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Controversies in Multiple Sclerosis

People with MS should consume a low-salt diet – YES

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It is generally accepted that autoimmune diseases like multiple sclerosis (MS) arise from complex interactions between genetic susceptibility and environmental factors. In the last half-century, the incidence of autoimmune diseases, including MS, has increased dramatically in Western countries.[1] Given how quickly disease distribution changes have occurred worldwide, genetic factors seem an unlikely cause. Several epidemiological studies have linked MS risk to environmental and lifestyle factors.[2] Recently, the dietary contribution to MS incidence and severity has come under scrutiny, particularly consumption of "Western-style diets" characterized by high-fat, cholesterol, sugar, and processed foods with high content of salt (sodium chloride (NaCl)).

Clearly, increased sodium exerts negative impacts on several body systems including blood pressure, and cardiovascular and kidney functions. However, recent studies have also documented increased inflammatory innate and adaptive immune function resulting from increased NaCl. Two studies have shown that elevated NaCl concentrations, mimicking those found in the interstitium in animals fed high-salt diets, promote $CD4^+$ T cell differentiation to Th17 cells (critical effector cells in MS pathogenesis) in vitro.[3,4] This effect occurs via transcription factor NFAT5 and serum/glucocorticoid-regulated kinase1 (SGK1), both expressed on Th17 cells and induced by NaCl. Interestingly, SGK1 appears to govern NaCl homeostasis in other cells, enhancing Th17 differentiation in an IL-23-dependent manner. These experimental data correlated with in vivo observations, since high-salt diets accelerated onset and worsened experimental autoimmune encephalomyelitis (EAE), a finding dramatically reduced in SGK1-deficient mice. High-salt diets also increased interferon (IFN)-γ producing T cells in animal central nervous system (CNS), but not in peripheral immune compartments, suggesting NaCl may increase infiltration but not expansion of IFN-γ^+ effector T cells in target organs.[4] Similarly, in EAE mice, high-salt diets also promoted pro-inflammatory macrophages, inducing microglial cells and CNS macrophage activation, producing IL-1β which further enhanced Th17 responses.[5] Increasing NaCl concentrations also inhibited regulatory mechanisms mediated by M2 macrophages as well as mouse and human $CD4^+$ T regulatory cells (Tregs), evolved to limit immune-mediated inflammation levels and promote tissue injury resolution.[6,7] Thus, increased salt intake can disrupt immune response equilibrium by promoting pro-inflammatory macrophages and T cells.

Evidence of a direct influence of salt intake on autoimmunity and increased inflammation has only recently come into focus. We evaluated the association between salt intake (measured by urinary Na excretion) and MS disease activity in two separate cohorts.[8] We observed positive correlations between relapse rates and sodium intake after multivariate analysis adjusted for age, gender, disease duration, smoking status, Vitamin D levels, body mass index, and treatment. In the first cohort of 70 relapsing-remitting MS patients followed for 2 years, relapse rates were 2.75 or 3.95-fold higher in patients with medium (2–4.8 g/day) or high (> 4.8 g/day) sodium intake levels compared to a baseline group of patients (taking World Health Organization (WHO) recommended levels of < 2 g/day). Additionally, a statistically significant correlation was found between sodium intake and MRI activity, including T2 lesions and the combined unique activity (CUA) (combination of new Gd^+ lesions and new or enlarging T2 lesions). Individuals with high sodium intake had 3.4-fold greater chance of developing new lesions on MRI; results later replicated in a cross-sectional study involving 52 relapsing-remitting patients. No significant correlation was detected between daily sodium intake and serum levels after multivariate adjustment, nor was there correlation between serum sodium and clinical or radiological disease activity, suggesting that if NaCl has any causal role beyond its association, it does not occur in the peripheral blood. The study could not demonstrate that increased salt intake is related to an increased risk of developing

MS. We are aware that this study has some limitations, namely, small cohort size and lack of evaluation of other diet components or commensal microbiota. So, although association between increased salt intake and MS activity was demonstrated, causality cannot be claimed.

A recent case-control study evaluating the association between salt intake and the risk of pediatric onset of clinically isolated syndrome (CIS) and relapsing-remitting MS assessed dietary salt intake using the Block Kids Food Screen.[9] Results did not support association between sodium intake and MS susceptibility in children. The association between increased sodium intake and conversion from CIS to MS and MS activity was recently assessed in patients receiving IFN-β-1b.[10] Sequential 24-hour sodium excretion levels were not associated with conversion to clinically definite MS during a 5-year follow-up, or with clinical or MRI outcome, suggesting salt intake does not influence MS disease course or activity. Discrepancies between these results and ours may be explained by differences in (1) patient selection (CIS vs relapsing-remitting MS; pediatric vs adult onset MS); (2) study design; and (3) population genetic background, possibly impacting interaction between genetic and environmental factors in the context of sodium-induced CNS inflammation.

Comorbidities are known to impact MS course.[11] A high-salt diet is associated with increased risk of hypertension which has a detrimental impact on MS affecting clinical outcomes including walking speed, self-reported disability, and depression.[12] Interestingly, macrophages residing in skin interstitium modulate local electrolyte composition in response to extracellular NaCl hypertonicity, through secretion of vascular endothelial growth factor,[13] and renin-angiotensin system blockade can modulate immune response and affect EAE course.[14]

Overall, experimental evidence and preliminary clinical data would indicate that elevated salt intake in MS could worsen disease. Therefore, dietary salt restriction as a complementary measure in addition to standard medical care might benefit MS patients. However, strong clinical and epidemiological evidence is still lacking, and the intervention remains to be definitively proven as a useful therapeutic intervention. Prospective controlled clinical trials with larger cohorts should be designed to address the relevance of direct and indirect effects of increased salt intake on the course of MS. Additionally, excess salt content in diet should be investigated as a potential environmental MS risk factor.

Declaration of Conflicting Interests

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