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KETOGENIC DIET AND ITS POSSIBLE EFFECTS ON MULTIPLE SCLEROSIS: ANTI-INFLAMMATORY POTENTIAL, MITOCHONDRIAL FUNCTION AND MICROBIOTA

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Abstract

Multiple sclerosis affects 2.5 million people in the world. It is a chronic, inflammatory and neurodegenerative pathology of the central nervous system. The disease has genetic and environmental causes.

It is known that environmental factors are critical in activating the autoimmune response. Ketogenic diets, dietary regimens characterized by a reduced intake of carbohydrates (<20 grams per day), activate hepatic gluconeogenesis which provides glucose production starting from lipids and proteins. The ketone bodies, which are a by-product of gluconeogenesis, can determine relevant effects on multiple sclerosis.

In this work, starting from the available scientific literature, we will try to highlight the potential benefits induced by the ketogenic diet in multiple sclerosis.

Keywords: *Ketogenic Diet, Multiple Sclerosis, Mitochondria, Micorobiota.*

Introduction

Most multiple sclerosis (MS) patients start with a disease form characterized by an acute phase of activation followed by a partial or complete symptoms remission. In relapsing multiple sclerosis cases, acute episodes indicate autoimmunity activation phenomena that lead to a partial loss of myelin sheath in different areas of the central nervous system (optic nerve, brain, spinal cord). Inflammatory focal lesions cause signs and symptoms such as vision changes, weakness, numbness and tingling, intestinal and bladder disorders. Fatigue, depression and cognitive disorders are also frequently found in patients with multiple sclerosis [1]. Inflammatory and neurodegenerative phenomena play an important role in disease evolution. Neurodegeneration is associated with affected focal areas atrophy. Most people with multiple sclerosis (85-90%) debuts with relapsing form (MSRR). Only 10% of MS cases have since the onset of the disease, the progressive form with an early neurological decline (MSPP). People with relapsing multiple sclerosis (MSRR), more gradually over the years, experience neurodegenerative processes even in the absence of new inflammatory lesions (MSSP). Scientific research has confirmed a multifactorial genesis of multiple sclerosis. Genetic predisposition and environmental factors contribute to disease pathogenesis. Some environmental factors, identified as risk factors for multiple sclerosis are indicated below: low levels of vitamin D, sun exposure, smoking, and viral agents. Directly linked to the purpose of this work, obesity plays a well-known role as a risk factor. There is no doubt that diet represents a constant meeting possibility for the organism and environment. Accordingly, dietary factors may play an important role in disease controlling progression and symptoms management. Concerning multiple sclerosis pathophysiology, at the moment we do not have a completely clear picture. Considering the hypothesis of peripheral autoimmunity for multiple sclerosis, some studies have identified immune system loci linked to disease risk [1].

The demyelination process is associated with the reduction of oligodendrocyte precursor cells, loss of mature oligodendrocytes and infiltration of macrophages and T-cells [2-3].

From a morphological point of view, it is possible to trace how structural damage occurs in typical multiple sclerosis lesions in four different patterns. Pattern I and II are very similar to those found in autoimmune encephalomyelitis mediated by T-cells or T-cell plus antibody (schema II). Pattern III and IV show oligodendrocytes damage and degeneration, reminiscent of virus-induced demyelination or toxins [2]. Histological analysis of lesions highlights localized inflammation, demyelination, and neuronal and axonal injury in white and gray matter. A neurodegenerative model holds oxidative stress responsible for mitochondria dysfunction, chronic energy insufficiency, possible redistribution of ion channels and finally cellular damage or death [1].

Studies show that the early stages of MS development are largely driven by the inflammatory process and the inflammation itself while the progression of MS is mainly driven by mitochondrial dysfunction. Mitochondria appear irregular in their shape and structure accompanied by molecular and biochemical abnormalities. A study conducted on experimental autoimmune encephalitis (EAE) mouse models and on MS patients showed that alterations in mitochondrial DNA repair or, more generally, damage to mitochondrial DNA, atypical mitochondrial gene expression and altered enzyme activity of mitochondria are involved in development and progression of MS. In addition, an energy deficiency resulting from altered mitochondria, which in turn lead to an increase in ROS production, affects various metabolic pathways, causing cell damage, including greater demyelination and inflammation in neurons, glia and tissues that are affected by the SM [4].

Methods

Review of concepts.

Discussion

It is possible that ketogenic diets are able to act on the immune response and produce positive effects on patients with multiple sclerosis. Animal models confirm this hypothesis but sufficient data on

humans are still lacking. Obesity is a risk factor for multiple sclerosis and diet is a potentially modifiable factor that could affect the progression of the disease. A recent study shows a link between eating habits and degree of disability or severity of symptoms. An extensive cross-sectional study showed an association between dietary quality and an active lifestyle with less fatigue, depression, cognitive impairment and pain. The term ketogenic diet indicates a particular dietary model characterized by a higher lipid intake and low carbohydrate content. This dietary model can simulate (from a metabolic point of view) fasting state. In low-carbohydrate conditions, metabolism undergoes a shift towards energy production through beta-oxidation of fatty acids and the production of ketonic bodies. Concerning this work, it is not relevant to highlight the metabolic and physiological implications of ketosis but to indicate any of the possible essential mechanisms through which a ketogenic diet may determine beneficial effects on immunological, inflammatory and neurodegenerative components that influence the evolution of the disease. Ketogenic diets have demonstrated the capacity to reduce the formation of reactive oxygen species by acting on uncoupling proteins. Oxidative phosphorylation is known to generate ROS. It is also recognized that there is a correlation between ROS production and potential difference through the internal mitochondrial membrane. UCPs proteins act on the potential difference by facilitating the entry of protons into the mitochondrial matrix. Although uncoupling proteins could reduce ATP production in oxidative phosphorylation, the net effect of the phenomenon, as a result of the reduced production of ROS, is better mitochondrial energy efficiency. Ketone bodies, easily mobilized by blood, reach and pass the blood-brain barrier and act on the regulation of important signaling pathways involved in cellular antioxidant potential and increased production energy in the brain tissue. Beta-hydroxybutyrate and acetoacetate ketone bodies exhibit dependent dose inhibitory activity on different classes of HDAC histone deacetylase. Beta-hydroxybutyrate promotes histone H3 acetylation on lysine 9 and 14 and influences genes transcription regulated through FOXO3A. Among these genes are also those that lead to the expression of mitochondrial antioxidant enzymes superoxide dismutase and catalase. The ketogenic diet also acts on the activation of the NRF-2 pathway [5]. Recent animal and human studies have shown that ketogenic diets may reduce inflammatory parameters in both blood and cerebrospinal fluid. In a mouse model of experimental autoimmune encephalitis (EAE), the ketogenic diet produces reversion of motor disability, better learning, and memory, increased the volume of the hippocampus and remyelination of periventricular lesions. This effect has been related to the suppression of the production of inflammatory cytokines and the increase in neuronal repair processes [6]. The anti-inflammatory effect of this dietary model may be explained by inhibition of the NLRP3 inflammasome operated through beta-hydroxybutyrate independently of hunger-induced mechanisms such as AMPK, autophagy or inhibition of the glycolytic pathway [5]. KD has shown, due to its reduced amount of calories and carbohydrates, a neuroprotective effect demonstrating a high capacity to reduce ROS production in the brain, decrease inflammatory and pro-apoptotic activities, improve mitochondrial functions and increase the expression of the molecular chaperones which will prevent the aggregation of polypeptides, generating complexes that could be toxic. The caloric restriction dictated by KD allows to increase the levels of neuroprotective factors such as some neurotrophins such as the brain-derived neurotrophic factor (BDNF), or neurotrophin-3-NT-3 and the neuritrophic factor derived from the glial cell line (GDNF). It has been noted, also, that the anti-inflammatory effect can reduce the levels of the main component of the inflammatory process represented by NFKB, blocking the synthesis of certain interleukins (such as IL1β, IL2, IL4 and IL6), tumor necrosis factor (TNF) and suppressing the activity of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) [7].

Another recent study shows that a ketogenic diet o caloric restriction may inhibit systemic expression of some key enzymes such as COX1, COX2, and ALOX5 involved in pro-inflammatory eicosanoid biosynthesis. The expression of COX1 and COX2 in human peripheral lymphocytes is reduced

by ketogenic diets. This data may explain the beneficial effects experienced in patients with multiple sclerosis. The potential mechanisms by which ketogenic diets may reduce COX/LOX gene expression are not fully understood. It is likely that during the initial phase of mitochondrial adaptation to the ketogenic diet, ROS is involved in regulating gene expression of many important enzymes [2]. In a pilot study on the effects of a particular ketogenic diet (MAD) on twenty patients with relapsing-remitting multiple sclerosis, there was a positive effect on the sense of fatigue, depression, and weight. Observance of the maintenance of the dietary regimen was verified through daily urine tests. After a six-month period, it was possible to observe a reduction in body fat and BMI ($p< 0.0001$), a recovery in the score of fatigue ($p = 0.002$) and depression ($p< 0.0001$). Leptin detection, another inflammatory parameter, was also significantly reduced after three months ($p< 00001$) [3]. It is evident, from the amount of scientific literature produced, the importance of the role of the microbiota in the state of health and different pathologies. The study of the microbial community present at the intestinal level both at the qualitative and quantitative level is fundamental to understand the role of this complex biome and its interaction with the host through the production of molecules of energy value and regulation of important functions in humans. The human microbiota consists of microorganisms belonging to the Bacteria, Archaea and Eukarya. The new technologies available for genetic material sequencing (NGS) and the evolution of bioinformatics systems for data analysis, provided us with the tools suitable for assessing the qualitative and quantitative composition of the microbiota. The role of food and especially dietary fiber is important in microbiota modulation in terms of species diversity. The fibers can be degraded and fermented with the production of SCFA (short-chain fatty acids). These important compounds provide energy to human enterocytes and function as signal molecules in host relationships. A diet rich in sugars and fats but deficient in dietary fiber, modulates the microbiota in inflammatory mode by inducing metabolism to produce harmful substances. Cellulose, hemicellulose, pectins and resistant starch can be metabolized with butyrate, propionate and acetate production that, in addition to the energy function, play a role in regulating the immune system and inflammatory processes. Although ketogenic diets are increasingly used in the treatment of various pathologies, few is known about its possible impact on the intestinal microbiota [6]. Few experimental studies are currently available on the effect of VLCKD diets on the gut microbiota. Referring to multiple sclerosis, one study highlighted the role of a VLCKD, a particular type of low-calorie ketogenic diet, on microbiota. [8-9] Patients with multiple sclerosis are known to have damage to the fermentative function of the colon. In these dysbiotic cases, the production of SCFA is compromised and increases the formation of harmful molecules with a negative health impact. The VLCKD diet was able to fully recover the fermentative function of the microbiota in the colon. This was achieved through two successive phases. The first showed a significant reduction in microbial diversity and quantity, while in the second, which lasted 23-24 weeks, a recovery of the baseline state and subsequently a significant overcoming of that state was noted [9].

The KD has demonstrated the ability to inhibit the NF-kB inflammatory pathway, decrease oxidative stress, and improve mitochondrial function and biogenesis, emerging as a plausible dietary approach in treating neurodegeneration associated with RRMS [10]. In MS mouse models a ketogenetic dietetic regimen showed improvements in both cognition and physical function suppressing inflammatory markers [11].

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