doi:10.2478/enr-2026-0009

Current perspectives on the pathogenesis of multiple sclerosis: A minireview

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Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system characterized by inflammation, reactive gliosis, and progressive neuroaxonal damage resulting in heterogeneous clinical and histopathological manifestations. As MS often leads to disability at a young age, it represents a substantial socio-economic burden in developed countries. The etiopathogenesis of MS is multifactorial and incompletely understood, involving genetic, immunologic, and environmental factors. Recent research highlights immune responses to Epstein-Barr virus, blood-brain barrier disruption, microbiome-gut-brain axis alterations, oxidative damage, and mitochondrial dysfunction. Studying patients with newly diagnosed MS without significant comorbidities provides insight into early disease mechanisms before disability development or long-term treatment effects. This mini-review focuses on early vascular and metabolic alterations that may contribute to MS, including lipoprotein subfractions as markers of incipient atherosclerosis, endothelial dysfunction as an initiating vascular event, and autonomic nervous system imbalance during disease progression. It also addresses insulin sensitivity as a key metabolic factor alongside chronic inflammation and oxidative damage as interconnected mechanisms driving tissue injury. Metabolic changes reflecting neuronal impairment, mitochondrial dysfunction, and astroglial activation are detectable in both lesional and normal-appearing white matter in early stages. Reduced antioxidant capacity supports a role of oxidative damage in MS pathogenesis. Accelerated vascular aging, independent of traditional cardiovascular risk factors, may progress from endothelial dysfunction to structural atherosclerotic changes. Subtle alterations in lipoprotein profiles further suggest an increased risk of atherosclerosis, potentially influenced by inflammatory activity and oxidative damage, with possible sex-specific differences. Autonomic dysfunction appears to develop secondary to disease progression rather than as a primary driver of pathogenesis.

Keywords: multiple sclerosis, inflammation, lipoproteins, autonomic nervous system dysfunction, oxidative stress

The authors would like to dedicate this research article to the Endocrine Regulations 60th anniversary.

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Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory immune-mediated demyelinating disease of the central nervous system (CNS) leading to neurodegeneration and diverse clinical and histopathological features. Early observations include Sir Augustus d'Este (1794–1848) diaries, scientific characterization in 1838 by Sir Robert Carswell (1793–1857), and the introduction of "Sclérose en plaques" by Jean-Marie Charcot (1825–1893). The modern term "multiple sclerosis" emerged in the 1950s.

It remains under investigation which pathological processes play a primary role in the etiopathogenesis of MS and which represent consequences or concomitant features of the disease. Therefore, studies focusing on patients with newly diagnosed MS without significant comorbidities may help to elucidate mechanisms involved at early stages of the disease, when symptoms are not yet fully developed and the disease course has not been influenced by treatment.

Patients with MS are at increased risk of cardiovascular and metabolic diseases, even in the absence of traditional risk factors (Yang et al. 2022). Mitochondrial dysfunction has been proposed as a potential underlying mechanism contributing to neurodegeneration through oxidative damage, induction of apoptosis and insufficient energy production (Rey et al. 2022). In this context, particular attention has been directed toward cardiovascular and metabolic alterations present in early MS.

This mini-review aims to provide an integrated perspective on the pathogenesis of MS by linking metabolic, vascular, and autonomic mechanisms, with a particular focus on early disease stages. It offers a concise overview of the clinical characteristics, epidemiology, and current understanding of the disease to provide context for these mechanisms. In particular, it examines early vascular and metabolic alterations potentially contributing to MS, including lipoprotein subfractions as markers of early atherogenesis, endothelial dysfunction, and autonomic nervous system imbalance. It further addresses insulin sensitivity, chronic inflammation, and oxidative damage as interconnected mechanisms involved in tissue injury.

Epidemiology and etiopathogenesis. Globally, ~2.9 million people have MS, with prevalence increasing with latitude. High rates are reported in Europe, Canada, northern USA, and southern Australia; lower prevalence occurs in Asia and sub-Saharan Africa (Boutitah-Benyaich et al. 2025).

MS typically begins between 20 and 40 years; ~10% present in childhood/adolescence, usually females, with slower progression but earlier transition to secondary progressive MS (Filippi et al. 2018).

Women are affected by MS 2–3 times more than men. Relapse rates decrease during pregnancy, and modern disease-modifying therapies (DMTs) prevent postpartum relapses. Breastfeeding further reduces the risk of relapse (Compston and Coles 2008). Women typically show a milder course with sensory symptoms and frequent relapses, whereas men experience faster progression with more severe motor and cognitive impairment (Ryan and Mills 2022).

MS often begins as a clinically isolated syndrome (CIS) affecting myelin-rich regions with early symptoms, such as sensory disturbances, numbness or tingling. Common presentations include optic neuritis (~25%), brainstem symptoms (diplopia, trigeminal neuralgia), and cerebellar signs (coordination impairment, tremor). Additional features are motor dysfunction, sphincter disturbances, erectile dysfunction, cognitive changes, and depression (Compston and Coles 2008; Filippi et al. 2018).

MS is characterized by a focal CNS demyelination driven by immune-mediated mechanisms. Generally, MS is classified as an autoimmune disease due to female predominance, increased relapse risk in puberty and postpartum, and pregnancy-associated improvement, though no definitive autoantigen has been confirmed (Ryan and Mills 2022). Myelin-specific T lymphocytes can be activated via molecular mimicry following exposure to foreign antigens in genetically susceptible individuals. Several candidate autoantigens have been proposed, but evidence is inconclusive (Filippi et al. 2018; Thompson et al. 2018; Van Noort et al. 2023).

MS etiopathogenesis is multifactorial, involving genetic (*HLA-DRB1*15:01~HLA-DQB1*06:02~a1*), immunological, and environmental factors (Boutitah-Benyaich et al. 2025). Epstein-Barr virus (EBV) infection is strongly implicated in increasing MS risk 32-fold (Van Noort et al. 2023). Additional factors include other infections, gut microbiome composition, smoking, vitamin D deficiency, limited sunlight, obesity, and diet (Penesova et al. 2018; Thompson et al. 2018). Mechanistic insights come from the experimental autoimmune encephalomyelitis (EAE) animal model (Ryan and Mills 2022).

Myelin, formed by oligodendrocytes in the CNS and Schwann cells in the peripheral nervous system, consists of approximately 40% water. Its dry weight is predominantly formed by lipids (70–85%) and

a smaller protein fraction (15–30%). Cholesterol, phospholipids (e.g., lecithin, sphingomyelin), and glycolipids (e.g., galactosylceramide) are the principal lipid components. Cholesterol in the CNS is synthesized locally due to the blood-brain barrier (BBB). In MS, BBB disruption may allow the peripheral lipoproteins to enter the CNS, potentially altering cholesterol homeostasis. MS pathology involves inflammation, demyelination, reactive gliosis, and neuroaxonal injury contributing to both reversible symptoms and permanent disability (Figure 1).

Central pathological features of MS are focal demyelinating lesions around postcapillary venules with BBB disruption (Filippi et al. 2018; Boutitah-Benyaich et al. 2025). Although the precise mechanism underlying BBB permeability changes remains unclear, both direct effects of cytokines and chemokines (e.g., TNF, IL-1β, IL-6) produced by microglia, astrocytes, and endothelial cells, and indirect leukocyte-mediated injury are implicated.

Activated leukocytes (including T and B cells, monocytes, and macrophages) migrate across the BBB, mediated by interactions between leukocyte integrins and endothelial cell adhesion molecules (CAMs). Therapeutic blockade of this interaction is exploited clinically with natalizumab. Within active lesions, activated T lymphocytes secrete proinflammatory cytokines (IL-17, IL-6, IL-23, TNF-α) and recruit immune cells, leading to myelin and oligodendrocyte damage, reactive gliosis, and neuroaxonal degeneration (Filippi et al. 2018). Microglial activation may be protective or may contribute to neurodegeneration.

The vascular hypothesis attributes MS pathogenesis to endothelial dysfunction and BBB breakdown (Zierfuss et al. 2024), whereas the mitochondrial hypothesis implicates oxidative damage, apoptosis, and energy failure (Rey et al. 2022). Remyelination occurs via oligodendrocyte precursor cells restoring saltatory conduction, which may contribute to clinical recovery and has been well characterized in experimental models (Cunniffe and Coles 2021). Clinical trials are investigating agents such as clemastine, opicinumab, biotin, and bexarotene (Cunniffe and Coles 2021). Neuroaxonal loss begins early affecting both white and gray matter with lesion volume correlating weakly with clinical disability and cognitive impairment (Filippi et al. 2018).

Clinical forms and manifestations. Based on the clinical course descriptors, MS is classified into several forms (Figure 2) commonly referred to as the Lublin-Reingold classification (Lublin et al. 2014):

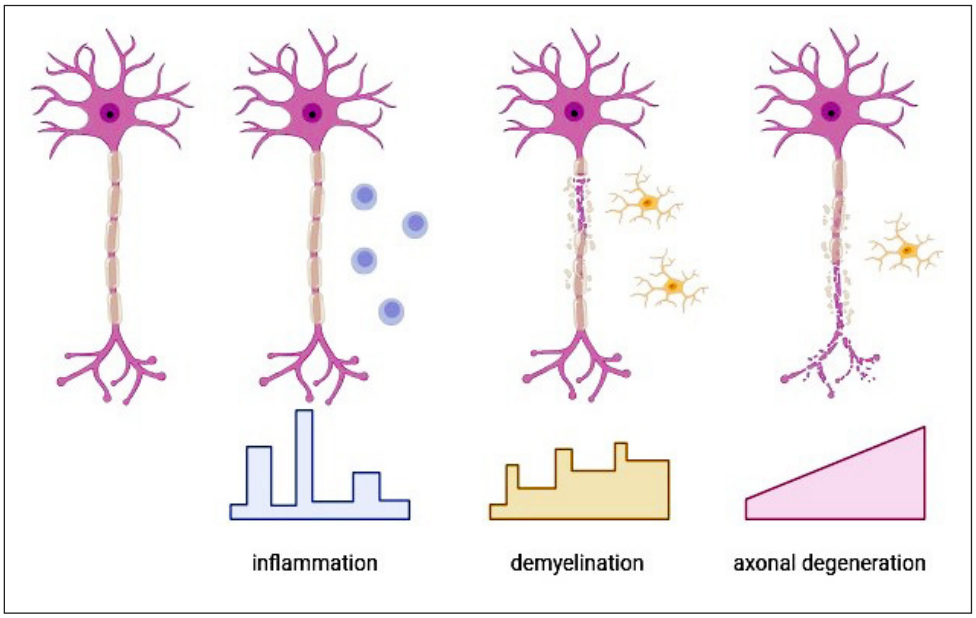

Figure 1. Relationship between pathological processes in a neuron and the severity of clinical symptoms over time. Schematic representation of the relationship between severity of clinical symptoms (y-axis) and disease course over time (x-axis) in relation to individual pathological processes icluding inflammation, demyelination, and axonal degeneration. The histograms illustrate the relative contribution of each pathological process at different disease stages showing how their involvement changes over time in a descriptive model of disease progression without representing quantitative data. Adapted from Compston (2020). (created in BioRender.com)

- **Relapsing-remitting MS (RRMS)** is the most common phenotype, affecting approximately 80–85% of patients. It is characterized by acute disease attacks followed by months- to years-long periods of complete or partial remission, which may occur spontaneously. After 10–20 years, approximately 50–65% of patients develop secondary progressive MS.
- **Secondary progressive MS (SPMS)** involves gradual and sustained neurological deterioration with or without superimposed relapses.
- **Primary progressive MS (PPMS)** accounts for 15–20% of cases and is more common in men. It is characterized by continuous worsening of neurological function from disease onset with rare remissions.

Two additional clinical designations are recognized:

- **Clinically isolated syndrome (CIS)** refers to the first clinical episode suggestive of inflammatory demyelination that does not yet meet the criterion of dissemination in time.
- **Radiologically isolated syndrome (RIS)** describes incidental MRI findings highly suggestive of demyelination in the absence of clinical symptoms, although not considered a true MS phenotype due to the lack of clinical manifestation. Individuals with RIS require monitoring as symptomatic disease may subsequently develop (Lublin et al. 2014).

Clinical manifestations of MS depend on the localization of demyelinating lesions and axonal degeneration and arise from impaired or slowed nerve impulse conduction along affected pathways. Accordingly, symptoms are highly variable and most commonly involve the motor, sensory, visual, and autonomic systems.

Characteristic signs include Lhermitte's sign, described as an electric shock-like sensation radiating along the spine or into the limbs upon neck flexion, and Uhthoff's phenomenon, a transient worsening of neurological symptoms associated with increased core body temperature (e.g., after exercise, sauna exposure, or hot bathing) (Compston and Coles 2008).

RRMS typically begins with sensory disturbances, unilateral optic neuritis, diplopia, limb weakness, gait ataxia, and sphincter dysfunction. Fatigue is common, often worsening in the afternoon, and sometimes accompanied by an elevated body temperature. Some patients experience recurrent brief stereotypical symptoms such as paroxysmal pain or paresthesias, trigeminal neuralgia, episodic dyspraxia or dysarthria.

Less commonly, early MS may manifest predominantly with cortical symptoms (e.g., aphasia, apraxia, visual field deficits, early cognitive decline) or extrapyramidal features such as chorea or rigidity. Additional manifestations include cognitive impairment, depression, emotional lability, dysarthria, dysphagia,

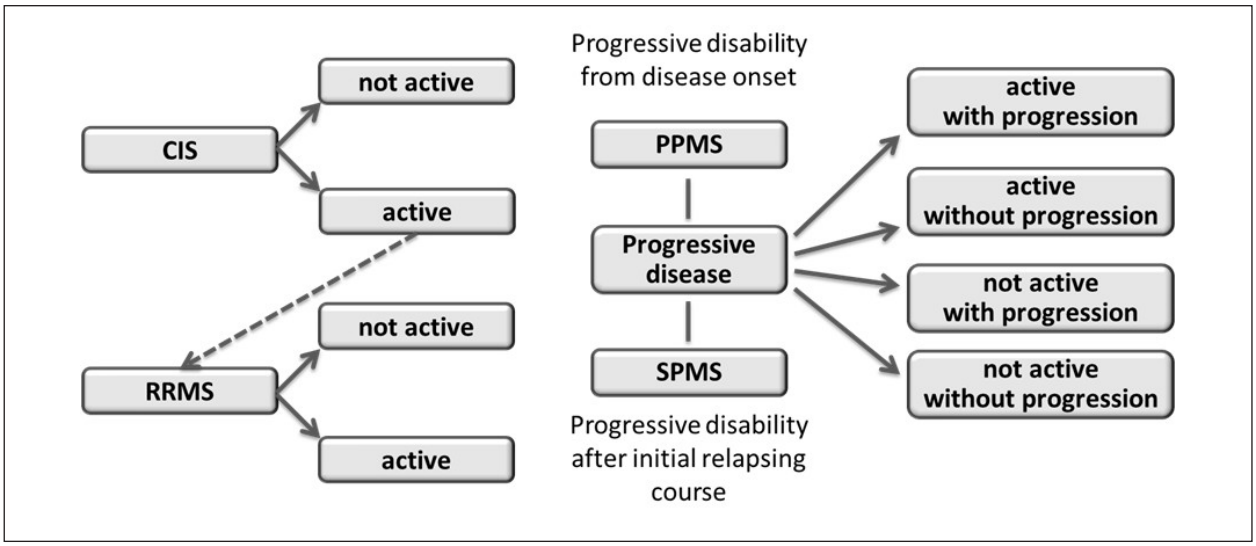

Figure 2. Schematic representation of the phenotype classification of relapsing and progressive multiple sclerosis (MS). Disease activity is assessed by the presence of clinical relapses and/or MRI activity (gadolinium-enhancing lesions new or enlarging T2 lesions), while progression is determined by clinical evaluation at least once annually. Abbreviations: CIS – clinically isolated syndrome; PPMS – primary progressive multiple sclerosis; RRMS – relapsing-remitting multiple sclerosis; SPMS – secondary progressive multiple sclerosis. Adapted from Lublin et al. (2014).

vertigo, progressive quadriparesis, sensory loss, ataxic tremor, pain, sexual dysfunction, and spasticity (Compston and Coles 2008).

Patients with PPMS typically present with gradually progressive spastic paraparesis due to upper motor neuron involvement. Relapses are absent, and neurological decline is continuous with subsequent development of symptoms such as muscle spasms and weakness, cognitive impairment, visual loss, dysarthria, dysphagia, pain, fatigue, and sphincter dysfunction (Compston and Coles 2008). The principal clinical features are summarized in Table 1.

Diagnosis relies on the revised McDonald criteria (Thompson et al. 2018), with clinical findings and MRI assessing lesions and their dissemination in time and space. Supportive investigations include cerebrospinal fluid analysis for oligoclonal bands, evoked potentials, and MRI-based brain volumetry (Compston and Coles 2008; Boutitah-Benyaich et al. 2025). Neurofilament light chain (NfL), a structural component of the neuronal cytoskeleton, has emerged as a promising biomarker of axonal injury. Released into the interstitial space following axonal damage, NfL can be detected in cerebrospinal fluid and blood, potentially even before the first clinical manifestation of MS (Dimitriadou et al. 2026). Disability in MS is commonly assessed using the Expanded Disability Status Scale (EDSS). The EDSS evaluates seven functional systems: pyramidal, cerebellar, brainstem, sensory, sphincter, visual, cognitive/mental, and mobility and self-care abilities, ranging from 0 (normal) to 10 (death).

MS remains incurable but treatable, with life expectancy reduced by approximately 7 years (median disease duration ~40 years). The primary cause of death is MS itself or infection-related complications, while other causes reflect the general population. Suicide risk is higher, likely reflecting increased depression. The availability of disease-modifying therapies has improved the disease course, reducing severe disability and MS-related mortality (Kuutti et al. 2025).

Interplay of lipoproteins, insulin sensitivity, and inflammation in multiple sclerosis

Patients with MS exhibit an increased risk of cardiovascular and metabolic diseases, including atherosclerosis and features of metabolic syndrome; however, direct causal associations remain incompletely defined (Yuksel et al. 2021; Yang et al. 2022). Dietary patterns may contribute, as high intake of saturated fatty acids, particularly of animal origin, has been associated with increased MS mortality. Current recommendations limit saturated fat to <10% of total energy intake (Penesova et al. 2018).

Chronic inflammatory immune-mediated diseases, such as rheumatoid arthritis, are associated with dyslipidemia, metabolic syndrome, and cardiovascular risk, supporting the hypothesis that MS itself may promote atherosclerosis even in the absence of traditional risk factors (Yuksel et al. 2021; Cacciapaglia et al. 2022).

While elevated low-density lipoprotein (LDL) cholesterol and triglycerides are well-established drivers of atherosclerosis, high-density lipoprotein (HDL) cholesterol plays a more complex role (Lorkowski and Smith 2022). Epidemiological studies initially demonstrated an inverse association between HDL levels and coronary heart disease. However, genetic and pharmacological trials failed to confirm a causal protective effect of elevated HDL (Chiesa and Charakida 2019; Lorkowski and Smith 2022). Very high HDL levels may even increase risk, indicating a U-shaped relationship between HDL concentration and mortality (Lappegard et al. 2021).

Table 1
Symptoms of multiple sclerosis
Overview of the principal clinical manifestations of multiple sclerosis according to the site of central nervous system involvement

Site of involvement	Symptoms
Optic nerve	Unilateral painful vision loss, blurred vision, visual field defects, reduced visual acuity, impaired color vision
Brainstem	Diplopia, nystagmus, ophthalmoplegia, hearing disturbances, vertigo, dysphagia, dysarthria
Cerebellum and cerebellar pathways	Postural and intention tremor, clumsiness, impaired balance and coordination, gait ataxia
Spinal cord	Weakness, limb stiffness, spasticity, bladder dysfunction (incontinence or urinary retention), erectile dysfunction, constipation, sensory disturbances (tingling, burning, stabbing sensations)
Brain cortex	Cognitive impairment (attention, reasoning and decision-making deficits, later dementia), signs of upper motor neuron involvement

Adapted from Compston and Coles (2008) and Filippi et al. (2018).

Thus, attention has been shifted from HDL quantity to quality, namely particle composition and function.

HDL exerts multiple atheroprotective effects, including reverse cholesterol transport (RCT), anti-inflammatory activity, antioxidant properties, and endothelial protection (Chiesa and Charakida 2019; Lorkowski and Smith 2022). In inflammatory states, HDL remodels to incorporate acute-phase proteins such as serum amyloid A (SAA), which can impair cholesterol efflux capacity and convert HDL to a pro-inflammatory particle (Fogelman 2015; Chiesa and Charakida 2019). Dysfunctional HDL particles have been identified in atherosclerotic plaques. This system likely evolved to combat acute viral and bacterial infections in times of shorter life expectancy, but may now paradoxically promote chronic vascular damage and increase mortality risk through atherosclerotic complications (Fogelman 2015).

HDL is synthesized mainly in the liver and partially in the intestine consisting of a hydrophobic lipid core surrounded by a protein surface. Apolipoprotein A1 (ApoA1) predominates in discoidal "nascent" HDL particles. At the same time, mature spherical HDL contains apolipoprotein A2, enzymes such as lecithin-cholesterol acyltransferase, acute-phase proteins including SAA, complement components, and numerous other proteins and lipids (Chiesa and Charakida 2019; Lappegard et al. 2021). ApoA1 is the principal apolipoprotein in HDL, while apolipoprotein B (ApoB) predominates in LDL (Oesterle et al. 2017).

HDL exerts anti-inflammatory effects by inhibiting adhesion molecule expression, reducing macrophage migration, and stimulating endothelial nitric oxide (NO) synthase (Chiesa and Charakida 2019). ApoA1 may also contribute to neuronal regeneration and cognitive preservation. Inflammatory microenvironments, including those in MS, promote chemical modifications of ApoA1 (oxidation, glycation, and carbamylation), converting HDL from an anti-inflammatory to a pro-inflammatory, contributing to atherogenesis (Jorissen et al. 2017; Lorkowski and Smith 2022).

HDL and LDL are highly heterogeneous in size, density, structure, lipid-to-protein ratio, and function (Lorkowski and Smith 2022). Subfraction analyses using ultracentrifugation, NMR spectroscopy, gradient gel electrophoresis or ion mobility reveal diverse particle profiles, though results are method-dependent and not directly comparable (Lappegard et al. 2021). Individual subfractions may differ in atherogenic potential such that patients with similar total HDL or LDL cholesterol can exhibit markedly different cardiovascular risk. For example, small dense LDL (sd-LDL) particles are strongly associated with cardiovascular disease, insulin resistance, type 2 diabetes, and metabolic syndrome. In contrast, large LDL particles confer less risk (Rizvi et al. 2021).

In contrast, the cardioprotective relevance of individual HDL subfractions remains debated. Larger HDL subfractions are generally considered more protective, whereas small HDL may have the opposite effect. Inflammatory conditions may alter HDL composition and function (Lappegard et al. 2021). In obesity and inflammatory states, small HDL predominates, and large HDL is reduced. Similar trends appear in MS, where alterations in HDL subfractions have been associated with BBB permeability, lesion formation, disability progression, and cognitive impairment (Siddiqui et al. 2023) suggesting that lipid-mediated signaling in immune cells may contribute to disease pathogenesis. However, it remains unclear whether changes in lipid profiles contribute to disease pathogenesis or are secondary consequences of the primary disease process.

Reduced insulin sensitivity and hyperinsulinemia have been observed in patients with MS, independent of inflammation or physical activity levels (Penesova et al. 2015). Insulin resistance, commonly associated with dyslipidemia, affects lipoprotein concentration, particle size and subfraction distribution (Rizvi et al. 2021). Inflammatory cytokines further drive pro-atherogenic lipid changes by altering HDL-associated enzymes and apolipoproteins, leading to reduced HDL cholesterol and impaired anti-inflammatory, antioxidant, and reverse cholesterol transport functions (Chiesa and Charakida 2019). Lipid profiles have been linked to MS activity and progression, suggesting chronic inflammation contributes to dyslipidemia, atherosclerosis, and cardiovascular disease.

In longer-standing MS (8–10 years), pro-atherogenic changes include higher LDL and total cholesterol and increased small LDL and HDL fractions associated with accelerated disability progression (Jorissen et al. 2017). Whole-body and peripheral insulin sensitivity were reduced, and insulin response increased following oral glucose (Penesova et al. 2015). In patients with MS, intermediate-density lipoprotein B (IDL-B) subfraction negatively correlated with insulin resistance and hyperinsulinemia (Radikova et al. 2018), suggesting that metabolic changes may precede lipoprotein alterations.

Sex-specific differences are evident: in female patients with MS, total and large HDL correlated

negatively and intermediate HDL positively with inflammatory cytokines, whereas these associations were absent in controls or male patients (Radikova et al. 2020). Altered lipoprotein levels are reported in patients with MS. Men with MS exhibit higher HDL, particularly the small HDL fractions (Radikova et al. 2020), consistent with reports in lean patients with RRMS with prolonged disease (Jorissen et al. 2017).

Overall, HDL functionality depends more on protein composition than particle size. Larger HDL subfractions are generally atheroprotective, while small HDL may exert opposite effects (Lappegard et al. 2021). In atherosclerosis, HDL shifts from large to small subfractions (Fogelman 2015) and systemic inflammation can convert HDL from anti- to pro-inflammatory and impair its anti-atherogenic function.

Increased small HDL and LDL subfractions in MS are linked to disability progression and cardiovascular risk (Jorissen et al. 2017), highlighting sex-specific differences and the potential importance of HDL composition over size (Radikova et al. 2020).

Autonomic dysfunction in multiple sclerosis

The autonomic nervous system (ANS) controls, among other functions, heart rate, blood pressure, respiration, gastrointestinal tract function, and bladder function. Autonomic abnormalities affect 45–85% of patients with MS and include bladder, sexual, and gastrointestinal dysfunction, cardiovascular dysregulation, and thermoregulatory disorders (Racosta and Kimpinski 2016; Sirbu et al. 2020). The spectrum and severity of autonomic symptoms depend on the disease phenotype, progression rate, disability, lesion location, and clinical activity. Manifestations range from subtle changes in autonomic function to clinically overt signs such as impaired sphincter control or orthostatic hypotension (Findling et al. 2020).

Cardiac autonomic dysfunction in patients with MS correlates with inflammation, neurodegeneration, fatigue, rare cardiovascular complications, and treatment-related consequences (Findling et al. 2020). It may contribute to disability and cardiovascular complications during disease progression. Subclinical signs include altered heart rate variability (HRV), abnormal heart rate, and blood pressure. Parasympathetic dysfunction tends to appear later and is linked to progressive forms and disability (Sirbu et al. 2020). In contrast, cardiac sympathetic dysfunction manifesting as HRV changes and orthostatic intolerance correlates with inflammation and clinical activity appearing in earlier disease stages and predominating in patients with RRMS (Sirbu et al. 2020).

Interactions among the ANS, neuroendocrine, and immune systems have prompted investigation of their roles in MS pathogenesis (Racosta and Kimpinski 2016). However, it remains unclear whether autonomic dysfunction represents a primary factor in MS pathogenesis or a consequence of structural changes in critical regulatory autonomic pathways in the brainstem, spinal cord, hypothalamus, and cerebral cortex. While autonomic abnormalities appear even in early disease stages, data on newly diagnosed patients are limited. Early dysfunction has been associated with fatigue, challenging the traditional view of MS as a pure CNS disorder and suggesting involvement of the peripheral nervous system (Adamec et al. 2021).

In patients with newly diagnosed MS, normal catecholamine and cardiac autonomic responses to postural (orthostatic test) and non-postural (Valsalva maneuver) blood pressure changes as well as to mental stress (Stroop test) were found indicating preserved cardiovascular autonomic control at disease onset (Imrich et al. 2021). Similarly, the hypothesis that reduced insulin sensitivity drives increased sympathetic activity and lipolysis was not supported since only a weak correlation between sympathetic activity and triglycerides was observed, likely reflecting inflammation rather than primary autonomic dysfunction (Hardonova et al. 2021). Therefore, autonomic dysfunction in patients with MS does not appear to be a primary factor in disease pathogenesis, but rather develops secondarily with disease progression, namely inflammation and immune system activation.

Advances in proton magnetic resonance spectroscopic imaging (MRSI) allow assessment of the metabolic activity of MS lesions within the CNS without signal contamination from normal-appearing tissue. The metabolite profile and ratios expressing neuroaxonal integrity, inflammation, de- and remyelination, astrocytic proliferation, and glio-neuronal metabolism provide insight into lesion stage and disease activity. They could serve as a potential marker of disease progression (Kirov et al. 2017).

Changes in various spectra found in areas with lesions indicate decreased neuroaxonal integrity, mitochondrial dysfunction, astrocytic activation, and gliosis, together with early inflammatory activity with less pronounced de- and remyelination (Imrich et al. 2021). Diffuse glial abnormalities are present in the non-lesional white matter of patients with

MS, suggesting that even brain areas not affected by acute lesions participate in disease pathophysiology (Kirov et al. 2017). This suggests that neuronal, mitochondrial, and glial alterations may not be confined exclusively to areas affected by inflammatory processes, but may also be nonspecifically present in other brain regions (Imrich et al. 2021).

Overall, these findings suggest that autonomic dysfunction in early MS is secondary rather than primary, emerging with disease progression and associated with metabolic and structural changes in both lesioned and normal-appearing white matter (Imrich et al. 2021; Hardonova et al. 2021).

Oxidative damage in multiple sclerosis

Oxidative damage. Despite its widespread use, the term "oxidative stress" has been criticized for conceptual imprecision as commonly assessed markers may reflect oxidative damage rather than a clearly defined pathophysiological stress state. Oxidative stress results from an imbalance between the production of pro-oxidative compounds and the capacity of the biological system to detoxify these reactive products. Pro-oxidative substances include reactive oxygen and nitrogen species (RONS), sulfur-containing organic compounds, and enzymes such as myeloperoxidase. Antioxidant defenses comprise repair enzymes, free radical scavengers, and preventive antioxidants (Liguori et al. 2018). When these systems are balanced, redox homeostasis is maintained; disruption due to increased pro-oxidative factors or impaired antioxidant capacity leads to oxidative stress.

Persistent predominance of pro-oxidative factors, due to excessive production, accumulation, or intake, or to insufficient antioxidant defence, results in damage to important biological molecules and structures. Oxidative stress contributes to aging and to the pathogenesis of numerous diseases including cancer, neurodegenerative disorders, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, metabolic disorders, atherosclerosis, and cardiovascular diseases (Liguori et al. 2018).

Reactive oxygen species (ROS) such as superoxide ($\bullet O_2^-$), hydroxyl radical ($\bullet OH$), singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), and organic peroxides are generated mainly in mitochondria and are natural by-products of oxygen metabolism. Under physiological conditions, ROS regulate phosphorylation, transcription factor activation, apoptosis, immune responses, differentiation, and cell signaling. However, excessive ROS production occurs during inflammation, immune activation, ischemia, infection, cancer, mental stress, aging, and intense physical exercise. Environmental stressors (UV and ionizing radiation, pollutants, heavy metals), xenobiotics, smoking, alcohol consumption, and certain food processing (smoked products, overheated fats) further increase ROS generation, thereby causing an imbalance that leads to damage of essential cellular molecules, including oxidation of lipids and lipoproteins, proteins, and nucleic acids.

Oxidative damage alters protein structure and enzyme activity, induces mutagenesis through nucleic acid oxidation, and disrupts cellular membranes via lipid peroxidation. Oxidation of lipoproteins, particularly small dense LDL, plays a central role in atherogenesis. Additionally, oxidative stress reduces NO bioavailability, thereby impairing vasodilation and blood pressure regulation and promoting endothelial dysfunction (Khosravi et al. 2019).

The organism's defense against oxidative injury is referred to as a total antioxidant capacity (TAC). Antioxidant systems include enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) as well as non-enzymatic molecules including glutathione, vitamins C and E, α-lipoic acid, bilirubin, uric acid, carotenoids, flavonoids, albumin, and metal-binding proteins (Yevgi and Demir 2021).

Oxidative damage and the nervous system. In the CNS, ROS participate in neuronal stability, synaptic plasticity, apoptosis, and immune signaling. However, the threshold between physiological and pathological ROS activity is narrow (Padureanu et al. 2019). Oxidative stress is considered to be a key contributor to MS pathogenesis (Sanabria-Castro et al. 2024). Activated macrophages and astrocytes produce large amounts of RONS, leading to axonal injury and neurodegeneration (Dong and Yong 2022). ROS directly damage nucleic acids, proteins, and lipids, including myelin components (Rodrigues et al. 2021).

The CNS is particularly vulnerable due to high metabolic activity, resulting in increased oxygen consumption; abundant polyunsaturated fatty acids, which are susceptible to oxidation; and relatively limited antioxidant reserves (Pegoretti et al. 2020). Patients with MS exhibit reduced TAC and increased markers of lipid and protein oxidation in serum and cerebrospinal fluid, both during relapse and remission (Padureanu et al. 2019; Rodrigues et al. 2021). Some earlier studies have reported compensatory increases in antioxidant enzyme activity likely

reflecting adaptive responses to minimize oxidative cellular damage (Ortiz et al. 2009).

Oxidative stress also promotes endothelial dysfunction, a subclinical stage of atherosclerosis characterized by the inability of an artery to dilate adequately in response to an appropriate stimulus (Vanhoutte et al. 2017; Hardonova et al. 2023). Dysfunction of cerebral endothelial cells facilitates leukocyte adhesion and migration into the CNS, potentially contributing to MS pathogenesis. Patients with MS exhibit increased cardiovascular and cerebrovascular risk that cannot be fully explained by traditional risk factors (Palladino et al. 2020). Moreover, higher Framingham risk scores predict greater disability progression and relapse risk (Petruzzo et al. 2021).

Mitochondrial dysfunction represents a central mechanism linking oxidative stress to neurodegeneration (Rey et al. 2022). Impaired oxidative phosphorylation increases RONS production and reduces ATP synthesis, promoting DNA damage, altered gene expression, defective repair mechanisms, and inflammatory activation (Pegoretti et al. 2020; Rey et al. 2022).

Markers of oxidative stress, including reduced TAC, are detectable even in newly diagnosed patients with MS (Sivakova et al. 2019). Interventions augmenting TAC may prevent or slow the progression of endothelial dysfunction (Hardonova et al. 2023). Although structural vascular changes may not be present initially, functional vascular impairment appears to develop progressively and correlates with disease duration and disability (Kemenyova et al. 2015). The findings suggest that oxidative stress might be the connection between neurodegeneration and accelerated atherosclerosis (Kollar et al. 2022).

Oxidative damage and immune cells. The homeostatic imbalance between RONS production and their neutralization by natural antioxidant systems in immune cells plays an important role in the pathogenesis of MS. Patients with MS have been shown to exhibit significantly increased superoxide anion production in peripheral blood mononuclear cells (PBMCs). When further investigation was conducted into which immune cells could be responsible for this increase, the results pointed to T lymphocytes (Gonzalo et al. 2019). Results that improve the picture of oxidative imbalance have also been demonstrated in a recently published study, in which the authors isolated subsets of CD4+ T, CD8+ T, and B cells from PBMCs of patients with MS using magnetic separation. In these cells, the ability of repair mechanisms to control oxidative DNA damage was measured. These preliminary results suggest that patients with MS have reduced repair efficiency of oxidative DNA damage in CD4+ and CD8+ T cells (Filipek et al. 2025). In addition, reduced antioxidant potential of CD4+ T cells has been observed in patients with MS, who have been shown to have significantly reduced activity of antioxidant enzymes such as SOD and GPx (De Riccardis et al. 2015). These results suggest that T cells from patients with MS have increased ROS production and, on the other hand, reduced ability to neutralize them. Therefore, T cells in these patients may be more susceptible to oxidative stress. These oxidative stress-related processes have been shown to contribute to T cell activation, inflammatory cytokine production, and facilitation of T cell migration and infiltration into the CNS, which are key processes that enhance the autoimmune response in MS (Gulow et al. 2024).

Demonstration of the deeper mechanisms by which oxidative imbalance can potentiate T cell influence on MS pathogenesis has been performed primarily in animal models. Interestingly, a high-glucose diet was shown to exacerbate autoimmune responses in the EAE animal model by promoting Th17 cell differentiation. This process was mediated by increased mitochondrial ROS production in T cells (Zhang et al. 2019). However, it is important to note that the influence of ROS on Th17 cell differentiation has not been confirmed in another study, in which the authors report conflicting results (Fu et al. 2017). Multiple studies have shown that Th17 cells play a key role in the pathogenesis of MS (Moser et al. 2020), so the effect of ROS on their differentiation is a potential target for future studies.

The key role of regulatory T cells (Treg) in the immune system is to maintain immune balance, and their dysfunction is a hallmark of autoimmune diseases. Mitochondrial metabolism is critical for Treg function, as the metabolism of these cells is dependent on oxidative phosphorylation. However, Treg cells in the EAE model have been shown to exhibit increased mitochondrial oxidative stress and a heightened DNA damage response. These processes have been associated with cell death in Treg cells in the mouse EAE model. In addition, the activities of the mitochondrial antioxidant enzymes manganese SOD and CAT were significantly reduced compared with the control group. On the other hand, when Treg cells or animals were treated with an ROS scavenger, the Treg cell death and DNA damage were inhibited under *in vitro* and *in vivo* conditions. At the same time, Th1 and Th17 autoimmune responses were attenuated (Alissafi et al. 2020). These findings

suggest that ROS-targeted therapy in MS may reduce inflammation and enhance anti-inflammatory processes.

A highly cited study (Haider et al. 2011), in which immunohistochemical staining was performed on paraffin-embedded archival autopsy material from patients with MS, showed that oxidative damage in the CNS may indirectly affect T cells. These authors analyzed oxidized lipid epitopes in MS lesions for the first time allowing them to look at oxidative damage to multiple cell types in the CNS. They have identified acute oxidative damage in oligodendrocytes, axons, and neurons in MS lesions at various stages. The results of this study showed that oxidative damage was partially related to inflammation, which was determined based on the number of CD3+ T cells and human leukocyte antigen D (expressed on macrophages and microglia) in lesions. These findings suggest that oxidative damage in MS lesions may exacerbate inflammation and, in turn, activate demyelination and axonal or neuronal damage, possibly mediated by recruited T cells. This study also showed that T cells were affected not only directly by oxidative damage, but also likely indirectly by processes in MS lesions (Haider et al. 2011).

Antioxidant therapy. Antioxidant therapy aims to counteract oxidative damage by reducing pro-oxidant exposure (e.g., smoking cessation) enhancing endogenous antioxidant defenses, or supplementing exogenous antioxidants. It has been hypothesized as a potential adjunctive treatment for multiple diseases including MS. Most studies on antioxidant therapy focus on atherosclerosis and cardiovascular outcomes. Although experimental studies have shown promising results, clinical trials in cardiovascular disease and MS have produced inconsistent findings. Dietary antioxidants such as vitamins C and E and beta-carotene are associated with reduced cardiovascular and oncological mortality in epidemiological studies (Penesova et al. 2018), yet interventional trials remain inconclusive.

Other natural antioxidants under investigation include glutathione, coenzyme Q10, tetrahydrobiopterin, folic acid, α-lipoic acid, carnitine, melatonin,

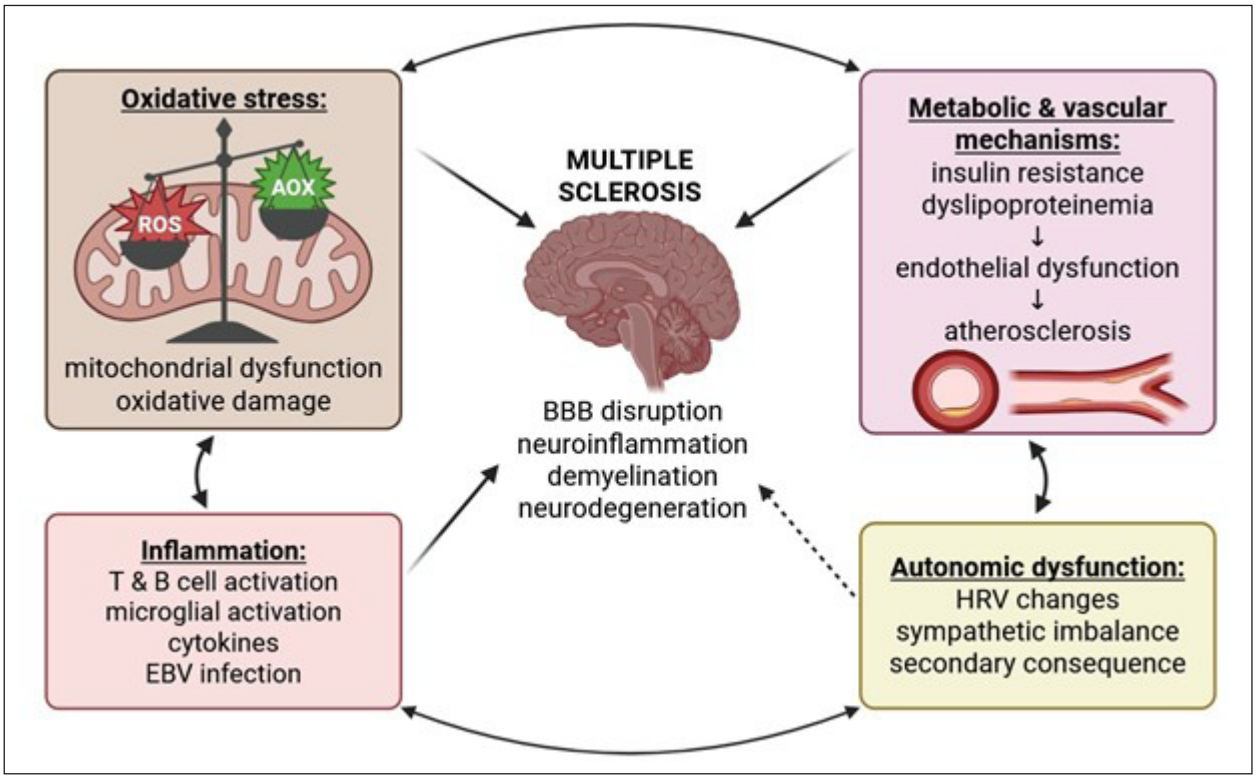

Figure 3. Model of multiple sclerosis (MS) pathogenesis and progression. The model integrates systemic immune, metabolic, vascular, and neurobiological interactions driving MS pathogenesis and progression. MS is characterized by blood-brain barrier disruption, neuroinflammation, demyelination, and neurodegeneration with primary contributing mechanisms including oxidative stress, immune activation and metabolic-vascular dysfunction with mutual interactions between these pathways. Autonomic dysfunction is depicted as a secondary process. Abbreviations: AOX – antioxidants; BBB – blood-brain barrier; EBV – Epstein-Barr virus; HRV – heart rate variability; ROS – reactive oxygen species. (created in BioRender.com)

and polyphenols (resveratrol, quercetin, catechins, curcumin) from olive oil, fruits, vegetables, tea, coffee, cocoa, and red wine (Bartekova et al. 2021). Results are variable and often limited by dosing, bioavailability or study design. Synthetic antioxidants and glutathione precursors, such as N-acetylcysteine, have also shown mixed outcomes.

Oxidative stress promotes atherosclerosis through oxidized LDL formation, therefore, reducing oxidative stress and LDL levels may limit LDL oxidation. LDL can be lowered through lifestyle interventions, such as physical activity and dietary modification or pharmacotherapy. Statins, fibrates, and ezetimibe are established treatments with statins reducing endogenous cholesterol synthesis via HMG-CoA reductase inhibition and lowering cardiovascular risk partly through pleiotropic effects including improved NO bioavailability, endothelial progenitor cell mobilization, and reduced CRP levels (Oesterle et al. 2017).

In MS, different compounds have been studied including curcumin, melatonin, coenzyme Q10, polyphenols, β-glucans, omega-3 PUFAs, and vitamins A, D, E, and C. Melatonin has antioxidant and immunomodulatory effects, but has minimal impact on disability. Coenzyme Q10 improves antioxidant markers without altering MS progression in preclinical EAE models (Pegoretti et al. 2020). Vitamin D, beyond its role in calcium and bone metabolism, exerts antioxidant and immunomodulatory effects. Patients with MS often exhibit reduced vitamin D levels. Experimental studies suggest a protective role of vitamin D in autoimmune diseases; however, human studies including patients with MS have yielded inconsistent results (Penesova et al. 2018).

Edaravone, an antioxidant and neuroprotective agent approved in Japan for acute ischemic stroke and amyotrophic lateral sclerosis, demonstrates inhibition of ROS production in preclinical MS studies (Villar-Delfino et al. 2022). Fingolimod, used in MS therapy, may exert antioxidant effects in addition to its immunomodulatory effects (Yevgi and Demir 2021). GLP-1 receptor analogs demonstrated neuroprotective, neurotrophic, anti-inflammatory, and antioxidant effects in animal EAE models (DellaValle et al. 2016; Ammar et al. 2022) and possess established safety in type 2 diabetes. The clinically relevant anti-inflammatory and antioxidant effects of these drugs were demonstrated in a meta-analysis evaluating 40 clinical trials in patients with diabetes (Bray et al. 2021). Patients with MS treated with teriflunomide, glatiramer acetate, IFNβ 1b, dimethyl fumarate, and cladribine show a significant increase in intracellular SOD-1 levels in T cells. It has been shown that higher levels of this enzyme are associated with increased Treg cell proliferation capacity (Rubino et al. 2021). Overall, while oxidative stress represents a plausible therapeutic target in MS, clinical evidence for antioxidant therapy remains limited and requires further investigation.

Summary

Patients with MS exhibit an increased risk of atherosclerosis and related complications even in early stages associated with subtle lipoprotein profile alterations influenced by inflammation and oxidative stress, with possible sex-specific differences. Autonomic nervous system dysfunction appears secondary to disease progression rather than a primary driver of MS pathogenesis. Early MS is not characterized by direct autonomic involvement in dyslipidemia or glucose metabolism disturbances, but is linked to immune activation. Subacute and early reparative lesion stages show metabolic alterations reflecting neuronal impairment, mitochondrial dysfunction, astroglial activation, and gliosis in both lesional and normal-appearing white matter of patients with MS. Oxidative stress markers, including reduced TAC, are present from early stages and likely contribute to both MS pathogenesis and accelerated atherosclerosis with functional vascular changes preceding structural alterations.

Acknowledgements

The authors sincerely acknowledge the long-standing collaboration with colleagues from the 1st Department of Neurology, Faculty of Medicine, Comenius University and University Hospital, Bratislava, Slovakia, particularly Prof. Peter Turcani, MD, PhD; Prof. Branislav Kollar, MD, PhD; and Assoc. prof. Pavel Siarnik, MD, PhD. Their continued cooperation, clinical expertise, and constructive discussions over the years have been highly valuable to this work.

This work was supported by the grants of the Slovak Research and Development Agency APVV-21-0261, APVV-23-0629; Scientific Grant Agency of the Ministry of Education, Research, Development and Youth of the Slovak Republic and the Slovak Academy of Sciences VEGA 2/0163/26 and VEGA 2/0041/25.

Conflict of interest: *The authors declare no conflicts of interest.*

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