.28), suggesting that physical comorbidities are associated with an apparent increase in MS disability progression.¹³

In a study examining the association between vascular comorbidities and MS, investigators enrolled 8983 patients in the North American Research Committee on

FIGURE 1. Highest Frequency Autoimmune Comorbidities in Patients With MS



SLE indicates systemic lupus erythematosus. Adapted from reference 3.

Multiple Sclerosis Registry and evaluated the differences in time from symptom onset or diagnosis until ambulatory disability in patients with or without vascular comorbidities.¹⁴ Multivariable proportional hazards models, such as sex, race, age at symptom onset, year of symptom onset, socioeconomic status, and region of residence were adjusted. Participants who reported 1 or more vascular comorbidities at time of diagnosis had an increased risk of ambulatory disability, with an increasing risk associated with the number of vascular conditions reported (adjusted HR for early gait disability, 1.51; 95% CI, 1.41-1.61). The risk of ambulatory disability (adjusted HR for unilateral walking assistance, 1.54; 95% CI, 1.44-1.65) also increased. In patients without vascular comorbidities, the median time between diagnosis and need for ambulatory assistance was 18.8 years compared with 12.8 years for patients with vascular comorbidities. Regardless of where they present, vascular comorbidities appear to increase the risk of disability progression in MS.¹⁴ These results suggest that the treatment of vascular comorbidities on disease progression should be investigated further.

The prevalence of psychiatric comorbidities is particularly high.⁴ Depressive disorders have been observed in up to 50% of individuals with MS, which is roughly 2 to 3 times higher than the general population,¹⁵ and despite the availability of therapies, depressive disorders remain underdiagnosed and undertreated. The treatment of anxiety and depression is an unmet need in patients with MS. The use of screening tools to help assess whether a mental health test is needed (eg, Hospital Anxiety and Depression Scale, Patient Health Questionnaire) to further improve a patient's individual treatment plan has been shown to be successful in patients with MS.²

Poor diet quality can also negatively affect disability

in patients with MS. Results from an online survey of 2399 participants with MS showed that 22.5% were overweight and 19.4% were obese, according to World Health Organization standards.¹⁶ Patients who were obese, overweight, or had a history of smoking or were currently a smoker were associated with greater risks of other comorbidities, such as cardiovascular disease. Mild-to-moderate alcohol consumption, healthy diet, and moderate exercise were associated with a decreased risk for comorbidities and increased likelihood of greater quality of life (QOL).¹⁶

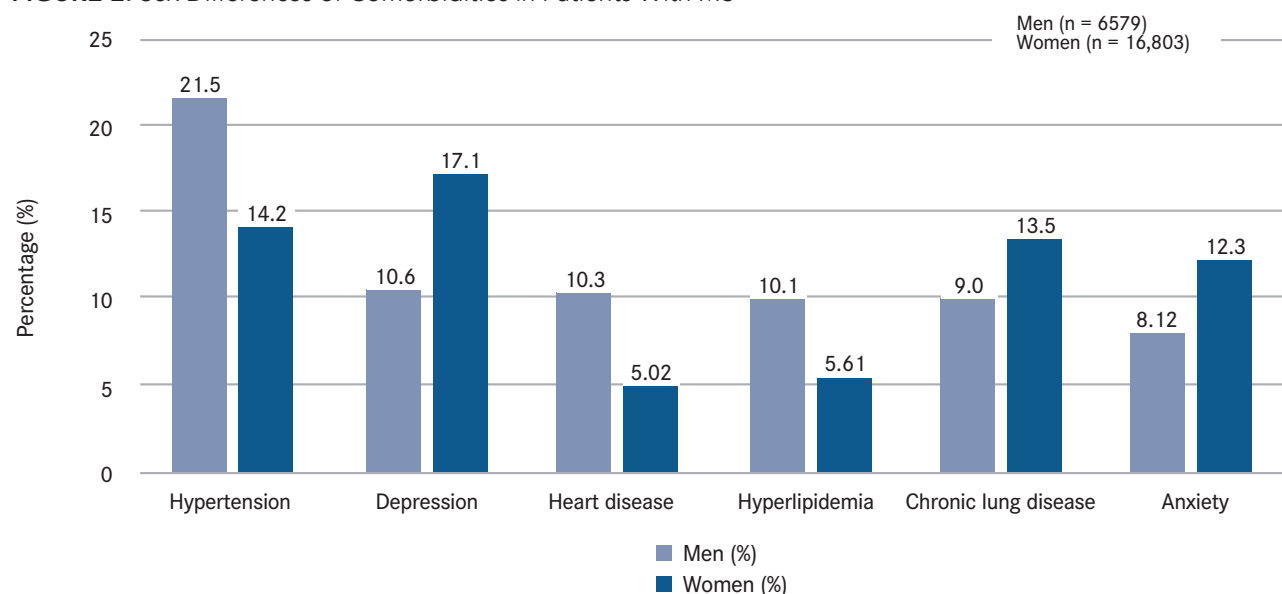
A recent study investigated the relationship between diet quality, disability, and symptom severity in MS patients.¹⁷ Using the North American Research Committee on Multiple Sclerosis Registry's dietary screener questionnaire, researchers measured diet quality and disability status with Patient-Determined Disease Steps (PDDS) and symptom severity with proportional odds models and adjusted for age, sex, income, body mass index (BMI), smoking status, and disease duration.¹⁷ Questionnaire responses showed that participants with diets higher in fruits, vegetables, legumes, and whole grains, and lower in added sugars and red meat, had lower levels of disability (proportional odds ratio [OR] for quartile (Q) 5 vs Q1, 0.80; 95% CI, 0.69-0.93). This group also had lower depression scores (proportional OR for Q5 vs Q1, 0.82; 95% CI, 0.70-0.97). According to the survey data, healthy diet and a composite healthy lifestyle are associated with reduced disability and symptom burden in MS.¹⁷

Patients with MS who smoke cigarettes are at greater risk for increased blood-brain barrier disruption, greater brain atrophy, and higher lesion counts.¹⁸ In a study that compared MRI characteristics in smokers and nonsmokers with MS, never-smokers had lower mean EDSS scores than ever-smokers and active smokers, indicating the significant risk to both disease course and disability from smoking.¹⁸

Smoking and obesity leave patients with MS at a higher risk for comorbidities associated with greater adverse effects and more rapid progression of disability.² The United States Preventive Services Task Force recommends screening for abnormal blood glucose in adults who are overweight and aged 40 to 70 years. Those younger than 35 years should regularly be evaluated if an increased cardiac risk is prevalent (eg, diabetes, tobacco use, obesity, hypertension).² Physicians should also consider regular evaluation of vascular comorbidities, such as diabetes, hypertension, and ischemic heart disease, as this risk can increase with age.²

Multiple Sclerosis and Cognitive Impairment

Comorbidities of MS disease course and disability have also been shown to negatively affect cognition and

FIGURE 2. Sex Differences of Comorbidities in Patients With MS

MS indicates multiple sclerosis.
Adapted from reference 4.

health-related QOL.² Because MS is a progressive disease characterized by widespread lesions in the brain and spinal cord, as well as axonal and gray matter damage, cognitive impairment is common and can affect social engagement and vocational activities. Memory deficits are present in 40% to 65% of patients with MS.^{19,20}

Neuroplasticity of cognitive functions is often evident in patients with MS. Neuroplasticity is the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function, and connections to cope with cognitive impairments.²¹ In patients with MS who are demonstrating significant cognitive impairment and disease progression, maladaptive neuroplasticity may come at the cost of other cognitive functions. Recent studies have applied neuroimaging techniques to establish outcomes, and researchers have successfully applied various neuroimaging techniques to study the effects of cognitive rehabilitation in patients with MS.²¹ Future research should identify adaptive versus maladaptive neuroplasticity associated with specific cognitive rehabilitation programs within all MS phenotypes to find the most effective cognitive rehabilitation interventions for individuals with MS.

Diminished visual and verbal memory, executive functions, and processing speed have been observed in patients with MS who have sleep disturbances and apnea.²² Effective treatment may offer new opportunities to improve cognitive functioning in this patient population.²² Tobacco use also has also been linked to cognition in those with MS. The results of one study showed that

29.2% of nonsmokers and 60% of heavy smokers, both with MS, had cognitive impairment.²³

Several cognitive exercises have been shown to improve learning and memory in patients with MS. A study that examined the efficacy of the modified Story Memory Technique (mSMT) to improve learning and memory abilities in patients with MS consisted of 10-session behavioral interventions, teaching context and imagery to facilitate learning. The double-blind, placebo-controlled, randomized clinical trial included 86 patients with MS, separated into either the treatment group (n = 41) or the placebo control group (n = 45). Patients completed questionnaires assessing everyday memory for the baseline neuropsychological assessment, had a repeat assessment immediately post treatment, and had a long-term follow-up assessment 6 months after treatment. After therapy, patients in the treatment group were assigned to a booster session or a non-booster session group to examine the efficacy of monthly booster sessions in facilitating treatment effects over time. Results showed that the treatment group demonstrated a significantly improved learning slope relative to the placebo group post treatment. It was determined that the mSMT has an impact on improving learning and memory in patients with MS.²⁴

Cognitive leisure activities (eg, reading) influence greater brain growth, vocabulary knowledge, and involvement in hobbies, all of which are linked to increased ability to cope with MS and diminished cognitive impairment.²⁰ In a study examining maximal lifetime brain volume and disease-related cognitive impairment, researchers

analyzed the relationship of cognitive reserve through lifestyle changes in 62 patients with relapsing-remitting or secondary-progressive MS. Investigators also evaluated cognitive efficiency and memory. Higher education ($P = .03$) and increased leisure ($P = .001$) were associated with better cognition. Intellectual leisure activities included reading, art, writing, playing instruments, and structured games.²⁵ The investigators concluded that patients may be able to preserve brain reserve and protect cognitive efficiency through disease-modifying therapies and being proactive about their brain health.²⁵

The Role of Lifestyle Interventions in Management

Given the impact of MS on cognition and the growing emphasis on the role of comorbid conditions, brain preservation and comprehensive brain health via lifestyle interventions, in concert with cognitive exercises, are increasingly recognized as important factors in the broader management of patients with MS. Although data are limited, preventing, minimizing, and appropriately managing comorbidities can potentially help to reduce their negative affect on MS and optimize outcomes.^{2,7,9,13}

Lifestyle interventions potentially improve QOL in patients with MS.²⁶ For effective management of comorbidities through lifestyle, patients must be willing to practice healthy habits, such as reducing/eliminating tobacco and alcohol use, maintaining a healthy weight from eating a healthy diet and increasing physical activity, lowering weight and BMI, increasing sleep, and reducing stress.^{26,27} Dietary habits have been shown to affect inflammation. For instance, red meat has been shown to enhance inflammation, while omega 3 polyunsaturated fatty acids diminish inflammation. Patients should be encouraged to focus on and remedy lifestyle risk factors that can negatively affect cognitive brain function and vascular effects.²⁶

In addition to adapting lifestyle changes to impact the outcomes of certain comorbidities, cardiorespiratory fitness has been studied to uncover ways to improve volumes of deep gray matter involved in cognitive and motor functions in patients with MS.²⁸ In one study, investigators evaluated the impact of cardiorespiratory fitness on 35 patients with clinically definite MS who were relapse-free for 30 days, aged 18 to 64 years, able to walk with or without assistance, had the willingness and ability to complete self-assessments, and had a physician's approval for exercise. The mean disease duration was 11.4 years ($SD = 7.5$).²⁸ Physical activity regarding cardiorespiratory fitness was assessed and accommodated if a patient had a disability (eg, seated stepper), while brain volumes were measured by oxygen consumption and MRI. The results showed that cardiorespiratory fitness is associated with deep gray matter volumes

and has an impact on cognitive and motor function in patients with MS.²⁸

Vitamin D supplementation could also improve cognitive performance. In a study analyzing the relationship between vitamin D levels and cognitive impairment, investigators examined 88 patients with MS who had a vitamin D deficiency compared with those who had sufficient levels of vitamin D. The change in cognitive performance was examined after 3 months of a vitamin D₃ oral replacement. Cognitive performance was tested at baseline and follow-up using the Montreal Cognitive Assessment, Stroop, Symbol Digit Modalities, and the Brief Visuospatial Memory tests. Results showed that the vitamin D₃ replacement improved cognitive performances in patients with MS after 3 months, resulting in a significant betterment in QOL.²⁹

In addition to diet and physical well-being, lifestyle interventions in individuals with MS should encompass emotional wellness.¹⁰ For instance, many patients may not know with how to deal with such psychological comorbidities as stress, anxiety, fatigue, and depression. Meditation can serve as an adjunct to treatment, as it can reduce stress levels, improve a patient's well-being and QOL, and decrease morbidity.³⁰ A mixed methodology study that included participants attending an MS workshop for patients found that 25% of attendees practiced relaxation and meditation activities in the past 12 months. Attendees of the workshop found that meditation and relaxation were either somewhat helpful or extremely helpful at improving MS symptoms. They reported improved sleep, reduced spasticity, eased muscle tension, and increased well-being.^{30,31}

Mindfulness-based interventions, such as mindful breathing and movement, may also benefit QOL and mental health in patients with relapsing-remitting MS, according to a global review of randomized controlled trials. All studies included in the global review reported on QOL, mental health, physical, and psychosocial measures that had a 3- to 6-month follow-up period.³² Mindfulness practices were shown to benefit QOL, mental health, and certain aspects of physical health in patients with MS, but given the limitations of the data, investigators noted that additional high-quality studies are needed to assess the benefits of mindfulness further.³²

Conclusions

As the integral role of comorbidities in MS disease course and the resulting disabilities continue to be elucidated, management strategies increasingly emphasize comprehensive brain health and preservation. Although limited, data supporting the therapeutic potential of lifestyle interventions demonstrate the potential of wellness efforts to reduce disease inflammation, relapse, and

symptoms. As the treatment landscape continues to expand with the development of new disease-modifying therapies, a healthy lifestyle—ranging from diet and fitness, to mindfulness and medication—is an important adjunct to optimal therapeutic regimens.

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