

Intermittent Fasting and Adding More days to Life

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ABSTRACT

Intermittent fasting (IF) is currently one of the world's most popular health and fitness trends. Several IF patterns have been studied. Not all were shown to be equally effective. Also, each person's experience of intermittent fasting is individual, and different styles will suit different people. The potential health benefit list of IF is long: accelerated weight loss, reduced inflammation, lower cholesterol, longer lifespan, blood sugar stabilization, and prevention of type 2 diabetes. Emerging research suggests IF may also lead to a healthier brain, longer life, and even aid cancer treatment. Placing time restrictions on feeding has been shown to have broad systemic effects and trigger similar biological pathways as caloric restriction. One key mechanism responsible for many of these beneficial effects appears to be "flipping" of the metabolic switch. The metabolic switch typically occurs in the third phase of fasting when glycogen

stores in hepatocytes are depleted and accelerated adipose tissue lipolysis produces increased fatty acids and glycerol. Just changing the timing of meals, by eating earlier in the day and extending the overnight fast, significantly benefited metabolism even in people who didn't lose a single pound.

Key words: Weight loss; Caloric restriction; Fasting; Circadian rhythm; Metabolic switch

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Abbreviations

Calorie Restriction (CR); Intermittent Fasting (IF); Randomized Controlled Trials (RCTs); Glycated Haemoglobin (A1c) (HbA1C); Alternative Day Fasting (ADF); Epworth Sleepiness Scale (ESS); Insulin-like Growth Factor 1 (IGF-1); Total Cholesterol (TC); Interleukin-2 (IL-2); Chronic Kidney Disease (CKD); Epithelial Growth Factor (EGF); Psoriasis Area and Severity Index" (PASI)

LETTER TO THE EDITOR

With over 50% of the adult population in the UK currently classified as overweight or obese, accompanied by an increased risk of type 2 diabetes and cardiovascular disease, finding more effective strategies to manage these conditions remains imperative^[1]. In 2016, World Health Organization (WHO) reported that more than 1.9 billion people in the world were overweight and over 650 million people were obese which has tripled in number since 1975^[2]. To date, the most robust intervention efficient in warding off the aforementioned cellular markers of aging is calorie restriction (CR) that involves the administration of a well-balanced, nutrient-dense diet that reduces calorie intake by 20%-40% without malnutrition^[3]. It is the only non-genetic intervention that has consistently been found to extend both mean and maximal life span across a variety of species^[4]. Randomized trials demonstrate that intentional weight loss reduces type 2 diabetes, retards aging-related functional decline; and increases cognitive and physical function; and increases lifespan^[5]. Modest weight losses of 5%–10% have been associated with

significant improvements in cardiovascular disease risk factors (i.e., decreased HbA1C levels, reduced blood pressure, increase in HDL cholesterol, decreased plasma triglycerides) in patients with T2D^[6]. In addition to the weight loss effects and metabolic improvements, several other beneficial effects of therapeutic fasting have been described including improvements in lipid profiles, osteoarthritis, healing of thrombophlebitis, healing of refractory dermal ulcers and tolerance of elective surgery^[7]. Recent findings indicate that meal timing is crucial, with both IF and adjusted diurnal rhythm of feeding improving health and function, in the absence of changes in overall intake. Lowered intake of particular nutrients, rather than of overall calories, is also key, with protein and specific amino acids playing prominent roles^[8]. Importantly, long-term exposure to a CR diet might also cause substantial side effects like amenorrhea, osteoporosis, decreased fertility and libido (due to reduced testosterone in men), impaired wound healing and increased susceptibility to infections^[9,10]. Fasting is distinct from caloric restriction (CR), in which daily caloric intake is chronically reduced by up to 40 %, but meal frequency is maintained^[11]. The cellular and molecular mechanisms by which IF improves health and counteracts disease processes involve activation of adaptive cellular stress response signaling pathways that enhance mitochondrial health, DNA repair and autophagy^[12]. Recently, studies in both in vitro and in vivo models have shown that IF improved the chemotherapeutic response to cisplatin, doxorubicin, cyclophosphamide, oxaliplatin, sorafenib, mitoxantrone, gemcitabine, etoposide, temozolomide and tyrosine kinase inhibitors in models of glioma, neuroblastoma, melanoma, fibrosarcoma and breast cancer, colon cancer, pancreatic cancer, hepatocellular cancer and lung cancer^[13]. IF regimens that induce the metabolic switch have the potential to improve body composition in overweight individuals. Moreover, IF regimens also induce the coordinated activation of signaling pathways that optimize physiological function, enhance performance, and slow aging and disease processes^[7]. Barnosky et al, 2014 detailed comparison of alternative day fasting (ADF) and IF over CR in reductions in insulin resistance, fasting insulin, and visceral fat mass and concluded that IF and ADF as alternatives to CR for weight loss and type 2 diabetes risk reduction in overweight and obese populations^[14]. Both central and peripheral clocks act to preserve the circadian rhythm of different tissue physiology via controlling “tissue-specific gene expression”^[15]. Couto et al, 2018 reported that magnitude of adipose and skin response to time of day was around twice that of hours fasting^[16]. Epworth Sleepiness Scale (ESS) score to assess relation between IF and daytime sleepiness reported conflicting results, reviewed by Almeneessier et al, 2018. Some studies reported a significant increase in daytime sleepiness, whereas other studies demonstrated no significant changes^[17]. However, overnight fasting, or fasting during sleeping hours, is associated with a nocturnal rise in plasma free fatty acids (FFA), ghrelin, growth hormone, and increased hepatic gluconeogenesis. Adipose tissue (AT) orchestrates the cycling of triglycerides (TG) by controlling the uptake, esterification, and release of FFA to meet the metabolic demands of the liver and muscle tissue. Hence, integration of circadian rhythms and eating may be beneficial^[18]. Current evidence suggests that as little as 10 min of high intensity exercise can improve metabolic health and aerobic capacity and alternative day fasting can reduce obesity-associated changes in body composition, fasting insulin and glucose concentrations^[19]. Studies in rodents have demonstrated that restricting the availability of food to the normal nighttime feeding cycle improves metabolic profiles and reduces the risk of obesity and obesity-related conditions, such as nonalcoholic fatty liver disease,

and chronic diseases, such as diabetes and cancer^[20]. Fasting periods with various patterns are found in most religions. In fact, this ascetic practice is referenced in the Old Testament, as well as other ancient texts such the Koran and the Mahabharata. Muslims, for example, fast from dawn until dusk during the month of Ramadan, while Christians, Jews, Buddhists, and Hindus traditionally fast on designated days or periods. For instance, Ramadan IF was linked with improvements in cardiometabolic risk factors^[21,22]. Studies reported that total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and blood glucose have been improved after Ramadan compared to before Ramadan among athletes. Rahbar et al, 2019 concluded that fasting in Ramadan independent of anthropometric measures decreases IGF-1, IL-2, and serum lipid levels^[23]. As Smoking has been forbidden during fasting of Ramadan, studies revealed a significant reduction in second-hand smoke levels in public places^[24]. Even with no advice on lifestyle changes, there are consistent-albeit transient-reductions in weight and fat mass with the Ramadan fast, especially in people with overweight or obesity^[25]. Ramadan IF might be associated with decrease in sexual desire, frequency of sexual intercourse and serum FSH level^[26]. Resistance training (weight lifting) in a fasted state affects the post-workout anabolic response to weight training more favorably than training after a fed-state, but only when a carbohydrate/protein/leucine mixture was ingested following a heavy resistance training session^[27]. Also, Frawley et al, 2018 reported that fasted resistance exercise relies more heavily on fat metabolism than carbohydrate^[28]. Other studies have found similar reliance on fat as a fuel source during fasted aerobic exercise^[29-32]. Remarkably, IF during early adulthood, and also during mid-life, was sufficient to extend lifespan, indicating a “memory” effect. Hormesis is a phenomenon by which “low-level” toxic stress elicits response mechanisms that protect against similar but higher-level stresses associated with aging. Given that intermittent starvation in early life led to increased post-IF starvation resistance in addition to increased lifespan, hormesis could play a role^[25]. One of metabolic effects of IF is intermittent ketosis known for its appetite suppression effect resulting in voluntary calorie reduction. In terms of meal timing, skipping breakfast is similar to IF^[33]. Although several studies reported associations between breakfast skipping and fatigue at noon, worsens memory and higher body mass index as well as increased prevalence of obesity-related chronic illness; deficient in total energy, vitamins and minerals, increased risk of central adiposity, and risk of insulin resistance and cardio-metabolic disorders^[34]. There are two basic varieties of the IF diet. The most popular variation is time-restricted feeding. It may be used in three variants: 16/8, 18/6 and 20/4. 16:8, consisting of a 16-h fast, and then an 8-h nutritional window. Another protocol consists of a 24-h fasting period, alternated with a 24-h eating period, repeated two or three times a week. There are two possible systems, 5:2 or 4:3. In the 5:2 system, in which caloric restriction is used for two days a week, and a regular diet for 5 days^[35,36]. However, IF should not be used by children, pregnant women, and people performing heavy physical work^[37]. Also, menstruating women, the elderly, sick people, and long-distance travelers are waived from this Ramadan fasting^[38,39]. Given the stress of fluid deprivation and subsequent electrolyte changes, kidney physiology is often significantly impacted. This is especially true among those with chronic kidney disease (CKD), predisposing them to acute tubular injury. Additionally, dehydration is a major precipitating factor for renal stone development^[40-42]. Antunes et al, 2017 stated that fasting increase the sensitivity of tumor cell lines to cisplatin-induced cells, and also of those cell lines particularly

resistant to any pharmacological treatment^[43]. In another study, fasting was found to modulate the IGF-1 receptor (IGF-1R)/epithelial growth factor (EGF) receptor (EGFR) and the Akt/mTOR pathways, which are dysregulated in obesity and may lead to skin cancer^[44]. However, Bragazzi et al, 2019 concluded that physicians should be instructed in recognizing rare dermatological disorders associated with fasting, such as *Prurigo pigmentosa* (PP)^[45]. Damiani et al, 2019 reported significant decrease in the “Psoriasis Area and Severity Index” (PASI) score after the Ramadan fasting^[38]. IF would be a useful tool in distressful condition to improve learning and memory by downregulation of the putative molecular factors involved in neuro-inflammation, although chronic stressors are generally well-known for adverse effects on the body particularly cognitive decline^[46]. To improve health, the goal should be to lose weight by reducing the total amount of calories consumed, rather than focusing on when those calories are consumed^[47]. 4-8 h time restricted feeding reduces caloric intake (without calorie counting) and significantly decreases fat mass without changing lean mass in young resistance trained men. Gabel et al, 2018 revealed that 8-h time restricted feeding produces mild caloric restriction and weight loss, without calorie counting. It may also offer clinical benefits by reducing blood pressure^[48]. Altering body composition in such a manner may be advantageous to the athlete for various biomechanical, aesthetic, and locomotive reasons, thereby increasing the likelihood of competitive success in a target weight-class (e.g., combat sports, weight lifting), weight-sensitive sports (e.g., endurance events, ski jumping), or aesthetically judged sports (e.g., gymnastics and bodybuilding)^[49]. IF regimens may be a promising approach to lose weight and improve metabolic health for people who can tolerate intervals of not eating, or eating very little, for certain hours of the day or days of the week. If proven to be efficacious, these eating regimens may offer promising nonpharmacologic approaches to improving health at the population level with multiple public health benefits^[50].

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