Is the Timing of Energy Restriction More Crucial than Calorie Intake for Individuals with Multiple Sclerosis?

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Introduction

The ongoing SARS-CoV-2 pandemic has had a profound global impact, both in terms of public health and the socio-economic landscape. In response to this crisis, health authorities worldwide have taken significant measures, with one of the most consequential being the widespread vaccination campaign.

This mass vaccination effort, aimed at combating the pandemic, has been implemented using newly approved vaccines. However, due to the limited real-life experience with these vaccines, concerns have arisen regarding their safety. Particularly, individuals with chronic autoimmune conditions such as Multiple Sclerosis (MS) have expressed apprehension, fearing potential adverse effects stemming from abnormal immune responses triggered by the vaccination.

Reports of MS relapses following SARS-CoV-2 vaccination have been documented, adding to the anxieties surrounding the vaccines. Nonetheless, multiple studies conducted across various regions, including Europe and early-starting vaccination countries, have yielded reassuring findings about the safety of the SARS-CoV-2 vaccines in MS patients [1,2].

Multiple Sclerosis (MS) is a Central Nervous System (CNS) disorder that stems from an autoimmune and degenerative process. Its hallmark features include focal neurological deficits, which result from inflammatory demyelinating lesions in the CNS. This complex condition arises from a combination of genetic and environmental factors, making it a multifactorial disease.

Among the various factors that contribute to the risk of developing MS, having a positive family history of the disease stands out as the most influential. Additionally, certain environmental determinants can modify an individual's risk, such as prior infection with the Epstein-Barr Virus (EBV), vitamin D deficiency, childhood obesity, and smoking [3].

Recent research highlights the role of diet in the risk and progression of MS. Studies indicate that women who are overweight or obese during early adulthood (18-20 years old) face a 2-2.25 times higher risk of developing MS compared to those with a normal Body Mass Index (BMI). These findings emphasize the significance of maintaining a healthy weight in the context of MS susceptibility [4].

Both chronic Energy Restriction (ER) and Intermittent Energy Restriction (IER) have shown promise in protecting against autoimmune demyelination in animal models of Multiple Sclerosis (MS). In studies conducted on mice and rats, chronic ER has been found to result in an increase in endogenous corticosterone levels, a decrease in pro-inflammatory cytokines like IFN-g and IL-6, and modulation of adipokine levels such as leptin and adiponectin. Additionally, it has been observed to influence the composition of the gut microbiome [5].

Researchers have also explored the potential benefits of ER in people with MS (pwMS). Chronic ER has proven to be safe, feasible, and has shown to improve mood and quality of life measures in pwMS. In a randomized trial comparing 15 days of IER with a normal diet in 16 pwMS undergoing corticosteroid treatment for MS relapses, IER was well tolerated and led to a reduction in leptin levels without altering adiponectin levels [6,7]. These findings suggest that both chronic ER and IER could be valuable approaches for managing MS and warrant further investigation.

In a recent publication in eBiomedicine, Fitzgerald et al. conducted a study to investigate the impact of either chronic or intermittent Energy Restriction (ER) on immune and metabolic biomarkers in individuals with multiple sclerosis (pwMS). The study involved thirty-six pwMS who were randomly assigned to receive one of three diets: a control diet (100% calorie needs), daily ER (providing 78% of calorie needs), or intermittent ER (providing 100% calorie needs for 5 days a week and only 25% for 2 days a week). Out of the participants, 31 successfully completed the study (11 in the intermittent ER group, 11 in the daily ER group, and 9 in the control group) [8,9].

Although the study sample was relatively small, it yielded several noteworthy findings that contribute to our understanding of ER in pwMS. Firstly, this study is the first to compare the effects of intermittent ER to chronic ER in pwMS through a randomized approach. Despite similar outcomes in terms of weight loss and weekly calorie intake, the two ER diets had distinct effects on circulating immune cells. Notably, pwMS who were assigned to the intermittent ER group experienced a significant reduction in effector memory and Th1 T cell subsets, accompanied by a proportional increase in nayve subsets. No such changes were observed in the daily ER group. Secondly, this study represents the first of its kind to describe the impact of ER on the plasma metabolome in pwMS. The metabolome analysis revealed a general increase in acyl carnitine metabolism for both ER diets, as well as significant changes in phosphatidylethanolamine and plasmalogens. Once again, the observed changes were more pronounced in the intermittent ER group compared to the chronic ER group. These findings contribute valuable insights into the effects of ER on immune and metabolic markers in pwMS and warrant further investigation.

Despite the numerous systemic benefits of daily Energy Restriction (ER), it can be challenging for many individuals to adhere to. As an alternative, intermittent ER has long been proposed as a more practical and feasible option. However, the comparison between the two regimens in individuals with multiple sclerosis (pwMS) has been limited, leaving the question of their relative effects unanswered. In this paper, Fitzgerald and colleagues shed light on this matter, reporting that intermittent ER (IER) has more profound effects on both the metabolome and the immune system compared to daily ER in pwMS [10].

The positive impact of IER on brain health has been attributed to the alternating periods of negative and positive energy balance, leading to an intermittent metabolic switch from glucose to fatty acids and ketones as the primary fuel source for cells. The data from metabolome studies further confirmed that the IER group showed more significant alterations in metabolites related to fatty acid use compared to individuals on a chronic ER regimen.

While more research is necessary to fully understand the underlying mechanisms behind the beneficial effects of ER in pwMS and other neuro-inflammatory diseases, these findings suggest that IER may not only be more feasible but also more effective in reducing neuro-inflammation and preventing neurodegeneration compared to daily ER. In the future, an IER

approach could potentially serve as a valuable complementary therapeutic intervention to enhance the effects of Disease-Modifying Therapies (DMTs).

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