



NATURAL MEDICINE JOURNAL **RESEARCH GUIDE**

EXPLORING THE CLINICAL APPLICATIONS OF **INTERMITTENT AND PROLONGED FASTING**

A REVIEW OF THE EFFICACY, SAFETY,
AND PHYSIOLOGY OF FASTING

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Introduction

The spiritual and religious roots of fasting can be traced back to ancient Greece and the Old Testament, continuing presently during the holy month of Ramadan; and the movement to have fasting enhance health began back in the mid-1800s.¹ Prior to the Neolithic period that ushered in agricultural advances, humans were built to adapt and survive during cycles of food scarcity. Over the past several decades there has been a resurgence in the scientific literature regarding the potential health benefits of various types of fasts that take advantage of the innate survival mechanisms hard-wired into the human body.

Fasting is the abstinence or limitation of food intake during a set period of time. We now know that fasting creates physiological changes that positively impact

Types of Fasts At-A-Glance

INTERMITTENT FASTING (IF) = Creating daily fasting and eating intervals

COMMON TYPES

- Time-Restricted Eating (TRE), also known as “overnight fasting,” creates a window of time each day when food can be consumed. Typical fasting windows are 12 to 16 hours.
- The 5:2 Diet where any 2 days of the week include a low-calorie fast.
- The Alternate-Day Fast where the fast is every other day.

BENEFITS

- Weight loss
- Body fat loss
- Blood sugar management
- Lower cholesterol
- Lower blood pressure

PROLONGED FASTING (PF) = A fast lasting longer than 48 hours

COMMON TYPE

- Water-only Fasting
- Fasting Mimicking Diet (FMD) that extends the fasting period to 5 consecutive days

BENEFITS

- Supports cellular cleansing and renewal
- Weight loss
- Maintenance of lean body mass
- Reduced waist circumference
- Supports overall health

health and longevity.² This guide will focus specifically on the research and clinical applications of intermittent and prolonged fasting.

One of the hallmarks of any fast, including intermittent and prolonged fasting, is to shift the body from utilizing glucose as fuel to fatty-acid-derived ketones, efficiently transitioning from fat storage to fat mobilization.³ This switch leads to many health effects including weight loss, better blood glucose control, improved stress resistance, and reduced inflammation.⁴ Because of the mechanisms activated during prolonged fasting, this eating pattern can help reduce the risk of many illnesses associated with aging including cancer, dementia, diabetes, and heart disease.⁵

Physiology of Fasting

Fasting is evolutionarily embedded in human physiology on a cellular level that is fueled by a persistent need for energy to survive and thrive. Intermittent and prolonged fasting moves the body into a state of ketosis after glycogen levels are depleted, forcing the body to get energy from adipose tissue and protein stores.⁶ This is significant because ketones are a much more efficient energy source compared to glucose and ketones also do not generate as much free radical activity.⁷

Intermittent and prolonged fasting have also been shown to positively influence mitochondria, DNA, and autophagy. Intermittent fasting stimulates cells to activate autophagy, which removes cellular debris and repairs damaged cellular components leading to proper cell health and regeneration.⁸ This intracellular clean-up is critical to cellular rejuvenation. Among the many net effects of autophagy are positive influences on immune function, including reduced inflammation.

Fasting also helps down-regulate 3 key pathways associated with cellular aging and growth: IGF1, mTOR, and PKA. The protein and carbohydrate restriction associated with intermittent and prolonged fasting creates positive changes in growth factors and nutrient signaling to help reduce the risk of illness and delay accelerated aging. Other downstream factors that impact and regulate aging that are influenced by both forms of fasting include PI3K, AMPK, FOXOs, and sirtuins.⁹

Via the various nutrient-sensing pathways, fasting also prompts genetic expression in the circadian system and supports metabolic homeostasis.¹⁰ This is significant because it is well-known that disruptions in circadian rhythm can negatively impact health.

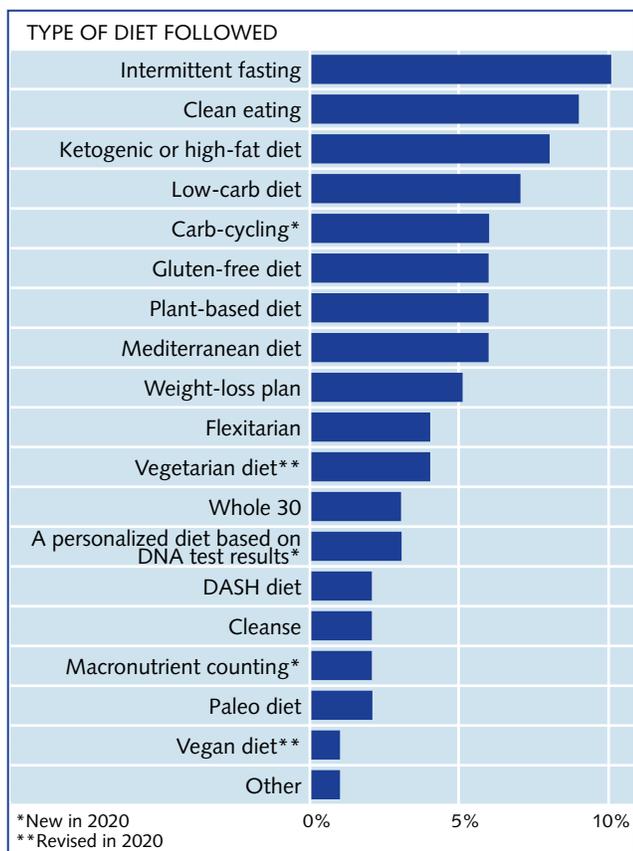
Intermittent and Prolonged Fasting Research

The authors of a 2021 literature review in *Nature Aging* concluded, “In humans, the alternation of fasting and refeeding periods is accompanied by positive effects on risk factors for aging, diabetes, autoimmunity, cardiovascular disease, neurodegeneration, and cancer.”¹¹ The physiology of both forms of fasting clearly explains how this therapeutic intervention can have such diverse and beneficial health effects.

For example, based on ongoing pre-clinical and clinical studies many of the same pathways positively influenced by fasting may be relevant when cancer is present, including IGF-1, mTOR, and autophagy. To date, the research on cancer has focused on both short-term and prolonged fasting as an adjuvant to chemotherapy. A 2019 review found that short-term fasting may help enhance the efficacy of some chemotherapy medications while protecting healthy cells and reducing drug side

Growing Popularity of Intermittent Fasting

In 2020, intermittent fasting became the #1 category in diet and nutrition in the United States.



Source: International Food Information Council. 2020 Food & Nutrition Health Survey.

effects.¹² Studies in this area are ongoing. In addition to influencing intracellular signaling cascades and increasing autophagy, prolonged fasting is also being studied for its influence on anticancer immunity and helping healthy cells be more stress resistant.¹³

Obesity is a key risk factor for cancer and other illnesses such as cardiovascular disease and diabetes. As a result, weight loss and preserving and building lean body mass can be significant health benefits of intermittent and prolonged fasting. Weight loss is also a common reason practitioners recommend fasting to their patients. A 2019 review of 12 different studies featuring 545 participants found that intermittent fasting resulted in a significant decline in body mass index, fasting glucose levels, insulin resistance, fat mass, and leptin.¹⁴

Ongoing clinical research indicates that intermittent fasting can help reduce some of the key risk factors associated with cardiovascular diseases such as obesity, high cholesterol, hypertension, and metabolic syndrome.¹⁵ A 2020 randomized controlled trial demonstrated that prolonged fasting also improved markers of metabolic syndrome in patients with type 2 diabetes.¹⁶

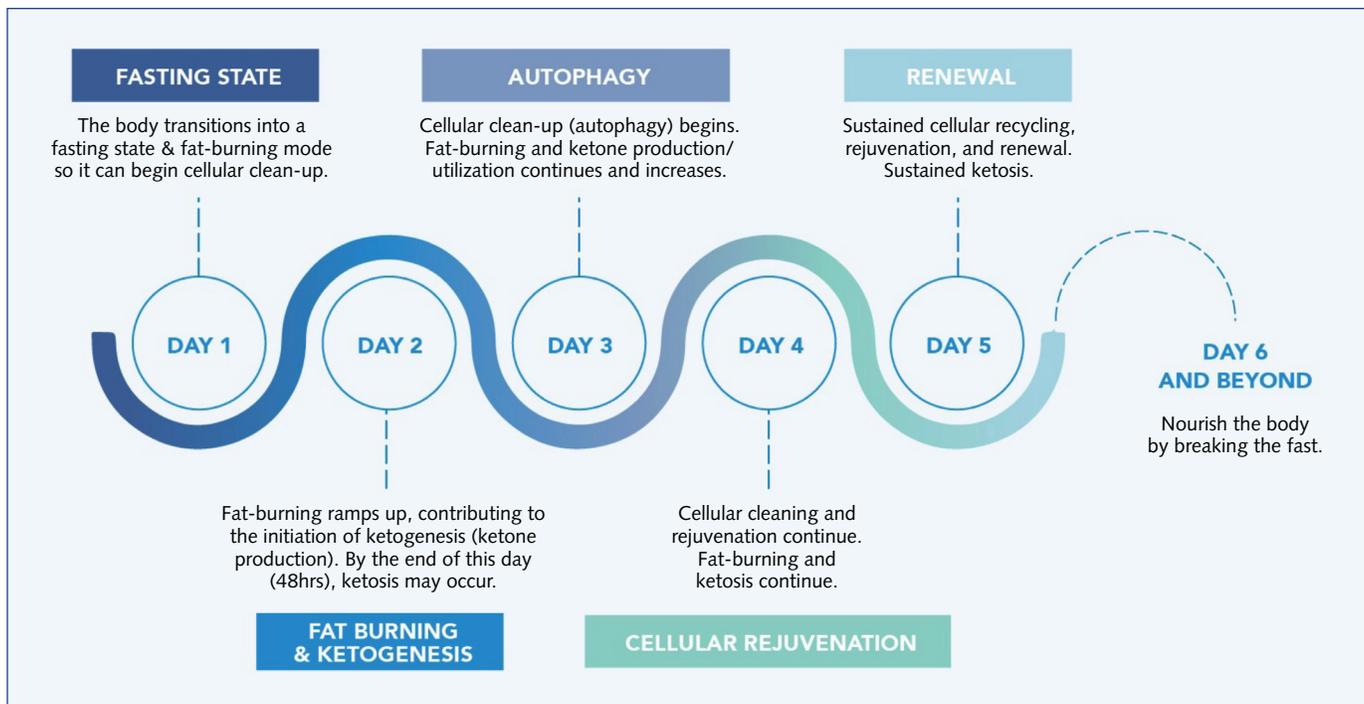
In vitro, *in vivo*, and some human clinical trials have all shown that prolonged fasting may also affect cognition.¹⁷ A 2019 review concluded that intermittent fasting has the potential to prevent vascular dementia, a neuroinflammatory condition characterized by cognitive and synaptic dysfunction, thus supporting the need for additional clinical research in this area to determine the

Extending the Intermittent Fast

The studies on intermittent fasting typically feature a fasting period of 12 to 16 hours with research on Ramadan religious fasting being about 16 hours, and efficacy appearing to be enhanced with longer fasts up to 18 hours.²⁰ This type of extended intermittent fast can be hard for some patients to sustain, which can impact adherence and fasting efficacy.

A 2021 randomized, controlled, parallel-arm study found that eating a 200 calorie FMD nutrition bar following a 15-hour overnight fast did not interfere with the physiological ketogenesis associated with the overnight fast when compared to participants doing an extended water fast and breakfast.²¹ This is significant because eating the bar may mitigate fasting-associated side effects while potentially enhancing compliance and intermittent fasting sustainability.²²

Table 1: The FMD Cycle



true potential impacts of fasting on these states.¹⁸ A 2019 observational study featuring 1,422 participants that fasted for up to 21 days demonstrated both physical and emotional wellbeing benefits.¹⁹ In that study, of the 404 participants with pre-existing health issues, more than 84% who did the prolonged fast reported an improvement.

Emerging research is demonstrating that prolonged fasting via a Fasting Mimicking Diet (FMD) may provide benefits similar to water fasts or intermittent fasting while also promoting intracellular cleanup and regeneration, but studies are ongoing and early.

Fasting with Food

Significant research has now determined that ingesting certain foods during a 5-day period once a month can have the same physiological effects as fasting without food for a prolonged period.²³ This form of FMD is a scientifically designed, structured 5-day meal plan carefully engineered to deliver the exact micro- and macro-nutrient ratio required to optimize nourishment but mimic fasting to ensure users enter and stay in a fasting state. The plant-based restricted-calorie meal program was carefully designed to provide the rejuvenating effects of fasting at the cellular level, while still providing the body with nourishment.

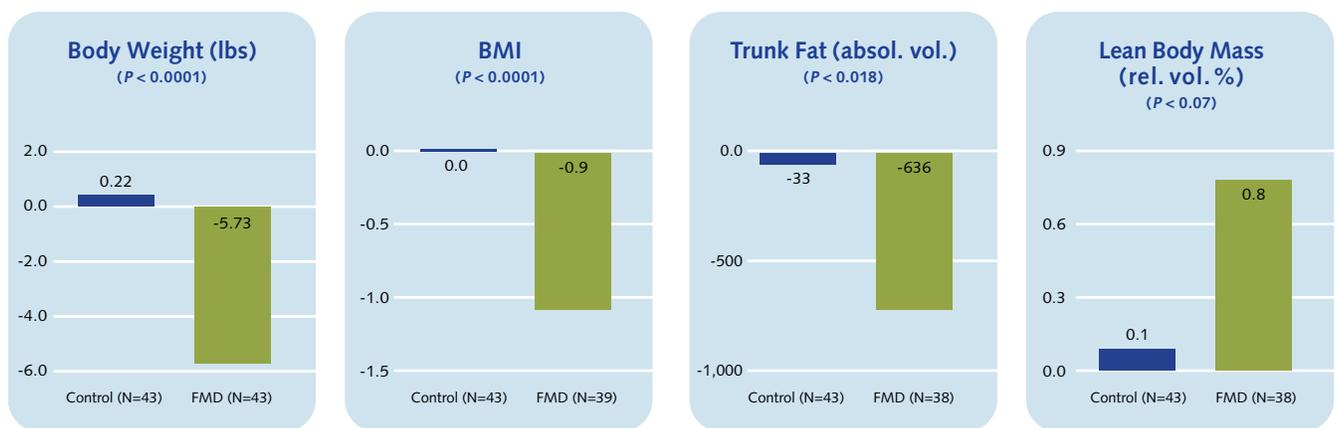
Each day the meals provide the following:

- Protein = 9-11%
- Complex carbohydrates and fiber = 43-47%
- Fats (emphasizing Omega-3 fatty acids) = 44-46%
- Calories = 700 to 1100

This combination of good fats, low protein, and specific low carbohydrates creates a fasting state while not triggering the 3 key nutrient sensing pathways mentioned previously: IGF-1, mTOR, and PKA. During the 5 days, the body goes from a fat-burning state to a state of cellular rejuvenation and renewal (Table 1). Keep in mind, however, that it is not only the amount of macronutrients that is important. FMD is designed to provide the exact amounts of macro-nutrients in precise combinations of those nutrients to provide nutrition while remaining in a fasting state, which has been validated via preliminary pre-clinical research.

FMD Research

As of June 2021, there have been more than 30 different clinical trials performed specifically looking at FMD from a variety of perspectives and in a variety of patient populations. Here we review the more recent and compelling studies evaluating FMD beginning with a 2017 paper published in *Science Translational Medicine*.²⁴ This crossover study featured 100 healthy adults. For 3 months the participants followed FMD for 5 days per



These charts show the degree of weight loss, decreased BMI, abdominal fat loss, and maintenance of lean body mass after a 3-month cycle of FMD compared to the control diet.

Source: Wei M, Brandhorst S, Shelehchi M, et al. Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease. *Sci Transl Med.* 2017;9.

month or an unrestricted diet and then were crossed over to follow the other diet for an ensuing 3 months. In both arms, the FMD led to reduced body weight, including visceral and total body fat; lowered blood pressure; and decreased IGF-1. This study also looked at markers of aging and age-related diseases and found that the FMD resulted in improved BMI and maintenance of healthy diastolic blood pressure and IGF-1 compared to baseline.

Preliminary *in vitro* and *in vivo* research demonstrates that FMD may play a beneficial role in cases of hormone-receptor-positive breast cancer.²⁵ Studies of FMD use as adjuvant therapy are still ongoing, however, and results are not conclusive at this time.

FMD also shows potential with inflammatory illnesses and autoimmunity. Similar to intermittent fasting, *in vivo* animal research has shown that FMD may positively impact inflammatory bowel disease.²⁶ In that study, FMD reduced markers of intestinal inflammation and promoted gut microbiome health.

Regarding autoimmunity, a 2016 *in vivo* animal study demonstrated that FMD reduced symptoms of multiple sclerosis with a complete reversal of all symptoms occurring in 20% of the animals.²⁷ In that paper, the researchers also considered the potential effectiveness of FMD in the treatment of relapsing-remitting multiple sclerosis in humans although studies are pending in this area as well.

In addition to efficacy, research has also addressed issues of safety, feasibility, and other clinical considerations. The developers of FMD strongly caution that it is being studied in all of these conditions, and FMD studies are in the early stages and many more pre-clinical and clinical trials will be required before results are conclusive. FMD should not be used for the diagnosis, treatment, cure, or prevention of any disease.

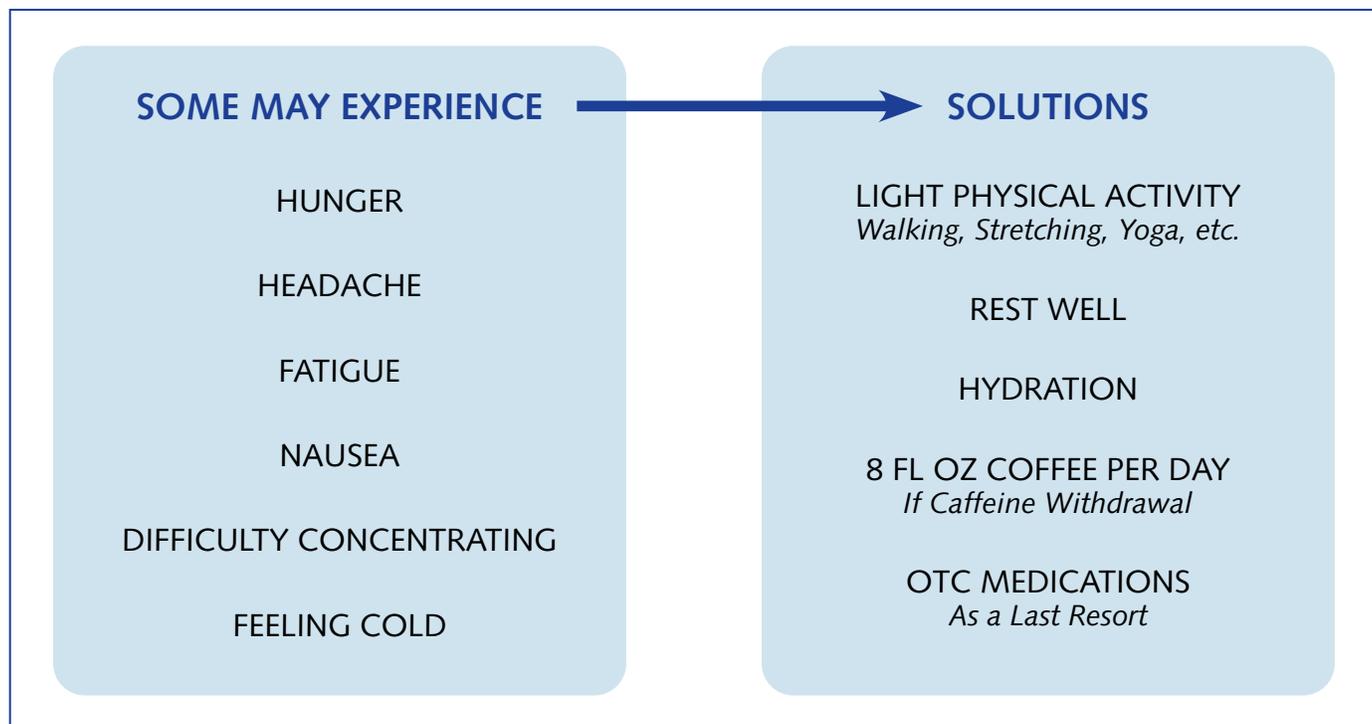
Clinical Considerations

In general, fasting is considered safe.²⁸ A 2016 cohort feasibility study involving people diagnosed with cancer receiving chemotherapy demonstrated that prolonged fasting was not only feasible but was also considered safe for this patient population.²⁹

However, as with many integrative therapy interventions, appropriate clinical oversight is preferred with prolonged fasting as certain patient populations may need to avoid this type of diet. Following is a list of patients who should not fast, including utilization of an FMD:

- Women who are pregnant or breastfeeding
- Children under the age of 18
- Patients with significant dietary restrictions
- Patients who are malnourished, underweight, or have a known, suspected, or present/past diagnosis of an eating disorder
- Patients who have symptoms or are being treated for an active infection or those at risk of recurrent infection

Optimizing the Patient Experience



While there is no specific research on fasting contraindications, clinical experience indicates that fasting and FMDs are not known to interfere with common medications such as aspirin or other NSAIDs, proton pump inhibitors, OTC allergy medications, or statins; however, there may be interactions with these medication categories:

- Hypoglycemic agents = monitor and adjust to avoid hypoglycemia
- Blood pressure medications = monitor and adjust to avoid electrolyte imbalance, dehydration, or hypotension (Note: weight loss can lead to lower blood pressure, so medications should be reassessed accordingly)
- Hormone therapy (thyroid, sex hormone replacement, or steroids) = although highly patient dependent, monitor and adjust accordingly and ensure the patient is on a stable regimen before fasting

As with any fasting program, side effects of FMD may occur such as fatigue, headache, and difficulty concentrating. Clinicians have a variety of methods to ease these and other side effects to help optimize the patient's fasting experience. During the prolonged fasting period, strenuous exercise and exposure to high temperatures

such as saunas or extreme cold environments should be avoided. Adverse events can be more common with extreme fasts such as water fasting, with hypertension and dizziness/fainting being the most commonly reported side effects of water fasting.³⁰

Conclusion

Fasting is an adaptive response to restricting food intake for a set period of time that creates physiological changes in the human body. The research regarding the benefits of intermittent and prolonged fasting has grown considerably over the past decade. While fasting is not indicated for all patients, it's clear that certain patient populations may experience diverse and vital health benefits from these forms of fasting.

There are many different types of fasting strategies making it a tool that can be customized for the individual patient. For patients who have difficulty with highly restrictive fasting regimens or those new to fasting, FMD is a viable option. For those patients utilizing the intermittent/overnight fasting strategy, FMD nutrition bars may help enhance efficacy and sustainability. For practitioners utilizing fasting as a health-enhancing strategy, future research should validate current practices as well as bring better precision to the application of fasting as a therapeutic tool.

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