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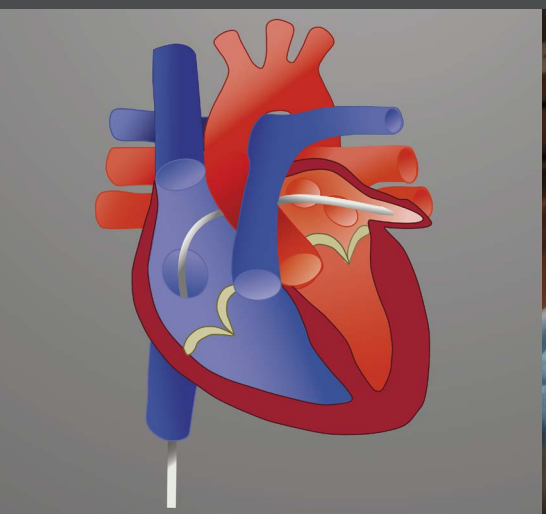

Virginia Mason Franciscan Health™

Intermittent Fasting

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INTRODUCTION

Based on nutritional data from the National Health and Nutrition Examination Survey (NHANES) from 2017 to 2020, 41.9% of U.S. adults are obese.[1] Obesity is associated with heart disease, stroke, and type 2 diabetes, which are among the leading causes of premature death in the United States.[2] In addition, obesity has been associated with certain types of cancer, including breast cancer, colon cancer, adenocarcinoma of the esophagus, liver, pancreatic and gallbladder cancer, thyroid cancer, ovarian cancer, and multiple myeloma.[3]

In conjunction with the rising rates of obesity, over the past several decades, Americans have begun to eat more frequently. In the 1970s, the majority of children ate 3 meals per day without snacks, while by 2004 Americans were eating on average 5 meals per day.[4] In 2015, one study found that U.S. citizens were eating approximately 10 times per day, from about 8 am to 11 pm, equivalent to an eating window of 15 hours per day.[5] Although many factors may be contributing to the rising rates of obesity, including an increase in sedentary lifestyles and a decrease in the nutritional quality of food consumed, increased meal frequency may also be an important consideration.

Intermittent fasting, otherwise known as time-restricted eating, is currently one of the most popular weight-loss strategies used by U.S. adults according to the International Food Information Foundation.[6] Patients favor intermittent fasting because weight loss is perceived as similar to traditional "diets" using daily caloric restriction but easier to maintain. Amidst the medical community, interest in fasting began in 1997, when Weindruch published an article in the New England Journal of Medicine describing the fact that caloric restriction extended the lifespan of animals, possibly through a drop in free radical generation.[7]

BACKGROUND

Over billions of years, during times of scarce energetic resources, prokaryotes developed cellular mechanisms which allowed them to survive while avoiding age-dependent damage which could threaten their fitness.[8] For example, under caloric restriction, bacteria increase their lifespan from about 36 hours to 84 hours, worms from about 25 to 40 days, mice from about 120 weeks to 200 weeks.[7] In addition, based on meta-analyses spanning from 1934 to 2012, caloric restriction increases lifespan from 14% to 47% in rats and 4% to 27% in mice, depending on strain and sex.[9] With alternate-day feeding, the average lifespan in rats can increase as much as 80%, depending on gender, age, diet, and genetics.[10]

Interestingly, it has been observed that rodents placed on caloric restriction tend to eat all their food within a short period of time and then spend the rest of the day fasting. As a result, recently, researchers have questioned whether the increase of lifespan seen with caloric restriction is related to fasting rather than simply caloric restriction.

DEFINITIONS

In research, daily caloric restriction – which many patients refer to as "dieting" – is defined as reducing daily caloric intake by

Compared to daily caloric restriction, intermittent fasting may preserve lean body mass and resting energy expenditure. Credit: Monkik/iStockphoto

Table 1. Definitions

Daily Caloric Restriction*
Reduce calories 20-40% but maintain meal frequency
Fasting
No or minimal amounts of calories for a period of time
Traditionally 12 hours – 3 weeks
Intermittent Fasting
Switching between eating and fasting on a recurring schedule
Examples include periodic fasting, alternate day fasting & time-restricted eating
Starvation
Chronic nutritional insufficiency from extreme fasting
Results in degeneration and death

* Note: daily caloric restriction ("dieting"), fasting, intermittent fasting and starvation all can result in caloric restriction. However, with daily caloric restriction, meal frequency is maintained. In starvation, the caloric restriction is so extreme, it results in degeneration.

Table 2. Types of Intermittent Fasting

Daily Time Restricted Eating • 14 hours fasting, 10-hour eating window • 16 hours fasting, 8-hour eating window • 18 hours fasting, 6-hour eating window
Alternate Day Fasting • 1 day fasting, 1 day in which eating permitted
Periodic Fasting (5:2 Fasting) • 2 days fasting, 5 days in which eating permitted

20% to 40% while maintaining meal frequency **(Table 1)**. Fasting describes a state when one does not consume calories for a period of time. Traditionally, fasting has been done as part of religious practice in many cultures around the globe, and fasting in this context is usually done for a period of 12 hours to 3 weeks.

Intermittent fasting refers to the practice of switching between eating and fasting on a recurring schedule. There are several types of intermittent fasting (**Table 2**). Alternate day fasting means that one fasts for 24 hours every other day. Periodic fasting is often used to refer to 5:2 fasting, in which fasting occurs for 2 days of the week, and eating is permitted for the other 5 days of the week. Time-restricted eating means that one is fasting for a regular period of time each day. Common examples include a 16:8-hour schedule or a 14:10-hour schedule. In the former, one would eat within an 8-hour window and fast for the rest of the day, while in the latter, one would eat within a 10-hour period, and fast for the remaining 14 hours of the day. Starvation is an extreme level of fasting which results in chronic nutritional deficiency, degeneration, and death.

Daily caloric restriction, fasting, and intermittent fasting all tend to result in caloric restriction. The difference is that with daily caloric restriction, one maintains meal frequency, while with intermittent fasting or fasting, meal frequency is restricted.

PHYSIOLOGY

During fasting, glycogen in the liver depletes over a 12-to-24-hour period, depending on activity level. As glycogen stores decrease, the body begins to break down fat for fuel into fatty acids, which are converted in the liver to ketone bodies. On average, ketones begin to occur at about 8 to 12 hours, by 24 hours of fasting, ketone levels can reach 0.2–0.5 mmol level, and by 48 hours, ketone levels are approximately 1-2 mmol.[11,12]

Although ketones serve as fuel for the body, they are also important signaling molecules which affect cell and organ function. For example, when beta hydroxybutyrate (BHB) enters mitochondria, the electron transport chain decreases its generation of superoxide radicals.[13] In addition, BHB increases the NADPH generated by the Krebs cycle, which helps to generate reduced forms of glutathione, vitamin C, and vitamin E.[14,15] Effectively, BHB protects the cell by decreasing oxidative stress.

In mammals, fasting shrinks the size of all organs except the brain and the testes.[6] From an evolutionary standpoint, it makes sense that there would be a high demand for excellent cognitive function when animals are hungry and hunting for food. Alternate day fasting in rodents improves learning and memory, synaptic plasticity, and behavioral tests of motor and sensory function.[16,17]

In the brain, BHB demonstrates several potential neurocognitive benefits. It binds to hydroxycarboxylic acid receptor 2 (HCAR2) in the brain, leading to a decrease in nuclear factor kappa beta (NFkB), which decreases neuroinflammation.[12] It also increases generation of sirtuin 1 (SIRT1), a deacetylase which has been associated with health and longevity benefits.[12] SIRT1 increases recycling of damaged mitochondria, increases biogenesis of mitochondria, and protects against apoptosis of neurons.[18,19] BHB also increases brain derived neurotrophic factor (BDNF), which has been shown to promote neuron growth, learning, memory, synaptic plasticity, and protects against Alzheimer's disease in animals.[19] It also improves parasympathetic tone, which leads to improved gut motility, and lower blood pressure – similar to what is seen with routine exercise.[20]

Fasting and caloric restriction improve autophagy.[21] Autophagy refers to a natural process by which the body recycles old cells and cell components – such as beta amyloid in the brain - for energy. Oshumi was awarded the 2016 Nobel Prize in Physiology and Medicine for research on autophagy and described the link between impaired autophagy and diseases including neurodegenerative disorders such as Alzheimer's and Parkinson's, ophthalmologic issues, myopathies, autoimmune diseases including systemic lupus, and cancer.[22] Fasting has been explored in research for some of these conditions because of its ability to support tissue repair via autophagy.[23,24]

With fasting, the body must oscillate between the glucose-dependent fed state and the ketone-dependent fasting state. This phenomenon is known as "metabolic switching."[25] Stress resilience refers to the body's capacity to accomplish metabolic switching with greater ease. During the fed state, the body activates the mTOR pathway, which leads to increased synthesis of proteins and lipids, and an anabolic state of growth and synthesis. In contrast, during the fasting state, the mTOR pathway is inhibited, which leads to global inhibition of protein synthesis, recycling of dysfunctional proteins by autophagy, DNA repair, and a decrease in inflammation.[26] Repeated metabolic switching, with consequent increase in stress resilience, has been shown to improve overall insulin sensitivity and lipid metabolism while reducing visceral adiposity, inflammation, and blood pressure.[24] This may be similar to exercise, in which the body repeatedly undergoes physiologic stress under calculated conditions - such as an increase in heart rate and blood pressure - which then over time leads to improved metabolism and resilience.

In summary, fasting improves insulin sensitivity and glucose metabolism. It has been shown to improve antioxidant regeneration, increase autophagy, and drop inflammation. Fasting is thought to be neuroprotective via several different mechanisms, including neuron growth and mitochondrial biogenesis, and it has also been shown to improve parasympathetic tone, with an improvement in blood pressure, resting heart rate, and gut motility. In addition, fasting allows the body to spend time in repair and autophagy, and balances the growth and anabolic processes of the fed state.

COMPARING DAILY CALORIC RESTRICTION TO FASTING

Both daily caloric restriction ("dieting") and fasting restrict calories; the difference is in the eating window. Thus, researchers have questioned if the benefits of fasting are simply related to caloric restriction, or to fasting itself.

One key difference between daily caloric restriction and fasting lies in that with fasting, metabolic switching occurs. As noted above, repeated metabolic switching leads to stress resilience which improves insulin sensitivity and lipid metabolism while reducing visceral adiposity, inflammation, and blood pressure. In addition, although daily caloric restriction and fasting both result in weight loss, some studies suggest that fasting preserves lean body mass while daily caloric restriction does not. One review comparing alternate-day fasting with daily caloric restriction of 15% to 60% found that an equivalent weight loss and fat mass loss with both interventions, but with alternate-day fasting, participants preserved more of their lean body mass.[27] Another review comparing time-restricted eating with daily caloric restriction also found that both interventions resulted in similar amounts of weight loss and fat mass loss, while maintaining lean body mass.[28] Lean body mass is important to protecting the body's capacity to burn calories at rest, also known as the "resting energy expenditure" (REE). If REE drops when a patient is losing weight, this can contribute to a plateau of weight loss.[29] Because fasting may help maintain lean body mass, it may be more effective in avoiding the plateau that often occurs with weight loss regimens. In addition, increases in lean body mass improve bone mass, which decreases risk for osteoporosis.

Is Timing of Meals Important?

In terms of metabolic effects, timing of meals may be as important as the type of meal we eat. One study supervised every meal for 5 weeks for two groups of prediabetic men.[30] Each group received the same meals; only the timing differed. One group ate 3 meals within a 12-hour window, between 8 am to 8 pm, and the other ate the same number of meals and calories in a 6-hour window, between 8 am to 2 pm. Early time-restricted eating resulted in a large mean drop in insulin levels by about 26 mU/L, and mean insulin levels remained 25% lower even in the 7-week washout period, with those with higher baseline levels having greater decrease. Blood pressure also decreased in the time-restricted eating group by about -11/10 mm Hg, as well as 8-isoprostane, a measure of oxidative stress. In addition, men in the time-restricted eating group self-reported decreased appetite in the evenings. Another study compared two groups of women with metabolic syndrome and a bone mass index (BMI) of 32 or greater.[31] Both groups ate 1400 kcal/day, but one group ate 700 kcal for breakfast while the other, 700 kcal for dinner. Women who ate 50% of their calories for breakfast had 2.5-fold drop in waist circumference and visceral fat loss, 33% drop in triglycerides, and the area under the curve for insulin response was 25% lower.

In summary, timing of meals may be just as important as type and amount of food for weight loss. Studies suggest that eating the same meal at dinner instead of at breakfast can increase the insulin response to food by approximately 25-50%.[32,33] Having a greater insulin response to food increases hunger, perceived sweetness of food, and food intake.[34] Higher insulin levels also increase adipose tissue growth and lead to weight gain. Thus, the ideal window for weight loss with daily

time-restricted eating would ideally include the morning and end early in the day, such as from 8 am to 2 pm.

CLINICAL APPLICATIONS

Clinical studies on the role fasting for cognitive function in humans is an area of ongoing research. Most studies have been done on caloric restriction, which refers to decreasing calories beyond what is habitual without malnutrition. All types of fasting will generally achieve caloric restriction. A one-year randomized control trial of 80 obese patients with mild cognitive impairment (MCI) found that those who did caloric restriction of 500 kcal per day had improved verbal memory, executive function, and global cognition compared to the control group.[35] Both groups had minimal amount of weight loss. Another randomized control trial of 220 healthy, normal weight adults found that those who did caloric restriction of 25% for 2 years had improved working memory on neuropsychiatric testing.[36] In addition, Ooi and colleagues found enhanced cognitive function in older adults with MCI who did regular periodic fasting compared to a group who did not fast over a period of 3 years.[37]

There is preliminary data suggesting possible benefit for fasting in autoimmune disease, including multiple sclerosis and rheumatoid arthritis. In a pilot study of 60 patients with relapsing-remitting multiple sclerosis, patients were assigned to a control diet for 2 months, a ketogenic diet for 2 months, or a fasting mimicking diet for 7 days followed by the Mediterranean diet for 6 months.[38] At the conclusion of the study, the ketogenic and fasting arms reported better health-related quality of life score (HRQOL) compared to the control. A randomized control trial is currently underway to examine the role of fasting and the ketogenic diet for MS.[39] In addition, a pilot study of 27 patients with rheumatoid arthritis found that fasting for 7 days followed by a gluten-free vegan/vegetarian diet for 12 months improved C-reactive protein (CRP), sedimentation rate, morning stiffness, and number of swollen joints.[40]

Preliminary studies suggest that fasting in some patients with cancer is safe and may decrease side effects related to chemotherapy. In one study, 13 patients with stage I/II breast cancer receiving standard of care chemotherapy who were randomized to fast 24 hours before and after chemotherapy had less hematologic toxicity.[41] A feasibility study of 20 patients receiving platinum-based chemotherapy for multiple tumor types - including breast, ovarian, and uterine cancers – found that fasting 48 to 72 hours prior to chemotherapy resulted in a trend towards decreased neutropenia and neuropathy.[42] A pilot study of 30 patients with gynecologic cancers receiving chemotherapy found that those who did a fast of 96 hours during 50% of chemotherapy cycles, while eating a regular diet for remaining cycles, had a lower toxicity score during fasting cycles, less stomatitis, and fewer chemotherapy delays.[43] Although there has been concern about weight loss in patients undergoing chemotherapy, no trials have found severe weight loss.[44] In addition, studies are currently underway to evaluate intermittent fasting for prevention of tumor recurrence and progression, including for breast cancer, colon cancer, and prostate cancer.[45] In summary, there is preliminary data suggesting possible benefit for chemotherapy-related side effects, but more studies need to be done to further evaluate the risks and benefits.

Contraindications

Contraindications to fasting include pregnancy, breastfeeding, eating disorders, low BMI, diabetes, and children.

SUMMARY

Intermittent fasting is currently popular with patients because weight loss is perceived as easier to maintain than with traditional diets with caloric restriction. Compared to daily caloric restriction, intermittent fasting may preserve lean body mass and resting energy expenditure, which may help prevent plateauing during weight loss. Fasting has been shown in animals to increase lifespan and may have metabolic benefits beyond weight loss. These include lowering inflammation, improving insulin sensitivity, neuroprotection, mitochondrial biogenesis, and improving parasympathetic tone – including blood pressure, resting heart rate, and gut motility. In addition, fasting allows the body to spend time in repair and autophagy, and balances the growth and anabolic processes of the fed state. Clinical studies on fasting is an area of ongoing research, with preliminary studies suggesting possible benefit for rheumatoid arthritis, MS, cognitive function, and side effects of chemotherapy. Further studies are needed, and some are underway, including for MS and cancer.

REFERENCES

1. US Centers for Disease Control and Prevention. Adult Obesity Facts. Centers for Disease Control Prevention. Last reviewed May 17, 2022. https://www.cdc.gov/obesity/data/adult.html. Accessed June 13, 2023.
2. US Centers for Disease Control and Prevention. Obesity and Cancer Risk. Centers for Disease Control Prevention. Last reviewed last reviewed: July 13, 2022. https://www.cdc.gov/cancer/obesity/index.htm. Accessed on Feb. 18, 2023.
3. Popkin BM, Duffey KJ. Does hunger and satiety drive eating anymore? Increasing eating occasions and decreasing time between eating occasions in the United States. *Am J Clin Nutr.* 2010 May;91(5):1342-7. doi: 10.3945/ajcn.2009.28962.
4. Gill S, Panda S. A Smartphone App Reveals Erratic Diurnal Eating Patterns in Humans that Can Be Modulated for Health Benefits. *Cell Metab.* 2015 Nov 3;22(5):789-98. doi: 10.1016/j.cmet.2015.09.005.
5. International Food Information Council. 2020 Food & Health Survey. June 10, 2020. https://foodinsight.org/2020-food-and-health-survey/ Accessed Feb. 18, 2023.

6. Weindruch R, Sohal RS. Seminars in medicine of the Beth Israel Deaconess Medical Center. Caloric intake and aging. *N Engl J Med.* 1997 Oct 2;337(14):986-94. doi: 10.1056/NEJM199710023371407.
7. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. Cell Metab. 2014 Feb 4;19(2):181-92. doi: 10.1016/j.cmet.2013.12.008.
8. Swindell WR. Dietary restriction in rats and mice: a meta-analysis and review of the evidence for genotype-dependent effects on lifespan. *Ageing Res Rev.* 2012 Apr;11(2): 254-70. doi: 10.1016/j.arr.2011.12.006.
9. Goodrick CL, Ingram DK, Reynolds MA, Freeman JR, Cider N. Effects of intermittent feeding upon body weight and lifespan in inbred mice: interaction of genotype and age. *Mech Ageing Dev.* 1990 Jul;55(1):69-87. doi: 10.1016/0047-6374(90)90107-q.
10. Cahill GF Jr. Starvation in man. *N Engl J Med.* 1970 Mar 19;282(12):668-75. doi: 10.1056/NEJM197003192821209.
11. Browning JD, Baxter J, Satapati S, Burgess SC. The effect of short-term fasting on liver and skeletal muscle lipid, glucose, and energy metabolism in healthy women and men. *J Lipid Res.* 2012 Mar;53(3):577-586. doi: 10.1194/jlr.P020867.
12. Norwitz NG, Hu MT, Clarke K. The Mechanisms by Which the Ketone Body D-β-Hydroxybutyrate May Improve the Multiple Cellular Pathologies of Parkinson's Disease. *Front Nutr.* 2019 May 14;6:63. doi: 10.3389/fnut.2019.00063.
13. Sato K, Kashiwaya Y, Keon CA, et al. Insulin, ketone bodies, and mitochondrial energy transduction. *FASEB J.* 1995 May;9(8):651-8. doi: 10.1096/fasebj.9.8.7768357.
14. Veech RL, Todd King M, Pawlosky R, Kashiwaya Y, Bradshaw PC, Curtis W. The "great" controlling nucleotide coenzymes. *IUBMB Life.* 2019 May;71(5):565-579. doi: 10.1002/iub.1997.
15. Lee J, Seroogy KB, Mattson MP. Dietary restriction enhances neurotrophin expression and neurogenesis in the hippocampus of adult mice. *J Neurochem.* 2002 Feb;80(3):539-47. doi: 10.1046/j.0022-3042.2001.00747.x.
16. Singh R, Lakhanpal D, Kumar S, et al. Late-onset intermittent fasting dietary restriction as a potential intervention to retard age-associated brain function impairments in male rats. *Age* (Dordr). 2012 Aug;34(4):917-33. doi: 10.1007/s11357-011-9289-2.
17. Norwitz NG, Hu MT, Clarke K. The Mechanisms by Which the Ketone Body D-β-Hydroxybutyrate May Improve the Multiple Cellular Pathologies of Parkinson's Disease. *Front Nutr.* 2019 May 14;6:63. doi: 10.3389/fnut.2019.00063.
18. Rahman S, Islam R. Mammalian Sirt1: insights on its biological functions. *Cell Commun Signal.* 2011 May 8;9:11. doi: 10.1186/1478-811X-9-11.
19. Singh P, Hanson PS, Morris CM. SIRT1 ameliorates oxidative stress induced neural cell death and is down-regulated in Parkinson's disease. *BMC Neurosci.* 2017 Jun 2;18(1):46. doi: 10.1186/s12868-017-0364-1.
20. Rothman SM, Griffioen KJ, Wan R, Mattson MP. Brain-derived neurotrophic factor as a regulator of systemic and brain energy metabolism and cardiovascular health. *Ann N Y Acad Sci.* 2012 Aug;1264(1):49-63. doi: 10.1111/j.1749-6632.2012.06525.x.
21. Bagherniya M, Butler AE, Barreto GE, Sahebkar A. The effect of fasting or calorie restriction on autophagy induction: A review of the literature. *Ageing Res Rev.* 2018 Nov;47:183-197. doi: 10.1016/j.arr.2018.08.004
22. Mizushima N, Levine B. Autophagy in Human Diseases. *N Engl J Med.* 2020 Oct 15;383(16):1564-1576. doi: 10.1056/NEJMra2022774.
23. Antunes F, Erustes AG, Costa AJ et al. Autophagy and intermittent fasting: the connection for cancer therapy? *Clinics* (Sao Paulo). 2018 Dec 10;73(suppl 1):e814s. doi: 10.6061/clinics/2018/e814s.
24. Yang Z, Goronzy JJ, Weyand CM. Autophagy in autoimmune disease. *J Mol Med* (Berl). 2015 Jul;93(7):707-17. doi: 10.1007/s00109-015-1297-8.
25. de Cabo R, Mattson MP. Effects of Intermittent Fasting on Health, Aging, and Disease. *N Engl J Med.* 2019 Dec 26;381(26):2541-2551. doi: 10.1056/NEJMra1905136. Erratum in: N Engl J Med. 2020 Jan 16;382(3):298. Erratum in: *N Engl J Med.* 2020 Mar 5;382(10):978.
26. Gudden J, Arias Vasquez A, Bloemendaal M. The Effects of Intermittent Fasting on Brain and Cognitive Function. *Nutrients.* 2021 Sep 10;13(9):3166. doi: 10.3390/nu13093166.
27. Varady KA. Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss? *Obes Rev.* 2011 Jul;12(7):e593-601. doi: 10.1111/j.1467-789X.2011.00873.x.
28. Anton SD, Moehl K, Donahoo WT, et al. Flipping the Metabolic Switch: Understanding and Applying the Health Benefits of Fasting. *Obesity* (Silver Spring). 2018 Feb;26(2):254-268. doi: 10.1002/oby.22065.
29. Byrne NM, Sainsbury A, King NA, Hills AP, Wood RE. Intermittent energy restriction improves weight loss efficiency in obese men: the MATADOR study. *Int J Obes* (Lond). 2018 Feb;42(2):129-138. doi: 10.1038/ijo.2017.206.
30. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metab.* 2018 Jun 5;27(6):1212-1221.e3. doi: 10.1016/j.cmet.2018.04.010.

31. Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. *Obesity* (Silver Spring). 2013 Dec;21(12):2504-12. doi: 10.1002/oby.20460. Epub 2013 Jul 2.
32. Bo S, Fadda M, Castiglione A, et al. Is the timing of caloric intake associated with variation in diet-induced thermogenesis and in the metabolic pattern? A randomized cross-over study. *Int J Obes* (Lond). 2015 Dec;39(12):1689-95. doi: 10.1038/ijo.2015.138.
33. Van Cauter E, Shapiro ET, Tillil H, Polonsky KS. Circadian modulation of glucose and insulin responses to meals: relationship to cortisol rhythm. *Am J Physiol.* 1992 Apr;262 (4 Pt 1):E467-75. doi: 10.1152/ajpendo.1992.262.4.E467.
34. Rodin J. Insulin levels, hunger, and food intake: an example of feedback loops in body weight regulation. *Health* Psychol. 1985;4(1):1-24. doi: 10.1037//0278-6133.4.1.1.
35. Horie NC, Serrao VT, Simon SS, et al. Cognitive Effects of Intentional Weight Loss in Elderly Obese Individuals with Mild Cognitive Impairment. *J Clin Endocrinol Metab.* 2016 Mar;101(3):1104-12. doi: 10.1210/jc.2015-2315.
36. Leclerc E, Trevizol AP, Grigolon RB, et al. The effect of caloric restriction on working memory in healthy non-obese adults. *CNS Spectr.* 2020 Feb;25(1):2-8. doi: 10.1017/S1092852918001566.
37. Ooi TC, Meramat A, Rajab NF, et al. Intermittent Fasting Enhanced the Cognitive Function in Older Adults with Mild Cognitive Impairment by Inducing Biochemical and Metabolic changes: A 3-Year Progressive Study. *Nutrients.* 2020 Aug 30;12(9):2644. doi: 10.3390/nu12092644.
38. Choi IY, Piccio L, Childress P, et al. A Diet Mimicking Fasting Promotes Regeneration and Reduces Autoimmunity and Multiple Sclerosis Symptoms. *Cell Rep.* 2016 Jun 7;15(10):2136-2146. doi: 10.1016/j.celrep.2016.05.009.
39. Friedemann P, Principal Investigator, Charite University, Berlin, Germany. Nutritional Approaches in Multiple Sclerosis. NCT03508414. Updated July 29, 2021. Accessed Feb 18, 2023. https://clinicaltrials.gov/ct2/show/NCT03508414
40. Kjeldsen-Kragh J, Haugen M, Borchgrevink CF, et al. Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. *Lancet.* 1991 Oct 12;338(8772):899-902. doi: 10.1016/0140-6736(91)91770-u.
41. Bauersfeld SP, Kessler CS, Wischnewsky M, et al. The effects of short-term fasting on quality of life and tolerance to chemotherapy in patients with breast and ovarian cancer: a randomized cross-over pilot study. *BMC Cancer.* 2018 Apr 27;18(1):476. doi: 10.1186/s12885-018-4353-
42. Dorff TB, Groshen S, Garcia A, et al. Safety and feasibility of fasting in combination with platinum-based chemotherapy. *BMC Cancer.* 2016 Jun 10;16:360. doi: 10.1186/s12885-016-2370-6.
43. Zorn S, Ehret J, Schäuble R, et al. Impact of modified short-term fasting and its combination with a fasting supportive diet during chemotherapy on the incidence and severity of chemotherapy-induced toxicities in cancer patients - a controlled cross-over pilot study. *BMC Cancer.* 2020 Jun 22;20(1):578. doi: 10.1186/s12885-020-07041-7.
44. Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. *Nat Rev Cancer.* 2018 Nov;18(11):707-719. doi: 10.1038/s41568-018-0061-0.
45. Clifton KK, Ma CX, Fontana L, Peterson LL. Intermittent fasting in the prevention and treatment of cancer. *CA Cancer J Clin.* 2021 Nov;71(6):527-546. doi: 10.3322/caac.21694.