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Multiple sclerosis and circadian rhythms: Can diet act as a treatment?

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Abstract

Multiple sclerosis (MS) is an autoimmune inflammatory and neurodegenerative disease of the central nervous system (CNS) with increasing incidence and prevalence. MS is associated with inflammatory and metabolic disturbances that, as preliminary human and animal data suggest, might be mediated by disruption of circadian rhythmicity. Nutrition habits can influence the risk for MS, and dietary interventions may be effective in modulating MS disease course. Chronotherapeutic approaches such as time-restricted eating (TRE) may benefit people with MS by stabilizing the circadian clock and restoring immunological and metabolic rhythms, thus potentially counteracting disease progression. This review provides a summary of selected studies on dietary intervention in MS, circadian rhythms, and their disruption in MS, including clock gene variations, circadian hormones, and retino-hypothalamic tract changes. Furthermore, we present studies that reported diurnal variations in MS, which might result from circadian disruption. And lastly, we suggest how chrononutritive approaches like TRE might counteract MS disease activity.

KEYWORDS

chrononutrition, circadian clock, immunity, metabolism, multiple sclerosis, retino-hypothalamic tract, time-restricted eating

1 | INTRODUCTION

Multiple sclerosis (MS) is an autoimmune inflammatory and neurodegenerative disease of the central nervous system.[1] The disease typically manifests in young adults (between 20 and 40 years of age) and affects more women than men (female-to-male ratio of 3–4:1).[2] MS affects more than 2 million people worldwide and is the leading cause of permanent neurological disability in young adults.[1]

The relapsing–remitting subtype of MS (RRMS) is defined by recurrent episodes of neurological dysfunction brought on by acute inflammatory demyelination.[1] In contrast, primary and secondary progressive MS (PPMS and SPMS) is characterized by progressive neurodegeneration leading to irreversible neurological disability.[1] While only 10%–15% of people with MS (pwMS) feature a progressive disease course from onset (PPMS), many people with RRMS convert to secondary progressive MS (SPMS) within 20 years.[1] However, even in the earliest stages of MS, including in patients who have just experienced their first episode of inflammatory demyelination, neurodegeneration occurs.[3,4]

MS features inflammatory plaques that, depending on their location, can lead to a variety of neurological symptoms. The most common early syndromes include monocular visual loss from optic neuritis,[5] ataxia brought on by a cerebellar lesion, a double vision brought on by brain stem dysfunction, or limb weakness or sensory loss from transverse myelitis[1] (Figure 1). However, one of the most prevalent and debilitating symptoms throughout the disease is fatigue, a severe reduction of physical or mental energy.[6]

There is growing evidence that MS is associated with a disruption of circadian rhythms, which represent the oscillating physical, mental, and behavioral patterns repeating around every 24 h.[7] However, our understanding of the impact of circadian rhythms on MS remains vague. Furthermore, it is unclear whether circadian disruption and fatigue associated with sleep disturbances in MS[8,9] are a consequence of MS-related inflammation and neurodegeneration; or, instead, whether circadian disruption is an actual cause for developing MS (chicken or egg). The latter is supported by studies showing that shift work, as an external cause of circadian disruption, is associated with a higher risk of developing MS.[10,11] However, it should be noted that sleep disorders in MS may also arise independently of the clock, e.g., due to nocturia (waking up to urinate at night) or pyramidal and sensory disability leading to restless legs syndrome.[12,13]

While a broad range of immunomodulatory drugs is available to prevent MS attacks and decelerate disability accumulation,[14,15] the disease is currently incurable.[1] Therefore, dietary interventions have been suggested as a safe addition to immunotherapy to attenuate the disease course.[16–18] In this review, we summarize the current

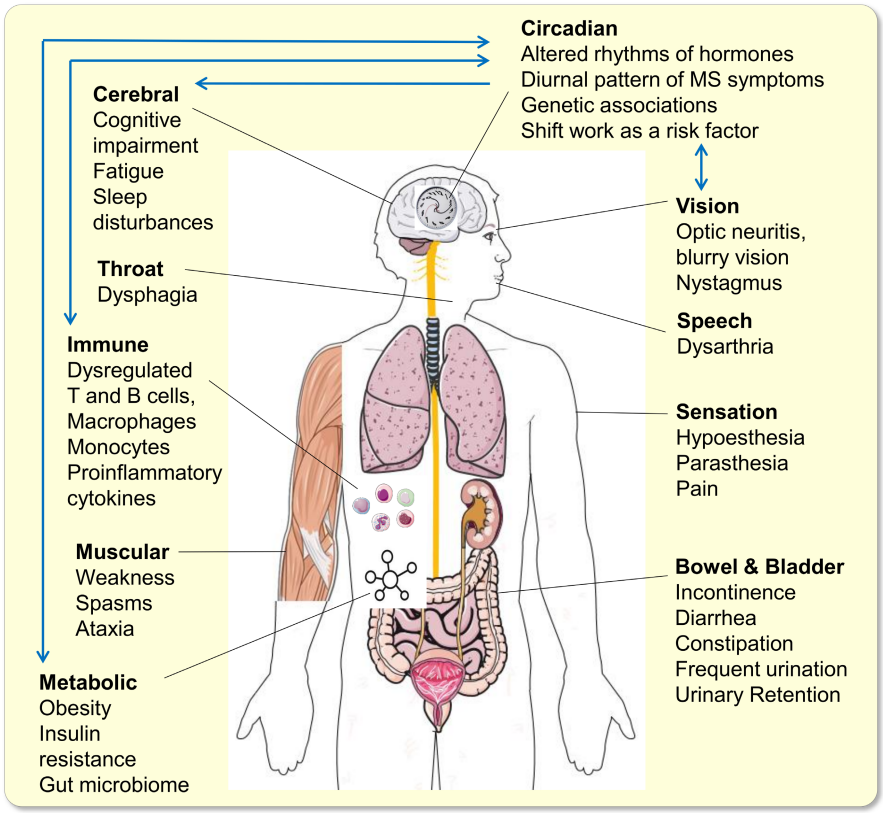

FIGURE 1 Main symptoms and functional disturbances in multiple sclerosis. Besides neurological symptoms, including cognitive impairment, fatigue, sleep disturbances, vision, speech, and sensation disturbances, pwMS can show immune, metabolic, muscular, and digestive dysregulations. Notably, alterations of circadian rhythmicity also observed in MS may contribute to or, in turn, caused by neurological, immune, metabolic, and digestive dysfunctions (as shown with blue arrows). The figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

knowledge on diets and circadian disruption in MS. Furthermore, we postulate that time-restricted eating (TRE) could be an effective treatment in MS by modulating circadian rhythms.

2 | IMMUNE, NEUROLOGICAL, AND METABOLIC DYSFUNCTIONS IN MS

2.1 | Immunopathogenesis, neuropathology, and diagnosis of MS

MS is an autoimmune demyelinating and neurodegenerative disease associated with derailments of the innate and adaptive immune system. While its entire immunopathogenesis is not fully clear, current notions posit that T and B cells, macrophages, monocytes, and microglia (endogenous phagocytes of the CNS) are involved,[19–27] (Figure 1).

It is unclear where and how the initial trigger of an autoimmune response to the CNS occurs; the primary contact could be in cervical lymph nodes, and the adaptive immune system might be stimulated by molecular mimicry or novel autoantigens. The innate immune system could be activated through environmental factors such as dietary or smoke constituents, bacteria, or viruses at mucosal surfaces.[19,20] The transmigration of peripherally activated immune cells into the CNS is facilitated by a permeable blood–brain barrier that precedes inflammation and subsequent demyelination reflected by focal inflammatory white matter lesions that are visible on brain magnetic resonance imaging (MRI) and represent key diagnostic and predictive measures in clinical practice.[28–30]

Most of these focal and disseminated demyelinating white matter lesions ("plaques") of the brain, brainstem, cerebellum, spinal cord, and optic nerve show a perivenous location which points to an association of the cerebral vasculature with lesion formation.[31–33] The so-called central vein sign is now considered an emerging imaging biomarker of MS, as it rarely occurs in relevant MS mimics.[34,35] In acute focal white matter lesions, axonal transection is a characteristic feature. The extent of axonal damage and, thus, the destructiveness of a lesion may vary across anatomical regions and between patients.[36] In recent years, the neurodegenerative component of the disease has been re-emphasized; manifold neuropathological and advanced neuroimaging studies have shown cortical lesions and cortical and deep gray matter damage from the earliest disease stages that contribute significantly to long-term disability, including cognitive impairment[37–39] (Figure 1). Also, the optic nerve and retina, which are part of the CNS, are frequently affected from early on, as mirrored by numerous optical coherence tomography (OCT) studies showing retinal atrophy with loss of axons and retinal ganglion cells in eyes with and without prior optic neuritis.[40–43] Lesions and more subtle tissue damage in the spinal cord that predominantly manifest in the cervical cord significantly contribute to disability, especially impaired ambulation with reduced walking distance and bowel–bladder problems[44] (Figure 1). A diagnosis of MS is currently made according to the current version of the so-called McDonald criteria,[45] which are heavily based on radiographic findings and enable a diagnosis of MS after the first typical clinical event in many patients. Current research aims to improve prognostication of the disease course with advanced MRI methods, sophisticated retinal imaging, and serum-borne biomarkers such as the neurofilament light chain.[46,47] However, the value of these measures for the management of individual patients remains to be shown.

2.2 | Metabolic disturbances in MS

Overweight and obesity are associated with an increased risk of MS.[48,49] Further, pwMS often show other metabolic disturbances such as insulin resistance and changes in glucose and lipid homeostasis and the gut microbiome[20,48–50] (Figure 1). In particular, dysregulations in glycolysis, Krebs cycle, electron transport chain, pentose phosphate pathway, and glycogen metabolism were observed in pwMS.[50] Interestingly, while changes in glucose homeostasis typical of type 2 diabetes, such as hyperinsulinemia and decreased insulin sensitivity, were observed in pwMS, they seem unrelated to chronic inflammation or physical inactivity.[51] Furthermore, the levels of multiple plasma lipids and ketone bodies, the fatty acid oxidation pathway and involved enzymes, and the metabolism of eicosanoids, lipoproteins, and cholesterol were altered in MS, and, in part, correlated with its clinical aspects.[50] Altered metabolic pathways of carbohydrates and lipids in pwMS may lead to further cellular damage, such as oxidative stress, which might be responsible for systemic complications. These metabolic abnormalities may be detected through altered levels of related metabolites in the blood and cerebrospinal fluid of MS patients. Notably, a hypothetical relationship between such metabolic changes and the immune system in patients with MS has been proposed.[50]

Interestingly, cellular and whole-body inflammatory and metabolic processes are also under strong circadian control.[52,53] Therefore, their dysregulations might be, at least in part, induced by circadian disruption in MS.

2.3 | Dietary approaches in MS

Available pharmacological therapies in MS have limited effect on disability progression and may confer a risk for serious adverse events.[1,14] Therefore, the development of novel and non-pharmacological approaches to support the combat of MS progression is a crucial unmet medical need. In particular, dietary approaches may improve the patients' disease course and quality of life. Indeed, the high consumption of saturated and trans-fatty acids, red meat, sugar-sweetened beverages, and refined cereals induces the production of Th17 cells and proinflammatory cytokines.[54] In contrast, the Mediterranean diet (rich in fruits, vegetables, whole grains, and polyphenols),[55–58] the Paleolithic diet (characterized by the high consumption of leafy green vegetables, plant proteins, soy, nuts, and the reduction of processed food),[59,60] the Swank diet (based on limited saturated fat intake),[60,61] and McDougall diet (based on carbohydrates of plant origins)[62] are associated with a low MS risk or attenuate some MS symptoms such as fatigue. Furthermore, caloric restriction reduces the risk of postprandial inflammation, protects against oxidative damage, improves the quality of life, and attenuates the progression of MS in experimental models and several human trials.[63,64] Finally, the ketogenic diet, which is low in carbohydrates and high in fat and induces ketone increase in circulation, might result in anti-inflammatory and neuroprotective effects and improve the quality of life, fatigue, and depression in MS patients.[17,18,57,65,66] Nevertheless, most previous dietary trials in MS were underpowered, and therefore, provided no convincing data yet that dietary approaches may delay MS onset or improve the disease course. Furthermore, whether dietary interventions can counteract circadian disturbances associated with MS described in the next chapter remains unclear and needs to be investigated in future clinical trials.

3 | CIRCADIAN DISTURBANCES IN MS

3.1 | Circadian rhythms and MS risk

The endogenous circadian clock plays a significant role in how humans adapt their physiology and behavior to changes between day and night. Like in all mammals, the human circadian clock consists of a master clock, located in the suprachiasmatic nucleus of the hypothalamus, and a peripheral clock.[52] Almost every tissue in the body contains peripheral oscillators controlled by the master clock. Circadian rhythms are demonstrated in the tissue transcriptome, circulating metabolome, metabolic hormones, adipokines and cytokines regulating cholesterol, carbohydrate, lipid, and energy metabolism.[67–71] For a detailed review of the current knowledge on the mammalian circadian system, please refer to a recently published review.[72]

Circadian rhythms play a critical role in innate and adaptive immunity,[73–75] metabolic regulation, and contribute to the pathophysiology of neurodegenerative and metabolic diseases.[52] As such, circadian disruption is increasingly considered a contributor to autoimmune diseases.[74] pwMS show metabolic and immunological disturbances such as derailment of physiological T- and B-lymphocyte functions, alteration of innate immune responses, and in many cases, also changes in glucose and lipid homeostasis and gut microbiome.[20,48–50] The circadian release of immune cells is controlled by hormones like melatonin and cortisol, which again are regulated by the suprachiasmatic nucleus. Indeed, an animal study showed that TH17 cell differentiation follows the circadian clock.[76] Nevertheless, data on circadian rhythms of immune cells in MS are still very limited, in contrast to other autoimmune diseases such as type 1 diabetes, where phase shifts of 3–5 h in the circadian peak of blood levels have been demonstrated for B and T cells and their naive and effector memory subsets.[77] Circadian disruption might thus contribute to metabolic and immune cell dysregulation and malfunction in MS (Figure 2).

Notably, the circadian–immune connection is bidirectional, so immune challenges and mediators (e.g., cytokines) can affect the circadian rhythms at multiple levels.[78] Indeed, lipopolysaccharide injections in rodents alter the rhythmicity of the circadian clock in several organs.[79,80] Furthermore, the intravenous administration of a bolus dose of endotoxin to healthy human subjects synchronizes and suppresses clock gene expression in peripheral blood leukocytes.[81] In agreement with this, in septic shock patients, molecular rhythms in immune cells are substantially altered and decreased compared to healthy young men.[82] Therefore, immune dysfunction per se might induce circadian dysrhythmicity observed in MS, supporting the abovementioned chicken-or-egg discussion.

3.2 | Circadian variations in biomarkers and MS symptom

Multiple processes and biomarkers demonstrated circadian rhythms in pwMS. An RNA analysis showed that gene expressions are subject to the time of day in MS.[83] Furthermore, diurnal variations were found in serum markers of oxidative stress (nitric oxide, carbon dioxide, and uric acid),[84] hematologic biomarkers,[85] and cytokines[86,87] in MS.

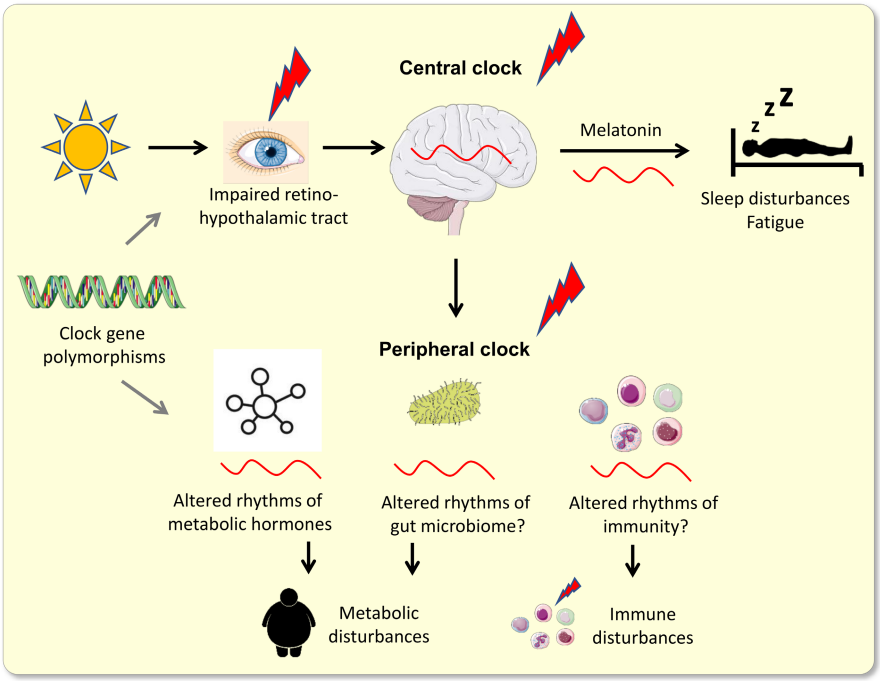

FIGURE 2 Circadian disturbances in MS. Evidence suggests that both central and peripheral rhythmicity are disturbed in MS. Processes and rhythms affected in MS are designated with a lightning symbol and red oscillating lines, respectively. Ganglion cell atrophy, including intrinsically photosensitive ganglion cells, and impaired retino-hypothalamic tract integrity lead to impaired central clock synchronization by the light/dark signals. Several studies showed altered rhythms of melatonin secretion, which might contribute to sleep disturbances and fatigue in MS and might be explained by altered central clock rhythmicity. Peripheral rhythm changes in MS were shown for some metabolic hormones, such as leptin and corticosterone, which, together with altered gut microbiome composition, might contribute to the change of metabolic functions in MS. In turn, altered immune rhythms might contribute to immune disturbances in MS. However, whether other metabolic rhythms, the rhythmicity of immune cells and immune mediators, as well as gut microbiome, are affected by MS, still needs to be investigated. Notably, MS is associated with genetic polymorphisms within several clock genes, confirming a role of genetic factors in MS predisposition. The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

A range of studies showed diurnal variations in MS symptoms. MS symptoms, particularly fatigue and pain, increase over the day,[88,89] while muscle strength decreases.[90] Both objective and subjective cognitive performance of pwMS decreases over the day.[91] In contrast, another study showed that walking patterns remained stable, while it confirmed that fatigue increased over the day.[92] A wrist actigraph study identified circadian patterns in motor activity, possibly due to a hyperactive hypothalamus–pituitary–adrenal axis and higher cortisol awakening response.[93] Furthermore, circadian temperature variations are associated with motor function fluctuations.[94] Even the effect of corticosteroid treatment, which is given to treat an acute MS attack, differs in the day and night.[95,96]

3.3 | Clock genes in MS

Clock genes are responsible for intracellular timekeeping, generating roughly 24-h rhythms in physiology and behavior.[7] Interlocked transcriptional–translational feedback loops, including the transcription factors, aryl hydrocarbon receptor nuclear translocator-like (ARNTL, also called BMAL1), clock circadian regulator (CLOCK), period (PER1, PER2, PER3), cryptochrome (CRY1, CRY2), retinoic acid-related orphan receptors (RORs), and nuclear receptor subfamily 1 group D (NR1D1/2 or Rev-Erb/ß) make up the master clock mechanism found in almost every cell.[53] The expression of so-called clock-controlled genes, which comprise important metabolic transcription factors and enzymes causing circadian oscillations of metabolic processes, is regulated by one cycle of this molecular machinery, which lasts roughly 24 h.[52,53,97]

A study in experimental autoimmune encephalomyelitis, an animal model of MS, showed that the clock gene BMAL1, a main constituent of the molecular clock, and the time of day in myeloid cells are associated with immune cell accumulation and activation.[98] Genetic variability in the ARNTL and CLOCK genes might be associated with MS risk.[99] A specific genotype of PER3, a clock gene controlling circadian rhythm and sleep, is associated with

accelerated MS disease course[100] (Figure 2). Furthermore, differential expression and frequency of low-frequency variants were observed in MS families for six genes involved in circadian entrainment/rhythm.[101] The expression of *Per2* in the liver showed altered circadian rhythms in an animal model of MS.[102]

3.4 | Circadian hormones in MS

Melatonin, a natural hormone, is produced in a circadian rhythm by the pineal gland. Its main role is the control of the sleep–wake cycle. However, also antinociceptive, antidepressant, anxiolytic, and immunomodulatory properties have been described.[103] Several studies have investigated the role of serum melatonin levels in MS.

Melatonin levels are lower in pwMS compared to controls.[103] Lower melatonin levels are associated with longer MS disease duration, increased neurological disability, and a higher frequency of sleep disruptions.[104] A disruption of the circadian melatonin rhythm in the form of an abnormal proportion of overnight melatonin was associated with higher disability and fatigue severity.[105] Melatonin also inhibits demyelination and boosts remyelination in pwMS.[106] Interferon beta, a common MS immunomodulatory drug, led to an increase in melatonin levels in pwMS.[107] Caution might be required regarding corticosteroids, which represent the standard treatment for an acute MS attack: a study in both pwMS and an animal model of MS showed that corticosteroid therapy leads to a downregulation of melatonin serum levels.[108] However, as high-dose corticosteroid therapy is usually only given during an acute MS attack, this is probably not the reason for the results reported above.

Only a few studies have investigated the effect of melatonin supplementation in MS. A randomized, double-blind, placebo-controlled, crossover trial investigated melatonin for the treatment of nocturia in pwMS.[109] However, there was no significant treatment effect among the 26 pwMS who completed the study.[110] A case–control study that investigated the effect of melatonin supplementation found that melatonin acts as antioxidant and improves sleep in pwMS.[111] Interestingly, the seasonality of MS disease activity was linked to melatonin release.[105,112,113]

Another hormone that was linked to the course and severity of MS is the glucocorticoid hormone cortisol. Lower cortisol levels were linked to despair, weariness, and urinary dysfunction, while higher cortisol levels were linked to anxiety and depression.[114] Like melatonin, cortisol is produced in a circadian rhythm and controlled by the central clock in the suprachiasmatic nucleus. Altered circadian cortisol release in the form of an increase in the cortisol awakening response, an increase in cortisol within 20–30 min after awakening, which was associated with neurological disability worsening[115] and fatigue, was found in pwMS.[115–117] There seems to be no influence of MS disease-modifying treatment on the cortisol awakening response.[115] One of the two aforementioned studies found an association of depression with the cortisol awakening response,[116] while the other did not.[115]

Notably, glucocorticoids are also involved in regulating energy metabolism and immune reactions and demonstrated altered rhythmicity in the animal model of MS.[102] In the same model, leptin, a metabolic hormone secreted by adipose tissue and regulating energy homeostasis, satiety, neuroendocrine function, and immune function, also demonstrated altered rhythms,[102] which might provide a link to the metabolic disturbances in MS. Notably, leptin is regulated by glucocorticoids so that leptin and cortisol show an inverse circadian rhythm.[118] However, in pwMS, leptin rhythms have not been studied yet.

3.5 | Retino-hypothalamic tract integrity

Information about the length of day and night is delivered via photosensitive retinal ganglion cells over the retino-hypothalamic tract to the nucleus suprachiasmaticus of the hypothalamus, the corresponding control centers of the CNS. Those intrinsically photosensitive, melanopsin-expressing ganglion cells (ipRGCs), which constitute a small subset (~1%) of the retinal ganglion cells, control pupil response. The function of the ipRGCs can be measured with post-illumination pupil response (PIPR) to a blue light stimulus, which achieves the maximum stimulation of ipRGCs, compared to a red-light stimulus. Multiple studies investigated PIPR in neurologic and neuro-ophthalmic diseases.[119] Indeed, several studies found reduced melanopsin-mediated PIPR in conditions associated with ganglion cell atrophy, e.g., glaucoma.[119] While some of the studies did not find any abnormalities in PIPR despite severe ganglion cell damage, it is of note that most of the studies featured low sample sizes.[119] Only one study investigated the melanopsin-mediated pupillary restriction response in MS.[120] They found a reduced PIPR to blue light in MS eyes compared to controls, which was associated with retinal ganglion cell atrophy.

Retinal ganglion cells are the cell bodies of the axons forming the optic nerve. Ganglion cell atrophy was found in 79% of pwMS in a post mortem histological evaluation.[121] In vivo, the ganglion cell integrity can be measured as the thickness of the combined ganglion cell inner plexiform layer (GCIPL) from OCT scans.[41] A systematic review and meta-analysis found that in pwMS, there is pronounced thinning of the GCIPL in eyes with previous optic neuritis.[122] However, to a lesser

effect, also in eyes with no optic neuritis, the GCIPL is reduced,[122] presumably due to subclinical or chronic neurodegeneration of trans-synaptic retrograde degeneration originating from posterior visual pathway lesions.[123] As such, it seems plausible that also ipRGCs are affected by MS-related atrophy. As a consequence, one would expect retino-hypothalamic disruption and impaired circadian rhythms. While this has not been investigated in MS, studies have shown an association of reduced melanopsin-mediated PIPR with sleep disturbances in ophthalmic diseases featuring ganglion cell damage.[124,125]

Because of the presumably impaired retino-hypothalamic tract integrity in MS patients, the responsiveness of the master clock to light in these subjects might be disturbed. Two studies investigated the effect of bright white light therapy for treating fatigue in pwMS.[126,127] Both studies revealed an improvement in fatigue scores after light therapy. However, neither of the studies revealed a significant treatment effect of bright white light when compared to sham therapy with dim red light.[126,127] Although both studies feature low sample sizes and did not investigate the effects of light therapy on circadian rhythmicity in MS, their results indicate that the effectiveness of light therapy might be limited in MS, potentially as a consequence of retino-hypothalamic tract impairment. External stimuli mainly affecting the peripheral clock instead of the master clock, e.g., chrononutritional tools, might be more effective than light in treating pwMS.

4 | FUTURE DIRECTIONS: DIETARY APPROACHES AS A CHRONOBIOLOGICAL TOOL IN MS

Whereas circadian research initially focused on the investigation of the clock machinery organization and circadian disruptions upon various diseases, in the last years, the idea of strengthening and maintaining circadian rhythms for treating diseases, i.e., circadian medicine or chronomedicine, was developed.[128] In this paradigm, factors known to influence the circadian system (zeitgebers), such as light, food, melatonin, and exercise, are used as therapeutic approaches to bolster and reset circadian rhythms.[128] In agreement with this paradigm, in MS, circadian rhythm disruption is apparently not only a symptom but also a risk factor for MS and its progression over time. Therefore, therapeutic approaches to strengthening and maintaining circadian rhythms might be a tool to improve MS symptoms and decelerate disease progression.

As mentioned above, because of the presumably impaired retino-hypothalamic tract integrity in MS patients, external stimuli mainly affecting the peripheral clock instead of the master clock, such as dietary approaches, might be more effective as chrononutritional tools in MS patients than light. Indeed, the interaction between circadian clocks and metabolic functions is reciprocal, i.e., (1) central and peripheral circadian clocks control metabolic processes in relevant tissues (liver, adipose tissue, muscle, pancreas, etc.), and (2) nutrients and metabolites, in turn, can act as powerful zeitgebers for peripheral clocks.[52,53] As an example, in mice fed with a high-fat diet (HFD), altered rhythms of the core clock and a reorganization of the whole circadian transcriptome were observed.[129] In humans, a switch to the isocaloric HFD altered the oscillation of the core clock genes in blood monocytes and affected the centrally driven cortisol rhythm.[130] Along with food composition, calorie intake and timing are important nutritive factors to alter the circadian rhythms of the core clock and other enes and proteins.[53,131]

In recent years, TRE attracted great attention as a promising non-pharmacological approach in circadian medicine for the prevention and treatment of chronic diseases such as diabetes, obesity, and cardiovascular diseases. TRE (or time-restricted feeding, TRF, if applied in animals) is an eating pattern whereby the daily caloric intake is limited to a time interval of less than 12 h.[132] While feeding to the "wrong" circadian phase (e.g., upon the shift work or night eating) induces circadian disruptions and has negative health effects,[133] restricting feeding to the "right" circadian phase (i.e., active phase) appears to restore normal rhythms, especially in peripheral tissues and improve health outcomes. In rodents, TRF during the dark phase increased the amplitude of circadian rhythms of the gene expression compared to the ad libitum feeding[134] and, combined with a caloric restriction, effectively extended the life span.[135] Furthermore, it was protective against high-fat diet-induced obesity, glucose intolerance, hepatic steatosis, and inflammation and improved nutrient utilization and energy expenditure.[134,136] The beneficial effect of TRF in mice was shown also for high-sucrose and high-fructose diets and even in pre-existing obesity and metabolic disturbances.[136]

Similarly, in humans, TRE in form of the religious daytime dry fasting (whereas food is consumed in the night) showed impacts on the circadian system, advancing the circadian phase in blood monocytes by 1.1 h.[137] Another trial on 10-h daytime eating restriction revealed that TRE restores the 24-h profile of adipose tissue transcriptome including rhythms of core clock genes in obese men.[138] Furthermore, TRE trials demonstrated improvements in glucose regulation, insulin sensitivity, blood lipid levels, blood pressure, oxidative stress markers, and quality of life measures, although the effects may differ between early and midday/late eating windows.[139–142] Some studies showed that TRE affects the gut microbiome, which

might contribute to the described metabolic effects of TRE.[143] However, these findings are not yet advanced enough to lead to actionable evidence. Notably, TRE also reduced levels of C-reactive protein and proinflammatory cytokines,[140,144,145] improved sleep quality, and resulted in subjects feeling more energetic.[146,147] Furthermore TRE induces autophagy[142] and mild elevation of the ketone bodies[148] in the fasting phase, which might contribute to the TRE-induced changes in circadian rhythms.[149] Notably, although most TRE trials demonstrated weight reduction, some studies demonstrated improvements in metabolic and inflammatory parameters without significant body weight loss,[140] suggesting that shortening the eating window induces beneficial effects independent of weight loss.

Taken together, although TRE acts via multiple metabolic mechanisms induced by the change of the eating/fasting duration,[132] there is strong evidence of its modulating impact on the circadian clock. Therefore, it could be hypothesized that TRE would stabilize circadian clocks, restore immunological, metabolic, and possibly neurological functions, and combat the disease progression in pwMS (Figure 3). However, a TRE approach accompanied by investigations of the circadian rhythmicity of metabolic and immunological function has not yet been studied in MS.

Till now, only two clinical trials investigating the effects of 8 h TRE in subjects with MS are registered on ClinicalTrials.gov. The aims of the first study, an 8-week trial, are to determine preliminary efficacy of TRE for reducing symptom burden, improving inflammatory markers, and reducing cardiometabolic risk among adults with RRMS as well as the TRE safety and acceptability of TRE (NCT04389970). The second study, a 6-month trial, compares the TRE impact with continuous caloric restriction vs. no intervention (NCT02846558). However, the question if TRE can restore circadian rhythmicity in MS is not addressed in these trials and has to be a subject of future research.

Other dietary approaches used in MS and mentioned in Chapter 3 might act at least in part via the circadian clock. Firstly, the ketogenic diet, which is low in carbohydrates and high in fat, might affect circadian rhythms due to the increase in the ketone bodies. Secondly, other forms of intermittent fasting, which means the abstinence from food for different periods[150] (such as alternate day fasting involving a combination of no-eating days with eating days or modified fasting with consumption of 20%–25% of energy requirements on fasting days) might affect circadian rhythms and improve metabolic and inflammatory parameters in MS. Intermittent fasting effects on circadian rhythms were mostly shown in animals and depend on the day time of the food intake. Food intake at the inactive phase results in arrhythmic clock gene expression, whereas feeding at the active phase induces rhythms similar to ad libitum feeding.[151] In humans, most studies show a decrease in glucose and insulin in circulation, improvement of blood lipids, and reductions in inflammatory markers, although different fasting regimens make the data very heterogeneous.[152] The beneficial effects of intermittent fasting could be explained by weight loss and a higher fasting duration; however, exact mechanisms affecting circadian rhythms still need to be elucidated.

Finally, calorie restriction (CR) without any limitation of the eating time can restore circadian rhythms, improve metabolic and inflammatory factors, and even extend the life span in rodents.[153] Notably, in Drosophila, the lifespan effects of CR are mediated by an increased amplitude of clock genes regulating lipid metabolism.[154] Several mouse studies confirmed that CR synchronizes the peripheral

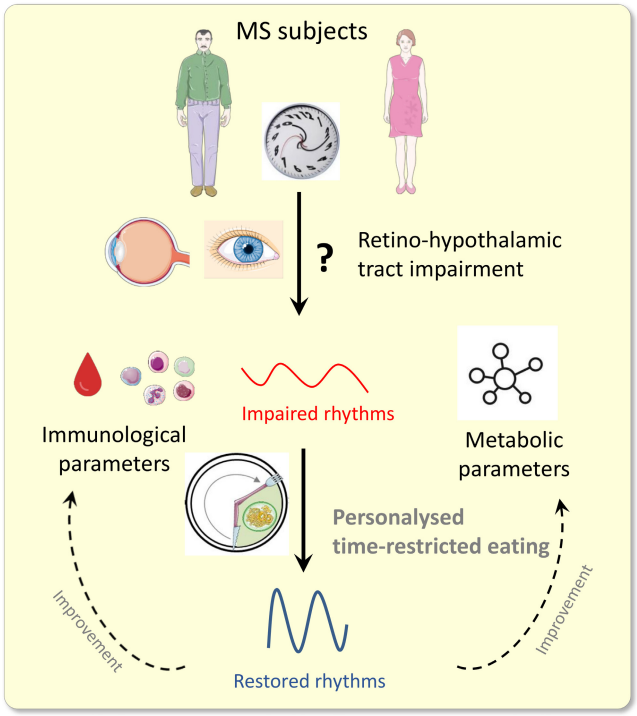

FIGURE 3 Time-restricted eating as a chrononutritive tool for the entrainment of circadian rhythms in MS. In later life, a reduced sensitivity of the master clock to light, imbalances of neurotransmitters, and desynchronization of SCN neurons lead to a decrease in the overall amplitude of its firing rhythm. In turn, a weaker SCN output signal reduces the strength of downstream oscillators in central and peripheral tissues. In metabolic diseases such as obesity and T2D, circadian rhythms are also reduced or dysregulated. Providing other zeitgebers, such as scheduled meals, which act on the circadian system via extra-SCN pathways, may entrain the circadian system and restore circadian rhythms. The figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

clock and can also affect the SCN clock, which synchronizes biochemical processes and metabolic functions. As in rodents, a hypocaloric diet was shown to affect the clock gene expression in human adipose tissue.[155] Currently, five human trials studying the effects of CR or comparing CR effects with other diets (ketogenic diet and intermittent fasting) are registered on ClinicalTrial.gov. Notably, there is evidence suggesting that intermittent fasting might be more feasible and more effective at reducing neuroinflammation and metabolic dysfunctions and preventing neurodegeneration compared to continuous CR.[156]

5 | CONCLUSIONS

Multiple sclerosis is an autoimmune inflammatory and neurodegenerative disease accompanied by disruptions of circadian rhythmicity. Chrononutritive approaches such as TRE may represent a promising strategy to stabilize circadian rhythms and clock-controlled metabolic and immune functions in MS and to counteract MS progression. However, given the disease's complexity, future carefully controlled studies are needed to elucidate TRE effects on circadian rhythms in MS and underlying molecular mechanisms.

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CONFLICT OF INTEREST STATEMENT

There are no competing interests to declare.

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