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Multiple sclerosis and the relation to the excessive consumption of sodium chloride: a systematic review

Esclerose múltipla e sua relação com o consumo excessivo do cloreto de sódio: uma revisão sistemática

Paula Laderuski Wolf*, Thaynara Zanineli Stevanato, Simone Martins de Oliveira, Heber Amilcar Martins

ABSTRACT

Multiple Sclerosis is an autoimmune disease demyelinating which affects mainly the central nervous system, because it is influenced by genetic and environmental factors. This research aims to point the relationship between sodium chloride consumption and the likely triggering and/or worsening of Multiple Sclerosis (MS), an autoimmune disease. The selected articles were analyzed according to the systematic literature review to ascertain the possible relationship between the worsening of the pathophysiology of multiple sclerosis and the consumption of sodium chloride. The systematic literature review followed the following databases: BVS, Science Direct, PubMed, and Web of Science. From the articles found, a previous selection was made, in which 13 articles were selected, based on keywords related to sodium chloride and multiple sclerosis, referring to studies made *in vitro* and *in vivo*. It has been demonstrated the relationship between MS physiopathology and the overconsumption of salt is negative in five research and positive in others. Thus, despite the favorable results, indicating the relationship between sodium consumption and Multiple Sclerosis, further research is suggested, due to the diversity of methodology and populations used in each study.
Keywords: Dietary sodium chloride. Dietary sodium. Multiple sclerosis.

RESUMO

A Esclerose Múltipla é uma doença autoimune desmielinizante que afeta preferencialmente o sistema nervoso central, pois este sofre influência de fatores genéticos e ambientais. Esta pesquisa tem como objetivo evidenciar a relação do consumo de cloreto de sódio e o provável desencadeamento e/ou agravamento da Esclerose Múltipla (EM), uma doença autoimune. Foram analisados artigos selecionados de acordo com a revisão sistemática de literatura, com intuito de averiguar a possível relação entre o agravamento da fisiopatologia da esclerose múltipla e o consumo de cloreto de sódio. A revisão sistemática de literatura seguiu as seguintes bases de dados: BVS, Science Direct, PubMed e Web of Science. A partir dos artigos encontrados, realizou-se uma seleção prévia, em que foram selecionados 13 artigos, com base em palavras-chave relacionadas ao cloreto de sódio e a esclerose múltipla, utilizando de estudos *in vitro* e *in vivo*. Apresentou-se a relação entre a fisiopatologia da EM e o consumo exacerbado de sal negativa em um total de cinco estudos e positiva nos demais. Desse modo, apesar dos resultados favoráveis, indicando a relação entre o consumo de sódio e a Esclerose Múltipla, ainda se sugerem novas pesquisas, devido à diversidade de metodologia e às populações usadas em cada estudo.
Palavras-chave: Cloreto de sódio na dieta. Esclerose Múltipla. Sódio na dieta.

University Center of Maringa – Unicesumar, Maringa, PR, Brazil.
*paula_wolf_11@hotmail.com

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INTRODUCTION

It is known that processed foods have a significant impact on individual health because of huge amount of sodium and glutamate in their composition (Barros, 2008) According to the World Health Organization (WHO, 2016), consumption above 2 grams per day is considered excessive, thus harmful to an individual's health. However, most of the population, due to an industrialized diet, consumes higher values than indicated. This feeding system, called hypersodic, results in cardiovascular problems, such as blood pressure increases, and other complications, suchlike kidney problems (Borges, 2014). According to Krementsov et al. (2015), this hypersodic diet is a possible cause of Multiple Sclerosis (MS) physiopathology.

MS is an autoimmune demyelinating disease, which affects mainly the central nervous system (SNC). Its predominance increased in recent years (O'Gorman, Lucas & Taylor, 2012). It is estimated that in Brazil there is a rate of 35.000 people living with MS (Brasil, 2019). The main symptoms presented are fatigue, change in sleep, and paroxysmal symptoms (Oliveira & Souza, 1998).

MS development relies on genetic and environmental causes. According to Machado et al. (2012), MS physiopathology can be divided into phases: a) the T lymphocytes are activated in the bloodstream after an infection or a macrophage reaction, these macrophages recognize myelin sheath proteins as unsafe. The macrophages present these antigens to the T cells called T helper 1 (Th1) peripheral (Sobral & Dias, 2013), so that recognize myelin sheath proteins as autoantigens. Other substances can be identified as autoantigens; b) the T lymphocytes earn and grow your capacity: The lymphocytes corroborate in microglia as they express vascular adhesion molecules and release pro-inflammatory cytokines (Sobral & Dias, 2013) allowing them to cross the blood-brain barrier (BBB) and reach the central nervous system (CNS); c) lymphocyte T began destroying the myelin sheath: When lymphocytes reach CNS, they differ in phenotypes, because of the various cytokines released, besides secreting destructive factors to the myelin sheath. Remyelination can happen in acute conditions and injuries of MS. This phenomenon becomes continuous while new Th1 cells are activated, exacerbating the immune response, and causing neuronal dysfunctions (Sobral & Dias, 2013).

Dietary sodium consumption, in physiopathology, can influence the remittent-recurrent form of the disease. The device can be diverse, it is still not evident, but can generate changes in Th1 and Th17 cells. These would increase interleukins and the inflammatory state, salt backlog in some tissues, or even acting over circumventricular organs (CVO), which do not present a blood-brain barrier (BBB), in a way that enhances the inflammation process of MS in CNS (Krementsov et al., 2015).

The way of envisioned treatment in MS is immunosuppressive and immunomodulators (Silva & Silva, 2013), thus, the treatment is mainly pharmacological, presenting the first effective proven drug beta interferon, which is currently used in public health services, combined with others such as glatiramer acetate in other types of MS, by the Incorporation of technologies in the Unified Health System (CONITEC, 2019).

Considering this context, the work aims to present through a literature systematic review, the main updates on the relation between sodium chloride and the unleashing of MS.

MATERIALS AND METHODS

In the first research, it was selected papers that presented the correlation between sodium chloride/cooking salt and/or hypersodic dietary and the development or increase of MS physiopathology. The main question was the following: What is the connection between the possible growth and/or the increase of Multiple Sclerosis physiopathology and the cooking salt (NaCl)? For the answer, the software Mendeley Desktop® (Version 1.19.2; 2008-2018) was used for paper data compilation. There was no restriction of date, year, or any other for the text research, or the use of any connective between the keywords selected for it.

In the second research, for effective development of the literature review, it recurred for online research through the literature manager software Endnote® (free online version - version X8). PubMed and Web of Science Core Collection were the databases available with this software.

There were no dates, language, or data restrictions for both paper research, aiming to cover a vast number of papers related to the research subject. Nevertheless, it is important to highlight those databases as Virtual Health Library (VHL), and the Science Direct database was not available on the selected EndNote® version.

The research using "Any Field" or according to the keyword in any searched text description was done for the PubMed issues research, considering this the most wide-ranging available from this database. Furthermore, the connective "and" was used for the keywords search combination.

In addition, the database Web of Science has done the most wide-ranging research in this database, using keywords considering Title/Keywords/Abstracts. Moreover, the boolean operator "and" were used for the keyword's combination.

Used words combination

Through EndNote®, papers considering the physiopathology of MS disease and its connection to cooking salt were investigated. The terms used were based on Health Science Descriptors (HSD) in English,

of "word or term" class: "multiple sclerosis" "sodium chloride" "dietary sodium" dietary sodium chloride", sodium-restricted diet". The following combinations were used in both databases: "multiple sclerosis" and "sodium chloride"; "multiple sclerosis" and "dietary sodium"; "multiple sclerosis" and "dietary sodium chloride", "multiple sclerosis" and "sodium-restricted diet".

Combination results and eligibility and exclusion criteria

Through the research using PubMed, Science Direct, and VHL, the papers found were evaluated according to the exclusion and inclusion criteria based on titles. Those which presented terms such as "autoimmunity" and/or "autoimmune" and or "multiple sclerosis" and/or "salt" and/or "saline" and/or "sodium chloride" directed to abstract readings for framing on papers list, whose are part of the complete text, once the number of papers found in this selection was superior compared to the search made by EndNote®.

For the eligibility criteria, on the second search, made through the EndNote® database, the readings of each found paper titles and abstracts were made and the main criteria for inclusion of the text to the present study were to relate and discuss the physiopathology change of physio pathogeny of MS related to the consumption of sodium chloride or cooking salt. Papers that did not make the correlation were not selected.

Also, papers that made the correlation were literature reviews of any kind or meta-analysis, subject commentaries, papers without abstracts available because of past publishing, text counterparts, or texts without the main language as English. Therefore, comparative studies, cohort studies, experimental studies made *in vivo* and *in vitro*, observational studies, controlled randomized studies, and research support studies.

Paper analysis criteria

For an adequate text analysis from the selected ones, it was established criteria as the author, release year, study type, methodology, population, population age, the reference value of sodium chloride used, study durability, and results. This present systematic review was registered in any protocol database for systematic reviews.

RESULTS AND DISCUSSION

In the first research using the terms "multiple sclerosis" and "sodium chloride", the Science Direct database presented 8.222 papers as a total amount, making available 6.000 of them. PubMed database presented a total of 39 papers and VHL a total of 152, totalizing 6.191 papers. In the second selection, the terms used in combination were "multiple sclerosis, sodium-restricted diet." Science Direct database presented 2618 papers, PubMed database presented a total of six papers, and VHL a total of four, totalizing 2.628 papers. Hucke et al. (2016) were the only selected paper, as shown in Figure 1.

The selection made by EndNote® found a total of 208 papers, however, just 14 papers relating sodium chloride consumption in diets and changes in MS course were found. Among these articles, the work of Cortese et al. (2016) was similar to Cortese et al. (2017), being selected the one which was most recent and available. Consequently, 13 articles were selected for analysis and review, as shown in Figure 2, based on PRISMA method guidelines.

Populations

Due to the types of study diversity, the observed population varies between humans and animals, regularly, following ethical and normative research principles. Human studies are divided first by age. Of the majority of the papers concerned with grown-ups, two of them studies regardless of gender (Farez, Fiol, Gaitán, Quintan & Correale, 2017; Fitzgerald et al., 2017), one study addressing women (Cortese, Yuan, Chtnis, Ascherio & Munger, 2017), one study of age group 19-70 or above grown-ups diet, regardless of gender, without direct application, which means without a practical intervention of diet (Chenard, Rubenstein, Snetselaar & Wahls, 2019). Two studies were obtained on the pediatric age bracket (McDonald et al., 2016; Nourbakhsh et al., 2016). Besides this, studies selected made in animals were included, in the majority of mice, specified in species in each paper; (Kleinewietfeld et al., 2013; Krementsov et al., 2015; Hucke et al., 2016; Jörg et al., 2016; Deng et al., 2017; Hammer et al., 2017). It is important to highlight the consideration of gender and ethnicity of human beings for the observation in the majority of these studies. Also, the use of studies *in vitro* in this present study is highlighted, considering that they are components of a significant part of the theoretical resources of a substantial number of other selected studies.

Selected studies method

According to the type and methodology of the selected studies, the majority can be classified as experimental studies, with a total of eight studies (Kleinewietfield et al., 2013; Krementsov et al., 2015; Hernandez et al., 2016; Jörg et al., 2016; Deng et al., 2017; Fitzgerald et al., 2017; Conitec, 2019; Hammer et al., 2020), the others can be classified as observational studies (Farez et al., 2014; Nourbakhsh et al., 2016; Cortese et al., 2017; McDonald et al., 2018), totalizing four papers and one paper classified as comparative study (Chenard et al., 2019). Verifying the average usage of salt, the papers vary in their measure form: four studies (McDonald et al., 2016; Nourbakhsh et al., 2016; Cortese et al., 2017; Chenard et al., 2019) use mg/day, g/day, or mg. The seven remaining

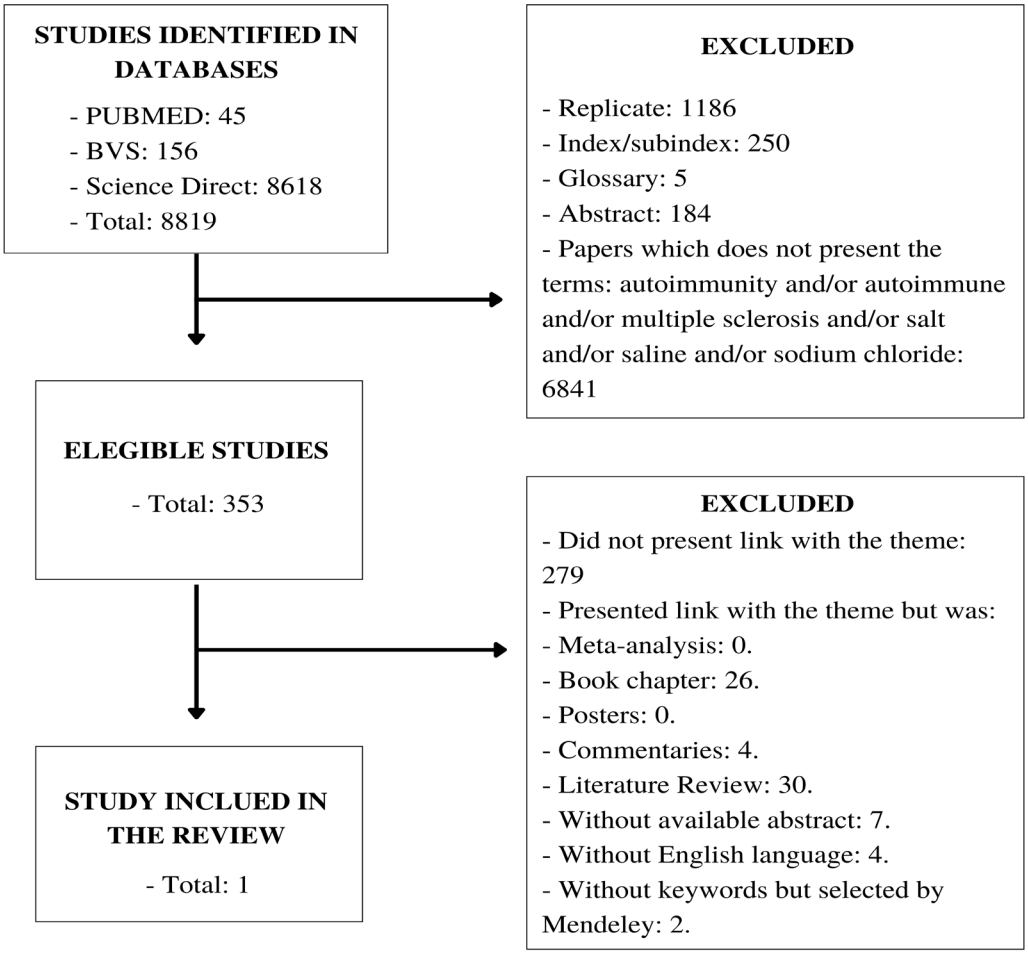

Figure 1. Mendeley Desktop® selection results.
Source: The authors.

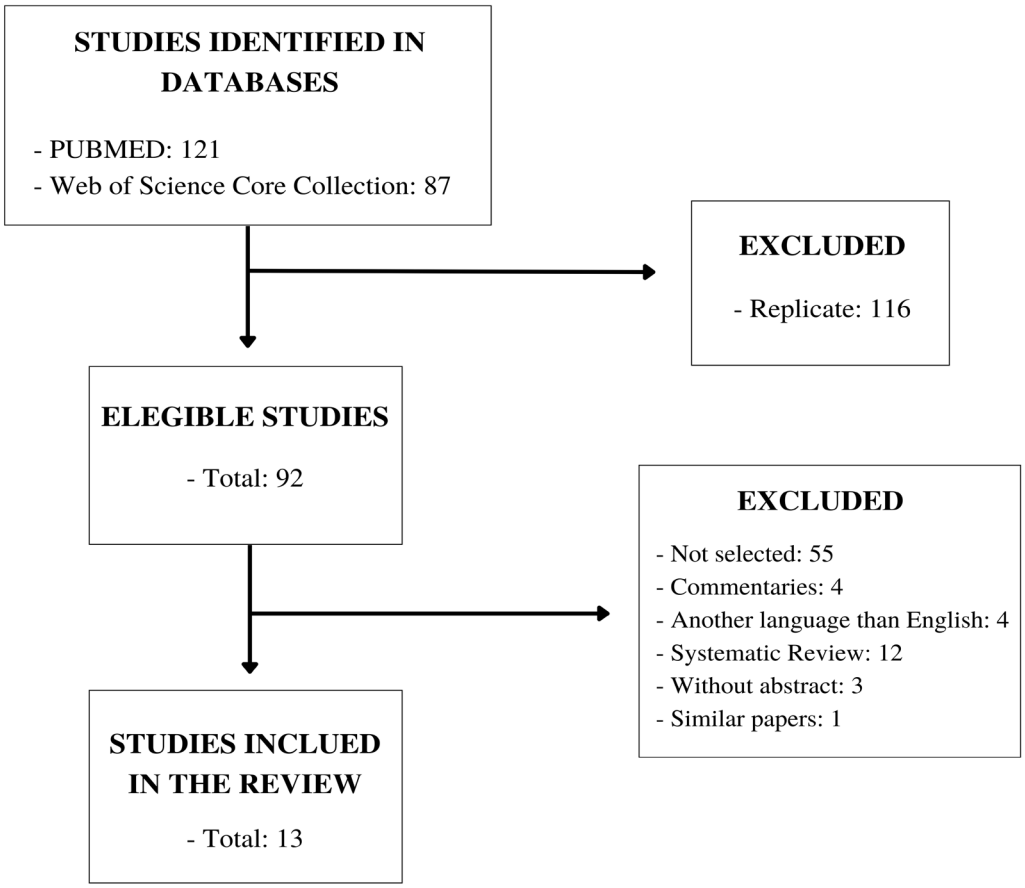

Figure 2. EndNote® selection results.
Source: The authors.

studies (Kleinewietfeld et al., 2013; Hernandez et al., 2015; Krementsov et al., 2015; Hucke et al., 2016; Jörg et al., 2016; Deng et al., 2017; Hammer et al., 2017), consider the measure in percentual and millimolar (mM). This choice is mostly related to the study type, once some papers applied specific diets and other food questionnaires for a valid sodium consumption analysis. Only two studies verified sodium eliminated in urine for investigation (Farez et al., 2014; Fitzgerald et al., 2017).

The duration time of these studies' analysis varied in years, five of them (Farez et al., 2014; McDonald et al., 2016; Nourbakhsh et al., 2016; Cortese et al., 2017; Fitzgerald et al., 2017; Chenard et al., 2019); in days and weeks in seven of them (Kleinewietfeld et al., 2013; Hernandez et al., 2015; Krementsov et al., 2015; Hucke et al., 2016; Jörg et al., 2016; Hammer et al., 2017; Chenard et al., 2019). There is a different system found by Deng et al. (2017), in which the author observed studies *in vivo* in months and *in vitro* with sodium distribution in analyzed cells in hours (Deng et al., 2017).

Effects of high concentration of salt on analyzed results

According to Table 1, it is observed that the relation between the physiopathology of MS and exaggerated salt consumption was negative in five studies, in a way that it excludes or does not conclude a correlation between salt consumption and MS. The other papers present a possibility, in that the diet full of sodium chloride can be related to changes of MS.

Initially, it is important to emphasize that the search terms used to find papers are extremely relevant, considering the differences between the Health Science Descriptors (HSD) and keywords. The descriptors have synonyms and a meaning, which embraces subjects and structures with different themes by order and relevance (Brandau; Monteiro & Braile, 2005).

After the analysis made from the research benchmark and its contents, it could be said the authors' majority support directly or inconclusively that the exposition to sodium chloride (cooking salt) can affect the MS disease course.

The papers, with human studies with a diet or a food questionnaire, showing the existence of a correlation between MS and the high consumption of cooking salt, use as standards values below or equal to 1.500mg/day (Arnett et al., 2019) or 2 g/day (WHO, 2016), as a daily limit of salt consumption, it allows an accuracy on studies, once they follow recent recommendations, this information is found on Table 1. In advance, the animal studies use percentual and values based on mouse diets, as identified in Table 2.

Although the facility of checking and applying sodium consumption in large studies employing questionnaires can also put aside the real consumption and metabolization of this element on body analysis (Cortese et al., 2017). It is important to remind factors like the number of notes the patient has according to the questionnaire, about meals, and other factors that can influence in assessments and measurements of the questionnaires (Bentley, 2006). It should be highlighted, also, comparative studies between questionnaires and the gathering of sodium excretion in 24 hours of urine present a difference between them, reporting the fact that questionnaires introduce an inferior variation compared to sodium intake real value (Bentley, 2006). A few studies verified sodium excretion in urine during analysis (Farez et al., 2014; Fitzgerald et al., 2017).

It is known that the sodium in urine means a reliable source of sodium intake, therefore, in a sample of adequate gathered urine, up to 90% ingested will be excreted in the urine, while there can be found variations according to year and ingested salt quantity (McLean, 2014). Tanaka's equation allowed the evaluation of larger populations and sodium excretion in 24 hours of urine (Tanaka et al., 2002; Farez et al., 2014; Fitzgerald et al., 2017).

Between the papers with experimental *in vitro* studies, all of them used the saline diet normal on mice treatment containing a NaCl percentual of 4% in feed and 1% in water, for realizing cells and its effects analysis in hypertonic solutions later (NaCl quantity varies according to each study and presented on Table 2). From these papers, which address the effects of hypertonic solutions in cells, we had evidence of the induction of cytokines production and immunostimulants (Hucke et al., 2016), as well the stimulation of a neuroinflammatory state, and Th17 cells proliferation (Jörg et al., 2016). Moreover, this Th cell polarization conjoined to the neuroinflammation corroborates for triggering autoimmune diseases (Hammer et al., 2017) as MS.

In contrast to *in vitro* studies, which presented the NaCl connection to Th17 cells induction, *in vivo* research denies the increase of Th17 and Th1 cells induced by hypersodic diets, expressing its function of increasing blood-brain barrier permeability, because this system corroborates to a neuroinflammatory state (Krementsov et al., 2015) commonly seen in autoimmune diseases.

According to the paper field branch approaching hypersodic diets, Deng et al. (2017) conclude that the high content of salt can develop astrocytes induction besides other cytokines, corroborating the assumptions made by Hernandez et al. (2015) which suggests the relation between diets with a high concentration of sodium, and with possible changes in intestinal microbiota, inducing pro-inflammatory responses in auxiliary lymphocytes T cells (CD4), contributing for autoimmune diseases development.

Besides the research relating hypersodic diets with autoimmune disease induction or a neuroinflammatory state, which corroborate diseases such as MS, a paper exposes the worsening of an inflammatory framework

in an already established disease. Farez et al. (2014) presented in their study an MS exacerbation in patients with average and high salt intake.

Differing from this branch, an author studied in this meta-analysis presented a randomized clinical study, questioning the influence of hypersodic diets on autoimmune diseases course, also, suggesting that salt ingestion does not influence the evolution or activity of diseases such as MS.

There is a standstill between two studies with the same research base, the analysis of sodium in urine and monitoring by magnetic resonance, but each one of them with a different conclusion, Farez et al. (2014) assume that hypersodic diets exacerbate the disease course, in contrast, Fitzgerald et al. (2017) deny this affirmation. These cohort studies have the capability of potentially confusing factors exclusion (as a variable diet in salt, during the study, the intestinal microbiota, stress, and other behaviors that can impact food preference). (Farez et al., 2014), allowing questions about the accuracy of the obtained conclusions by the studies.

Another important fact is the disparity between the results made *in vitro*, which means experimental, obtained by questionnaires, observational, or case-control studies.

Studies *in vitro* and *in vivo* were analyzed. Among *in vitro* studies, all of them were favorable to the connection between hypersodic solution and cytokines induction and an inflammatory state. Adversely to this conclusion, some *in vivo* studies denied in the majority (McDonald et al., 2016; Nourbakhsh et al., 2016; Cortese et al., 2017; Fitzgerald et al., 2017) the relation between high salt diets and autoimmune diseases, or were inconclusive about the subject as Chenard et al. (2019).

Through this disagreement between the study types and the respective results, considering the focus of this review, comparing studies and finding similarities and differences, it is questioned and evaluated which type of study evaluates in a trustworthy way the correlation between hypersodic diets and solutions, and their effects on cells, consequently, on the body, looking forward to autoimmune disease evolutions as MS.

Therefore, the studies used in this review present the prevail of experimental studies, considering the advantage of casualty in a demonstration related to an observational study (Bonita, Beaglehole & Kjellström, 2010). In this study, the relation between cause, hypersodic diet or solution, and the effect of inflammation were investigated.

Another advantage provided by experimental studies is the smaller interference of variables, considering the "environment" controlled, while observation studies depend on long duration, suffering external interferences (Bonita et al., 2010), it can modify the alimentary profile or the group study selection, insofar the observational studies analyzed in this review are in the same temporality of years and experimental studies just in weeks.

In addition to the salt quantity decrease, it is relevant to verify some authors put forward diets that include food with a lower sodium level as Chenard et al. (2019) study. In this, the Paleolithic-modified diet with selected food is an option for MS controlling. It is known that food influences on body's inflammatory state, as well as intermittent fasting which improved positively the inflammatory condition and the characteristic demyelination of the disease (Cabo & Mattson, 2019).

CONCLUSION

Based on the considerations, there is a larger number regarding favorable to sodium consumption and MS. However, the methodology diversity used makes the definitive conclusion difficult, because the experimental studies are, in most part, *in vitro* studies, turning it difficult to have a conclusion in human beings. Besides that, studies made on human beings demonstrate a substantial number of variables such as gender, age, methodology, and length of study, which difficult the standardization, and the accuracy of the results. Salt consumption, as demonstrated during this work, influences many aspects of the body, from the induction in an inflammatory state to the exacerbation of MS frames, but the evidence is still missing to prove how this mechanism reaches autoimmune diseases and how it could be controlled, what would change the disease course.

Table 1
Display of search data by authors according to the relation between Multiple Sclerosis physiopathology and the high intake of sodium chloride in human diet - Maringá, 2020.

Author/Year	- Study Type - Methodology - Population	- Population Age - Standard Value - Duration	Results
Chenard et al. (2019)	Wahls diet analysis comparative Unspecified Unspecified	Between 19 and 70 years or above - 1350 mg (1000 kcal) - 1350 mg (4184 kJ) Less than seven days	Inconclusive
Cortese et al. (2017)	Observational/Cohort - Use of Food Frequency Questionnaire (FFQ) - Human/ Female 80.920: NHS 94.511: NHS II	- 30 to 55 years (NHS) and 25 to 42 years (NHSII) Values change according to each applied questionnaire VR: 2.300 mg/day - 38 years	To exclude sodium consumption and the disease development
Farez et al. (2014)	- Observational/Cohort - Sodium in urine analysis and two groups MR - Human/Adult/Male and Female: 122 Group 1: 70 patients Group 2: 52 patients	- NA - RV: Basal intake (intake below 2 g/day), Average intake (2-4, 8 g/day) and above average (≥4,8 g / day) - Group 1 (Cohort): observed for 2 years	MS Exacerbation in patients with average and high salt intake
Fitzgerald et al. (2017)	- Randomized clinical study / Experimental Sodium in urine analysis and MR - Human/Adult (Europe and Canada) 468 patients	- NA - Average sodium excretion in urine from 24 hours identified as 3,7 g/day - 5 years	Suggests that the intake of salt does not have influence on course or activity of MS disease
McDonald et al. (2016)	- Human/Pediatric/Male and Female: - Study beginning: 631 patients - Study conclusion: 501 (170 cases and 331 monitoring) patients	- Cases: 15,2 years rate Monitoring: 14 rates - RV: 1000 mg/day 1 to 3 years; 1200 mg/day 4 to 8 years and 1500 mg/day 9 to 19 years. Obtained: Cases: 2044 mg/day (average) Monitoring:2030 mg/day (average) - Participants selected from 2011 to 2014	The study does not prove pediatric relation between salt consumption and MS development.
Nourbakhsh et al. (2016)	- Observational/Case-control - Questionnaire Block Kids Food Screener (NutritionQuest) - Human/Pediatric - 174 patients with CIS but started with 275.	- 15 years (average) RV per age: 1000 mg/day, 1 to 3 years of age;1200 mg/day 4 to 8 years; 1500 mg/day 9 to 19 years) Obtained:1975 mg rate. - Average observation: 1,8 years	Without relation between salt consumption and MS relapses
Deng et al. (2017)	- Experimental - Dosage *In vitro:* saline solution and control solution Diet *In vivo*: Diet normal (group 1) and HSD (group 2) for two mice groups - Animals/ Sprage-Dawley Mice in two groups: 1 and 2	- From 8 weeks to 1 year - *In vitro*: NaCl concentrated in 0/20/40/80 mM to NaCl 24h or 40mM for 6h / 12h / 24h. *In vivo*: Normal saline diet (water and food - group 1) and Concentrated diet of food with sodium in an 8% NaCl percentual and 1% saline solution (group 2) - *In vitro*: Unspecified -6h/12h/24h *In vivo:* Dietary from 30 to 60 days	The high content of salt can develop astrocytes induction besides other cytokines
Hammer et al. (2017)	- Experimental - Dosage: *In vitro*: Evaluate additional effects of saline solution in T CD4+ cells *in vitro* - Animals/Mice: Species unspecified.	- 10 to 12 weeks. - *In vivo:* Concentrated sodium food diet, containing NaCl in a percentual of 4% and tap water with a NaCl percentual of 1% - *In vitro:* NaCl in 40 mM compressions - *In vivo:* - 4 weeks diet - *In vitro:* - NA	Demonstrates an NaCl partially additive effect in cells Th polarization *in vitro* and in responses of Th cells in autoimmune neuroinflammation.
Hernandez et al. (2015)	- Experimental - Dosage: *In vitro.* Evaluate if the increase of NaCl *in vitro* sharply harms cells Treg function. - Animals/ Mice NSG male Species Unspecified	- 6 to 10 weeks of age. - *In vivo:* NSD, containing NaCl 0,4%. - *In vitro*: NaCl in 40 mM compressions *In vivo:* - 3 weeks diet - *In vitro:* - NA	Exposes the direct relation between a high salt cell and the deletion function losses of the cells Treg. Related to an induction of Tregs and IFNγ secretors. The work suggests in an inconclusive way the relation between diets with high concentration and changes in intestinal microbiota, inducing pro-inflammatory responses in CD4 effector cells and Treg channels, contributing for autoimmune diseases development.
Hucke et al. (2016)	- Experimental - Dosage: *In vitro*: Evaluate effects of saline solutions in macrophages derived from mice's' bone marrow. - Animals/ Mice	- 6 and 16 weeks - *In vivo:* NSD, containing NaCl 4% in food an 1% in water. - *In vitro:* NaCl in 20 mM or 40 mM compressions - *In vivo:* 1 week diet - *In vitro:* - NA	It shows that the addition of NaCl in macrophages provokes a strong pro-inflammatory effect characterized by the increase production of cytokines, increase of immunostimulants molecules and an increase of T cells proliferation. This macrophage phenotype induced by NaCl were accompanied by the increase of NF-kB and MAPK signaling pathways activation, aggravating SNC autoimmunity.

Continued

Table 1 Continued

Jörg et al. (2016)	- Experimental - Dosage: *In vitro*: Saline solution added to mice cells in order to defend a NaCl direct effect in cells Th17 in neuroinflammation - Animals/ Mice wild type	- 8 to 11 weeks of age. - *In vivo:* NSD, containing NaCl 4% in food an 1% in water. - *In vitro:* NaCl in 20, 40, or 80mM compressions - *In vivo:* 2 weeks diet - *In vitro:* 10 days.	It was shown that NaCl affects directly the neuroinflammation through Th17 cells, but it does not interfere in activation or maturation of dendritic cells.
Kleinewietfeld et al. (2013)	- Experimental - Dosage: *In vitro*: Evaluate saline solution effects in TH17 cells induction - Animals: Mice	- *In vivo:* NSD, containing NaCl 4% in food an 1% in water. - *In vitro*: NaCl in 10 mM compressions - *In vivo:* 1 week diet - *In vitro:* 12 days - *In vivo:* 1 week diet. - *In vitro:* 12 days	It was proven that small increases in NaCl concentrations are efficient for inflammatory cytokines stimulation as IL-17[a] in CD4 naive cells.
Krementsov et al. (2015)	- Experimental - Dosage: *In vitro*: 2 different genetic models of EAE chronic B6 disease and the type of SJL recurrent remission were evaluated with hypersodic food - Animals/ Mice wild type	- NA - *In vivo:* NSD, containing NaCl 4% in food an 1% in water. - *In vivo:* 3-to-4-week diet	Sodium enriched diets does not increase inflammatory responses by Th17 or Th1, by the way it presented a permeability increase of Blood Brain Barrier permeability.

Source: The authors.

Notes: RV: Reference Value; CIS: Clinically Isolated Syndrome; MS: Multiple Sclerosis; HSD: High Salt Diet; NA: Not Applicable.

Table 2

Display of search data by authors according to the relation between Multiple Sclerosis physiopathology and the high intake of sodium chloride in animal diet - Maringá, 2020.

Author/Year	- Study Type - Methodology - Population	- Population Age - Standard Value - Duration	Results
Deng et al. (2017)	- Experimental - Dosage *In vitro*: saline solution and control solution Diet: *In vivo* Normal diet (group 1) and HSD (group 2) for two mice groups - Animals/ Mice - Animals/ Sprage-Dawley Mice in two groups: 1 and 2	- From 8 weeks to 1 year - *In vitro*: NaCl in concentrated in 0/20/40/80 mM to NaCl 24h or 40mM for 6h / 12h / 24h. *In vivo*: Saline diet normal saline diet (water and food - group 1) and Concentrated diet of food with sodium in an 8% NaCl percentual and 1% saline solution (group 2) - *In vitro*: Unspecified - 6h/12h/24h *In vivo*: Dietary from 30 to 60 days	The high content of salt can develop astrocytes induction besides other cytokines
Hammer et al. (2017)	- Experimental Dosage: *In vitro:* Evaluate additional effects of saline solution in T CD4+ cells *in vitro* - Animals/Mice: Species unspecified.	- 10 to 12 weeks. - *In vivo:* Diet concentrated sodium food diet, containing NaCl in a percentual of 4% and tap water with a NaCl percentual of 1%. - *In vitro:* NaCl in 40 mM compressions - *In vivo:* - 4 weeks diet *In vitro:* NA	It demonstrates an NaCl partially additive effect in cells Th polarization *in vitro* and in responses of Th cells in autoimmune neuroinflammation.
Hernandez et al. (2015)	- Experimental - Dosage: *In vitro.* Evaluate if the increase of NaCl *in vitro* sharply harms cells Treg function. - Animals/ Mice NSG male. Species Unspecified	- 6 to 10 weeks of age. - *In vivo:* NSD, containing NaCl 0,4%. - *In vitro:* NaCl in 40 mM compressions - *In vivo:* - 3 weeks diet *In vitro:* NA	Exposes the direct relation between a rich diet in salt and the loss of suppression functions of Treg cells associated to INFγ secretors. The work suggests in an inconclusive way the relation between diets with high concentration and changes in intestinal microbiota, inducing pro-inflammatory responses in CD4 effector cells and T reg channels, contributing for autoimmune diseases development.
Hucke et al. (2016)	- Experimental - Dosage: *In vitro*: Evaluate effects of saline solutions in macrophages derived from mice's' bone marrow. - Animals/ Mice	- 6 and 16 weeks - *In vivo:* NSD, containing NaCl 4% in food an 1% in water. - *In vitro:* NaCl in NaCl in 20 mM or 40 mM compressions - *In vivo:* - 1 week diet - *In vitro:* - NA	It shows that the addition of NaCl in macrophages provokes a strong pro-inflammatory effect characterized by the increase production of cytokines, increase of immunostimulants molecules and an increase of T cells proliferation. This macrophage phenotype induced by NaCl were accompanied by the increase of NF-kB and MAPK signaling pathways activation, aggravating SNC autoimmunity.
Jörg et al. (2016)	- Experimental - Dosage: *In vitro*: Saline solution added to mice cells in order to defend a NaCl direct effect in cells Th17 in neuroinflammation - Animals/ Mice wild type	- 8 to 11 weeks of age. - *In vivo:* NSD, containing NaCl 4% in food an 1% in water. - *In vitro:* NaCl in NaCl in 20-, 40- or 80-mM compressions - *In vivo:* 2 weeks diet - *In vitro:* 10 days.	It was shown that NaCl affects directly the neuroinflammation through Th17 cells, but it does not interfere in activation or maturation of dendritic cells.

Continued

Table 2 Continued

Kleinewietfeld et al. (2013)	- Experimental - Dosage: *In vitro*: Evaluate saline solution effects in TH17 cells induction - Animals/Mice	- NA - *In vivo:* NSD, containing NaCl 4% in food an 1% in water. - *In vitro:* NaCl in 10 mM compressions - *In vivo:* 1 week diet - *In vitro:* 12 days	It was proven that small increases in NaCl concentrations are efficient for inflammatory cytokines stimulation as IL-17[a] in CD4 naive cells.
Krementsov et al. (2015)	- Experimental - Dosage: *In vitro*: 2 genetic models different from the disease: EAE chronic B6 disease and the type of SJL recurrent remission were evaluated with hypersodic food - Animals/ Mice wild type	- NA - *In vivo:* NSD, containing NaCl 4% in food an 1% in water. - *In vivo:* 3-to-4-week diet	Sodium enriched diets does not increase inflammatory responses by Th17 or Th1, by the way it presented a permeability increase of Blood Brain Barrier permeability.

Source: The authors.

Note RV: Reference Value; MS: Multiple Sclerosis; HSD: High Salt Diet; NA: Not Applicable.

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