



## Research Paper: The Association Between Salt and Potassium Intake with Multiple Sclerosis



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**Running Title** The Association Between Salt and Potassium Intake with MS

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### ABSTRACT

**Background:** The number of patients with Multiple Sclerosis (MS) is increasing in Iran. Studies have shown that high sodium chloride (salt) and low potassium intake are associated with the development of MS. High physiological salt concentrations can lead to the induction of Interleukin-17 (IL-17) accompanied by the excessive generation of helper T-17 cells (Th-17). This cytokine plays a critical role in the pathogenesis of autoimmune diseases. This is while potassium supplementation has a blocking effect on IL-17 production.

**Objectives:** Because of the role of salt and potassium in Th 17 development, we hypothesized that sodium chloride (NaCl) would be higher and potassium (K) would be lower in MS patients than healthy controls. Therefore, we investigated the association between salt and potassium intake with MS in Isfahan City population, Iran.

**Materials & Methods:** A case-control study containing 23 patients and 23 healthy controls was performed in Isfahan City, Iran, 2016. NaCl and K levels were measured in 24-h urine. Using the Chi-square test, the patients' laboratory values were compared with the healthy controls. The level of significance was set at  $P < 0.05$  in all analyses. All calculations were performed in SPSS, version 23.0.

**Results:** In this study, urine Na levels were somewhat higher in cases than in controls (Interquartile Range [IQR]; 160[140-211] mEq/24 h vs. 128[83-166] mEq/24 h) ( $P=0.027$ ). These results show a significant relationship between urine-Na and MS. Urine k concentrations were lower in cases than controls [IQR; 47(27-70) mEq/24 h vs. 50(29-56) mEq/24 h] but we did not find a significant difference between two groups ( $P=0.807$ ).

**Conclusion:** Based on this study, a high level of sodium intake may be associated with MS; however, we did not find a significant difference between patients and controls with regard to potassium level.

**Keywords:** Multiple Sclerosis, Sodium chloride, Potassium, Th 17 cells, Interleukin-17

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## Highlights

- High levels of sodium intake is associated with the development of Multiple Sclerosis.
- No significant correlation was found between potassium intake and the risk of MS.

## Introduction

**M**ultiple Sclerosis (MS) is a chronic inflammatory disorder of the central nervous system leading to both axonal damage and demyelination. This disease is more common in young adults [1, 2]. Common presentations of MS include sensory disturbance, visual loss, diplopia, limb weakness, and vertigo [3]. The number of patients with MS is increasing in developing countries such as Iran [4-6]. It seems that MS usually develops in genetically susceptible people as a result of environmental exposure. Several environmental factors, such as viral infection, vitamin D deficiency, smoking, obesity, sunlight exposure, and diet have been postulated as potential risk factors for the increasing incidence of autoimmune diseases such as MS [7-9].

The mean sodium intake in most Asian countries is over 100 mmol/d, while the recommended salt intake value by WHO is 80-90 mmol/d [10] and in many societies the mean potassium consumption is below 70-80 mmol/d, which is the value recommended by the WHO (1988, 2003). Previous research studies have shown that high salt intake is associated with the development of autoimmune diseases and aggravations of MS symptoms in patients, while potassium supplementation has a diverse effect [11, 12].

T helper 17 (Th 17) cells produce Interleukin (IL)-17, which is a pro-inflammatory cytokine. It plays a critical role in the pathogenesis of autoimmune diseases. High physiological salt concentrations have a direct effect on the induction of Th 17 cells and IL-17, which initiate pro-inflammatory signatures. However, potassium supplements block IL-17 production in T lymphocytes [11-14]. In this research, we performed a case-control study to investigate whether NaCl uptake in MS patients is one of the underlying factors of the disease.

## Materials and Methods

A total of 23 patients with Relapsing-Remitting Multiple Sclerosis (RRMS) were randomly selected from

Alzahra Clinic of MS, Isfahan, Iran. Then, 23 healthy controls matched with the cases based on gender and age were selected, too. The participants were recruited between October and June 2016, and all of them signed informed consent forms. Furthermore, the Ethics Committee of Isfahan Research Committee of Multiple Sclerosis approved this project.

## Study samples

The MS patients, aged 15-46 years, would be included in this study if they were clinically diagnosed with MS with a relapsing-remitting course for more than 1 year. Exclusion criteria were the presence of renal disease, diabetes insipidus, and adrenal disorders. In addition, the patients using diuretics were excluded from this study.

## Sodium chloride (NaCl) and Potassium measurements

The levels of sodium chloride (NaCl) and potassium were measured in 24 hours of urine. To confirm that the high level of sodium in urine is not due to the elevated level of sodium in the blood, we also measured the level of blood sodium. In addition, the blood creatinine level and Glomerular Filtration Rate (GFR) were also measured in all cases and controls to rule out kidney diseases. All the measurements were performed in one laboratory and by the same technicians.

## Statistical analysis

All analyses were performed in SPSS (version 23.0). We used the Chi-square test to compare NaCl and potassium level in 24 hours of urine between cases and controls. Conditional logistic regression was performed to determine the effect of daily sodium and potassium intake on the development of MS. The level of significance was set at  $P < 0.050$  in all analysis.

## Results

In this study, a total of 46 subjects (23 cases and 23 matched controls for sex and age) were included. The Mean $\pm$ SD age of cases and controls was  $27\pm 7$  years. In

each group, 5 (22%) males and 18 (78%) females were studied. Serum sodium concentrations were in the normal range, and none of the cases or controls had hyper- or hypo-natremia (Mean±SD: 139±2 mEq/L vs. 139±2 mEq/L, respectively) (P=0.262). Urine sodium level was relatively higher in cases compared to controls (Interquartile Range [IQR]; 160 [140-211] mEq/24 h vs. 128 [83-166] mEq/24 h), which is probably due to higher sodium intake in the patients. The difference in the level of urine sodium between the two groups of cases and controls was significant (P=0.027). Urine potassium concentration was lower in cases compared to controls (IQR; 47[27-70] mEq/24 h vs. 50[29-56] mEq/24 h). However, this difference was not significant (P=0.807). Table 1 presents the level of the measured variables and the significant differences between the two groups.

## Discussion

There are several reasons to postulate that sodium and potassium intake is involved in MS. Recent studies have shown the complex effects of sodium on different cellular components which are involved in central nervous system autoimmunity [15].

First of all, the high salt condition can activate the MAPK (p38/Mitogen-Activated Protein Kinase) pathway leading to upregulation of the transcriptional factor NFAT5 (Nuclear Factor of Activated T-cells 5), which enhances the expression of sodium sensing serine/threonine kinase named SGK1 (Serum Glucocorticoid Kinase 1). SGK1 has been shown to be highly expressed in CD4+ T cells and has a pivotal role in Th 17 differentiation and induction of IL-17A production [8, 15]. Based on these studies, gene silencing or chemical inhibition of SGK1, p38/MAPK or NFAT5 can prevent the development of high-salt induced Th 17 cell [16].

Th 17 bias and IL-17A are involved in the pathogenesis of autoimmune diseases [17]. However, studies have shown that potassium is able to reduce IL-17 expression that has increased due to high levels of NaCl. In a recent

study performed by Wen et al. it is demonstrated that high potassium intake can block the effects of sodium on p38/MAPK-SGK1 signaling pathway. In addition, some research suggests that potassium supplements antagonize pathogenicity of salt by their antioxidant effects. Moreover, it has been hypothesized that elevated level of extracellular potassium can increase the activity of membrane sodium pump and results in hyperpolarization of the cell membrane and decreases oxidase activity [12].

The differentiation of Th 17 is crucial since these cells are the first ones that cross the blood-brain barrier [18] and upon interaction with antigen-presenting microglial cells in the CNS, a chemokine cascade is activated that recruits further immune cells, such as other T cells and inflammatory monocytes [15]. However, in addition to the increased production of Th 17 cells and IL-17A, excess dietary sodium intake can lead to autoimmunity by inhibiting the function of FOXP3+ Tregs (regulatory T-cells) that are involved in the maintenance of self-tolerance. People who frequently use processed food, characterized by high levels of salt, have an increased ratio of proinflammatory IL-17+/anti-inflammatory FOXP3+ T cells in comparison to individuals who have a low intake of processed food [19].

High-salt diets induce a proinflammatory Treg phenotype associated with an SGK1-dependent increase in IFN $\gamma$  (Interferon gamma) secretion which has been seen in patients with relapsing-remitting MS [11, 20]. Hernandez et al. have shown that under high-salt in vitro conditions, IFN $\gamma$  blockade by either monoclonal antibodies or shRNA-mediated knockdown can restore Treg function. Furthermore, shRNA-mediated knockdown or chemical inhibition of SGK1 in human Tregs inhibits IFN $\gamma$  secretion while restoring suppressive function [11]. In addition to the mentioned effects of sodium on autoimmunity, proinflammatory myeloid cells, including monocytes, macrophages, and microglial cells, also play a crucial role in inflammation of CNS [21].

**Table 1.** The measured variables (NaCl and potassium in 24 hours of urine and blood sodium) and statistical results

Variables	Case	Control	Wald	P
Na urine (IQR)	160(140-211) mEq/24 h	128(83-166) mEq/24 h	4.905	0.027
Na serum (Mean±SD)	139±2 mEq/L	139±2 mEq/L	1.260	0.262
K urine (IQR)	47(27-70) mEq/24 h	50(29-56) mEq/24 h	0.060	0.807

High concentrations of NaCl induce myeloid cell activation and promote the phosphorylation of members of the MAPK pathway in macrophages. Macrophages also produce high levels of chemokines, such as MIP (macrophage inflammatory protein-2) and CCL2 (C-C motif Ligand 2) which are strongly related to salt intake. CCL2 plays a pivotal role in the migration of inflammatory monocytes to the CNS during Experimental Allergic Encephalomyelitis (EAE, an animal model of MS) [15]. Moreover, studies have shown that intestinal epithelial cells play a significant role in the maintenance of self-tolerance.

In vitro studies have demonstrated that in high salt condition, induction of Na<sup>+</sup>-glucose co-transport in colon epithelial cells activates the Na<sup>+</sup>/H<sup>+</sup> exchanger 3. As these events occur, the intestinal permeability increases, leading to the entry of foreign immunogenic antigens that can induce autoimmune processes [15]. In addition, hyperosmolaric treatment of epithelial cells promotes the production of proinflammatory cytokines mediated by the MAPK pathway [22]. Furthermore, endothelial cells, which are in contact with plasma sodium, can respond to small increases in sodium level. Under in vitro shear stress conditions, high-salt condition promotes responsiveness to TNF $\alpha$  (tumor necrosis factor-alpha) in endothelial cells, which is characterized by enhanced expression of adhesion molecules such as E-selectin and VCAM-1 (vascular cell adhesion molecule 1) [11].

Under saltwater treatment, CCL2 is highly upregulated which promotes the adhesion of leukocytes to the brain microvasculature [23]. Therefore, sodium changes the phenotype of endothelial cells and results in immune cell infiltration to CNS which can lead to autoimmunity. Finally, recent studies have shown that high-salt diets can affect gut microbiota and gut flora might influence Th 17 cells and Tregs [11]. Thus, reducing salt intake and consumption of probiotic foods may have beneficial effects on autoimmune diseases.

## Conclusion

In this study, for the first time, we have shown that high levels of sodium intake are associated with the development of Multiple Sclerosis. Therefore, it can be considered as one of the risk factors for MS. However, while there are some hypothesis showing that potassium also plays a role in the development of MS, but we did not observe any significant correlation between potassium intake and the risk of MS. Additional studies are needed to investigate whether an alternation in dietary salt and potassium intake proves beneficial in MS.

## Ethical Considerations

### Compliance with ethical guidelines

The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (No. 397365). All the study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki (1957 Draft).

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### Authors contributions

Initial draft: Sarah Ghorbani; Writing, revision, and editing the manuscript: All authors; Funding acquisition: Sarah Ghorbani, Amir Hossain Mahmoudzadeh, Sina Raeisi; Providing resources: All authors; and Study supervision: Masoud Etamadifar.

### Conflict of interest

The authors declared no conflict of interest.

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