Energy restriction in people with multiple sclerosis: Is time more important than calories?

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Food has been one of the major evolutive driving forces for both humans and animals.[1] Our ancestors were used to strenuous physical exercise to obtain food, followed by periods of fasting. As a consequence, evolution favored individuals whose motor and cognitive skills functioned well during food scarcity.[1] The cognitive and physical benefits of fasting have been recognized for centuries, as demonstrated by the presence of prolonged periods in which people would refrain from eating in many religious cultures across the world. Intermittent energy restriction (IER) has been demonstrated to reduce neuroinflammation, enhance synaptic plasticity and promotes neuronal survival.[1]

Multiple sclerosis (MS) is an autoimmune and degenerative disease of the central nervous system (CNS). It's characterized by episodes of focal neurologic deficits, reflecting inflammatory demyelinating lesions in the CNS.[2] MS is a multifactorial disease arising from a complex interplay between genetic and environmental factors.[3] The strongest risk factor for MS is positive family history, while environmental determinants that could modify an individual risk include: Epstein-Barr virus (EBV) infection, vitamin D deficiency, childhood obesity and smoking.[3] A growing body of evidences suggest the importance of dietary factors in MS risk and disease course.[4] Women who are overweight or obese at the age of 18-20 years have a 2-2.25-fold higher risk of MS compared to women with a BMI within a normal range.[3]

Both chronic and IER have been demonstrated to protect against autoimmune demyelination in animal models of MS.[5,6] The effects of chronic ER in mice and rats include the increase in endogenous corticosterone, the decrease in pro-inflammatory cytokines, such as IFN-γ and IL-6, the modulation of adipokine levels, such as leptin and adiponectin, and of the gut microbiome composition.[5–7] Several studies have focused on potential beneficial effects of ER in people with MS (pwMS). Chronic ER has been demonstrated to be safe and feasible and to improve mood and quality of life measures in pwMS.[8] In a randomized trial of 15 days of IER versus normal diet in 16 pwMS being treated with corticosteroids for MS relapses, IER was well tolerated and reduced leptin without altering adiponectin levels.[7]

In a recent issue of *eBiomedicine* Fitzgerald et al., explored the effect of either a chronic or an intermittent ER on immune and metabolic biomarkers in pwMS. Thirty-six pwMS were randomized to receive a control diet (100% calorie needs), daily ER (78% of calorie need) or intermittent ER (100% calorie needs 5 days a week and 25% 2 days a week).[9] Thirty-one out of 36 participants finished the study (11 in the intermittent CR, 11 in the daily CR and 9 in the control group). Though the study sample was relatively small, this study exhibits a number of significant novelties that impact our knowledge about ER in pwMS. Firstly, this is the first randomized study comparing the effect of IER to chronic ER in pwMS. Despite being no different in terms of weight loss and weekly calorie uptake, the two ER diets show different effects on circulating immune cells. Notably, pwMS randomized to the intermittent ER group showed a significant reduction in effector memory and Th1 T cell subsets and a proportional increase in naÿve subsets. No changes were observed in the daily ER group. Secondly, this is the first study to describe the effect of ER on the plasma metabolome in pwMS. The metabolome analysis revealed a general increased in acyl carnitine metabolism in both ER diet and significant changes in phosphatidylethanolamine and plasmalogens. Again, the observed changes were more significant for the intermittent compared to the chronic ER group.[9]

Despite its systemic beneficial effects, daily ER may be difficult to undertake, for most people. Intermittent ER has long been proposed as a valuable and practically more feasible substitute. However, studies comparing the two regimens in pwMS were so far limited and the question about the comparability of their effects remained unanswered. In this paper, Fitzgerald and colleagues, reported how IER has more profound effects on the metabolome and the immune system compared to daily ER in pwMS.[9] The beneficial effects of IER on brain health have been linked to the alternation of periods of negative and positive energy balance, resulting in an intermittent metabolic switch from glucose to fatty acids and ketones as the major fuel source for cells.[10] Data from the metabolome studies confirmed that in the IER group alteration of metabolites

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linked to fatty acid use is more profound compared to people in chronic ER.

More studies are needed to unravel the mechanisms underlying the beneficial effects of ER in pwMS and other neuroinflammatory diseases. However, these data suggest that an IER might be not only more feasible, but also more effective at reducing neuroinflammation and preventing neurodegeneration compared to daily ER. In the future, a feasible dietary intervention might become a useful complementary therapeutic approach to enhance the effect of disease modifying therapies (DMTs).

Contributors

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Declaration of interests

All authors have no conflict of interests to disclose.

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