Less is more: effectiveness and feasibility of a fasting-mimicking diet programme in persons with type 2 diabetes in primary care

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Chapter 3

Intermittent fasting

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Abstract

Intermittent fasting, also known as intermittent energy restriction (IER), is gaining popularity as a dietary method for weight loss or health improvement. In this chapter, we will explain the physiology of IER, describe the different forms of IER and provide an extensive overview of the effects of IER. Several animal and human studies show that IER may have a positive effect on weight, fat distribution, metabolic health and other health parameters including inflammation, cognitive function, mental health and the gut microbiome composition. There is no evident superiority in the effect of IER on weight and fat loss when compared to continuous energy restriction, nor was there a difference in adherence to the diet. Only mild side effects have been reported by implementing IER, but there are risks to consider for some patient groups. Overall, IER seems a viable option when considering different dietary methods.

Intermittent fasting methods

Intermittent fasting is rapidly gaining popularity as a contribution to a healthy lifestyle and a method to lose weight. The necessity for effective lifestyle interventions arises from the world-wide increasing problem of obesity and its related diseases. Since not all individuals seem to be able to adhere to continuous energy restriction (CER), it is interesting to look at other methods for lifestyle change. Ideally, health care providers should be able to offer patients a variety of effective lifestyle changes that have proven to be effective for prevention and treatment of these obesity-related diseases, in order to match an individual's needs and capabilities(1, 2). Intermittent fasting, in literature also known as intermittent energy restriction (IER), could be an interesting option(3).

IER is an overarching term for several dietary regimens(4). It includes diets that apply water-only fasting for recurring periods, alternating with periods without dietary restrictions as well as diets alternating periods with reduced energy intake with periods without restrictions. Usually the low-calory periods allow a maximum of 25% of normal caloric intake. The periods of energy restriction are very diverse and differ from hours to several days. We will discuss most used IER regimens (**Figure 1**).

Time-restricted feeding (TRF) refers to no energy intake, or a restricted amount of energy intake, for a period of 12-20 hours a day. Early time restricted feeding refers to a period of reduced energy intake in the evening. When this period of reduced energy intake takes place in the morning, it is called late time-restricted feeding. Alternate day fasting (ADF) is a regimen in which one day of eating ad libitum is alternated with a day of fasting or severe energy reduction. A minimum of two consecutive days of fasting or strongly reduced energy intake is referred to as periodic fasting (PF). Often used is the 5:2 diet, with two consecutive days of fasting and five days of no restrictions per week. A fasting-mimicking diet (FMD) comprises complex, fiber-rich carbohydrate and healthy fats, while it lacks refined carbohydrate and contains less than 10 energy% protein. Although an FMD typically offers some 25% of normal caloric intake, it induces a physiological response that mimics the response to water-only fasting because it provides just minute amounts of readily available glucose and amino acids. An FMD however does provide for essential nutrients such as vitamins and minerals(5, 6). The various IER methods are summarized in **Figure 1**.

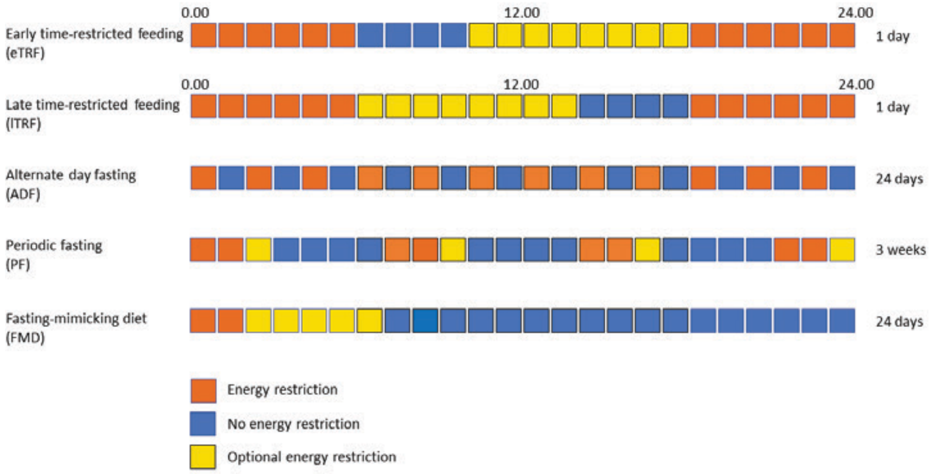

Figure 1. Intermittent energy restriction methods.

Physiology of IER

Fasting activates several cellular and molecular mechanisms, leading to a 'metabolic switch' in which the body switches from utilizing and storing glucose, to mobilizing fat(4, 7). Lipids in adipocytes are metabolized to free fatty acids and released in the blood, from where they are transported to hepatocytes and other tissues to serve as fuel(4)(**Figure 2**). Moreover, hepatocytes convert free fatty acids into ketones, which become an important energy source alongside free fatty acids as an alternative to glucose. These processes usually start after 12-36 hours of fasting, depending on several factors. First, hepatic glycogen stores must be depleted before significant amounts of ketones are produced. How long this takes depends on how extensive the initial glycogen content was at the beginning of the fast. Secondly, it depends on the level of energy expenditure during the fast. Besides being used as energy source, ketones are also potent signaling molecules activating several cellular pathways(7). These activated pathways enhance intrinsic defense against oxidative and metabolic stress, facilitate the removal or repair of damaged molecules, promote DNA repair, stimulate mitochondrial biogenesis and promote cell survival, while synthesis as well as growth and reproduction are minimized. Collectively, this improves resistance of cells and organs to stress. In a subsequent feeding period, tissue-specific processes of growth and plasticity are activated, and structural and functional tissue remodeling is initiated. The combination of fasting and re-feeding periods facilitates systemic and cellular responses that carry over into the fed state and seem to improve physical and mental performance as well as resistance to disease(4, 7-9).

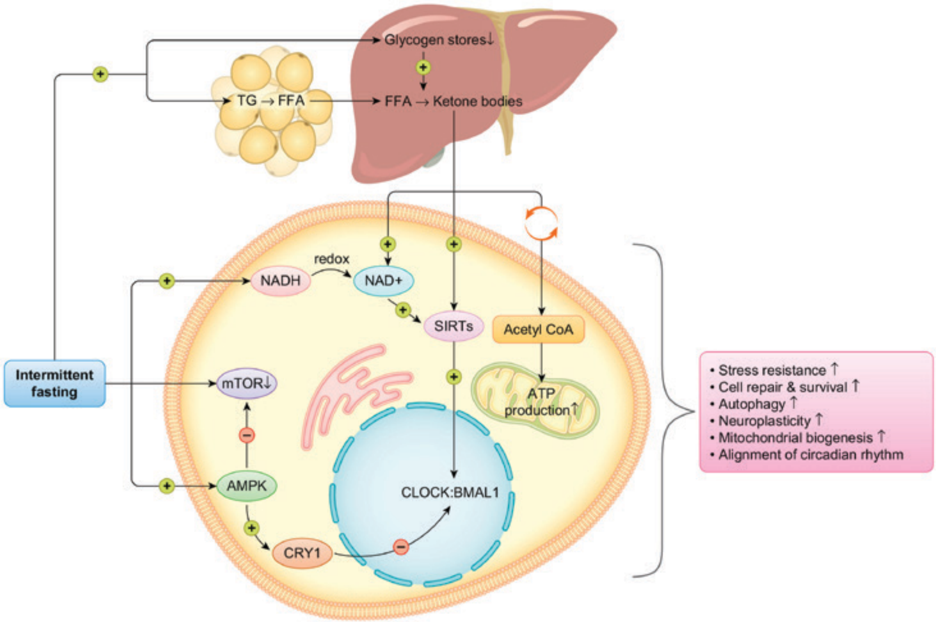

Figure 2. The effects of intermittent fasting.

TG: triglycerides; FFA: free fatty acids; NAD: nicotinamide adenine dinucleotide; SIRT: sirtuins; mTOR: mammalian target of rapamycin; AMPK: adenosine monophosphate protein kinase; CRY1: Cryptochrome 1; CLOCK:BMAL1: circadian locomotor output cycles kaput: brain and muscle Arnt-like 1; acetyl CoA: acetyl coenzyme A; ATP: Adenosine triphosphate. Reprinted from Clinical Nutrition, Volume 40, Issue 9, 5122 – 5132. Veldscholte, Karlien et al. Intermittent fasting in paediatric critical illness: The properties and potential beneficial effects of an overnight fast in the PICU

Effect of IER on health parameters in animal models

Several animal models have been used to study the effect of IER. In rodents, it has been shown that IER can have a beneficial effect on life span and several health parameters(6, 10). For example, the average life span of rats was increased by 30% when put on an ADF diet from the age of ten weeks, compared to rats with an ad libitum diet(10). Also in mice, extended longevity was seen when put on a bimonthly four-day FMD(6). In lower species such as yeast, nematodes and fruit flies IER led to an increased lifespan as well(6, 11). The effects of IER on weight and fat, metabolic parameters and other health parameters in animal models will be discussed below.

Effect of IER on weight and fat in animal models

Overall, compared to controls fed ad libitum, mice on IER showed changes in body weight and/or fat distribution (**Figure 3**). TRF prevented obesity and accumulation of lipids in the liver while retaining muscle mass in mice on a high fat diet(4). The same effects were observed in a study with mice on ADF combined with a high fat diet(12). Compared to the mice on ad libitum high fat diet, weight gain was reduced, epididymal fat pads were smaller and hepatic triglyceride content was lower. Concordant with these results, mice on a high fat diet combined with IER showed decreased energy intake, body weight, fat mass and fat cell size as well as reduced adipose tissue inflammation and fibrosis(13). Mice on a high fat diet combined with a 4-day FMD twice a month did not develop obesity. Compared to mice fed with the control diet their body weight was 13,5% higher, whereas in mice fed with the obesogenic diet without FMD, body weight was 97.29% higher after 18 months(14). The obesogenic diet without FMD also led to a significant accumulation of both visceral and subcutaneous fat compared to the control diet and obesogenic diet + FMD. The control and FMD group showed similar body fat content and the FMD group had lower ratio of visceral adipose tissue (VAT) to subcutaneous adipose tissue(SAT) (percent VAT/SAT) compared to the obesogenic diet and control diet groups.

In another study with mice on an alternate day modified fasting with 85% energy restriction no significant change in bodyweight was observed(15). Interestingly though, the proportion of subcutaneous fat increased, whereas the proportion of visceral fat decreased. This is in concordance with a study examining the plasticity of adipose tissue in response to fasting and refeeding in mice, where it was observed that during fasting lipids were consumed in visceral adipose tissue, whereas during refeeding, lipids were predominantly recovered in subcutaneous tissues(16). Mice on a 4-day FMD twice a month, with an ad libitum chow diet in between for 18 months, only demonstrated a trend for reduced total adipose tissue and a reduction in visceral fat deposits compared to a control group, with no change in subcutaneous adipose tissue volume(6). Lean body mass remained the same in the intervention and control group. The effects were seen even though the total amount of calories consumed by the control mice on ad libitum diet and the mice on FMD was the same. FMD mice remained on the same weight for the first 4 months but did lose weight afterwards. In mice on an ADF intervention, weight loss was also seen, however no significant change in inguinal and epididymal adipose tissue mass was measured(17). Though not tested, the authors proposed that the net weight loss was the result of skeletal muscle decrease. In this trial, adipocyte size was significantly reduced in both inguinal and epididymal adipose tissue, while total tissue mass had not changed, suggesting an increase in adipocyte number. Also, an increase in adipose tissue triglyceride metabolism was measured, with higher rates of lipolysis, increased plasma FFA concentrations, augmented gluconeogenesis and de novo lipogenesis.

In conclusion, several IER regimes can prevent obesity, lipid accumulation in the liver, and fat accumulation in fat pads in mice on a high fat diet. Furthermore, mice on IER exhibit an altered adipose tissue distribution, physiology and structure, even in absence of weight loss (**Figure 3**).

Figure 3. Effects of intermittent fasting regimes on body composition related parameters in mice.

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Effect of IER on metabolic parameters in animal models

Besides the effects of IER on weight and fat distribution, effects of IER on plasma glucose and insulin levels, resting blood pressure and heart rate in mice and rats are also reported.

In a study with mice on ADF, reduced serum glucose and insulin levels were measured although overall food intake and body weight were similar, suggesting an effect of IER apart from caloric intake(18). TRF can reverse high-fat food induced obesity with impaired glucose tolerance, elevated plasma glucose and insulin levels in mice(4). Also, a four-day FMD twice a month in non-obese mice reduced glucose and insulin levels(6). However, these levels returned to normal within 7 days of re-feeding. Compared to rats on an ad libitum diet rats on ADF showed improved glucose metabolism(19). Blood pressure and resting heart rate both progressively decreased during the first month and maintained the same level during the following 6 months. Furthermore when exposed to stressors, rats on ADF showed a smaller increase in blood pressure, heart rate, ACTH, corticosterone and epinephrine levels compared to control rats on an ad libitum diet. Additionally, studies found favorable lipid profiles in rodents on ADF compared to the controls(4).

The results of the above-mentioned studies indicate beneficial effects of IER on glucose tolerance, blood pressure, heart rate and lipid profile in rodents (**Figure 4**).

Figure 4. Effects of intermittent fasting regimes on metabolic parameters in mice.

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Effect of IER on other health parameters in animal models

Other health parameters evaluated in animals on an IER diet include physical function, inflammation, cancer and skin lesion incidence, bone mineral density, mental health indicators and gut microbiota composition.

Physical function including running endurance, balance and coordination are better in rats on ADF compared to ad libitum fed controls(7). Mice on 4-day FMD cycles twice a month starting at middle age, showed reduced tumor incidence, delayed onset and a major reduction in the number of skin lesions compared to controls(6). The FMD group also had a reduced number of tissues with inflammation, less severe ulcerating dermatitis and a higher femoral bone density.

In older mice on the same FMD, improved cognitive performance and hippocampal neurogenesis was found. Furthermore, brain neurons are protected against dysfunction and degeneration in different animal studies with ADF diets(4). Animal models with epilepsy, Alzheimer disease, Parkinson disease or stroke all show beneficial effects when put on ADF. Furthermore, ADF seems to improve cognitive performance, even when started later in life(4). Cognitive function improvement was seen in multiple domains, including spatial memory, associative memory and working memory(20).

IER also affects gut microbiome composition(21). ADF shifts gut microbiome composition towards an abundance of Firmicutes while most other phyla occur less, along with an elevation of the favorable fermentation products acetate and lactate. The authors suggested that it might be due to the change in microbiome that white adipose tissue browning was promoted, and metabolic homeostasis improved. In germ free mice without gut microbiota, the beneficial effects of ADF on several indicators of metabolic function were less obvious. The metabolic effects of gut microbiota were also demonstrated in a study where germ-free mice received fecal transplants from obese and lean mice(22). When receiving a fecal transplant from obese mice their body- and fat mass increased and they developed the obesity-associated metabolic phenotype, whereas this effect was not seen when they received a fecal transplant from lean mice. These results suggest that alteration of the gut microbiome can influence the metabolic phenotype.

IER was also suggested to have positive immunomodulatory effects, at least partly mediated by the gut microbiome in multiple sclerosis mouse models(23).

Figure 5. Effects of intermittent fasting regimes on several parameters in mice.

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Taken together, IER interventions result in positive effects on several health parameters including physical health, tumor incidence, cognitive function, skin lesions, bone mineral density and immune disorders (**Figure 5**). An alteration of the gut microbiome composition by IER possibly plays a role in the metabolic improvement. **Figure 6** gives an overview of some of the positive effects seen in literature upon using FMD, one of the IER methods.

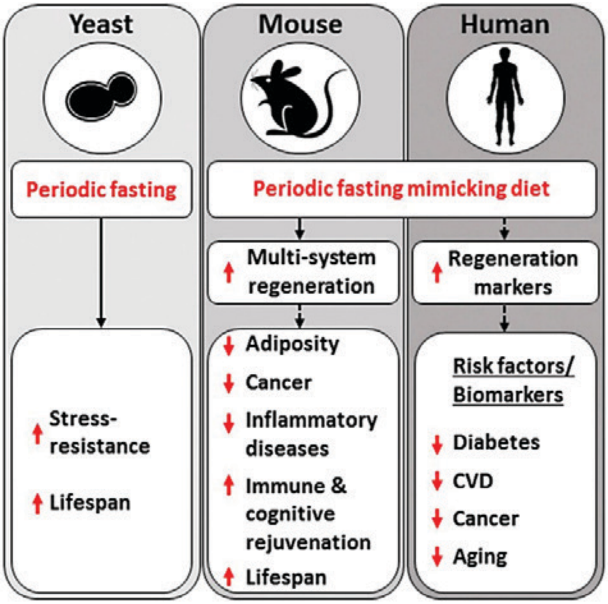

Figure 6. Graphical Abstract.

Reprinted from Cell Metabolism, Volume 22, Issue 1, 2015. Sebastian Brandhorst, In Young Choi, Min Wei, Chia Wei Cheng, Sargis Sedrakyan, Gerardo Navarrete, Louis Dubeau, Li Peng Yap, Ryan Park, Manlio Vinciguerra, Stefano Di Biase, Hamed Mirzaei, Mario G. Mirisola, Patra Childress, Lingyun Ji, Susan Groshen, Fabio Penna, Patrizio Odetti, Laura Perin, Peter S. Conti, Yuji Ikeno, Brian K. Kennedy, Pinchas Cohen, Todd E. Morgan, Tanya B. Dorff, Valter D. Longo. A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan. Pages 86-99. With permission from Elsevier.

Effect of IER on health parameters in humans

In the last decades, more research has been performed exploring the effects of IER on body weight, fat mass as well as metabolic and other health parameters in humans. An overview of observed changes by use of IER in humans is illustrated in **Figure 7**.

Effect of IER on weight and fat in humans

In IER interventions in humans, fat mass loss is usually achieved along with weight loss. In a review including 40 studies implementing multiple forms of IER, 37 of the 40 studies demonstrated weight loss(24). Three studies with lean participants showed no average weight loss. Fat mass was reported in 23 trials, of which 20 reported a decrease. The other three trials tested lean persons or had only a decrease in one of the IER intervention arms. Fat-free mass was measured in 17 trials and of these, nine reported a decrease and eight reported no change. BMI and waist circumference were reported in 13 articles, 10 reported a decrease in BMI and 12 a decrease in waist circumference. The three studies that measured hip circumference all showed that it was reduced by IER. This review shows that almost all IER interventions have a positive effect on both weight and fat, and only in lean persons weight and fat remain similar.

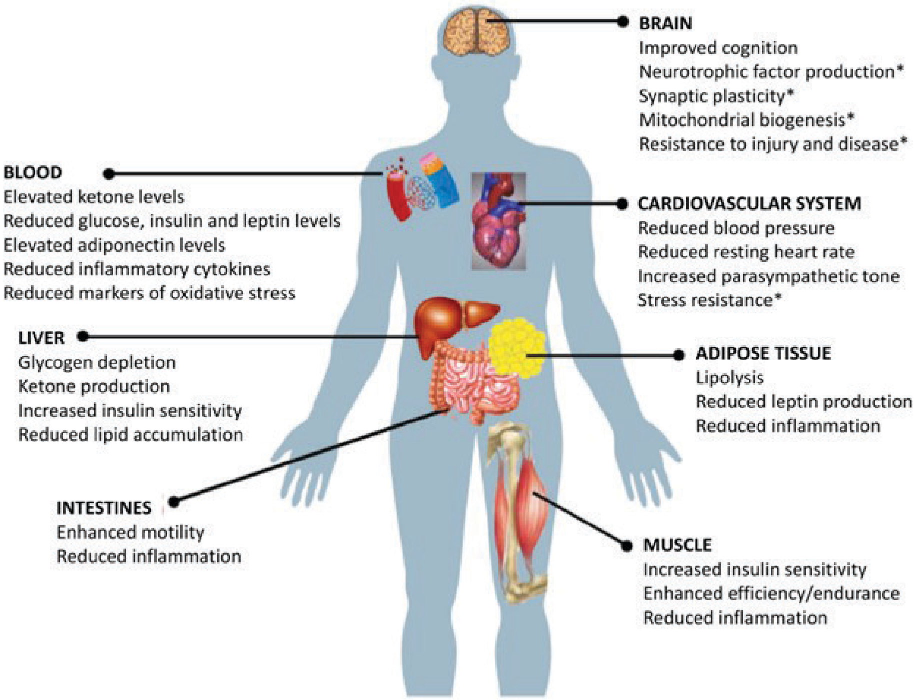

Figure 7. Examples of functional effects and major cellular and molecular responses of various organ systems to IF.

In humans and rodents, IF results in decreased levels of circulating insulin and leptin, elevated ketone levels, and reduced levels of pro-inflammatory cytokines and markers of oxidative stress. Liver cells respond to fasting by generating ketones and by increasing insulin sensitivity and decreasing lipid accumulation. Markers of inflammation in the intestines are reduced by IF. The insulin sensitivity of muscle cells is enhanced and inflammation reduced in muscle cells in response to the metabolic switch triggered by fasting and exercise. Emerging findings further suggest that exercise training in the fasted state may enhance muscle growth and endurance. Robust beneficial effects of IF on the cardiovascular system have been documented and include reduced blood pressure, reduced resting heart rate, increased heart rate variability (improved cardiovascular stress adaptation), and resistance of cardiac muscle to damage in animal models of myocardial infarction. Studies of laboratory animals and human subjects have shown that IF can improve cognition (learning and memory); the underlying mechanisms may involve neurotrophic factors, stimulation of mitochondrial biogenesis and autophagy, and the formation of new synapses. IF also increases the resistance of neurons to stress and suppresses neuroinflammation. *Demonstrated in animal models but not yet evaluated in humans. Reprinted from Obesity, Volume: 26, Issue: 2, 2017, Pages: 254-268. Flipping the Metabolic Switch: Understanding and Applying the Health Benefits of Fasting. Anton SD, Moehl K, Donahoo WT, et al.

Another review focused on the amount of weight and fat lost by different IER interventions. A body weight reduction of 3-9% was achieved in 12-24 weeks in IER interventions with intermittent complete fasting 1-2 days per week(25). Comparable effects were found in IER interventions with ADF with 25% of calories on fasting days with reductions in body weight reductions of 3-7% in 3-12 weeks. Body fat was reduced by 3-5.5% in these interventions, with most of the weight loss due to fat loss, however a part of the weight loss was fat-free mass.

Part of the loss of total fat is the loss of visceral fat. A review summarizing the impact of seven IER interventions on visceral fat, showed reductions of 4-7% after 6-24 weeks treatment(26). In these interventions, the visceral fat loss was mostly paralleled by the percentage of weight loss. It should be noted that visceral fat loss was not measured directly but estimated by measurements of waist circumference.

Proportionally in a study with three ADF interventions of eight weeks an average weight loss of approximately 4 kg was due to 3 kg fat mass loss, 1 kg fat-free mass loss and 0.075-0.135 kg visceral adipose tissue loss (measured by DXA)(27). However, fat-free mass loss might be depending on the body composition of the subjects, for in obese women on IER, fat-free mass loss was approximately 10% of overall weight loss, whereas within non-obese subjects it was as high as 30%(15, 28, 29).

Overall, almost all IER interventions result in weight loss, ranging from 3 to 9%, partly by loss of fat-free mass, but primarily by loss of fat. Concerning long-term effects evidence is limited. One study with 6 months follow-up after the intervention reported no difference in weight regain between a IER and CER intervention(30). More research is needed to draw conclusions. Studies of visceral fat measurements other than waist circumference are scarcely available at this moment and to our knowledge, no data of IER on ectopic fat including hepatic, cardiac and intramyocellular triglyceride stores is currently available.

More research with more defined mechanisms, for example Magnetic Resonance Imaging, will be necessary to gain more insight in the effect of IER on fat distribution.

Effect of IER on metabolic parameters in humans

In addition to the positive effect of IER on fat mass, effects on different metabolic parameters have been observed.

Glucose homeostasis is one of them. In healthy individuals IER regimes do not appear to affect fasting glucose levels(5, 15, 29, 31). However, patients with prediabetes on an ADF diet showed a 3-6 % reduction in fasting glucose(15, 29, 31). A significant decrease in glucose of 11.8 ± 6.9 mg/dl was also observed in obese patients on an FMD(5). Studies with IER regimens ranging from 8-24 weeks also showed a decrease in fasting insulin levels of 11%-57% after 3-24 weeks(32). The largest decrease in insulin levels was seen in the studies with the highest energy restriction. This effect on fasting insulin levels was independent of the prediabetes status of participants. Insulin resistance was also reduced by IER(32). This effect was more pronounced in studies with greater weight loss. In type 2 diabetes patients on IER consisting of 75% energy restriction on five consecutive days every five weeks for 15 weeks HbA1c was normalized in 47% of the patients(33). IER consisting of energy restriction one day every week for 15 weeks led to a normalized HbA1c in 31% of the patients, compared to 8 % in the control group(33). Although the differences between the groups were clinically relevant, they were not statistically significant. This beneficial effect on HbA1c was independent of the effects of IER on weight loss.

Variable results of the effect of IER are found on total and LDL cholesterol concentrations. Some trials report a reduction in total cholesterol of 6-21% and LDL cholesterol from 7-32%, while others report no effect(32). Significant reductions in total and LDL cholesterol were only found in studies in which participants had elevated cholesterol. Triglyceride concentrations decreased in the majority of IER studies, with reductions of 16-42%(32). This effect was dependent on the amount of weight loss.

Also, systolic and diastolic blood pressure decline in patients with borderline hypertension was dependent on weight loss(32). Only IER interventions that achieved 6-7% weight loss showed a decrease of 3-8% in systolic blood pressure and 6-10% in diastolic blood pressure after 6-24 weeks.

Taking all these results into account, IER interventions can have beneficial effects on glucose homeostasis, cholesterol, triglycerides and blood pressure in patients with elevated baseline measures. Most effects seem to be weight loss related, except for effects on insulin levels and HbA1c levels, which have been shown to decline by IER independent of weight loss. More long-term trials should be conducted to draw conclusions regarding the sustainability of the effects. Results from a study in which long-term metabolic effects of an intermittent FMD for 5 consecutive days every month for 1 year in patients with type 2 diabetes will maybe shed new light on this subject(34).

Effect of IER on other health parameters in humans

The effect of IER on many other health parameters has been examined, including inflammation related diseases, cancer and cognitive function. In one study with an ADF regimen in overweight patients with moderate asthma, pulmonary function and asthma symptoms improved(35). This reduction in symptoms was associated with significant reduction in inflammatory and oxidative stress marker levels in the blood. In the autoimmune disease multiple sclerosis, only two small pilot studies have been conducted, which show improvement following IER on several scales concerning well-being and quality of life(36, 37). IER has not yet been studied in rheumatoid arthritis patients, but a review looking at short term energy restriction interventions suggests a positive effect of fasting on subjective disease symptoms as well as rheumatoid arthritis activity(38).

Most clinical trials researching IER in cancer patients have so far focused on compliance and side effects, and only a few evaluated efficacy. Case studies suggest that IER can suppress tumor growth and extend survival(7). Use of a FMD as an adjunct to neoadjuvant chemotherapy for breast cancer showed no difference in toxicity between the FMD and the control group, while the control group received additional dexamethasone(39). A radiologically complete or partial response occurred significantly more often in the FMD group (OR 3.168). Also, a 90-100% tumor-cell loss was more likely to occur in patients on the FMD (OR 4.109). Cognitive function also can be positively influenced by use of IER, as several studies have demonstrated improvement in verbal memory, executive function, global cognition and working memory in persons on IER(7).

Concerning psychological and psychiatric effects, an ADF regimen in patients with obesity had a small but statistically significant effect on binge eating and depression(40). Purgative behavior and fear of fatness were unchanged, perceived body image was improved and restrictive eating was increased.

Research of the effect of IER on the human gut microbiome is still in its infancy. An increase in the abundance of several protective microbial families including Bifidobacteriaceae, Lactobacillaceae and Akkermansisaceae has been observed, suggesting fasting might be used to positively influence the gut microbiota(41).

In conclusion, relatively few studies have evaluated the impact of IER on inflammatory diseases, cancer, cognitive function, mental health and gut microbiome composition. Although these studies yielded promising results, there is not enough evidence to date to draw definitive conclusions. Further exploration of the benefits of IER in the treatment of several diseases is warranted.

The effect of IER versus CER on weight and fat in humans

IER is often compared with CER. Theoretically, IER could have advantages over CER concerning visceral fat loss, as IER produces more intense lipolytic stimuli compared to CER. Visceral adipocytes are more responsive to these stimuli compared to their subcutaneous counterparts, therefore IER might induce proportionally more visceral fat loss(42, 43).

A meta-analysis found a positive correlation between the ratio of visceral fat reduction and the degree of energy restriction, independent of weight loss. Since IER has periods with more energy restriction compared to CER, this might also favor IER(44).

There are some reviews and studies comparing the effect on weight and fat in IER and CER interventions. A review including twelve human trials concluded that the effect of IER appears to be comparable to CER with respect to weight loss, BMI, waist circumference, hip circumference, fat loss and free fat loss(24). Overall, most studies yielded no significant differences between the IER and CER interventions, some had better results with IER and others with CER. Another review also compared IER and CER interventions, and categorized the trails in short duration (8-12 weeks), which included 3 IER interventions, and moderate duration(13-30 weeks)(42), which included 2 IER interventions. Weight loss was found to be less in IER compared to CER (4.5% vs 8.8) in short duration trials. In moderate duration trials however, weight loss was similar between IER and CER (10.0% vs 8.8%). In two trials of 12 months, weight loss was not significantly different between the ADF and CER interventions. Relative to the control group total weight loss of -6.0% was observed in the IER group and -5.3% in the CER group in one trial(45). In the other trial this was -6.8 kg in the IER groups vs -5.0 kg in the CER group(46). Total fat reduction in short duration studies was also less in IER compared to CER interventions (9.0% vs 15.3%)(42). In studies of moderate duration IER reduced total fat mass more effectively than CER (18.0% vs 14.8%). However, in long-term trials, no difference was found in total fat mass loss between both groups(45, 46). Visceral fat, estimated by waist circumference, was reduced comparably between short-term IER and CER (5.5% vs 6.5%). In trials of moderate duration, IER showed a greater reduction in visceral fat compared to CER (9.0% vs 6.2%)(42). The effect on the ratio of waist circumference reduction to total fat mass reduction, showed opposite results, with greater reduction of the ratio in IER than CER (0.67 vs 0.42) diets in short duration trials, and no effect in moderate duration trials (0.45 for IER vs 0.41 for CER). In the long duration trials, also no significant difference in visceral fat loss was found between the two interventions(45, 46).

Concluding, in short-duration trials, IER interventions seem less effective on weight and fat loss compared to CER interventions, in moderate-duration interventions fat mass loss seems more effective in IER interventions, and in long-duration trials no difference was found between groups in weight loss, fat loss or visceral fat loss. No clear superiority of either IER or CER is apparent based on current data, but especially concerning visceral fat too few studies have been conducted to draw hard conclusions.

Sustainability of IER

Several factors are important for the sustainability of a lifestyle change such as IER. As persons are individually very different, one dietary regimen can be easy to follow for some but can be very hard to comply to for others. Adherence to CER often begins to decline at 6-8 weeks and progressively worsens thereafter(42). Some patients found IER less demanding, as the diet was easier to understand and follow compared to CER(47). Here we will describe current knowledge for IER diets concerning dropout rates, adherence to the intervention, feeling hungry, effect on mood and behavioral change over time.

Dropout can be an indicator of non-compliance. Fifteen IER interventions reported dropout rates ranging from 0-65%. Dropouts because of the inability to adhere to the diet were reported in 12 studies and ranged from 3-10%(24). However, overall dropout was similar in IER and CER intervention studies(24, 48). The proportion of people dropping out due to inability to adhere to IER or CER was only mentioned in two studies. Both showed a greater dropout rate due to inability to adhere to CER compared to IER(3, 49).

Although data concerning adherence are important for estimating sustainability of diets, to date these data are limited(50). Self-reported adherence varied widely between studies, with percentages of 43-97% after 3 months. In studies with one year of follow up, self-reported adherence was 21-44%. Dietary adherence did not significantly differ between IER and CER in a six-month ADF intervention(45).

Change in eating habits on the non-restricted days when conducting an IER is an interesting and important part of sustainability. Persons in a CER versus IER trial with a 2-5 IER regime, consumed 23% less calories than the prescribed amount on non-restricted days, which was comparable with the number of calories of the CER(3). This effect was also seen in an ADF intervention, where people ate less calories than instructed on the non-fasting days(45). However there was also a tendency of eating more than instructed on the fasting days.

Ability to adhere to IER might be better if people feel less hungry. Several studies report that subjects became habituated to the ADF regimen and felt very little hunger on the fast day, with no over-eating on the feast day, even feeling an increase of fullness and satisfaction(29, 31). Not all studies report this effect. Out of ten trials describing appetite, four demonstrated an increase of appetite and six a decrease or no significant effect. However, in all studies a significant weight loss was observed(24).

The effect of a diet on mood may also influence adherence. Unfortunately, only few trials report the impact on mood. Five trials showed that IER had a positive effect on mood, with bad temper only reported in 3% of the participants, however in a trial with lean participants, an overall worsening of mood was reported(24).

The combined results so far could indicate that for some persons CER is more suitable and for others IER, but overall, there is no evident superiority to either IER or CER regarding adherence to the diet.

IER interventions might be an option to try if former CER interventions were unsuccessful. Some participants felt less hungry and had a better mood on IER and experienced it less demanding than CER. Inter-individual differences in response to a dietary treatment are likely due to a combination of behavioral, environmental and psychosocial factors(50). It will be interesting to investigate the effect of IER on behavioral context – and consequences, and to investigate which cognitive, environmental or physiological factors influence adherence to IER. Conducting qualitative research with for example focus groups could therefore be useful. Furthermore, as not many trials incorporate treatment satisfaction or quality of life questionnaires, this could be an interesting and valuable addition to future research. Knowing more about the sustainability or IER can help doctors and patients in shared decision making on dietary interventions.

Potential risks of IER

While fasting, the human body has no or limited access to essential nutrients. After many weeks of continuous fasting (approximately 5-7 weeks in healthy adults), fasting converts into starvation, which causes vital organs and muscles to be consumed for energy(4, 51). Starvation has many effects on the body, including weight loss, diarrhea, delirium and eventually death. Since IER only applies fasting periods for a limited period of time, these adverse events are prevented. In trials of shorter, more frequent fasts, including periodic fasting and ADF, severe events have not been reported(4). More commonly, IER may cause mild adverse events such as dehydration, nausea, headaches, dizziness, syncope, weakness, feeling cold, feeling irritable, bad breath, low energy and hunger pangs(9, 40, 51-53). Usually, these side effects are mild and do not hinder participants in continuing the fasting period. In a review including nine IER trials, none of these trials reported any serious adverse events related to the dietary intervention(48). Many side effects are linked to dehydration. It is important to hydrate well during any fasting regimen, because the fluids must be replaced that would normally be consumed in foods(53). In general, when long-term intermittent fasting is undertaken, one must be aware of protein malnutrition and vitamin and mineral malnutrition(6, 54). If fasting is undertaken regularly, it might be necessary to use vitamin and/or mineral supplements(6, 53).

There are specific populations that have to be extra careful while fasting(53). Patients with diabetes should carefully consider if IER is the best suitable option for them and should not undertake this without the help of their physician. IER in combination with antidiabetic medication, especially sulfonylureas or insulin, can induce hypoglycemia. Treating physicians should adjust medication and, if necessary, plan additional glucose monitoring during the fasting periods for example flash glucose monitoring(55). Other populations should refrain from fasting all together, like pregnant and lactating women, young children, adults of advanced age and frail older adults(9). These groups have a higher risk of dehydration and not receiving the minimal amount of nutrients for growth and development.

Overall, for IER only mild side effects have been reported but there are some risks to consider.

Conclusion

Positive effects of IER on weight loss, fat mass loss, visceral fat loss, glucose tolerance and many other parameters have been observed in both animal studies and clinical trials. Although several studies have indicated that benefits of IER are dissociated from the effects on weight loss(7), no overall superiority of IER over CER was demonstrated. For individuals who have tried a CER intervention unsuccessfully or who are unwilling to try a CER intervention, an IER intervention could be an option. Safety should always be considered. Several trials report positive effects of IER on multiple health parameters, however further research is necessary to prove health improvement in the long term. Long term studies and long term follow up are necessary to create a better understanding of various possible benefits and harms of using IER.

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3

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