

# Cardiovascular Dysfunction in Multiple Sclerosis

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## ABSTRACT

*Multiple sclerosis (MS) is a chronic neurological condition, characterized by recurrent episodes of inflammation and demyelination of the central nervous system called relapsing-remitting episodes, and continuous axonal degeneration that leads to irreversible progressive invalidity.*

*Patients with multiple sclerosis present a higher mortality rate compared to the general population, and the excess of mortality may be explained by the increased cardiovascular risk and occurrence of cardiovascular disease. However, the exact pathways to cardiovascular dysfunction are not yet completely elucidated.*

*This review focuses on the most important mechanisms of cardiovascular dysfunction in MS, such as the cardiomyocyte structure alteration, the cardiovascular autonomous nervous system dysfunction, physical invalidity, oxidative stress and endothelial dysfunction, as well as the impact of cardiovascular risk factors in MS.*

*The latest evidence about therapeutic approaches for MS, such as immunomodulatory treatment, vitamin D supplementation and statins are also discussed.*

*There is little knowledge about the cardiovascular dysfunction in MS, and further research is required to improve the understanding of these complex mechanisms.*

**Keywords:** multiple sclerosis, cardiovascular dysfunction, immunomodulatory treatment

## INTRODUCTION

**M**ultiple sclerosis (MS) is a chronic neurological condition, characterized by recurrent episodes of inflammation and demyelination of the central nervous system leading to relapsing-remitting episodes and to continuous axonal degeneration with irreversible progressive invalidity (1).

MS is the main cause of non-traumatic neurological invalidity in young and middle-aged population, representing a major public health issue. The disease becomes clinically manifest in the early third decade of life, when the individual is economically and socially active, requiring higher costs than stroke or Alzheimer’s disease (2,3). Moreover, patients with MS have a lower life expectancy than normal population, but detailed data on mortality in MS is

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limited (4). Recent studies show that the median survival time from the onset of the disease is approximately 10 years shorter for these patients. Furthermore, MS is associated with an almost threefold increase in the risk for death, most of the data suggesting that this is due to cardiovascular disease (5, 6). Several large studies reveal the high occurrence of cardiovascular disease in patients with MS, demonstrating that the risk of ischemic heart disease, stroke or heart failure is significantly increased in this population (7). However, recent research shows controversial results regarding the risk of cardiovascular disease occurrence and death in MS people (8). □

### CARDIOVASCULAR DYSFUNCTION MECHANISMS IN MULTIPLE SCLEROSIS DISEASE

In the next paragraphs we will describe the main mechanisms for cardiovascular dysfunction in MS that have been studied by now: the myocyte function alteration, the cardiovascular autonomous nervous system dysfunction, the physical invalidity, oxidative stress and endothelial dysfunction, the impact of cardiovascular risk factors in early atherosclerosis development in MS, like the presence of inflammation, smoking, hypertension, type 2 diabetes mellitus, dyslipidemia, obesity, psychosocial stress and procoagulant status. The main described mechanisms are summarized in Figure 1.

#### Cardiomyopathies in neuromuscular disorders

Cardiomyopathies are generally characterized by abnormal structure, dimension or function of the left or right ventricular myocardium in the absence of arterial hypertension, coronary heart disease, valve abnormalities or congenital heart disease (9). The cause of cardiomyopathies caused by neuromuscular disorders is unknown, but there are indications that isoforms of mutated muscle proteins causing muscle disease are also expressed in the myocardium (10).

MS is a neuromuscular disorder, involving the upper motor neuron with demyelination, accompanied by a disruption in the ability of the nerves to conduct electrical impulses to and from the brain. Until today, there are no studies demonstrating the association between MS and the development of cardiomyopathies,

so research in this area should be intensified. Our study group started a protocol to determine the subclinical myocardial dysfunction in MS patients using the newest echocardiography techniques, which concluded that patients with MS, either treated or not, have subclinical biventricular systolic dysfunction with normal vascular function, suggesting an intrinsic myocardial impairment (11).

#### Cardiovascular autonomous nervous system dysfunction

The autonomous nervous system is affected in the course of MS due to the lesions of the regions responsible for autonomic regulation. Parasympathetic dysfunction is closely related to the progression of disability in patients with MS. In contrast, sympathetic dysfunction was associated to the clinical activity of MS (12). The main tests for diagnosing the cardiovascular autonomous dysfunction are: head up tilt test for assessment of impaired heart rate and blood pressure response to orthostatic challenge, deep breathing test, Valsalva maneuver, handgrip test and baroreflex stimulation (13).

A recent meta-analysis on cardiovascular autonomic dysfunction in multiple sclerosis from 16 studies including 611 patients showed that the proportion of patients with autonomic dysfunction was two-fold higher when using a threshold of one than when using a threshold of two abnormal autonomic tests (42.1% vs. 18.8%,  $p=0.006$ ). This is why the lack of consensus about the threshold for the diagnosis of autonomic dysfunction in patients with multiple sclerosis may cause problems of comparability in literature, and no threshold is completely acceptable for diagnosing it, although

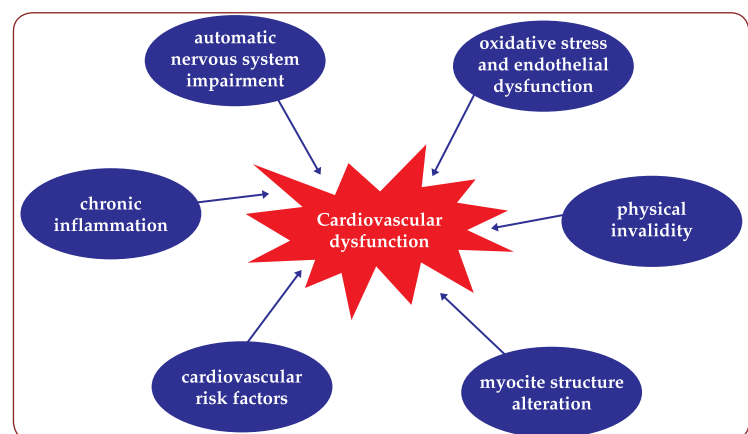


FIGURE 1. Main mechanisms of cardiovascular dysfunction in MS. Adapted after (17,19,30,43,52,69).

using the definition of at least one abnormal test is the approach that appears to have the greatest sensitivity (13).

### Physical invalidity

Sedentary behavior has been associated with increased risk of obesity, metabolic syndrome, type 2 diabetes and cardiovascular disease mortality. (14) Physical invalidity might be an important determinant of cardiovascular dysfunction in MS. MS patients are less physically active compared to healthy people and healthy sedentary individuals (15). Disability status and progression of the disease are associated with reduced physical activity, which, combined with other factors may lead to a higher susceptibility for subclinical atherosclerosis and cardiac dysfunction (16). On the other hand, MS does not prohibit adapted physical activity. Moreover, it has been established that quality of life in MS people is correlated with physical activity level. Studies showed that rehabilitation interventions like exercise training and educational intervention have a stronger effect on severity of patient-reported fatigue compared to the two most commonly prescribed fatigue medications (Amantadine and Modafinil) (17). The results of these studies suggest that rehabilitation interventions should be the initial treatment choice for people with MS who are reporting disabling fatigue. MS women that do low to moderate long-term physical activity have significantly less abdominal fat accumulation, lower levels of triglycerides, and lower levels of glucose. This may improve cardiovascular disease risk and contribute to important health-related benefits (18).

### Oxidative stress and endothelial dysfunction

Oxidative stress is defined as an imbalance between oxidants and antioxidants, in favor of the oxidants, leading to molecular damage (19). It increases with the biological aging process, and it independently causes a greater risk of cardiovascular disease. Endothelial cells and vascular smooth muscle cells produce reactive oxygen and nitrogen species which oxidize low-density lipoproteins (LDL). Oxidized LDL enters subendothelial spaces where they initiate atherosclerosis (20). Oxidative stress consequently leads to endothelial dysfunction, the early feature of atherosclerotic vascular disease, characterized by a decrease in nitric oxide

(NO) bioavailability and a concomitant increase in vascular superoxide (O<sup>-</sup>) formation. Loss of NO bioavailability precedes the development of overt atherosclerosis and is an independent predictor of adverse cardiovascular events (21).

Reactive oxygen species and reactive nitrogen species increase several times in MS (22). The central nervous system has a high susceptibility to oxidative stress due to the high rate utilization of the oxygen, the relatively poor antioxidants and the high concentration of polyunsaturated fatty acids. Multiple studies indicate an intense peripheral oxidative stress in MS patients (23). This may lead to endothelial dysfunction, arterial remodeling and stiffness, and at the end at overt atherosclerosis.

### Cardiovascular risk factors in multiple sclerosis

The major risk factors that promote the development of atherosclerosis are elevated low-density lipoprotein (LDL) cholesterol level, low high-density lipoprotein (HDL) level, cigarette smoking, type 2 diabetes, hypertension and a family history of coronary heart disease, ischemic stroke or peripheral arterial disease. Other conditions thought to increase the risk of atherosclerotic disease include abdominal obesity, hypertriglyceridemia, high plasma levels of lipoprotein (a) and homocysteine, hyperfibrinogenemia, the inflammatory marker C-reactive protein (CRP) and physical inactivity. Other emerging risk factors, including uric acid, psychosocial stress, encompassing external stressors (e.g. job stress life events and financial problems), and reactions to stress (e.g. depression, anxiety, psychosocial distress and sleep disturbances), have as well their contribution (24).

The cardiovascular risk factors are present in MS population and our review discusses the most frequent ones: (a) inflammation status, (b) smoking, (c) arterial hypertension, (d) type 2 diabetes mellitus, (e) dyslipidemia, (f) obesity, (g) psychosocial stress and (h) procoagulant status.

**(a) Inflammation.** Inflammation is considered to have an important role in atherosclerosis. Evidence indicates that inflammation, both focal and systemic, plays a key role in formation, destabilization and rupture of atherosclerotic plaques, leading to acute cardiovascular events (25).

High levels of CRP are associated with disease activity in MS (26). Cytokines are the principal mediators of immunity. MS is an immune-mediated disease with principal emphasis on the activated inflammatory cells. Studies indicate that pro-inflammatory cytokine levels such as IL-1, IL-6, TNF- $\alpha$  or IFN- $\gamma$  are increased in MS patients. On the other hand, the IL-10, which plays an important role in the regulation of immune responses and is considered the main anti-inflammatory cytokine, was decreased in MS patients when compared with healthy individuals (27).

**(b) Smoking.** Smoking is one of the major modifiable risk factors for coronary artery disease and the largest risk factor for coronary artery disease for those below the age of 45, especially women (28). Smoking leads to decrease NO levels, increased levels of NO synthase inhibitors, decreased NO synthase expression, increased production of oxygen radicals, and inflammatory reactions, resulting in augmented oxidative stress, endothelial dysfunction, subsequent arterial remodeling and stiffness and overt atherosclerosis (29). It also produces higher plaque instability, faster platelet activation and coagulation and increased mitochondrial damage in heart myocyte (29). Smoking significantly accelerates the onset of coronary artery disease presentation. The average smoker develops coronary artery calcification, a sensitive marker for early development of coronary artery disease, 10 years earlier than a non-smoker (30).

Cigarette smoking is one of the most postulated environmental risk factors linked to the onset and clinical course of MS in genetically susceptible individuals, along with the vitamin D level, latitude and Epstein Barr virus infection (31). The incidence of smoking is greater in MS people than in general population, leading to an excess of cardiovascular disease (32).

**(c) Hypertension.** For all ages and for all ethnic groups, hypertension has a direct relation with the incidence of cardiovascular events like stroke, myocardial infarction, sudden death, heart failure and peripheral artery disease (33). Most of the studies regarding hypertension in patients with MS concluded that incidence is the same as in the general population, 30-45 %. Marrie et al reported that 30% of 8983 patients with MS were hypertensive, percentage similar for the general population (34). Moreover, patients with MS who developed

hypertension had a faster progression of the disease and clinical disability (35).

**(d) Type 2 diabetes mellitus.** People with type 2 diabetes mellitus (DM) have a 2-3 times higher risk of myocardial infarction or stroke, independent of the association with other cardiovascular risk factors (36). Studies report different results regarding the prevalence of type 2 DM in MS patients. Hussein et al reported a higher prevalence of type 2 DM compared to general population (37), however, Marrie et al found similar prevalence (38). Patients with MS and type 2 DM may have a worse progression of disability compared to people without DM: a 29% increased risk of early gait disability, a 28% increased risk of requiring unilateral assistance and a 56% increased risk of requiring bilateral assistance for walking. However, DM determines increased disability compared to patients with MS without DM (39).

**(e) Dyslipidemia.** There is a direct relation between serum cholesterol and cardiovascular mortality and morbidity, as shown by important epidemiological studies. The cardiovascular risk grows with 2-3% with every 1% growth of serum cholesterol (40).

There is contradictory data regarding the lipid profile in patients with MS. Studies show only slightly elevated total cholesterol, LDL and triglycerides in these patients compared to controls. However, LDL cholesterol has a negative impact on acute inflammatory activity and disease course in MS patients (41). On the contrary, higher levels of HDL have a beneficial effect on course of the disease, which is consistent with the antioxidant and anti-inflammatory properties of HDL. EDSS worsening was associated with higher baseline LDL and total cholesterol levels, with trends for higher triglyceride. Higher HDL levels were associated with lower contrast-enhancing neurological lesion volume in MRI (42). Oxidized LDL was also high in the MS serum, as a marker of early atherosclerosis, and correlated with the disease activity (43).

**(f) Obesity.** Different methods have been used to quantify obesity, including body mass index, waist circumference, waist-to-hip ratio, waist-to-height ratio, but regardless of the chosen index, overall and central adiposity confer a greater risk for subsequent cardiovascular diseases, both in men and women (44). Approximately 50% of patients with MS are overweight or obese, the same with the general population



(45). Recent data suggest that childhood and adolescence obesity increases the risk of MS in females beyond established heritable and environmental risk factors (46).

**(g) Psychosocial stress.** The lifetime incidence of depression in patients with MS is 50%, nearly three times higher than in the general population (47). The mechanisms of depression are multiple. First, depression can be reactive following the diagnosis and the uncertainties about the prognosis and the future in general. Second, depression may be related to the release of proinflammatory cytokines such as interferon- $\gamma$ , TNF- $\alpha$  or IL-6 that can produce symptoms which reinforce an underlying tendency for depression. Third, structural changes in the brain due to neurodegeneration may contribute to the development of depression (48). By activating the inflammatory mechanisms and consequent acceleration of endothelial dysfunction and early atherosclerosis, patients with depression are at higher risk of developing cardiovascular disease.

**(h) Procoagulant status.** D-dimer concentrations were raised in MS patients serum, correlated with homocysteine levels. It has been demonstrated that axonal damage in MS lesions is associated with failure of fibrinolysis because of the inhibition of the plasminogen activator system (49). So, in MS patients, the procoagulant system is enhanced, while the fibrinolysis system is reduced. This may also contribute to cardiovascular disease.  $\square$

### THE INFLUENCE OF TREATMENT ON CARDIOVASCULAR DYSFUNCTION

There is no cure in MS, the treatments approved for use focus only on preventing relapses and on slowing down the progression of the disease. The treatment drugs are divided into first-line drugs: interferon beta (Avonex, Rebif, and Betaferon) and glatiramer acetate (Copaxone), injectable disease modifying treatments available for more than 15 years, and teriflunomide (Aubagio) and dimethylfumarate (Tecfidera), newcomer oral disease modifying treatments. The second line agents include fingolimod (Gilenya), natalizumab (Taysabri) and mitoxantrone (Novantrone). A third line is now available with alemtuzumab and some forth class experimental therapies. First class therapies have a good safety profile, but the clinical

response is often suboptimal, and there are still unknown issues about the right timing to switch for a second line agent of whether escalation therapy is an appropriate strategy (50). The use of mitoxantrone is limited by the cardiotoxicity effect, first time documented in the cure of cancer, because it may affect the structure of the cardiac myocyte and may cause irreversible cardiomyopathy, with reduced left ventricular ejection fraction and congestive heart failure (51). A recent metaanalysis showed that the incidence of significant heart dysfunction was almost 12% under mitoxantrone treatment. This is why recent guidelines recommend assessing cardiac function before each dose of mitoxantrone, regardless of the cumulative dose, and on an annual basis even after discontinuation, given the potential for delayed development of cardiotoxicity (52).

Vitamin D supplementation showed its positive effects in delaying the relapses and in modulation of the immune regulation (53). There is also research on the effect of statins on the course of MS, but the results of the latest metaanalysis (54) concluded that combination therapy of IFN beta plus statin is not able to reduce in a definite way the relapse rate or to prevent progression in MS. The analysis included only a small number of trials, so it is necessary to perform more randomized trials in order to establish the statins' precise indication.  $\square$

### CONCLUSION

Patients with MS have a higher mortality rate compared to the general population. The excess of mortality could be explained by the increased cardiovascular risk and occurrence of cardiovascular disease. The main mechanisms described so far are cardiomyocyte structure alteration, the cardiovascular autonomous nervous system dysfunction, physical invalidity, oxidative stress and endothelial dysfunction and the presence of cardiovascular risk factors in MS.

There is little knowledge about the cardiovascular dysfunction in MS, and subsequent research is required to improve the understanding of these mechanisms. Thus, our research group has started a study to investigate the cardiovascular dysfunction in MS, ongoing at this moment.

## Abbreviations

MS = multiple sclerosis;  
 LDL = low density lipoprotein;  
 HDL = high density lipoprotein;  
 EDSS = expanded disability status scale;  
 NO = nitric oxide;  
 CRP = C-reactive protein;  
 hs CRP = high-sensitivity C-reactive protein;  
 CVD = cardiovascular disease;  
 TNF = tumor necrosis factor;  
 IL = interleukine;  
 IFN = interferon;  
 DM = diabetes mellitus;  
 BMI = body mass index;  
 MRI = magnetic resonance imaging.

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