THE CARB-APPROPRIATE REVIEW

A MONTHLY RESEARCH REVIEW BY

CLIFF HARVEY PHD

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ABOUT CLIFF

Cliff Harvey PhD is an author, clinician, and researcher. He was one of the first clinical nutritionists to begin working with ketogenic and low-carb diets, way back in the 1990s and is also considered a pioneer in the area of mind-body integrative healthcare.

Cliff's early post-graduate work was in mind-body healthcare, while his master's research focussed on the use of medium-chain triglycerides to mitigate 'keto-flu' and encourage faster induction of nutritional ketosis.

His doctoral thesis continued to investigate keto-flu and ketogenesis, and the effects of different types of low-carbohydrate diets along with the individualisation of dietary prescription and how 'carbohydrate tolerance' varies from person-to-person.

He is a former world champion strength athlete, submission grappler, and author of several best-selling books, including *The Carbohydrate Appropriate Diet*, *Carb-Appropriate 101*, *Time Rich Cash Optional* and *The Credo.*

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THIS MONTH

ALL YOU NEED TO KNOW ABOUT FASTING

Key Findings:

- Fasting is considered generally to be safe.
- The majority of benefits from fasting are likely to result from control of energy balance (i.e. calorie restriction and 'auto-regulation).
- Fasting results in increased breakdown of dysfunctional and damaged tissue (autophagy and apoptosis).
- Fasting also results in improved 'fat-adaptation' (the use of fat for fuel)
- Fasting increases cortisol and stress-hormone levels but these return to normal with adaptation to fasting.
- Fasting is at least as effective as calorie-restriction for body-fat loss and improvement of cardiometabolic health measures but is more effective for reducing IGF-1.
- Fasting benefits asthma and autoimmune inflammatory conditions
- Fasting reliably reduces chemotherapy side effects and might improve survival times and reduce cancer growth.
- Fasting has been demonstrated to reduce blood pressure, and improve mood disorders, and skin health.

Fasting has recently re-entered the mainstream consciousness as a diet and lifestyle practice that is perceived as an easy and effective way to improve health. Fasting though is nothing new and has been a dietary strategy employed for mental, physical, and spiritual health for millennia. A 'natural' free-living human, throughout much of our existence as a species, would have gone through frequent periods of fasting, both day-to-day and periodically. Only very recently have we had an abundance of food which has caused fasting to be seen as outside of the norm. The adaptations that we have developed to respond to nutrient and energy scarcity allowed us to survive in varied environments and through times of scarcity. As it turns out, many of these adaptations are also beneficial to health and to our ability to not just survive but to thrive.

There have now been hundreds of studies on the effects of intermittent or periodic fasts of various types. For this article, a search of reviews and meta-analyses of these studies yielded 144 articles of which 64 were considered and 49 were included in this final summary.

WHAT IS FASTING?

Fasting is the act of *abstaining from all or some kinds of food or drink*. Fasting has traditionally been associated with spiritual and religious practices rather than the primarily health-focus we see today. Thus, most definitions qualify fasting with *'especially as a religious observance'.*

There is no quantified definition for fasting though, and it could be considered to be any period of abstention from food or restriction of calories that is outside the 'norm' of dietary patterns. So, it can vary from missing one or more meals per day (intermittent fasting) through to missing entire days of eating (as in alternate-day fasting) or having a couple of days a week in which nothing is eaten, or calories are strictly controlled (such as in 5:2 fasting).

Religious fasting is still common and is reflected in the dietary habits of millions of believers and the health impact of religious fasting has been documented among Buddhists, Hindus, Christians, and Muslims.[1] The most commonly observed religious fast carried out nowadays is the Ramadan fast of Islam. All adherents who are not ill, travelling, elderly, pregnant, diabetic, or menstruating, are expected to fast completely (without foods or liquids) between sunrise and sunset. Because the majority of the nearly 2 billion Muslims fast during this time, it's unsurprising that much of the research on fasting has been carried out during Ramadan.

WHY FAST?

Overall, the reviews of studies conducted so far show that fasting provides a range of health benefits,[2, 3] and that much of the benefit results from energy-restriction. By reducing the 'feeding window' available, people tend towards eating less overall because even if they 'overeat' during their non-fasting times, they do not eat more than they would have if not fasting. It has been observed in randomised controlled trials that fasting does not result in increased calorie intake during the non-fasting times.[2]

It has been observed in randomised controlled trials that fasting does not result in increased calorie intake during the non-fasting times

So, fasting is an effective way to achieve calorie-restriction, but it might also offer additional benefits by encouraging secondary processes such as reduced insulin-like growth factor (IGF-1), an anabolic chemical which, while beneficial to growth and repair, is also implicated in the development of cancer when produced in excess.

Fasting also increases autophagy and apoptosis (self-destruction and immune destruction of dysfunctional cells and tissues),[4] reduces monocyte-driven inflammation and might offer additional benefits over and above the restriction of energy intake.[5] Medically supervised fasts of 200-500 calories per day for 7-21 days have been shown to be beneficial for inflammatory disorders, reduce pain and inflammation, and improve mood and cognition, and are thought to work by also encouraging increased brain availability of serotonin, opioids, cannabinoids, and neurotrophic factors, along with neuroendocrine activation and by providing a mild stress response (which also results in the aforementioned reductions in monocyte driven inflammation and increased autophagy).[6]

Fasting also increases autophagy and apoptosis (self-destruction and immune destruction of dysfunctional cells and tissues)

Along with energy-restriction, fasting results in increased proportions of fat being used as fuel ('fat-adaptation') and the combination of fasting , fat-adaptation, and calorie restriction also improve glucose homeostasis (blood sugar control), blood lipids, and increase the availability of neuroprotective chemicals such as brain-derived neurotrophic factor (BDNF) which is critical to the repair and maintenance of the brain and central nervous system.[2]

In the studies performed to date (many of them on the Ramadan fast), fasting has been shown to be safe and with few, if any adverse effects. Water-only fasting equal to, or greater than two days has

similarly been shown to be incredibly safe overall.[7]

Common types of fasting

Type	Sub-type	Meals per day	Description
Intermittent fasting (IF)	14:10	2-3+	No food is eaten for a 14-hour window, i.e. between dinner and brunch
	16:8	2+	No food is eaten for 16 hours. I.e. between dinner and lunch
	20:4	1	One feeding window in the morning or evening. I.e. only feeding around dinnertime
	12:12	Usually 2	2 meals per day, typically breakfast and dinner
Alternate day fasting		Any	"Feed day" followed by "fast day" (usually 0-300 calories)
5:2 fasting		Any	5 "feed days" followed by 2 "fast days" (usually 0-300 calories)
Periodic fasting		3 or more days of fasting every 1-12 months or more	
Religious fasting	Lenten fast	Any	Traditionally avoidance of meat, dairy, eggs, sugar, and any intoxicants for 40 days. This resulted in energy-restriction
	Orthodox fast	Any	Similar to a Lenten fast
	Ramadan fast	1-2 feeding windows	Food (and liquids) are abstained from between dawn and dusk

What is 'autophagy'?

In simple terms, autophagy is a mechanism in cells of the body that removes unnecessary or dysfunctional components. The word itself means 'eating the self' (auto=self, phagy=to eat).

In more complex terms, it is a lysosomal degradation process which eliminates damaged organelles (cell components), long-lived misfolded proteins and invading pathogens. The function of autophagy is to remove damaged or dysfunctional cell components and recycle them into amino acids (and other

substrates) to be used as building blocks of tissues and for energy. The proper regulation of autophagy is essential for health and we are only just beginning to understand the implications of having this process running at the optimal level (i.e. consistent with our development over time.) In the modern food and lifestyle environment, it is highly likely that persistent stressors, such as food scarcity and heat stress have been largely eliminated, and we are also far less active than our forebears. These changes have led to a reduction in our biologically normal levels of autophagy. So, providing some of these 'stressors' in our lifestyle can positively impact the regulation of autophagy and helps to preserve our cell integrity and energy restriction by fasting or calorie-restricted diets are the most potent non-genetic stimulators of autophagy.[8]

The function of autophagy is to remove damaged or dysfunctional cell components and recycle them

Effects on catecholamines ('stress' hormones)

Fasting results in a significant increase in cortisol and other 'stress' hormones (and more than calorie-restriction) but this effect appears to attenuate back to baseline after several weeks, suggesting that there is no long term negative effect on cortisol status resulting from behavioural fasting.[9]

there is no long-term negative effect on cortisol status resulting from behavioural fasting

Effects on immunity

No significant effects on circulating immune complexes, immunoglobulins or c-reactive protein have been seen as a result of Ramadan fasting. However, there are small reductions in pro-inflammatory cytokines (interleukin 1β, interleukin 6, tumour necrosis factor-alpha).[10, 11] These 'pro-inflammatory cytokines' are chemical messengers for the inflammatory cascade and increased inflammatory cytokines are observed in inflammatory and autoimmune conditions. Reductions in these markers

are a key therapeutic target in conditions like lupus, rheumatoid arthritis, Crohn's disease and more.

FASTING VS CALORIE RESTRICTION

Intermittent fasting regimens have gained considerable popularity in recent years because many people find these diets easier to follow than traditional calorie-restriction approaches.

Intermittent fasting involves restricting energy intake on 1–3 days of the week and eating freely on the non-restricted days. Alternate-day fasting is a subclass of intermittent fasting, which consists of a "fast day" (75% energy restriction) alternating with a "feed day" (*ad libitum* food consumption). Recent findings suggest that fasting is at least as effective as calorie restriction for weight loss and the improvement of cardiometabolic risk markers (like glucose, fasting insulin, and insulin sensitivity).[12]

fasting is at least as effective as calorie restriction for weight loss

However, insulin-like growth factor (IGF-1) (high levels of which are implicated in cancer development and growth) might be reduced more by fasting than calorie-restriction. A systematic review of fasting vs calorie-restriction for the reduction of IGF-1 suggested that fasting significantly decreases IGF-1 levels (WMD: -28.87 ng/ml, 95% CI: −43.69, −14.05, I2 = 00%), an effect that was not seen in most calorie-restricted groups.

fasting significantly decreases IGF-1 levels, an effect not seen in most calorie-restricted diets

Only calorie restriction to less than 50% of habitual calories had a comparable effect on IGF-1.[13] Fasting was also 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.[14]

EFFECTS OF FASTING ON HEALTH CONDITIONS

Asthma

Among asthmatic patients, in a case-control study involving 15 asthmatic patients and 14 controls, fasting was shown to significantly decrease the inflammatory marker c-reactive protein but there was no significant difference in lung function tests or respiratory symptoms. This suggests that fasting is safe and may reduce inflammation for people with asthma.[10]

> fasting was shown to significantly decrease the inflammatory marker c-reactive protein

Autoimmune conditions

No significant effect (positive or negative) has been observed as a result of Ramadan fasting for systemic lupus, multiple sclerosis, or inflammatory bowel disease.[10] However, small reductions in important inflammatory markers of clinical importance to autoimmune conditions, particularly tumour necrosis factor-alpha have been observed.[10, 11]

Blood pressure

A majority of studies on the effect of fasting on blood pressure in hypertensive patients have shown significant reductions in systolic blood pressure. However, there appears to be little significant effect on diastolic blood pressure. Overall, fasting is considered to be a safe method that can help to reduce blood pressure in those with hypertension.[15]

Cancer

Both human and animal studies demonstrate that fasting is effective for reducing the side-effects of chemotherapy (organ damage, toxicity, immunosuppression, and weight loss) and suppress tumour growth and improve survival rates. For these benefits, a fasting duration of longer than 48 hours was found to be crucial. Because of these results, fasting is now considered an effective option to improve both quality-of-life and outcomes in cancer patients.[16]

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Cardiometabolic health

In a recent review published in 2015, six studies on intermittent fasting, featuring overweight or obese participants were analysed. A variety of fasting styles was used in these studies, from 5:2 to 3:4, through to 2:5 (days 'fed':'fasted'). All studies reported a decrease in blood pressure (up to 4%), fours studies reported decreased insulin concentrations (with three reducing mean insulin to within reference range. Additionally, and perhaps most importantly, attrition rates (how many people stopped the diets) were lower than typically seen in studies of weight management, at around 20%.[17] Calorie-restricted diet interventions for weight loss show attrition rates of around 36% (with a higher rate of attrition in low-fat, high-carbohydrate interventions).[18]

Ramadan fasts can also reduce triglyceride concentrations, total cholesterol, and increase HDL cholesterol in women.[19] In support of this, 85 studies (containing over 4000 participants) conducted in 23 countries between 1982 and 2019 have demonstrated that Ramadan fasting results in reductions in waist circumference, systolic blood pressure, fasting glucose, and triglycerides, while also increasing HDL cholesterol.[20] A meta-analysis of nine fasting studies (n = 746) found significant reductions in body fat and (non-significant) reductions in weight, waist circumference, total cholesterol, triglycerides, blood pressure, glucose, and insulin, with a non-significant increase in HDL cholesterol.[21]

attrition rates from fasting were lower than typically seen in studies of weight management

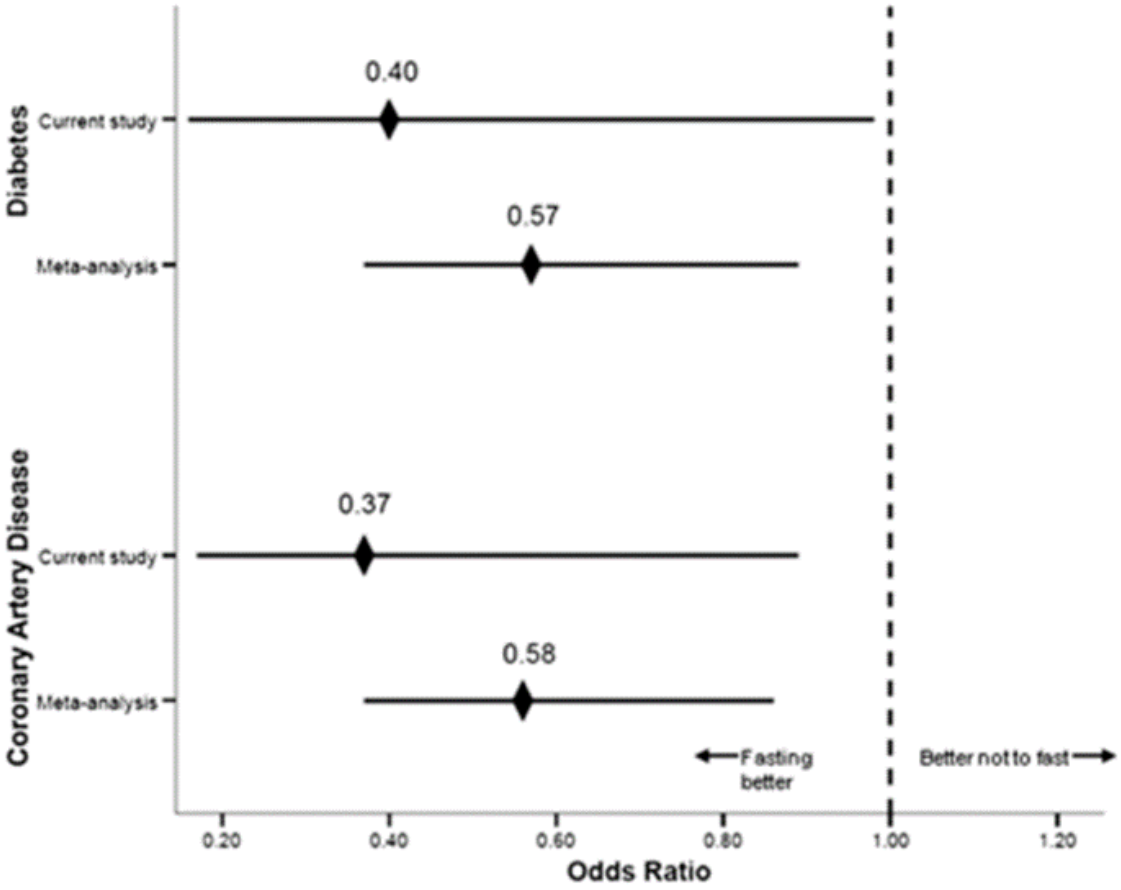


Figure 1. The association between periodic fasting and diabetes and coronary artery disease.[22]

Cardiovascular disease

Most studies have noted improvements in lipid profile from Ramadan fasting but not reductions in cardiovascular disease incidence or hospitalisation.[23] The incidence of cardiovascular events (stroke, myocardial infarction, and congestive heart failure) also, does not differ significantly between fasting and non-fasting periods.[24, 25]

Metabolic syndrome and diabetes

In patients with insulin-dependent (Type 1) diabetes, no change in glycaemic control has been observed and only minor effects (hypoglycaemic events, hyperglycaemia, or diabetic ketoacidosis) have also been observed, but these effects are considered to be trivial and not meaningful when compared to usual care. It has been concluded that Ramadan-style fasting is feasible for Type 1 diabetic patients under the care of a suitably qualified practitioner.[26, 27] Furthermore, Ramadan fasting is considered to be 'non-risky' for both controlled and partially controlled diabetes.[28]

Ramadan fasting is considered to be 'non-risky' for diabetes

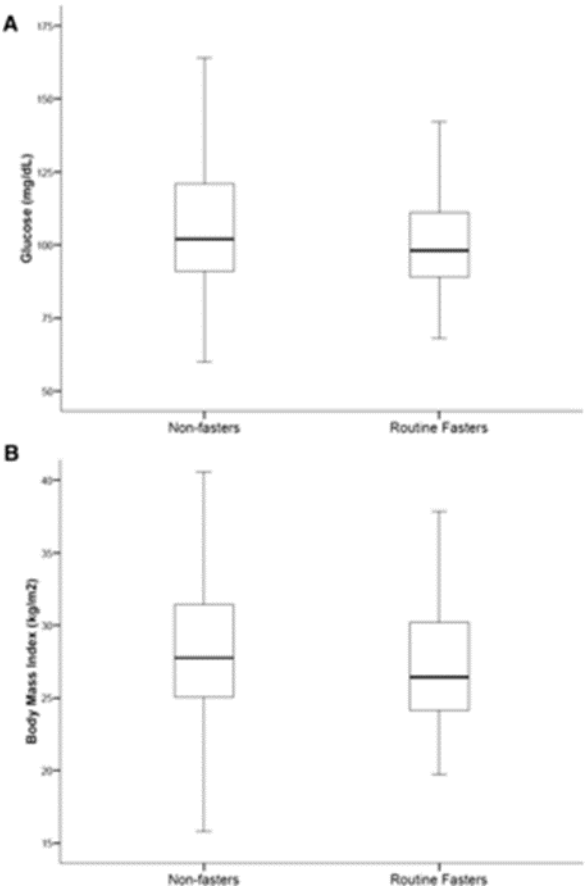


Figure 2. Differences in fasting glucose and BMI between fasters and non-fasters.[22]

Cognition

Some studies have shown executive function deficits from fasting, others have shown benefits or unclear results. In a review of ten scientific papers on short-term fasting also showed inconsistent results, with several studies reporting no observable differences as a result of fasting, and others showing deficits on tasks designed to test psychomotor speed, executive function, and mental rotation.[29]

Kidney function

Overall, reviews of the evidence suggest that there are no adverse effects on markers of kidney health (such as urea, uric acid, and creatinine) resulting from fasting.[30-32]

Mood disorders

In contrast to the equivocal findings for cognition, mood disorders seem to benefit from fasting.

mood disorders seem to benefit from fasting

In one study, eight days of fasting (300 kcal/day) resulted in a significant improvement in mood after the fifth day. In another, two weeks of fasting (250 kcal/day) resulted in over 80% of fasters showing rapid decreases in depression and anxiety scores, and improved depression and mania scores in bipolar disorders have been reported in fasting studies.[33]

Obesity and overweight

Intermittent fasting has become perhaps most popular among people wanting to lose fat and weight and those seeking to

maintain a healthy body weight and fasting has been demonstrated to be effective for the treatment of obesity.[34] Studies on people overweight or with obesity show that fasting is equal to calorie-restricted interventions for weight loss,[35, 36] and at least one study has suggested that fasting is superior to calorie-restriction for loss of body fat, and two studies report greater improvements in insulin resistance (as measured by insulin homeostasis) when compared to continuous energy restriction.[35] Interestingly, hyperphagia (overeating) is not observed in studies of intermittent fasting and in the 'fed' phases, people typically still achieve a 20% calorie restriction on habitual energy intakes.[35]

at least one study has suggested that fasting is superior to calorie-restriction for loss of body fat

Reviews of the effects of the Ramadan fast consistently show that there are significant reductions in weight and body fat resulting from the fasting period (e.g. body fat reductions of −1.46% [95% confidence interval: −2.57 to −0.35] p = 0.010). These reductions are greatest for those that have higher body fat levels and become non-significant for normal-weight people, however, loss of fat-free mass (i.e. muscle) can also be appreciable (approximately 30% of fat-mass). There is also a relatively consistent return to pre-fasting weight after the cessation of fasting (at ~2–5 weeks).[37, 38]

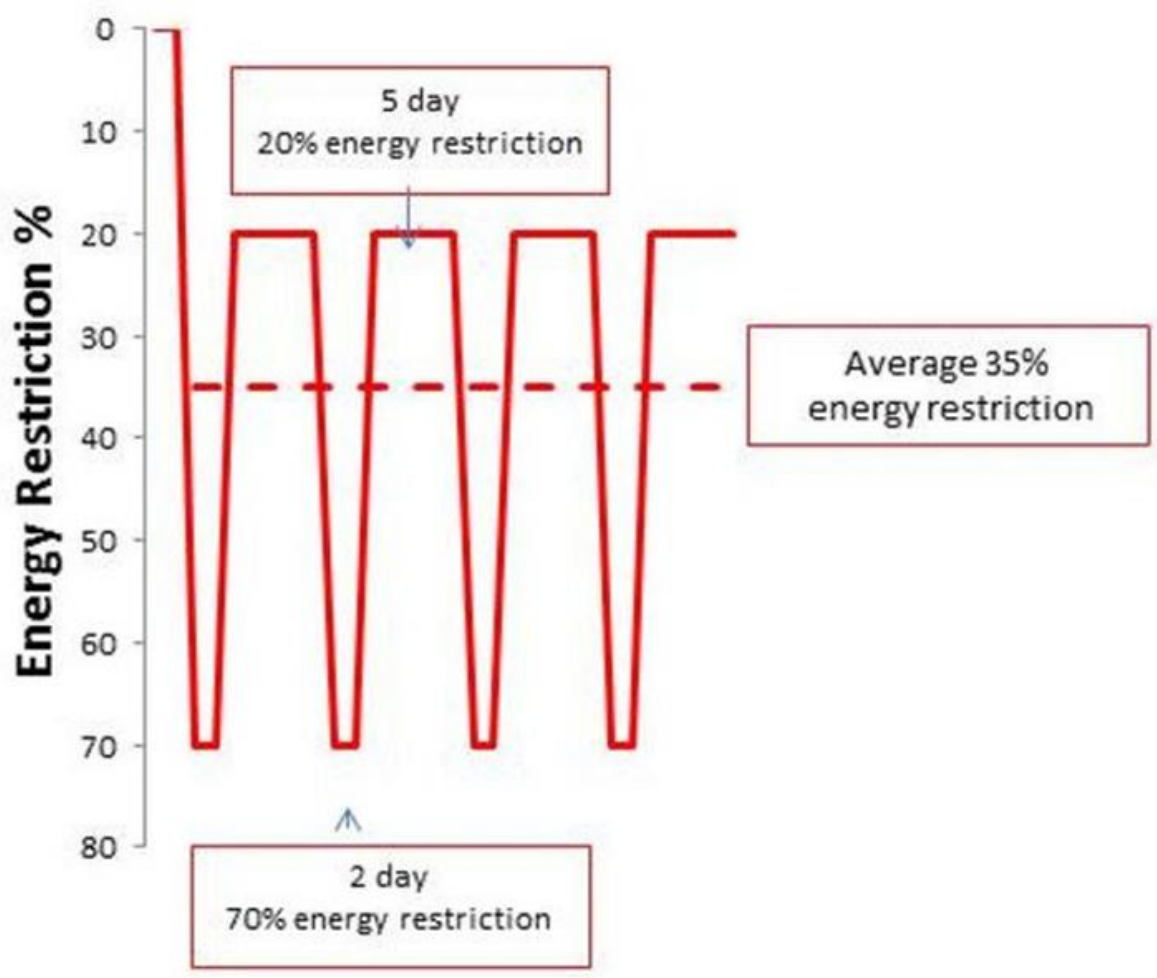


Figure 3. The overall effect on calorie intake resulting from fasting.

Maintenance of weight loss

One month of a weight maintenance fasting protocol (one day of fasting and six days of *ad libitum* Mediterranean diet) successfully maintained reductions in weight and improvements in insulin sensitivity that had been achieved over three months following a 5:2 fasting protocol for weight loss. However, other analyses have shown higher numbers of people continuing to follow a calorie-restricted diet vs fasting over 6 months (58% IF vs 85% calorie-restriction).[35]

Prevention of weight gain

There are currently no randomised controlled trials specifically on the prevention of weight gain among healthy, normal-weight people. Two studies have looked at metabolic effects of fasting in healthy adults and these have corrected for energy deficit by strictly controlling calorie intake on non-fasting days so as to not have an overall calorie deficit. It was reported that there was sustained hunger in fasters and difficulty maintaining normal activity

during fasting days in an alternate day fasting protocol.[35]

Performance

Overall, there appears to be no marked benefit or decrement resulting from fasting for physical or mental fitness.[39-41] Subjective feelings of fatigue or mental performance can show some decline, implying some level of 'stress' on the athlete, however, most of these studies also show that these measures may not result in decreases in performance.[41] Markers of inflammation related to this increase in stress have been observed in some but not all studies on Ramadan fasting.[10] Additionally, aerobic fitness may be compromised, while inflammatory marker IL6 is increased and along with epinephrine and norepinephrine ('fight or flight' stress-hormones) and fatigue levels. Importantly though, these measures returned to normal after approximately one week, suggesting that adverse stress effects abate with adaptation to fasting.[10] Markers of electrolyte and hydration status and kidney function do not change markedly during Ramadan.[42] Measures associated with cardiometabolic health LDL cholesterol, HDL cholesterol and the inflammatory marker c-reactive protein are improved by fasting in athletes, similar to the effects observed in non-athletes.[10]

Overall, there appears to be no marked benefit or decrement resulting from fasting for physical or mental fitness

Pregnancy and infant outcomes

No negative effects on outcomes such as foetal growth and development, intrauterine and early-life conditions, pre-term delivery, or markers of health status have been observed in those observing Ramadan while pregnant.[43-45] However, some micronutrients may be reduced in the breast milk of fasting mothers and both micro- and macronutrient intakes of some pregnant women during Ramadan have been found to be deficient.[44]

No significant differences have been observed in growth rates between children following or not following the Ramadan fast.[46]

In a survey of 108 obstetricians and gynaecologists, most physicians recommended against fasting in the second or third trimester, while fasting on the first trimester was controversial. Senior specialists were more lenient about fasting than younger specialists

(62% and 35%, respectively, $p = 0.01$) and religious and traditional physicians were more likely to permit fasting (the Yom Kippur fast) compared to their secular colleagues (53% and 25%, respectively, $p = 0.01$).[47]

Schizophrenia

In a prospective study on 100 patients with schizophrenia, there were increased lymphocytes, monocytes, fibrinogen and c-reactive protein, especially in schizophrenic patients with metabolic syndrome. This offers a significant contrast to other studies which have shown benefits to mental health conditions and to inflammatory disorders (note: inflammation and mental health are strongly linked). Further research is required to understand the implications of fasting for people with schizophrenia.[10]

Skin health

Fasting might be beneficial to the health of the skin and in treating pathology of this organ. Calorie restriction had previously been demonstrated to reduce skin irritation following topical retinol treatment (a common application for skin disorders such as acne) without reducing the treatment-effect of the medication.[48]

Wound healing can be either improved or worsened by fasting. It has been demonstrated that benefits to wound healing might come from increasing macrophage activity, increases in transforming growth factor-alpha (TGF-α), and the secretion of other factors that encourage tissue formation. However, fasting before and during wounding might have a detrimental effect, one which is reversed by feeding for several days before wounding and during the early recovery phase, likely due to increases in growth factors like IGF-1 and by increasing collagen production through anabolic signalling.[14] Calorie restriction and fasting are also likely to reduce the ageing of the skin by reducing rates of glycation and free radical and other damage along with distinct epigenomic signalling to slow ageing processes.[14]

Furthermore, fasting is also likely to reduce the incidence or severity of autoimmune-related disorders of the skin such as psoriasis.[14]

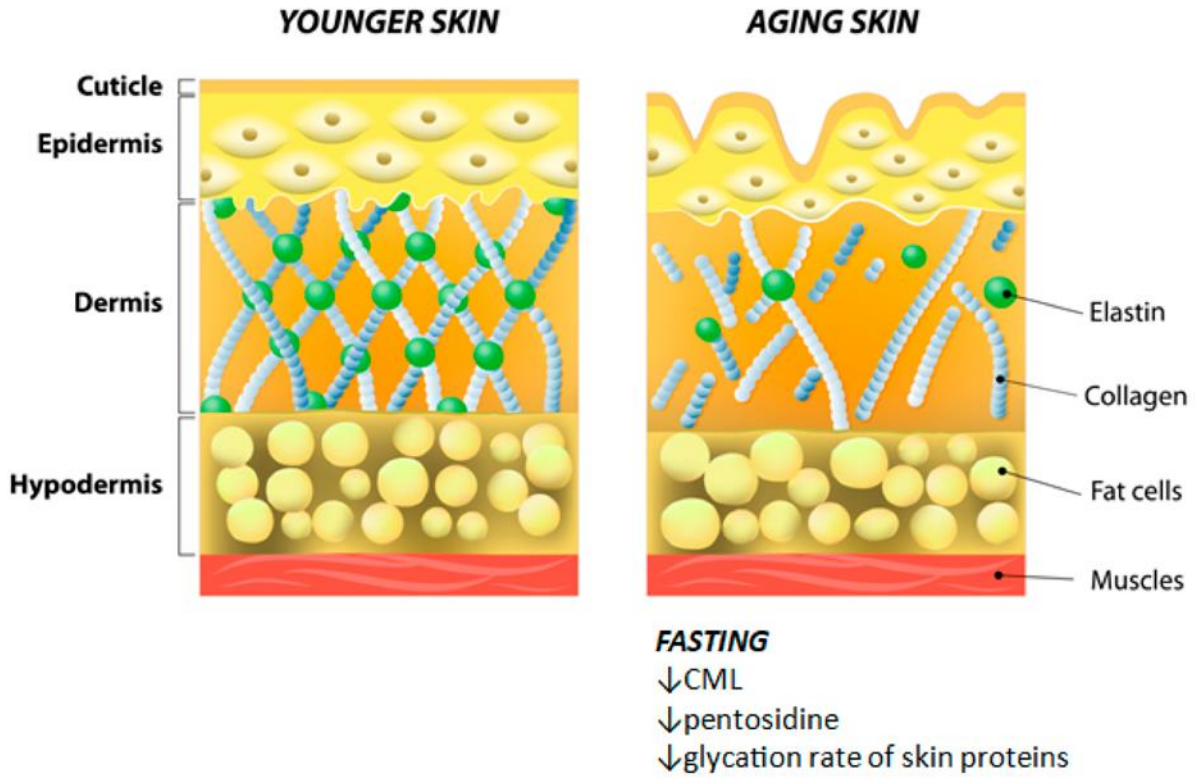


Figure 4. The anti-ageing effects on the skin from fasting.[14]

ADVERSE EFFECTS & CAUTIONS

Some studies have noted the adverse effects of Ramadan fasting. These have included headaches, heartburn, constipation, dehydration, decreased sleep quality, and anaemia.[49] There are also anecdotal suggestions that people with Gilbert's syndrome (a typically mild congenital condition marked by the liver not being able to process bilirubin) may have to modify fasts as energy and lipid insufficiency or long fasting periods can worsen bilirubin levels resulting in fatigue and mood disturbance, possibly related to neurotoxicity of very high bilirubin levels. Additionally, it has been suggested (again, anecdotally) that if someone is not sufficiently fat-adapted, they might experience symptoms similar to those commonly called 'keto-flu'. As we have demonstrated, keto-flu has the strongest association with energy-restriction, not how much carbohydrate is restricted (in a low-carb diet context)[50] and so, this makes sense.

CONCLUSIONS

Fasting, on the whole, is safe and effective for weight and fat loss and a range of health outcomes. It is at least as effective as calorie restriction for the improvement of body composition and cardiometabolic outcomes and may offer some particular benefits to the reduction of IGF-1, which has potential anti-cancer implications, and for the improvement of other processes that help to regulate the epigenome and the clearance of damaged and dysfunctional tissues from the body.

On the other hand, fasting is unlikely to benefit hypertrophy as it typically results in energy-restriction overall, even on non-fasting days and thus, it becomes more difficult to achieve a caloric surplus required for muscle growth. Fasting may also not benefit individuals who are behaviourally more comfortable with portion-control and planned energy-restriction. Enforcing a fasting protocol in contrast to one's behavioural tendencies is likely to lead to failure.

TAKE-HOME MESSAGE

Overall, for the improvement of health, energy must be kept in balance. If fasting helps you to do that, it is a useful intervention that is safe and effective and might have some additional benefits to health over and above energy-control. So, if you can stick to fasting, and it helps you to feel and perform at your best, do it. If it is more difficult for *you* to implement than another dietary strategy that gives you great results, don't!

IN THE LITERATURE

Fasting, inflammation, and autophagy

Dietary intake regulates the circulating inflammatory monocyte pool

Stefan Jordan, Navpreet Tung, Maria Casanova-Acebes, Christie Chang, Claudia Cantoni, Dachuan Zhang, Theresa H. Wirtz, Shruti Naik, Samuel A. Rose, Chad N. Brocker, Anastasiia Gainullina, Barbara B. Maier, Derek LeRoith, Frank J. Gonzalez, Felix Meissner, Jordi Ochando, Adeeb Rahman, Jerry E. Chipuk, Maxim N. Artyomov, Paul S. Frenette, Laura Piccio, Marie-Luise Berres, Emily J. Gallagher, Miriam Merad

Cell – bioRxiv preprint: https://doi.org/10.1101/582346

Summary

Caloric restriction is known to improve inflammatory and autoimmune diseases. However, the mechanisms by which reduced caloric intake modulates inflammation are poorly understood. Here we show that short-term fasting reduced monocyte metabolic and inflammatory activity and drastically reduced the number of circulating monocytes. Regulation of peripheral monocyte numbers was dependent on dietary glucose and protein levels. Specifically, we found that activation of the low-energy sensor 5'-AMP-activated protein kinase (AMPK) in hepatocytes and suppression of systemic CCL2 production by peroxisome proliferator-activator receptor alpha (PPARα) reduced monocyte mobilization from the bone marrow. Importantly, while caloric restriction improves chronic inflammatory diseases, fasting did not compromise monocyte emergency mobilization during acute infectious inflammation and tissue repair. These results reveal that caloric intake and liver energy sensors dictate the blood and tissue immune tone and link dietary habits to inflammatory disease outcome.

Highlights

- Fasting reduces the numbers of peripheral pro-inflammatory monocytes in healthy humans and mice.
- A hepatic AMPK-PPARα energy-sensing axis controls homeostatic monocyte numbers via regulation of steady-state CCL2 production.
- Fasting reduces monocyte metabolic and inflammatory activity.
- Fasting improves chronic inflammatory diseases but does not compromise monocyte emergency mobilization during acute infectious inflammation and tissue repair.

Comment

This study is one of my favourites of the year so far and it came to my attention quite serendipitously. I was asked to appear on *The AM Show* on TV3 (NZ) to talk about fasting and its effects on the immune

system and they specifically mentioned this study, which had been released in pre-print only a few days earlier (those journos were on to it this time!)

https://www.newshub.co.nz/home/shows/2019/08/how-could-intermittent-fasting-affect-the-immune-system.html

One of the things that attracted me to the study was that it used a novel combination of outcome testing in humans and backed that up with additional testing in mice where it would have been difficult or unethical to perform in humans. This led to a broader range of results and helped to bridge the divides between mechanisms (mostly shown in animals) and functional outcomes in the human subjects.

> fasting reduces monocytes (white blood cells) that increase inflammation

The study showed that fasting reduces monocytes (white blood cells) that increase inflammation. However, importantly, these levels were not decreased in those with already lower levels. This suggests that fasting does not simply *reduce* inflammation, but instead helps the body to properly regulate it.

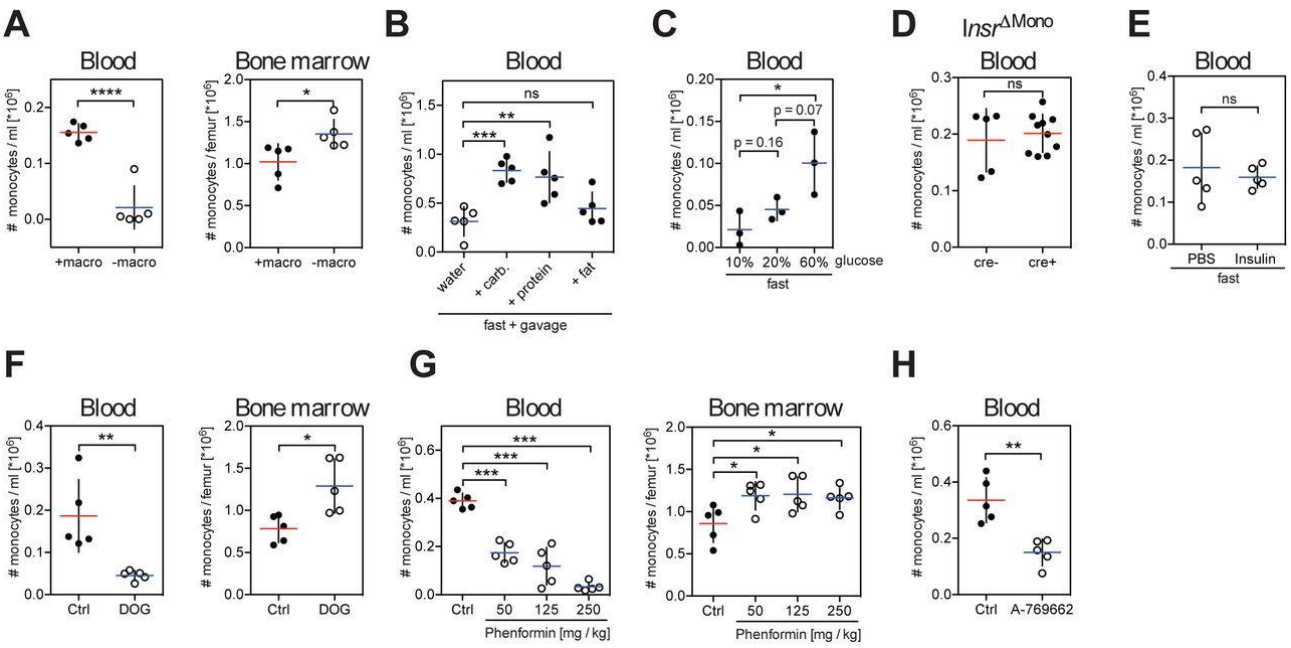
> fasting does not simply *reduce* inflammation but instead helps the body to properly regulate it

The authors also looked into the mechanism by which pro-inflammatory monocytes were increased and found that it was unlikely to be driven by cell-death or reductions in monocyte precursors, but instead appeared to be driven by sequestering of the inflammatory monocytes in the bone marrow. This further suggests that the body is adapting to fasting by moderating inflammation where it is unnecessary.

What drove the reduced inflammation?

Overall, energy-restriction drives the monocyte and inflammation-reducing properties of fasting. But importantly, both protein and fasting restore monocyte levels (and therefore return inflammation to pre-fasting levels) but fat does not. Furthermore, the size of the monocyte pool (the total number of inflammation-driving monocytes) depends on the amount of carbohydrate ingested (see figure below).

the total number of inflammation-driving monocytes depended on the amount of carbohydrate ingested



Because both protein and carbohydrate (but not fats) have a large insulin response, the researchers looked into whether insulin was the reason for the increase in monocyte numbers when animals were fed carbohydrate or protein but not fat. They found, however, that deleting the insulin receptor from mice did not change these results, showing that insulin is unlikely to be the reason. But, blocking glycolysis (the breakdown of carbohydrate for energy in the cell) *did* reduce monocyte levels to those similar to fasting. This effect is likely to be because of 'energy-sensing' within the cell. When energy availability is low (especially low energy from carbohydrate) mammalian 5'-AMP-activated protein kinase (AMPK) is activated and this acts as a signal to reduce monocyte release from bone marrow through various other channels (such as the peroxisome proliferator-activated receptor α (PPARα)).

PPARα itself has been implicated in the anti-inflammatory effects of fasting and in the present study, fasting-induced reduction of

monocytes was less efficient in mice which had the PPAR gene knocked out. Additionally, it was found that this signalling pathway was mostly driven by energy-sensing by the liver (via the AMPK-PPARα pathway) in response to caloric and carbohydrate intake. In addition, it was found that a ketogenic diet failed to affect peripheral monocyte numbers.

Fasting also affects many metabolic hormones and in this study, fasting resulted in very similar changes in levels of hormones like ghrelin (increased), and insulin, c-peptide, amylin, GIP, leptin, PP, and PYY (decreased). Most human (and mouse) subjects (67%) also had reduced CCL2 (also known as MCP-1) levels. This hormone is known to bind to a receptor (CCR2) found in abundance on monocytes and helps to regulate the release of monocytes from bone marrow. This provided another inter-related pathway by which fasting reduced monocyte-driven inflammation.

Fasting modifies the metabolic activity of monocytes

Fasting was also seen to have a profound effect on gene expression in monocytes (with more than 2700 genes in mice monocytes being differentially expressed due to fasting). Genetic expression changes unsurprisingly mostly related to cellular energy conservation (eIF2 signalling, protein ubiquitination, and mitochondrial function and oxidative phosphorylation). It was co concluded that "monocytes from fasting mice were reduced in their metabolic activity reflecting a quiescent functional state."

Fasting and chronic inflammatory disease

It is well known that fasting and calorie-restriction improve chronic inflammatory and autoimmune disorders, such as multiple sclerosis and rheumatoid arthritis.

In this study, gene modules associated with joint inflammation and rheumatoid arthritis were reduced. So, the researchers followed this line of enquiry in mice induced to develop an autoimmune disorder of a pre-clinical model for multiple sclerosis (EAE). A large reduction in myeloid cell accumulation was observed in the spinal cords of fasted mice with EAE, and intermittent fasting significantly improved the clinical symptoms of this disease. Genes related to inflammation and infiltration were also strongly downregulated in monocytes from fasting mice compared to non-fasting mice. This suggests that fasting can reliably improve auto-immune activity.

But....does this reduction in monocytes and inflammation impair the normal immune and repair responses?

The authors had observed reductions in key monocytes and resulting inflammation. While this is seen to be a 'good' thing, inflammation and the immune white blood cells (monocytes) are important to proper immune function, resistance to pathogens, and repair from illness and injury. So, the question was asked; would "changes in

monocyte functional state also compromise acute inflammatory reactions in response to tissue injury or pathogen invasion?"

It was found that emergency mobilisation of monocytes in response to a pathogen (Listeria) was no different when fasted to non-fasted. Neither immunity against Listeria infection nor wound healing were in any way impaired in fasting mice. This suggests that monocyte resp9nses to infection and injury are unaffected by fasting.

Take home points:

- Fasting reduces inflammation
- Fasting improves symptoms and clinical progression of an autoimmune disease
- The effects of fasting are due to an inter-related and complex web of biochemical and gene interactions
- These changes are signalled at the cellular level (especially in organs like the liver) by energy-restriction
- Energy restriction and the total volume of carbohydrate consumed are the key drivers of the beneficial effects of fasting
- Fasting did not negatively affect the ability of the body to respond to illness or wounds

HOW TO FAST

I fast daily (currently), mostly for the potential benefits to both lifespan and health span. How I fast, and how anyone else 'should' (or should not) fast is highly individual. As considered in the review in this issue, some people should perhaps not fast, or at the least should not fast aggressively, habitually. People for whom this may be true might include habitual under-eaters, under-eaters with Gilbert's syndrome, uncontrolled or poorly controlled diabetics who aren't being monitored by a suitably qualified practitioner, or those seeking to gain large amounts of muscle and failing to do so.

Apart from those instances, and for those wanting to try fasting, there are many different styles available and much discussion as to what is the 'best' way to fast. At least in my humble opinion, there simply is no best fasting method. There is simply what works for the individual and remember that what works for an individual is not just determined by their physiology but also by their behaviours within their unique psychosocial environment.

The major points of confusion are commonly:

1. How long should I fast?
2. When should I fast? (Particularly, should I fast in the morning or evening)

How long should I fast?

The answer to the first question is somewhat parsimonious. Fast for as long as you need to... Another way to conceptualise this is to think about how long you need to eat, or how many meals you can eat, in order to maintain a healthy bodyweight (for you). If eating the standard 3-meals per day makes it difficult for you to maintain your bodyweight, you might want to consider cutting back to 2 meals, or a shorter feeding window. If on the other hand, you are losing weight and you don't want to, you might consider a shorter fasting window or adding a meal or two to your day. Of course, all of this is predicated on the understanding that you are eating a diet that is based on natural, unrefined foods (to at least 80% of your overall nutrition), and if that's not the case, then THAT is the first step!

When should I fast?

The debate rages as to whether you should fast early (e.g. miss breakfast) or late (i.e. having a very early dinner, or missing dinner), or something in between!

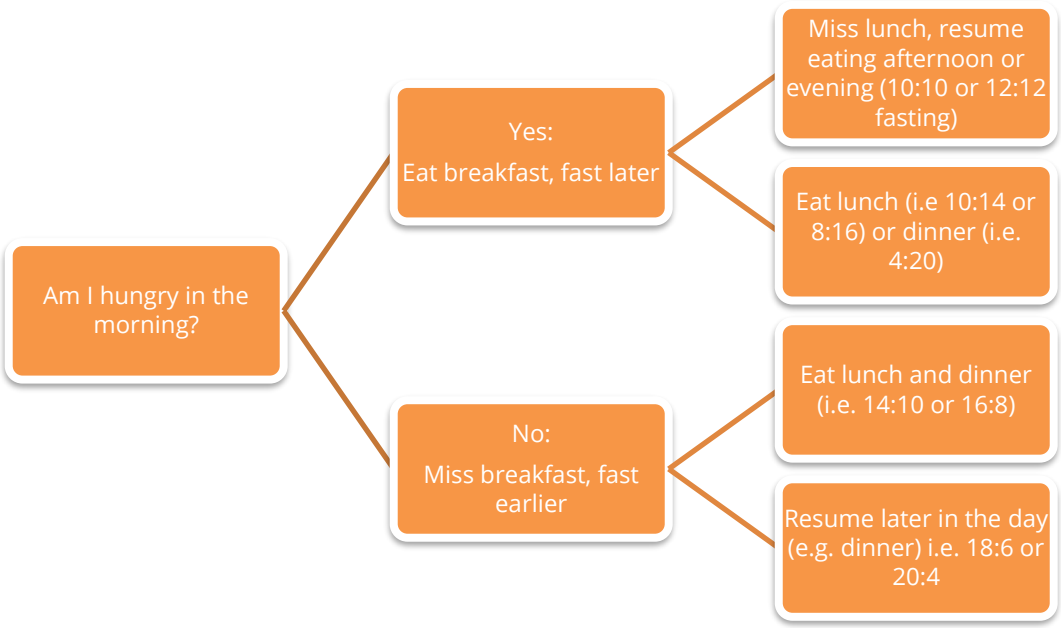
While different studies, and expert opinion will provide evidence for either style, the key is *what you can stick to.* Because there is likely to be a tiny difference between these styles over the longer term, in order to get optimal results, you should choose a style that fits your unique situation. The easiest way to evaluate this is to ask yourself the

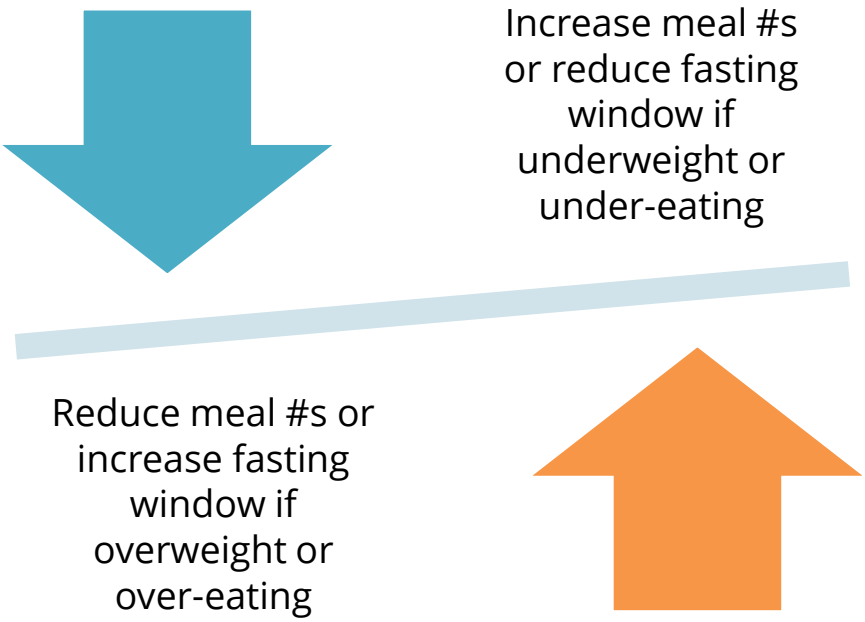
simple question: Am I hungry when I wake up in the morning?

If the answer is yes, then eat breakfast! Then, either miss lunch (12:12 fasting) and have your next meal at dinner or after work, or have lunch and a very early dinner, in order to provide for the fasting window that you want (i.e. 12, 14, 16, or more hours fasting).

If, on the other hand, you aren't hungry in the morning, there is no good reason to force yourself to eat. Omitting breakfast and then resuming eating either late in the morning, for lunch, late in the afternoon, or even at night, are all good strategies depending on the individual. One of the main considerations again is to a) make sure you are still eating a healthy diet containing plenty of protein and veggies, and b) make sure that you are taking in enough energy (and macros and micros) to thrive over the longer term.

Summary





Remember, that the first priority is always on food quality (natural, whole, unprocessed food) not finetuning fasting windows!

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Remember to check out our previous issues of The Carb-Appropriate Research Review

Previous topics have included:

Is Dairy Inflammatory?

Is a Keto Diet *Really* a 'Cure' for Cancer?

Can you be 'Heathy at Every Size'?

Do Low-Carb Diets Negatively Affect Female Hormone Balance?

All About Candida

And much more!

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