Narrative review

Intermittent Fasting and Caloric Restriction as an Adjunctive Treatment in Alzheimer's Disease and Multiple Sclerosis

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Abstract
Alzheimer's disease and multiple sclerosis are neurodegenerative disorders with expensive and complex treatments aimed at reducing the progression of symptoms. However, due to the lack of adequate therapies and the possible adverse effects caused by first-line treatments, it's necessary to implement better complementary therapeutic approaches that do not produce major side effects and improve symptoms. Caloric restriction and intermittent fasting have been shown to be novel and beneficial strategies in neurodegenerative diseases, through immune, metabolic, and physiological mechanisms. To determine the use of intermittent fasting and caloric restriction as a new treatment in multiple sclerosis and Alzheimer's disease, a narrative review of original articles in both national and international scientific journals, in English and Spanish languages with no greater obsolescence than five years. The use of caloric restriction and intermittent fasting have generated positive changes, producing a decrease in pro-inflammatory states, oxidative stress, and aging. Approaches that modulate disease progression and improve cognitive function of adenosine monophosphate kinase, insulin-like growth factor, and sirtuin enzyme pathways are considered, generating a neuroprotective effect.

Keywords
Intermittent Fasting, Caloric Restriction, Multiple Sclerosis, Alzheimer Disease, Cognition.

Resumen
Las enfermedades de Alzheimer y esclerosis múltiple son neurodegenerativas, con tratamientos complejos y de costos elevados, orientados a disminuir la progresión de la sintomatología. Sin embargo, a causa de la falta de terapias adecuadas y de los posibles efectos adversos ocasionados por tratamientos de primera línea, es necesario implementar mejores abordajes terapéuticos complementarios que no produzcan mayores efectos secundarios y mejoren la sintomatología de dichas patologías. La restricción calórica y el ayuno intermitente han demostrado ser estrategias novedosas y beneficiosas en enfermedades neurodegenerativas, a través de mecanismos inmunitarios, metabólicos y fisiológicos. Con el objetivo de determinar el uso del ayuno intermitente y la restricción calórica como tratamiento coadyuvante en esclerosis múltiple y enfermedad de Alzheimer, se realizó una revisión narrativa de artículos originales en revistas científicas, en idiomas inglés y español, de 2018 a 2022. El uso de la restricción calórica y ayuno intermitente han generado cambios positivos produciendo disminución de estados proinflamatorios, estrés oxidativo y envejecimiento. Se consideran abordajes que modulan la progresión de la enfermedad y mejoran la función cognitiva por vías de señalización de monofosfato de adenosina cinasa, factor de crecimiento similar a la insulina y la enzima sirtuina, generando un efecto neuroprotector.

Palabras clave
Ayuno Intermitente, Restricción Calórica, Esclerosis Múltiple, Enfermedad de Alzheimer, Cognición.

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Ayuno intermitente y restricción calórica como tratamiento coadyuvante en enfermedad de Alzheimer y esclerosis múltiple

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Introduction

Neurodegenerative diseases such as multiple sclerosis (MS) and Alzheimer's disease (AD) are characterized by a progressive loss of neurons and white matter that can lead to brain atrophy and different types of disability. Both diseases represent a health problem, as their prevalence has been increasing, and their treatments are considered complex.[i]

It is estimated that a total of 2.8 million people are living with MS worldwide, i.e. 35.9 per 100 000 population.[ii] MS is considered one of the main causes of disability in young patients, and its diagnosis is usually in the fourth decade of life.[iii] Regarding AD, the average age at which diagnosis is established is 65 years, although its onset at a younger age is increasingly frequent.[iv] In addition, it has been shown that AD is the cause of 60 to 80 % of all cases of dementia worldwide. The World Health Organization establishes that Latin America and the Caribbean will be the most affected, reaching 7.6 million patients by 2030.[v]

There are several drugs approved for MS, interferons being the first line of therapy, which cause flu-like effects in most patients.[vi] For this reason, it becomes necessary to find therapeutic alternatives that do not entail major side effects and can improve the symptomatology of these patients.[vii] Different nutritional approaches have been currently described as neuroprotective strategies for neurodegenerative diseases, but their mechanism of action is still under study.[viii]

Caloric restriction (CR) and intermittent fasting (IF) have been proposed as adjuvant treatments. However, the majority of clinical trials in which they are implemented have focused on overweight, metabolically compromised, or middle-aged populations. Therefore, it is necessary to adequately assess the potential benefits of these nutritional approaches.[ix]

The use of ketogenic diets such as IF and CR have demonstrated certain benefits in neurodegenerative pathologies and have been proposed as a novel strategy to improve symptoms in these chronic diseases.[x,xi] The relevance of these diets is greater due to the multiple benefits observed in patients with different metabolic pathologies. These diets also have been shown to significantly reduce cardiometabolic risk.[xii] In addition, these nutritional interventions have the advantage of not presenting side effects in addition to those caused by conventional treatment and even reducing them.[xiii]

The relationship between caloric intake, diet quality, and meal frequency with the gut microbiota and its role in regulating cellular pathways in diseases such as AD and MS has been described.[xiv] This regulation is believed to positively impact these diseases by promoting normal aging and delaying disease progression.[xv,xvi]

Methodology

A narrative literature review article was prepared by searching for original and review articles of clinical and preclinical studies in international scientific journals in English and Spanish, in databases such as PubMed, Embase, and sites of international organizations related to the topic of interest. The search terms used were "Intermittent fasting", "Caloric restriction", "Multiple sclerosis", "Alzheimer disease", and "cognition"; Boolean operators (AND, OR, and NOT) were incorporated to limit the bibliographic search. Articles with obsolescence not older than five years of publication, from 2018 to 2022, were cited.

Nutritional interventions in neurodegenerative diseases have a promising approach because of their ease of use, the paucity of associated adverse effects, and the theoretical improvement posed by their appropriate use. However, further investigation of these intervention strategies in neurodegenerative diseases is needed. For this reason, the present work seeks to determine the use of intermittent fasting and caloric restriction as adjuvant treatments for Alzheimer's disease and multiple sclerosis.

Results

Overview of intermittent fasting and caloric restrict

Obesity and overweight are among the most studied health problems with more non-pharmacological therapeutic alternatives. Among the diets that have emerged from different studies are IF and CR. The common results of these diets are weight reduction, lower oxidative stress, and improved cardiovascular health.[xvii] Both diets are considered ketogenic; they produce ketones from fatty acids metabolized by a glucose deficit. However, certain mechanisms differentiate these diets and by which they may be beneficial.[xviii]

IF consists of a pattern of food intake consisting of two periods: one of them is fasting, where no food is ingested, only non-caloric beverages or water; the other one

consists of the time in which food intake is allowed in a controlled manner. There are different modalities of IF depending on the number of hours in which the fasting is performed. Unlike CR, there is no limit to the number of calories ingested, only the time in which they are consumed.[xix]

Fasting periods in IF can vary from 12 hours to a full day. One of the most commonly used methods is 24 hours fasting followed by a full day with a regular eating pattern.[xx] Another protocol that can be classified as IF is the 5:2 method, in which fasting is for one day twice each week and eating food on a regular basis for the remaining five days. The fasting can also be for a certain number of hours, such as 12, 16, or 18 hours each day, and for the rest of the hours, only two meals are taken. While fasting for a full day produces more ketones, all methods have beneficial health effects.[xxi]

In IF, stored fatty acids are converted to ketones, which become the main energy source of the brain. These begin to be produced after 12 hours of fasting, as glycogen is consumed in the liver by glucagon. After a period of IF, insulin levels decrease due to reduced glucose utilization, thus regulating metabolism and improving insulin resistance. This was observed by Sutton *et al.* in their study, which showed that after IF insulin function was improved and insulin peaks were reduced. This metabolic change is what leads to a lower inflammatory state and overall better life prognosis caused by autophagy, a process by which damaged proteins and organelles in cells are eliminated.[xxii]

CR is also considered a ketogenic diet. Its main objective is the reduction of total caloric intake, up to 30 % less, without falling into malnutrition. Although its protective effects on the cardiovascular system are not as well studied as in IF, it has been shown in preclinical studies in mice that CR has a positive effect on weight reduction and increased longevity.[xxiii] A study by Il'yasova *et al.* showed that after two years of CR, oxidative stress levels decreased significantly, concluding that it improves the quality and prognosis of life.[xxiv] The same was corroborated by Redman *et al.*, who observed that patients with CR produced a lower amount of cellular oxidation markers.[xxv]

In CR, autophagy is the primary mechanism that generates the intended benefits of this diet. However, in this case, it is produced by the deficit of acetyl-CoA that leads to the deacetylation of the damaged proteins, which subsequently produces their destruction. This leads to an increased production of acetyl-CoA, which does not come directly from the diet but instead produces energy in the form of ATP. In addition, studies by Most *et al.* have shown that, in healthy adults, CR decreases circulating levels of tumor necrosis factor-alpha and cardiometabolic risk factors.[xxvi]

The effect of both CR and AI on weight, diabetes, obesity, hypertension and even some types of cancer has been extensively studied. In addition, several researches point out that these ketogenic diets, carried out in a controlled way, can lead to increase the average lifespan and prevent different diseases.[xxvii] The potential benefits on the prevention and progression of cognitive disorders of CR and AI through metabolic as well as immune and neurological mechanisms have now been highlighted.[xxviii] Such benefits of CR and AI on Alzheimer's disease and multiple sclerosis, as well as the possible physiological mechanisms involved, are discussed below.

Metabolic and immunologic effect of intermittent fasting and caloric restriction

Nutritional interventions aimed at the production of ketone bodies have shown benefits in neurodegenerative diseases. As previously mentioned, both proposed diets produce ketones, which are valuable sources of energy during periods of glucose deficiency. There are studies with animal models that show that the memory of animals with ketogenic diet was better than those with normal diet, suggesting that these dietary approaches may be beneficial in diseases such as AD and MS.[xxix] The mechanisms by which the neuromodulation process is achieved are: decreased glycolysis, change in oxidative stress, increased signaling and number of mitochondria and decreased molecules involved in neuroinflammation.[xxx]

Neuroinflammation is a defense mechanism that initially protects the brain, removing pathogens; however, when it persists, it is part of the pathophysiology in certain diseases,[xxxi] where both the innate and acquired immune systems are involved. For example, in MS, the acquired immune system prevails due to the invasion of T and B cells that characterize the disease.[xxxii] In AD, its occurrence is related to innate immunity since several regulators of this pathway are genetic risk factors for the development of the disease, while acquired immunity participates in the progression.[xxxiii]

The progression of these diseases can be modulated by anti-inflammatory mechanisms related to metabolism. The gut-brain axis, which represents a bidirectional system

between the central nervous system (CNS) and the gastrointestinal system, regulates inflammation and protects against oxidative damage.[xxxiv] In patients who practice IF and CR, it has been related to greater enrichment of the microbiota, increasing the levels of bacteria, mainly from families such as Lactobacillaceae, Bacteroidaceae, and Prevotellaceae, related to anti-inflammatory mechanisms.[xxxv]

Cignerella *et al.* describe the importance of the gut-brain axis, microbiota, caloric restriction, and their relationship in the clinical improvement of the autoimmune encephalomyelitis (EAI) model of MS in mice. After presenting their results found by histology and cytometry, they determined that CR generates an increase in regulatory T cells, anti-oxidative processes, less infiltration of inflammatory cells, and improvement in demyelination; establishing that these changes are caused by the microbiota exposed to CR. To prove this, they transplanted this microbiota to unexposed mice. The results were similar: demyelination studied by myelin basic protein, axonal damage studied by SMI-32+ protein and inflammatory cytokines IL-12 and IFN-Y were lower in these mice.[xxxvi]

Nutritional interventions have been successful in decreasing lymphocyte infiltration into the spinal cord, resulting in reduced demyelination after two cycles of CR in mice. Bai *et al.* subjected mice with EAI to CR with a 33 % decrease in calories three days a week, which generated a neuroprotective process with a decrease and regression in the accumulation of TDC4+ and IFN-Y cells in the CNS. Likewise, the proliferation rate increased, and the expression of neurotrophic factors and remyelination markers improved, generating a benefit in the inflammatory response and recovery of tissue damaged by demyelination in the CNS.[xxxvii]

In 2022, Fitzgerald *et al.* conducted a clinical study involving 36 MS patients who were followed for eight weeks. Different interventions were performed using three comparison groups: one group with daily caloric restriction in which patients received 78 % of their total calories, seven days a week; the second group with intermittent caloric restriction 5:2, decreasing calories two days a week to 25 % of the total and the control group where they received 100 % of their calories seven days a week. Lymphocyte levels were studied by flow cytometry at weeks 0, 4, and 8 in the three groups. It was found that patients in the intermittent CR group had significant reductions in TCD8+ and Th1 effector cells, a decrease in memory T cells, and an increase in immature T cells.[xxxviii]

Continuous monitoring of neuronal injury is key to determining the recurrence or remission of MS, which can be determined by neurofilament chains, being a marker of acute damage.[xxxix] Bock *et al.* conducted a study exploring serum neurofilaments in MS patients, finding that ketogenic diets for a period of six months decreased these markers of inflammation.[xl] Aging, oxidative stress, and inflammatory response are factors that are part of the pathophysiology of Alzheimer's disease. CR and IF regulate the above by modulating deacetylation activities and the inflammatory response.[xli] The aging process is an important factor as age is inversely proportional to neurogenesis. However, CR has been shown to mitigate microglia activation, thus alleviating chronic inflammation and preserving neurogenesis longer.[xlii]

Physiological effects of intermittent fasting and caloric restriction on cognitive function

It has been shown that through IF, a metabolic change is initiated in which there is a preference for energy extraction through lipolysis. In other words, there is greater utilization of stored fat in the form of lipids, which are subsequently metabolized into ketones, generating signaling effects and regulation of transcription factors in the neurons of the brain.[xliii] As previously mentioned, IF and CR affect the microbiota-gut-brain axis, relating directly to cognitive function through neural, endocrine, and immune pathways.[xliv]

AD is pathologically characterized by the presence of β-amyloid plaques that lead to neuronal death, leading to a decrease in cognitive abilities, from mild cognitive impairment to dementia.[xlv] Ooi *et al.* conducted a study with a three-year follow-up in 99 patients with mild cognitive impairment, divided into three groups: patients who performed IF regularly, another group that practiced IF irregularly, and those who did not perform IF. They determined that regular IF improves cognitive function through ketogenesis since ketone bodies act as a source of energy and increase the survival of neurons under hypoxemia conditions. In addition, it is related to the reduction of DNA damage through the production of repair enzymes, improving cognitive impairment by 73 % in those who performed IA regularly, compared to 2.7 % in the group that did not perform it ($p < 0.05$).[xlvi]

CR and IF are equally associated with blocking the accumulation of β-amyloid

in neurons. In the study by Shut *et al.* conducted in groups of mice injected with amyloid β in the hippocampus, it was shown that when these nutritional approaches were performed, there was a reduction in oxidative stress and improvement of synaptic plasticity, which was related to the protection of memory impairment.[xlvii]

Currently, there are theories of delayed aging related to the signaling pathways of adenosine monophosphate kinase (AMPK), insulin-like growth factor, and the enzyme sirtuin (SIRT1). The mechanism of such delay has not been fully determined; however, Ma *et al.* propose that the AMPK pathway is the most important in the delay of aging. To verify this, they performed an experiment with mice that were intervened in different nutritional ways, in which they found that in mice subjected to CR, learning and memory were increased, which was accompanied by an increase in the expression of AMPK, thus associating this kinase with a neuroprotective effect.[xlviii]

Patients with MS clinically show manifestations of cognitive impairment, including deficits in information processing and attention, impaired information processing speed, impaired working and long-term memory, and verbal fluency.[xlix] Wingo *et al.*, in a pilot study with 12 patients who underwent IF for eight weeks, determined that cognitive function in patients with relapsing-remitting MS improved through reduced inflammation and activation of autophagy. Similarly, this study attributes the importance of conducting more clinical trials in patients to determine the effects of this nutritional approach since the existing ones are in the preclinical phase.[l]

Conclusion

Intermittent fasting and caloric restriction are approaches that modulate the progression of Alzheimer's disease and multiple sclerosis through metabolism-related anti-inflammatory mechanisms via the gut-brain axis. In addition, they regulate antioxidative processes and decrease the infiltration of inflammatory cells into the nervous system. Similarly, CR and IF have demonstrated benefits in cognitive function through the AMPK, insulin-like growth factor and sirtuin enzyme pathways, generating delayed aging and a neuroprotective effect. However, most of the research is still in the preclinical phase, and many of these studies highlight the importance of conducting trials in patients to adequately define the effects of these nutritional interventions.

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