FASTING (CALORIE RESTRICTION)

Health and Longevity

In the previous section we discussed the evolution and history of fasting. We also spent time exploring the health benefits of weight loss and studies on the results of simple calorie restriction. We also discussed how many calories we should be eating. Now we can explore other ways to reduce our calories for weight loss and health — *fasting*.

There are not nearly the number of research studies about fasting on humans as there are about simple calorie restriction and much of our knowledge about fasting is from animal studies. I will be discussing primarily *human studies* and, when needed, comment on animal studies. Together we will figure out the best approach to a healthy lifestyle that we can use for both weight loss and maintaining our new bodies for the rest of our lives.

Potential Benefits of Fasting

Simply losing weight has numerous health benefits, but what are the benefits of *fasting*, if any? The primary result of fasting, as opposed to daily calorie restriction, is the production of *ketones*. Ketones start being produced around 12 hours into a fast and continue to slowly ramp up until about day 2 or 3 when ketone production rapidly increases (see section on physiology of fasting). I always prefer human studies when possible. Unfortunately, human studies are limited and, for the most part, are observational studies of religious fasting (Ramadan), studies of eating patterns and smaller experimental studies. The bulk of *scientific evidence* about fasting has predominately come from *animal studies*.

While we have several intermittent fasting studies with humans and weight loss, the literature is not very robust when it comes to human studies on health benefits of fasting (such as cancer, neurodegenerative disease, and aging).

Remember from the last section, starvation in many studies, shows a prolongation of life. Animals that eat only every other day live up to 30% longer than those that eat every day (Goodrick CL, 1983), they are resistant to diabetes (Anson RM, 2003), cancers (Berrigan D, 2002) (Lee C, 2012) and neurodegenerative disease (Duan W, 2003) (Halagappa VK, 2007) (Arumugam TV, 2010).

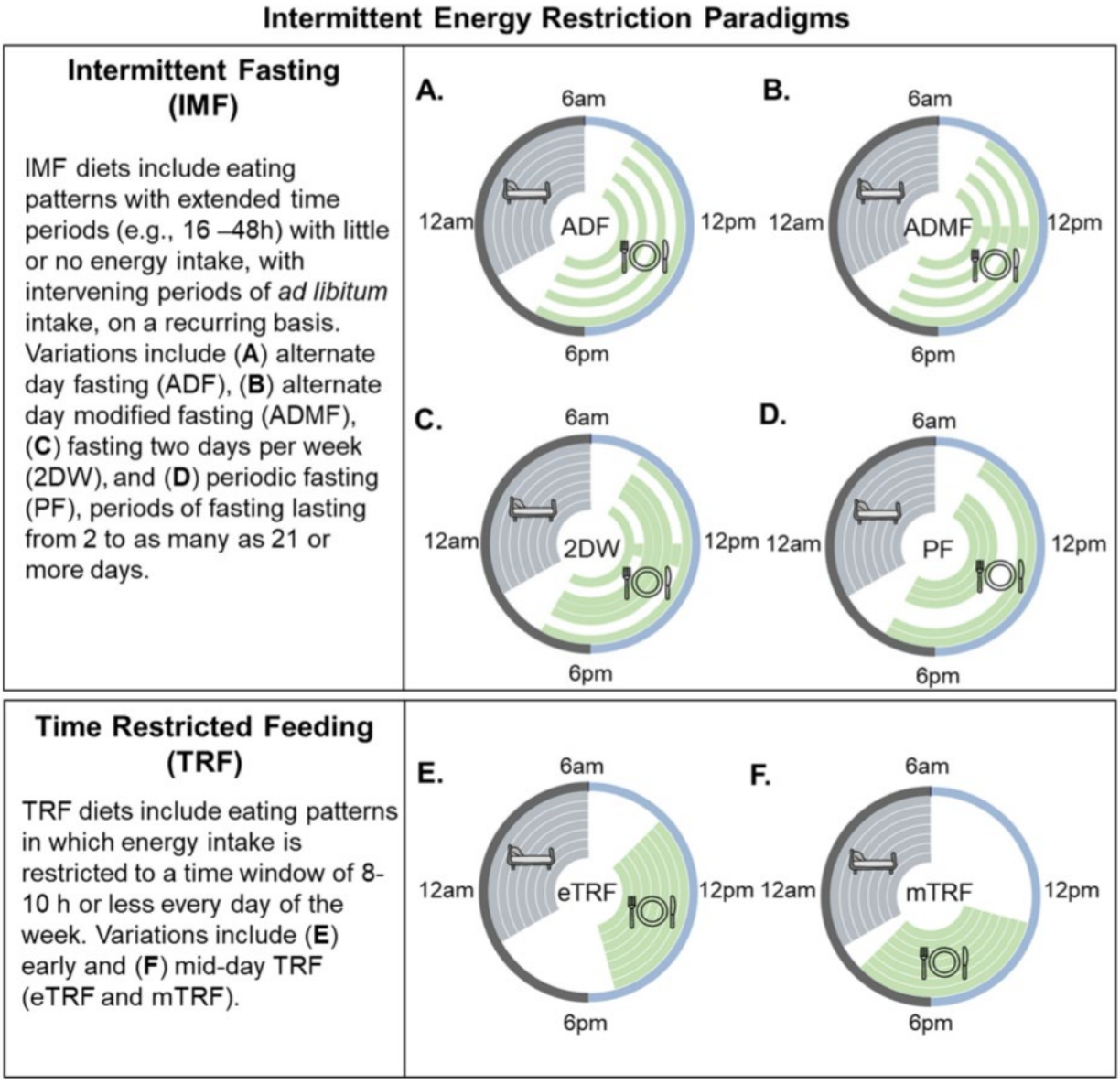
Flavors of Fasting

There does not appear to be one definition of Intermittent Fasting (IF) in available literature. IF is an all-encompassing term including many different forms of fasting which makes finding and comparing research papers difficult. The key with any method of fasting is that there is a period of food restriction alternating with periods of normal eating.

- **Time-restricted fasting (TRF)** – time-restricted (12 to <24 hours) fasting involves limiting the consumption of calories to a certain part of the day and fasting the other part. For example, eat during a twelve-hour window or an eight-hour window and not eating the rest of the day. The

16:8 diet is an example of this, you have a 16-hour fast each day followed by an eight-hour eating window.

- **Alternate-day fasting (ADF)** – involves alternating between a 24-hour fast followed by a 24-hour feast day. This can either be "complete", water only, or "modified fasting" allowing up to 25% of your normal calories on the fast day. One example of modified ADF is the 5:2 diet which has you fast two non-consecutive days each week allowing 500 calories on the fast days.
- **Periodic prolonged fasting (PF) or intermittent calorie restriction (ICR)** – This method has you fasting longer than 24 hours and the fast can last from one day to several weeks.



From Rynders et al. (Corey A Rynders, 2019)

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Intermittent Fasting Health Benefits

While animal studies show multiple health benefits including life extension from fasting, not all the benefits have been observed in humans. The lack of demonstrated benefits in humans are due to difficulties of performing the study and different physiologies between humans and test animals. Another issue is determining if the observed health benefit is the result of simply losing weight or something inherent to fasting *itself*.

One systematic review by Ganesan (Kavitha Ganesan, 2018) between 2000 and 2018 found 4 random controlled trials (not counting reviews or meta-analysis) in humans evaluating intermittent fasting. The criteria were 18-year-old and older, needed to be a randomized controlled trial, and looking at body weight as the primary subject. The four included studies (Varady KA B. S., 2013) (H LANTZ, 2003) (Bhutani S, 2013) (Leonie K Heilbronn, 2005) examined an ADF diet with 25% of normal calories consumed on the fast day and a normal diet on feast days. This study showed there was a significant reduction in fat mass, LDL and triglycerides.

Inflammation

One study looked at patients (human) with asthma and a BMI >30 (Johnson JB, 2007). The subjects were put on an ADF plan with 20% of calories on fasting days and normal eating on feast days. In 8 weeks, they lost 8% of their body weight. Measures of asthma improved significantly within 2 weeks. The authors commented that while major weight loss from surgery (13%) has some improvement in pulmonary function, this study showed improvements with only 4% weight loss suggesting that improvements were not just from weight loss, but from the ADF diet plan. Regarding the reasons for improvement, they opined that 1) weight loss reduces free radical production; and 2) ADF introduced a mild stress and the cells increased antioxidant systems in the body. This has also been demonstrated in rodents.

Heart Disease Protection

In obese subjects (BMI 30–39.99) ADF has been shown to reduce weight and visceral fat (Varady KA B. S., 2013). Cardiovascular benefits are also realized such as lower LDL of 20–25% and lower triglycerides of 15–30%, and lower blood pressure in obese subjects. The inflammatory marker, C-reactive protein, also decreased with the ADF diet.

As reviewed by Anton (Stephen D. Anton, 2018) cardiovascular risk factors are improved with a reduction of cholesterol from 6 to 21% and LDL by 7 to 32%. Triglycerides are reduced 16 to 42%. Systolic blood pressure drops 3 to 8% and diastolic by 6 to 10%. These blood pressure effects were primarily driven by weight loss.

A survey of persons presenting for coronary angiograms in Utah identified periodic fasting as preventive for coronary artery disease (CAD). The Church of Jesus Christ of Latter-day Saints (LDS or Mormons) undergo routine fasting one-day per month (first Sunday; no food for two meals), along with no smoking and other proscriptions. When patients were asked about their religious preference at the time of doing a coronary angiogram, 61% of LDS and 66% of all others had coronary artery disease (Benjamin D. Horne, 2008). A second survey of LDS members specifically asked about fasting and found that 64% of

persons fasting had CAD vs 76% of all others. Fasting, just one day per month, also had a lower diabetes risk.

Diabetes

The Mormon Church encourages intermittent fasting and the incidence of diabetes among those who fast was significantly less (Horne BD M. J., 2012). Another study of people with prediabetes (A1c between 5.5 and 6.5) showed that both TRF and ADF forms of fasting dropped fasting glucose by 3 to 6% (Varady KA B. S., 2009) (Varady KA B. S., 2013).

In general, some of the health benefits in intermittent fasting include:

- Improved glucose metabolism (Michelle Harvie, 2013) (Arguin H, 2012) (Harvie MN, 2011).
- Reduced inflammation (Faris MA, 2012) (Johnson JB, 2007).
- Reduced blood pressure (Harvie MN, 2011) (Varady KA, 2013) (KK Hoddy, 2014).
- Improved cardiovascular health (Horne BD, 2012) (Horne BD M. J., 2013) (Klempel MC, 2012) (Varady KA B. S., 2009).
- Increased resistance of cells to stress and disease (Wegman MP, 2015) (Johnson JB, 2007).
- Longevity - Animals that eat only every other day (alternate day fasting) live up to 30% longer than those that eat every day (Goodrick CL, 1983).

As commented upon by Anton (Stephen D. Anton, 2018) many of the beneficial effects of IF may simply be the effect of weight and body fat reduction, not necessarily a result of fasting itself.

Time Restricted Feeding (TRF)

In animal models, IF has been found to improve cardiometabolic health, reduce cancer incidence, slow tumor growth, regenerate organs by increasing stem cell production, and increase lifespan. In humans it appears that IF decreases body weight, insulin levels, blood pressure, inflammation, and appetite.

Most of the benefits of IF appear to be from simple calorie or energy restriction, however, TRF may have benefits beyond simple calorie restriction in both animals and humans. According to Jamshed (Humaira Jamshed, 2019) animal studies report TRF improves blood sugar control, blood pressure, lipids, fatty liver, inflammation, slows tumor growth, and increases lifespan, even when the total food intake is the same. Jamshed states the review of nine trials of TRF in humans showed improved cardiometabolic markers when calories are consumed early or in the middle of the day but either worsens or has no effect on these markers when consumed late in the day. It is theorized that our bodies circadian rhythms and clocks are the reason for this disparity. We know that many of our hormones peak in the morning and are lowest at night, suggesting that we need to eat in harmony with our clocks.

Time-Restricted Feeding (TRF) – HUMAN studies.

There are several studies in humans for ADF, yet relatively few human trials on TRF. There is a 2018 study of restricting your consumption of calories to just 8 hours daily (10am to 6pm) without any restrictions placed on the type or quantity of foods consumed. The subjects unintentionally ate approximately 300 fewer calories daily resulting in a 2.6% weight loss in 12 weeks (Kelsey Gabel, 2018). One advantage of TRF is unintentional, reduced-calorie consumption. Compared to ADF the weight loss

was less, probably because ADF resulted in a larger, unintentional calorie deficit (25-35%) compared to 20% in the TRF study. No improvement in insulin, triglycerides or other parameters were noted, most likely due to insufficient weight loss. Studies indicate it requires at least a 5% weight loss for improvements (Ryan DH, 2017) in biomarkers.

Observational studies on religious fasting is not an actual trial but rather an observation of peoples that have certain behaviors. Ramadan fasting requires a daily fasting window from sunrise to sunset with no other dietary restriction. One large analysis of 35 studies showed an average weight loss of 1.24kg from just not eating during the day (Sadeghirad B, 2012). Of note, this pattern, eating at night instead of daytime, is contrary to our normal biological clocks and the results might have been better if the fasting was at night instead of during the day.

A 2013 review of 30 studies showed that after Ramadan fasting, LDL and fasting blood glucose levels were decreased along with triglycerides (Kul S, 2013). Other studies show reduced inflammatory markers from Ramadan (Sarah J Mitchell, 2019) and lowering of diabetic markers (A1c) (Yeoh EC, 2015)

The Church of Jesus Christ of Latter-Day Saints encourages fasting and those who do have lower weight, lower glucose levels, less diabetes and coronary artery disease. On average they live 7.3 years longer than other white adults due to a lifestyle of not smoking, a vegetarian diet and regular exercise. They only eat TWO meals daily with the last meal in the afternoon.

What about ketosis? TRF of 6–8 hours really is not long enough to produce significant ketosis (that takes 2–3 days). However, many of the benefits of prolonged fasting can be seen. For example, autophagy (Mammucari, Schiaffino, & Sandri, 2008), the process of cleaning up our cells of unwanted junk which is fundamental to combat stress and preserve normal cell function. "*It is possible to speculate that dysregulation of autophagy could be associated with hypertension, obesity, diabetes mellitus and end organ damage*" (Gatica, Chiong, Lavandero, & Klionsky, 2015).

TRF may reduce many markers of inflammation which can have protective effects against coronary heart disease and atherosclerosis (Moro, et al., 2016). Fasting can also affect the circadian rhythm. In mice it is protective against obesity, liver disease and inflammation — even when fed a high-fat diet. TRF can also improve the antiaging mechanisms (Hatori, et al., 2012).

Rynders (Corey A Rynders, 2019) found that morning meal consumption on TRF lost more weight. Additionally, food intake at night (as in shift work) is linked to obesity, independent of energy intake. None of the reviewed studies compared TRF to CR. One of the reviewed studies showed that subjects who ate over 14 hours daily spontaneously consumed 20% *fewer* calories when restricted to a 10–12 hour window. They also had less hunger and improved sleep.

Early TRF (8am to 2pm) compared to later (8am to 8pm), showed improved glucose levels with increased ketones, and expression of anti-aging effects in humans (Humaira Jamshed, 2019). This is the first study in humans to look at TRF and gene expression and diurnal patterns in cardiometabolic risk factors in humans.

- 24-hour glucose levels were lower. When we eat dinner at 8 pm there is a prolonged increase in glucose throughout the night. Shifting the meal to mid-afternoon *or earlier* improved this.
- Elevated ketones (beta-hydroxybutyrate) in the morning. This helps reduce oxidative stress, preserve lean mass and decrease hunger.

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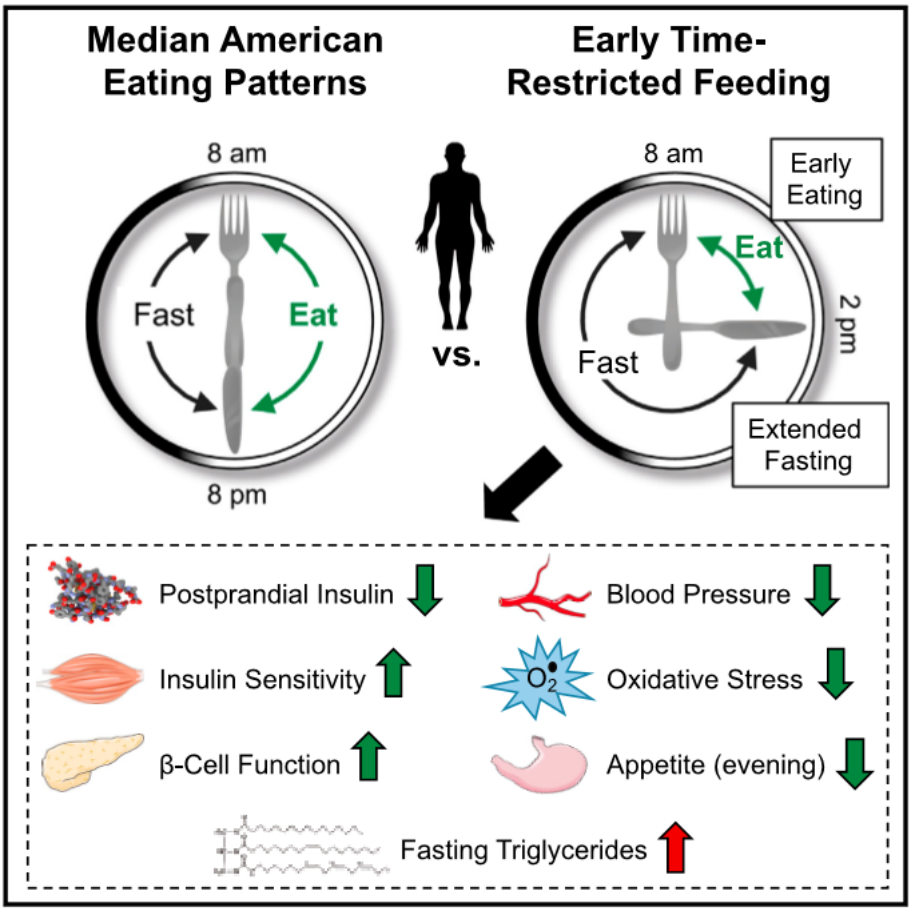
- Elevated BDNF (promotes brain growth and survival) in the evening.
- The author believes that a *shorter interval between meals* (still digesting) and *eating earlier in the day* promoted many of the anti-aging and autophagy gene activations and hormone changes.

Fasting, calorie restriction and the ketogenic diet all share many of the same pathways.



Highlights

- **Early time-restricted feeding (eTRF) increases insulin sensitivity**
- **eTRF also improves β cell function and lowers blood pressure and oxidative stress**
- **eTRF lowers the desire to eat in the evening, which may facilitate weight loss**
- **Intermittent fasting can improve health even in the absence of weight loss**

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CR vs IF For Weight Loss, Fat Loss And Fat Free Mass Sparing

In 2011, one of the leading researchers in weight loss (Varady, 2011) did a review of studies comparing IF vs CR. Here are some of the pertinent findings of this review:

> **Total Weight Loss:** Short-term CR of 25–60% (4 to 12 weeks) showed weight loss of 5–8% and at 13 to 24 weeks weight loss was 6–19%. The IF groups obtained 3–4% weight loss at 2–3 weeks and 6–8% weight loss at 8–12 weeks.

What we are hoping for is weight loss with sparing of FFM since muscle is our body's furnace and main metabolic source. Dietary restriction alone usually results in 75% of weight lost as fat, 25% lost as muscle (A. S. Ryan, 1995).

> **Fat and lean mass loss:** Varady made these observations on body fat and lean mass. The short-term trials (4–12 weeks) of CR reduced body fat by 10–20% and moderate-term (13–24 weeks) trials lost 11–34% of body fat. Fat-free mass only had minimal reductions of 1–4% short-term and 2–8% for moderate-term. These studies also showed that roughly 1 pound of muscle is lost for every 4–5 pounds of weight. Some studies tried to limit muscle loss with high protein diets which did not help.
>
> Varady reported that IF was similar to CR for body fat and lean mass reduction. Short-term studies had 11–16% fat mass lost with 1–4% fat-free loss. There were no moderate-term studies reporting fat and muscle loss. It did appear that a lower proportion of lean mass was lost (90% fat, 10% fat-free) in IF compared to CR (75% fat, 25% fat-free). The author pointed out that the difference could be a result of different methods of measurement.
>
> **Visceral fat** (the fat in the abdominal cavity, under the muscle) is the fat responsible for heart disease, blood pressure, elevated cholesterol and diabetes. Varady reported that the amount (relative percentage) of visceral fat loss was the same as total fat loss in the CR groups. This was not affected by diets that changed the amount of protein. IF diets had comparable amounts of visceral fat loss with CR.

Regarding weight loss maintenance, two of the human studies went out to 24 months and did not find any difference between CR and IF groups.

An extreme comparison is very-low-calorie-diets (VLCD), which provide less than 800 calories daily, vs alternate-day-fasting (ADF) (B A Alhamdan, 2016). Once the studies were adjusted for BMI and duration of the studies there was no significant difference between dietary methods for total weight loss or fat-free mass (muscle/bone). However, the ADF group did lose more total fat compared to VLCDs.

In 2016 Catenacci compared CR to ADF (Victoria A. Catenacci, 2016). In this study the participants could eat whatever they wanted on the feast days and no food on fast days. The CR group was assigned to a 400-calorie daily deficit. The ADF lost marginally more weight than the CR group with no significant difference in fat mass loss. The main difference showed up when the participants were followed up after the diet and regained weight. The CR group gained 1.2kg of fat and 1.1kg of muscle while the ADF group lost *another* 0.4kg of fat and gained 2kg of muscle.

A review (C S Davis, 2016) of the literature comparing calorie restriction CR to ADF found that at similar caloric levels there were similar amounts of weight loss. Seimon in his review also found similar weight loss effectiveness between intermittent fasting and CR (Radhika V Seimon, 2015). The comparative effectiveness in weight loss and cardiovascular risk factors was echoed by Sundfor (T M Sundfor, 2018)

A 2017 paper (John F. Trepanowski, 2017) highlighted the results of 100 people assigned to either an ADF group with 25% of energy needs on fasting days and 125% of energy needs on feast days, compared to a CR group at 75% of energy needs. This study had the participants follow the diet for 6 months and then followed for 6 more months *after* the diet. It is interesting, but not surprising, that the ADF group had the highest dropout rate of 38% compared to 29% for the CR group and 26% for the control group. The total weight loss was the same at 6 months, 6.8%, and similar at 12 months, 6% vs 5.3%. There were no significant differences between groups in fat mass, lean mass, or visceral fat mass at 6-or 12-months.

One note about the Trepanowski study is that the ADF participants tended to eat more on fast days and eat less (than the 125% of energy needs) on feast days. This shows that compliance to fasting is difficult with higher dropouts and less adherence than simple calorie restriction.

Another 2017 review of CR vs IF was done by Harvie (Harvie M, 2017). Harvie concluded that there is a lack of high-quality data to determine if IF or CR is better for weight loss. Harvie also concluded that no decision could be made whether one form of weight loss was better for visceral fat stores, adipocyte size, FFM, insulin resistance, metabolism and metabolic flexibility.

Also in 2017 a review by Mattson et al (Mark P Mattson, 2017) commented that the similar weight and fat free mass loss between IF and CR is really dependent on the protein content of the diet, rather than the pattern of energy restriction. Exercise also helps to maintain FFM during weight loss.

Regarding weight loss maintenance, Mattson commented that long term (>10% weight loss maintained >12 months) success for CR was between 20–50% of subjects depending on ongoing support. There are limited studies in humans for IF to compare with CR.

In Patterson's 2017 review of literature (Ruth E. Patterson, 2017) she commented that the sparse data on ADF (complete fasting on fasting days) does suggest that it can result in modest weight loss and improve some metabolic parameters. However, extreme hunger on the fasting days may prevent this from being a practical health intervention.

Patterson also reviewed modified ADF (eating 25% of daily energy needs on the fasting day). The studies that compared modified ADF to daily calorie restriction (CR) failed to show any benefit on weight loss. Two studies showed lower insulin levels compared to CR, but all other biomarkers were the same. Five reviews and meta-analyses (summarized by Patterson) failed to show any benefit of modified ADF over CR.

In 2018 a review of 11 studies directly compared CR with IF (Iolanda Cioffi, 2018). In this meta-analysis, the CR studies ranged in weight loss from 4.3% to 12.1% while the IF groups ranged from 5.2% to 12.9%. This review looked at fat loss and fat-free mass loss (muscle/bone) in both CR and IF groups and found no significant difference between groups.

Another 2019 review study compared both ADF and TRF to CR for weight loss (Corey A Rynders, 2019). Of 11 studies reviewed, 9 out of 11 showed comparable weight loss for ADF compared to CR. However, there was more body fat loss in the ADF groups compared to CR.

There is no clinically significant difference between calorie restriction and intermittent fasting regarding total weight loss, fat loss, or fat free mass loss.

Since there are no clinically significant differences between calorie restriction and fasting regarding weight loss, are there any potential health benefits from fasting?

Diabetes

When IF and CR are compared in humans there again appear to be similar effects. Limited studies on IF have been performed in humans and the results are mixed. In the review by Mattson, there are different outcomes for normal weight and obese subjects. Some also suggest a gender difference between men and women.

Cardiovascular Disease

Mattson again reported similar effects of IF and CR on blood pressure, triglycerides, increased LDL size. Only Hill reported a greater reduction in serum cholesterol with IF (14%) compared to 6% for CR (Hill JO, 1989).

A 2016 review of IF vs CR again confirmed that both are equally effective for weight loss (Michelle Headland, 2016) and further concluded that there is no evidence of superior effects on CVD risk markers (blood pressure, lipids, insulin, glucose).

Next, in 2018, Cioffi searched the literature comparing IF to CR for weight loss and cardiometabolic outcomes (Iolanda Cioffi, 2018). Her 11 trials included the 5:2 or similar diets and had the same conclusion as Headland, there were no differences.

Cancer

Again, from Mattson, there is no data regarding the effects of IF and cancer in humans. I previously mentioned that there are some 13 different cancers associated with obesity (Renehan AG, 2008). Unfortunately, we do not know if weight loss effects the cancer once it is detected, although it is reasonable to suppose that weight loss *before* developing cancer can help prevent its occurrence. There are biomarkers that are associated with the risk of cancer (insulin, cytokines, inflammation) which are believed to be mediators between obesity and cancer in humans.

In humans, circulating insulin-like growth factor-1 (IGF-1) does not change in response to CR or weight loss (they do change in mice studies). But IF and CR both increase the binding sites (proteins) for IFG and IGFBP-2 after fasting.

Interestingly, a 5 day per month fast of a low-protein, low-energy diet (34-54% with 0.25 grams protein/kg weight) with a “normal diet” the rest of the month lowered IGF-1 by 15%.

Adiponectin is a protein hormone produced by fatty tissue that helps regulate glucose levels and fatty acid breakdown. Adiponectin influences the body's response to insulin and helps the body's anti-inflammatory responses which protects against damage to the arteries, and cancer formation. In obesity, adiponectin levels are reduced. Adiponectin levels increase in CR only with large reductions in body and visceral fat (>10%) while some studies show a 30% increase in adiponectin during IF with just 4% weight loss and 11% body fat according to Mattson.

Finally, Mattson commented on other markers of inflammation. C-reactive protein (CRP) drops 2–3% for every 1% weight loss in both CR and IF. This holds true with other inflammatory biomarkers.

Longevity

Most studies on fasting are with research animals and while the results are very interesting, I am more concerned with human studies. Sometimes animals do not equate to human studies, for example, IGF-1 changes in mice with diet but does not necessarily change in humans. This is one reason why we need to be wary of what we hear and read in the lay press. Just because it works in animals does not mean it will work in humans.

Calorie restriction has consistently been found to extend both the maximum and average life span in many animal models. Prolonged calorie restriction extends the lifespan in a variety of species such as yeast, worms, fish, rats, and mice. And we already have seen that calorie restriction and weight loss has numerous health benefits. In humans, caloric restriction has improved health outcomes including heart, diabetes, oxidative damage and other biomarkers (Stephen Anton, 2013).

CONCLUDING THOUGHTS

The overall driving goal needs to be weight loss which has the largest effect on health. Just losing weight, if you are obese, helps (Ryan DH, 2017) prevent type 2 diabetes, blood pressure and HDL cholesterol. At 10–15% weight loss, sleep apnea and non-alcoholic fatty liver disease is improved. There is also improvement in quality of life, depression, mobility, sexual dysfunction, and urinary stress incontinence with just modest (5–10%) weight loss. Polycystic ovarian syndrome and infertility is improved with as little as 2–5% weight loss.

It is impossible to compare animal and human studies regarding the effects of IF. For example, Rothschild found the results of weight loss for TRF different in animal vs human studies making comparisons difficult (Rothschild J, 2014). The majority of the studies included in this section are human. Rothschild's review did find that in humans TRF may be effective for metabolic risk factors (lipids, glucose, insulin, and inflammatory markers).

IF is effective for weight loss and glucose control (Yongin Cho, 2019), however, for weight loss, overall calorie restriction must be involved, and it does not matter if you lose weight by CR or IF. The timing and frequency of meals along with daily fasting periods can contribute to weight loss, health, and longevity (reviewed and explained in another section). It appears that eating breakfast and consuming the bulk (70% or more) of your calories during the day is beneficial to weight loss. When combined with an extended fasting period of 16–18 hours and exercise, you have the best of all worlds. This would mean breakfast and lunch within a 5–6-hour time period and then an extended evening fast. On the other

hand, skipping breakfast, but not lunch, and eating dinner within five hours of lunch is also good, just not “as good.”

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