Perspective

Multiple Sclerosis and Sodium Toxicity: Controversy and Future Directions for Low-Salt Interventions

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Abstract: Salt intake is associated with multiple sclerosis; however, controversial findings that challenge this association rely primarily on methods that do not measure total sodium storage within the body, such as food surveys and urinary sodium excretion. In contrast, tissue sodium concentrations measured with sodium MRI confirm high sodium levels in multiple sclerosis, suggesting a role for sodium toxicity as a risk factor for the disease. Research on demyelination in the central nervous system has identified myelin phase transitions associated with increased salinity, which cause structural instabilities of myelin sheaths and add further evidence implicating sodium toxicity as a causative factor in multiple sclerosis. Inflammatory and immune responses in multiple sclerosis are also related to high sodium intake. In addition, salt is a potential mediating factor associating multiple sclerosis with comorbidities, including systemic lupus erythematosus, rheumatic arthritis, inflammatory bowel disease, and cardiovascular disease. Current confusion exists over classifying dietary sodium intake levels as low, normal, and high, and questions remain over levels of sodium restriction necessary for disease prevention. To reduce multiple sclerosis symptoms and prevent disease progression in patients, future research should investigate low-salt interventions with levels of sodium intake associated with ancestral hunter-gatherer tribes.

Keywords: multiple sclerosis; sodium toxicity; low-salt diet; high-salt diet; demyelination; myelin phase transition; tissue sodium concentration; urinary sodium excretion; ancestral sodium intake

1. Introduction

Multiple sclerosis (MS) is a chronic neurodegenerative disease associated with progressive demyelination of the central nervous system (CNS) [1]. A 2020 global epidemiological study reported 2.8 million people living with MS, with rising disease prevalence since 2013 [2]. The reported mean age of MS diagnosis is 32 years, and twice as many females as males live with the disease. MS is the leading cause of non-traumatic disability among young adults, and initial symptoms mostly affect people between 20 to 40 years of age [3]. MS symptoms commonly include muscle weakness, numbness and tingling, loss of vision, bladder problems, incoordination and imbalance, and gait impairment [4]. Among subtypes of MS, relapsing remitting MS (RRMS) is the most common type, in which approximately 85% of patients experience alternating periods of neurological symptoms and complete or partial symptom remission [5]. By about 19 years from the onset of RRMS, most untreated patients will have developed more severe neurological symptoms in secondary progressive MS (SPMS), but with continued periods of relapse and remission. In primary progressive MS (PPMS), onset and progressive severity of neurological symptoms occur without relapse and remission [5].

MS etiology is not completely understood, and more research is needed to investigate modifiable risk factors in the pathogenesis of the disease [2]. Current research supports the hypothesis that the risk of developing MS increases with global changes toward a 'Western-type lifestyle', which includes a high level of dietary salt intake that is hypothesized to be a factor in the pathogenesis of MS [6]. For example, using 24 h urine collection to

estimate sodium intake, Farez et al. observed a positive association of dietary sodium with exacerbation of symptoms in patients with RRMS [7]. Additionally, a recent systematic review found emerging evidence that dietary sodium is a risk factor for autoimmune responses and inflammation in the progression of MS, and sodium is a potential risk factor in the onset of the disease [8].

In contrast, controversial findings in 462 individuals in the BENEFIT clinical trial, based on dietary sodium intake estimated with 24 h urine collection, do not support the salt–MS hypothesis [9]. Additionally, a case–control study of pediatric-onset MS that estimated sodium intake from interviews did not find an association between MS onset risk with salt intake [10]. Nevertheless, although 24 h urine collection is the gold standard marker for dietary sodium intake, this method and other traditional methods to assess sodium intake, such as food surveys, do not indicate total storage of sodium in the body [11], nor do serum sodium levels provide sodium storage information.

Traditional sodium assessment methods raise concerns of bias when inferring sodium effects in the CNS from tightly regulated sodium concentrations in urine and peripheral blood [6]. For example, controversial findings in a study of wildtype PLP-hαSyn nine-month-old mice fed high salt for three months did not show a proinflammatory or neurodegenerative effect associated with autoimmune diseases such as MS [12], contradicting damaging effects of a high-salt diet on the CNS in an experimental autoimmune encephalomyelitis (EAE) model of MS using male C57BL/6J mice [13]. However, transient changes in dietary sodium intake under experimental conditions in lab mice may not be sufficient to initiate significant increases in tissue sodium storage affecting the CNS, especially if urinary sodium excretion is upregulated in the rodents. Another study found that a high-salt diet induced T-helper 17 (Th17) cells in the EAE model using wild-type C57BL/6 mice, but the study also found that corticosterone was released in response to defend against inflammatory T cell entry into the CNS by tightening the blood–brain barrier [14]. However, it is not clear if this immune mechanism is sufficient to prevent tissue sodium accumulation and storage in the CNS.

By contrast, earlier research that measured total body sodium in 81 female Beagle canines of approximately two years of age suggested that cells within the body can store large amounts of sodium [15], providing support for the salt–MS hypothesis. Moreover, findings from sodium magnetic resonance imaging in human clinical research rebut controversial claims based on traditional sodium measurements. The use of sodium-23 magnetic resonance imaging (^{23}Na MRI) provides better estimates of whole body sodium levels compared to estimated dietary intake and measured sodium excretion [16].

Imaging from ^{23}Na MRI has been suggested as a marker of tissue injury in MS [17]. Using ^{23}Na MRI in patients with RRMS, researchers detected higher sodium concentrations in brain lesions and in normal grey and white matter compared to healthy controls [18,19], and the researchers suggested that tissue sodium concentrations might serve as a predicting factor in clinical outcomes [18]. Similarly, a large cohort study of 70 patients with MS covering all subgroups found higher brain sodium concentrations using sodium ^{23}Na MRI [20]. Wang et al. [21] noted that a total increase in tissue sodium concentration (TSC) is associated with increases in intracellular sodium, loss of cell integrity, and cell death with increased extracellular volume. Other studies using ^{23}Na MRI found that skin concentrations of sodium can accumulate at levels above serum sodium levels [22]. A higher ^{23}Na MRI signal was also recently found in the skin of male patients with MS compared to healthy matched controls [23].

Summarizing evidence presented in the introduction, controversial findings that contradict the association of salt intake with MS pathogenesis are based on methods that only estimate dietary intake or measure levels of extracellular sodium tightly regulated by the kidneys, and cannot detect increased TSC throughout the body [8]. Furthermore, research needs to establish if a loss of cell integrity in MS causes increased TSC, or increased TSC causes a loss of cell integrity, or if other factors are involved. A potential factor that may cause both loss of cell integrity and increased TSC in MS is sodium toxicity, the

sudden acute effect of salt poisoning from excessive intake of sodium chloride [24], or, more generally, the long-term chronic effect of persistent dietary sodium overload [25].

2. Materials and Methods

The present perspective paper used a grounded theory method to retrieve and analyze findings from the research literature relevant to sodium toxicity and MS. Starting with a clean slate by removing all theoretical assumptions, grounded theory added rigor and objectivity to the paper's literature review and analysis [26]. Beginning with purposeful sampling [27], articles were selected by keyword searches using online search engines such as PubMed, Google, Google Scholar, and Scopus. Keywords included multiple sclerosis, demyelination, sodium, autoimmune disease, and dietary salt intake. References cited in selected articles were also searched for additional information and keywords. Selected articles included older foundational studies in addition to the most recent articles available. Research findings from retrieved articles were compared and categorized into concepts and themes. New knowledge was induced from a synthesis of associative, causative, and mediating relationships linking concepts and themes. Theoretical sampling refined the search and selection of additional articles to fill in knowledge gaps [26]. The grounded theory method continued as an iterative process until theoretical saturation contributed no additional new knowledge. Based on the emerging theory, the present perspective paper proposes insights and new directions for further research in the association of sodium toxicity with MS.

## 3. Sodium Toxicity and Demyelination

Axon degeneration in the CNS can be caused by injury, toxins, and genetic defects [28]. Bechtold and Smith [29] reviewed early studies of inflammatory demyelinating disease and reported that sodium ions can accumulate in axons, disturb axonal sodium ion homeostasis, and cause axonal degeneration. The authors described how the magnitude of degeneration in axons in patients with MS is correlated with the degree of neuroinflammation in demyelinating axonal lesions, which the authors attributed to potentially harmful concentrations of sodium.

The Nav 1.6 voltage-gated sodium channel is associated with increased neuroinflammation and axonal degeneration in genetically altered C57BL/6 mice in the EAE model of MS [30]. Additionally, neuroinflammation and axonal degeneration were reduced in an EAE model when dark agouti male rats were treated with the sodium channel blocker flecainide [31]. However, subsequent EAE studies found that treatment withdrawal of the sodium channel blockers phenytoin and carbamazepine in diseased C57BL/6 mice exacerbated symptoms and increased risk of death compared with healthy controls [32]. Another study found that tailored withdrawal of phenytoin in the EAE model prevented deaths in diseased C57BL/6 mice, but symptoms neared non-treatment levels [33].

Related to this, osmotic demyelination syndrome in humans, which affects the central pontine and extrapontine regions of the brain, is caused by rapid saline infusion in the clinical correction of hyponatremia [34]. Moreover, an early study of MRI revealed that demyelination of the central pontine occurs in several conditions, including MS [35], further implying an association between MS and sodium toxicity.

Recent research has discovered novel roles for lipid phase properties of myelin in the etiology and recovery from MS [36]. Beck and Shaharabani described the structure and function of the myelin sheath as a multilamellar complex composed of different types of proteins and lipids which circumscribe axons and preserve nerve conduction integrity by providing a layer of insulation [36]. The researchers also described how myelin's structure is undermined and its function is impaired in MS.

Biological membrane characteristics are determined by the distinctive organization of proteins and/or lipids, which can transition between a lamellar lipid phase, with cylinder shapes that add no curvature strain within the membrane, and hexagonal lipid phases including inverted-cone shapes (H_{II} phase) that induce a positive curvature strain within the membrane [37]. Beck and Shaharabani reported pathological phase transitions in the multiple membrane (multilamellar) stacked structure of myelin sheaths in MS, correlated with small variations in myelin lipid composition and reduced adhesiveness in myelin basic protein (MBP) [36]. Figure 1 shows in vitro and in vivo examples of normal myelin and myelin with structural instabilities caused by lipid phase transitions. The researchers noted that ion-specific structural instabilities are increased by elevated salinity (saltiness) and temperature, which change normal lamellar stacks to a disrupted inverted hexagonal phase.
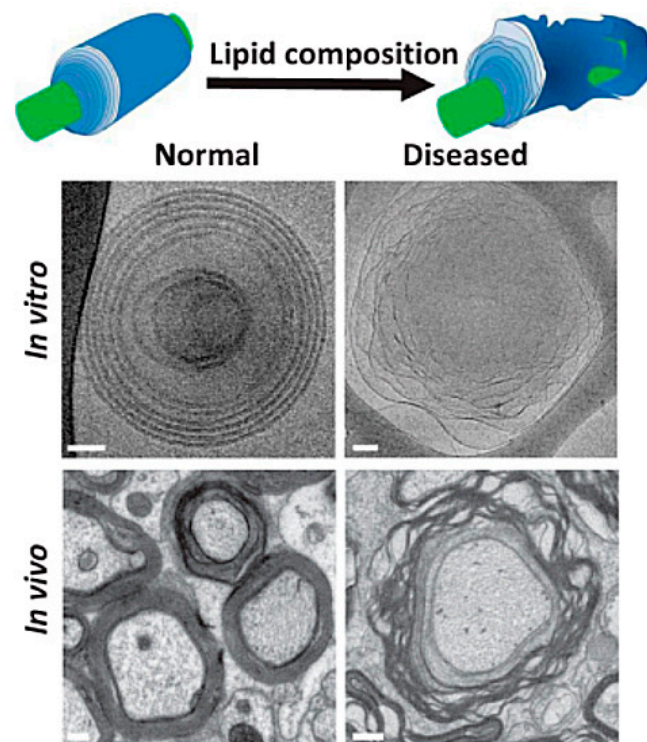
Figure 1. Normal myelin sheath membrane, in vitro and in vivo, and myelin with structural instabilities due to lipid phase transition, in vitro and in vivo [38].

More recent research on the molecular origin of MS corroborates findings of instability in diseased lipid membranes, which is associated with 25% lower membrane stiffness and lower binding strength of MBP [39]. Shaharabani et al. also reported that the temperature in which myelin phase transition occurs is 42 °C [40]. Of physiological relevance, high fevers or hyperpyrexia over 40 °C are associated with heat-induced injury to the CNS with axonal and myelin degeneration [41]. Furthermore, glandular fever or infectious mononucleosis caused by the Epstein–Barr virus is a risk factor for MS diagnosis [42], which may be mediated by myelin damage from exposure to high temperatures. "Fever is a common symptom of infectious and inflammatory disease" [43], and not only does salt indirectly contribute to increased CNS temperature by causing inflammation through salt-induced cytokine expression [44], but sodium chloride is also a pyrogen that directly causes fever by modulating the temperature-control function of the posterior hypothalamus [45]. Epstein–Barr viral infection is also associated with cytotoxic CD8+ T cell damage to the CNS during MS pathogenesis [46], and renal infiltration of CD8+ T cells was induced by a high-salt diet fed to Dahl–salt-sensitive rats [47].

Shaharabani et al. noted that myelin phase transition increases with sodium concentrations > 150 millimoles per liter (mmol/L), which is within the range found in vivo [40]. For example, normal serum sodium levels in rodents and humans are approximately 140 mmol/L, but higher sodium concentrations in lymphoid and interstitial tissue range from 160 to 250 mmol/L sodium [48]. Of relevance, serum sodium concentrations are sensitive to fluid overload in hypervolemia, and clinical hyponatremia should be classified as hypervolemic, hypovolemic, or euvolemic [49]. Clinical hyponatremia is most often hypervolemic due to fluid retention related to excessive sodium intake. In total, the reviewed evidence of salt and demyelination supports sodium toxicity as a cause of pathophysiological mechanisms related to the etiology of MS.

4. Salt-Related Inflammatory and Immune Responses in MS

This section briefly reviews several inflammatory and immune responses associated with dietary sodium and MS. Proinflammatory cytokines released from activated T cells, especially interleukin 17 (IL-17) induced by Th17 cells, are associated with disease activity in patients with MS [50]. Of relevance, increased sodium chloride concentrations under physiological conditions significantly enhanced induction of Th17 cells in male C57BL/6J mice and in blood samples from healthy humans [13]. Demyelinated lesions in the CNS are also infiltrated with increased levels of macrophages and T cells in people with MS, and blood levels of monocytes are increased [8]. Related to this, infiltration of macrophages in the CNS and levels of monocytes in the blood of healthy people increased with exposure to a high-salt diet [51]. When sodium levels were lowered in healthy people, proinflammatory cytokines IL-6 and IL-23 were reduced, whereas levels of the anti-inflammatory cytokine IL-10 increased.

A high-salt diet in EAE-diseased C57BL/6 mice also elevated CNS levels of macrophages and proinflammatory cytokines, including IL-6, IL-12, IL-23, and tumor necrosis factor alpha (TNFα) [52]. Additionally, a high-salt diet in male NSG immunodeficient mice reduced immunosuppressive function of forkhead box protein 3 (FOXP3+) T regulatory cells (Tregs) and increased interferon gamma (IFNγ) [53], a cytokine associated with neuroinflammation in MS [54].

5. MS Comorbidities Potentially Mediated by Sodium Toxicity

The following subsections describe the association of MS and several comorbidities with potential mediation by sodium toxicity as a common cause. These associations add supporting evidence for the salt–MS hypothesis, and suggest new directions for further research in the pathogenesis of conditions comorbid with MS.

5.1. Systemic Lupus Erythematosus and MS

Systemic lupus erythematosus (SLE) has rarely been reported to coexist in patients with MS, and differential diagnosis between the two diseases is often difficult [55]. Yet, both diseases have similar immune responses to salt intake [48], suggesting shared etiologies. For example, a high-salt diet in a murine model of SLE increased lupus nephritis progression and mortality, and a high-salt diet also upregulated Th17 cells in MRL/lpr mice [56].

5.2. Rheumatic Arthritis and MS

Self-reported rheumatic or rheumatoid arthritis (RA) was found to have a dose-dependent relationship with daily sodium intake in a case–control study in Spain [57]. Moreover, a nationwide retrospective cohort study in Taiwan found that patients diagnosed with MS had a higher subsequent diagnosis of RA compared to controls [58]. Patients with early RA were also found to have significantly higher sodium excretion than controls, even after controlling for nonsteroidal anti-inflammatory drugs, hypertension drugs, and smoking status [59]. Recently, a high urinary sodium-potassium ratio was associated with RA disease activity in patients, which the researchers suggested was linked to high sodium

intake and low potassium intake [60]. Taken together, these findings provide supporting evidence that high sodium intake mediates the association of MS with RA.

5.3. Heart Failure and MS

A Danish cohort study found that patients with MS had an increased risk of heart failure compared to the general population [61], and an increased risk of heart failure associated with MS was confirmed in a recent systematic review and meta-analysis [62]. Coincidently, another recent study using ^{23}Na MRI reported that patients with heart failure have extremely high levels of tissue sodium storage [63], inferring that increased risk of heart failure in patients with MS could be associated with high tissue sodium storage.

5.4. Inflammatory Bowel Disease and MS

Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, has been associated with a high-salt diet which induced gastrointestinal responses including "production of pro-inflammatory cytokines by intestinal mononuclear cells" [48] in eight-week-old female Balb/c mice [64] and eight-to-10-week-old female C57BL/6 mice [65]. Furthermore, a recently published systematic review and meta-analysis found that risk of IBD in patients with MS was higher than in controls [66], inferring that increased risk of IBD in MS could be associated with high salt consumption.

5.5. Ischemic Stroke and MS

A recent systematic review and meta-analysis found that people with MS have an increased risk of developing all types of stroke, especially ischemic stroke, compared to the general population [67]. A high-salt diet is a risk factor for acute ischemic disease [68], and salt restriction is an accepted lifestyle intervention in stroke prevention [69], implying that increased risk of ischemic stroke in MS is likely associated with high sodium concentrations.

5.6. Hypertension and MS

High blood pressure, or hypertension, is the most common risk factor for stroke [70], and hypertension's close relationship with dietary salt intake is well established [71]. In a case–control study, U.S. patients with MS were 48% more likely to have had hypertension than a control group [72]. A retrospective cohort study found that higher systolic blood pressure was associated with progressively worse MS-related disabilities [73]. A large cross-sectional study that examined 37 million electronic health records from across the United States found that hypertension was 25% more common in the MS population compared to the rest of the population. Similar to MS, hypertension is also associated with inflammatory and immune responses to high dietary salt [74,75], further implying sodium toxicity as a common causative factor.

5.7. Migraine, Non-Specific Low Back Pain, and MS

The prevalence of primary headache among MS patients is higher than in the general population, according to a systematic review and meta-analysis of global studies [76]. Migraine headaches in particular are often comorbid with MS [77], and evidence suggests that sodium chloride intake is associated with migraine headache pain [78]. Sodium chloride intake is also associated with posterior lumbar subcutaneous edema in non-specific low back pain [79]. Coincidently, a recent study of the French MS population found that the prevalence of lower back pain is two to three times higher than in the general population [80].

5.8. Obstructive Sleep Apnea, Anxiety, and MS

Patients with MS have a higher predisposition for obstructive sleep apnea compared to patients without MS [81]. Obstructive sleep apnea is associated with sodium chloride intake as fluid overload is redistributed toward the upper body [82]. Salt also increases anxiety by triggering the action of angiotensin II which facilitates the release of "fight or flight" adrenal

catecholamines from the sympathetic nervous system [82]. Of relevance, MS patients in a Canadian population have a 28.7% prevalence rate of anxiety disorders, self-rated with the Hospital Anxiety and Depression Scale, which is higher than the prevalence of anxiety reported in the general population [83].

5.9. Menstrual Disorders and MS

MS incidence is uncommon in people past ages 50 and 60 years [84]—the approximate ages of menopause and post menopause in women—and MS incidence is highest in females during childbearing years [85], although onset of the disease temporarily drops during the third trimester of pregnancy [86]. MS is also associated with a high prevalence of menstrual disorders [87,88], and menstrual disorders are associated with fluid overload [89], potentially related to increased interstitial sodium storage [11]. In the EAE model of MS, dietary salt worsened the disease only in female mice of the SJL/JCrHsd strain [90], suggesting involvement of sex-specific genetic factors. MS in human females is also associated with reproductive hormones [91] and with higher sodium sensitivity [11]. More research is needed to examine the relationship between menstrual disorders and greater exposure to sodium toxicity in MS.

Evidence implicating MS and comorbidities with sodium toxicity and other environmental factors challenges the prevailing concept of autoimmunity in MS [1] and in other related diseases including type I diabetes mellitus, Guillain-Barr syndrome, and myasthenia gravis [92]. Future directions in basic, epidemiological, and clinical research should continue to investigate etiological and epigenetic effects of sodium toxicity in MS and related comorbidities. Furthermore, lifestyle preventative measures should be investigated to modify dietary salt intake. Low-salt diet trials may show improvements in MS and comorbid conditions. However, separate trials should be conducted to directly link low salt as a causative factor in the pathogenesis of conditions comorbid with MS.

6. Future Directions for Low-Salt Interventions

According to a policy statement by the World Hypertension League [93], confusion exists over classifying dietary sodium intake levels as low, normal, and high, and questions remain over levels of sodium restriction necessary for disease prevention. Adding to the confusion, sodium constitutes only about 40% of the weight of dietary sodium chloride [94]. Based on "normal ancestral levels of salt intake and also on ranges of reduction in salt intake in clinical and population interventions," Campbell et al. published a Proposed Nomenclature for Salt Intake and for Reductions in Dietary Salt [93]. Rather than basing their nomenclature on contemporary salt consumption levels, the authors' cited sodium intake estimates of hunter-gatherer societies with low hypertension prevalence, such as the Yanomamo tribes of Brazil, whose people were each estimated to consume less than 100 mg sodium per day. The authors also referred to the clinical research of Walter Kempner and his effective treatments for hypertension using a rice and fruit diet containing 152 mg sodium per day [95]. However, the authors point out that more research is needed to investigate harm from sodium deficiency at ultra-low sodium intake levels below 100 mg. Furthermore, Kempner kept patients on a rice and fruit diet for two months, with extended treatments lasting many more months [95]—implying that elimination of excessive TSC requires long-term dietary changes. Future studies should use ^{23}Na MRI to measure the rate of TSC reduction in all subtypes of MS patients on low-salt diets.

Table 1 summarizes the proposed nomenclature for salt and sodium intake by Campbell et al. [93], which is supported by the World Hypertension League, World Action on Salt & Health, and the Australian Division of World Action on Salt & Health. The recommended salt level in the proposed nomenclature agrees with that of the World Health Organization and the International Society of Hypertension.

Table 1. Recommended daily sodium and salt intake nomenclature, based on the findings of Campbell et al. [93].

Nomenclature Term	Sodium mg	Salt g
Low intake	Undefined, likely <100	Undefined, likely <0.25
Normal ancestral level	<1000	<2.5
Recommended	<2000	<5.0
High	$\geq$2000–4000	$\geq$5.0–10
Very high	>4000–6000	>10–15
Extremely high	>6000	>15

Researchers have noted the need for "well-designed clinical studies with a sufficient cohort size" to address the effects of increased salt intake on MS pathogenesis and disease activity [96]. For future controlled clinical trials investigating effects of a reduced-sodium dietary intervention on MS symptom severity, relapse rate, and disease progression, the normal ancestral level of sodium intake (<1000 mg/day), derived mostly from whole natural foods without added salt, would provide an ideal experimental level. Coincidently, sodium levels of 500 mg or lower, which meet basal physiological needs according to the U.S. National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health [97], lie within the normal ancestral level of sodium intake. By contrast, U.S. average sodium intake is more than 3400 mg [94].

Finally, objections concerning policies that reduce salt intake include claims of increased cardiovascular disease risk, but these objections have been challenged, including a rebuttal by Campbell et al. who cited "inappropriate research methodology, lack of rigor in research, conflicts of interest and commercial bias" [98]. Figure 2 is a directed acyclic graph showing that dietary sodium overload and sodium toxicity are associated with MS symptoms, subtypes, and comorbidities (the dotted arrow), and that this association is mediated by CNS demyelination, tissue sodium storage, and inflammatory and immunes responses (solid arrows).
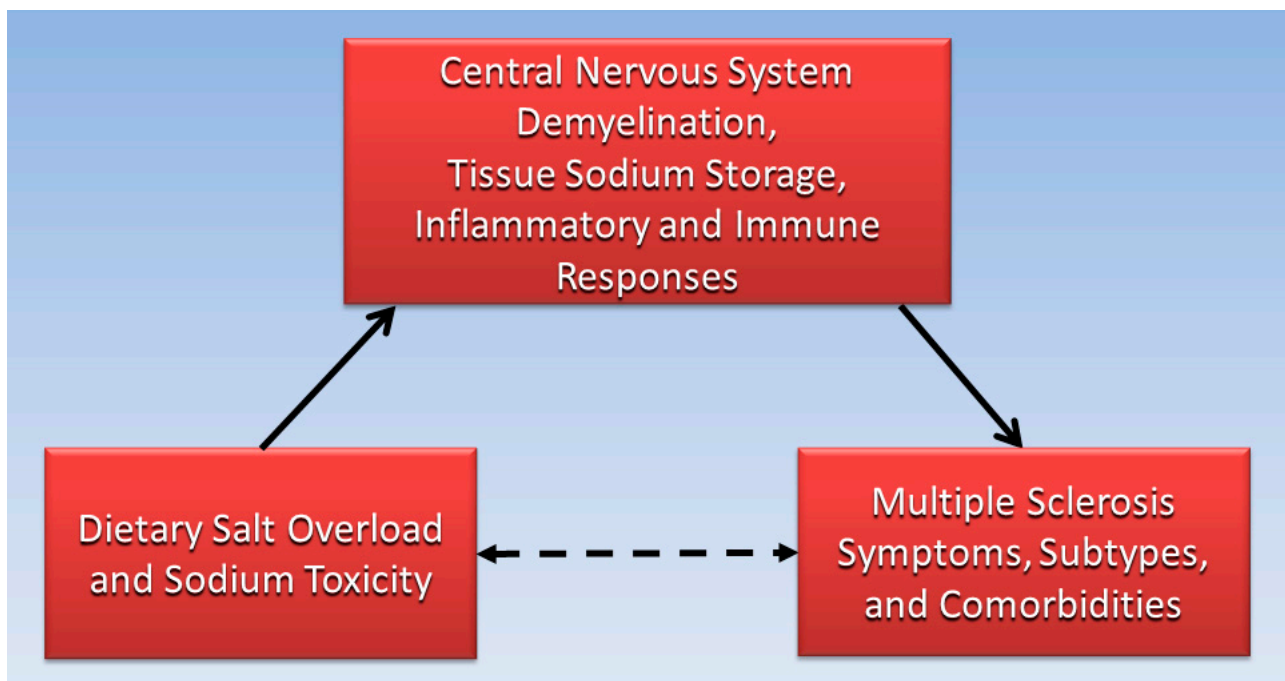
Figure 2. Mediation of sodium toxicity associated with MS.

7. Conclusions

Assessment methods of sodium intake using urinary sodium levels and food surveys do not measure tissue sodium concentrations associated with MS. [23]Na MRI detected higher sodium concentrations in brain lesions and in normal grey and white matter of patients with MS compared to healthy controls. Myelin phase transitions associated with increased salinity cause structural instabilities of myelin sheaths in the CNS, implicating sodium toxicity as a causative factor in MS. Inflammatory and immune responses in MS are related to high sodium intake levels. Comorbidities associated with MS are potentially mediated by responses to high sodium intake, providing additional evidence implicating sodium toxicity as a cause of MS. Future directions for low-salt interventions should investigate normal ancestral sodium levels below 1000 mg per day for reducing MS symptoms and preventing disease progression.

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Conflicts of Interest: The author declares no conflict of interest.

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