REVIEW

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Intermittent Fasting: A Heart Healthy Dietary Pattern?

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ABSTRACT

Dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean diet, have been shown to improve cardiac health. Intermittent fasting is another type of popular dietary pattern that is based on timed periods of fasting. Two different regimens are alternative day fasting and time-restricted eating. Although there are no large, randomized control trials examining the relationship between intermittent fasting and cardiovascular outcomes, current human studies that suggest this diet could reduce the risk for cardiovascular disease with improvement in weight control, hypertension, dyslipidemia, and diabetes. Intermittent fasting may exert its effects through multiple pathways, including reducing oxidative stress, optimization of circadian rhythms, and ketogenesis. This review evaluates current literature regarding the potential cardiovascular benefits of intermittent fasting and proposes directions for future research.

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KEYWORDS: Alternative day fast; Circadian; Diabetes; Dyslipidemia; Hypertension; Time-restricted feeding

INTRODUCTION

Although cardiovascular mortality rates have improved, the decline in mortality has recently ceased, and there has been an increase in mortality in 35- to 64-year-old males and females in the United States.[1] Obesity along with poor diet are important, modifiable contributors to the rise of cardiovascular disease with an estimated attributable risk of 13% to cardiovascular mortality.[2] There are several dietary interventions that have been shown to improve cardiovascular risk, including caloric restriction, which involves limiting calories consumed during a given period. Caloric restriction is linked to improvement in weight, blood pressure, and insulin sensitivity in humans.[3]

Intermittent fasting is a dietary intervention similar to caloric restriction, as it uses the principle of restricting food intake. However, intermittent fasting focuses on the timing of when one can consume meals either within a day or a week. Two overarching types of intermittent fasting are alternative day fasting and time-restricted fasting. In alternative day fasting, a subset may consist of 24-hour fasts followed by a 24-hour eating period that can be done several times a week such as a 5:2 strategy when there are 2 fast days mixed into 5 nonrestrictive days. For time-restricted fast programs, variations include 16-hour fasts with 8-hour feeding times, 20-hour fasts with 4-hour feed times, or other similar versions. Although both caloric restriction and intermittent fasting may result in overall decreased caloric intake, this is not integral to intermittent fasting. Intermittent fasting has been linked to better glucose control in both humans and animals.[4,5] However, long-term adherence to caloric restriction is low, whereas adherence to intermittent fasting may be more promising.

Given the similarity between these 2 diets, it is plausible that intermittent fasting could confer cardiovascular benefits

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as well. This dietary pattern has also shown potential benefit in slowing the progression of neurodegenerative diseases like Alzheimer and Parkinson diseases.[6] In this review, we explore the potential benefits of intermittent fasting for improving cardiovascular health.

CLINICAL SIGNIFICANCE

- Modifying the dietary pattern can lead to better cardiovascular outcomes.
- Intermittent fasting may benefit cardiovascular health by improving obesity, hypertension, dyslipidemia, and diabetes.
- Potential mechanisms of this diet involve reducing oxidative stress, syncing with the circadian system, and inducing ketogenesis.

MECHANISMS

There are several proposed mechanisms for how intermittent fasting could lead to better cardiovascular outcomes (Figure 1). The oxidative stress hypothesis supports decreased oxidative insult.[7] A second theory, the circadian rhythm hypothesis, is associated more with intermittent fasting than caloric restriction, indicating a mechanism unique to intermittent fasting. A third theory involves intermittent fasting inducing a ketogenic state, which has been linked to decreases in cardiovascular risk factors.

Oxidative Stress Hypothesis

The oxidative stress hypothesis states that decreased energy intake causes mitochondria to produce fewer free radicals.[7] After 8 weeks of alternative day fasting, patients who were obese with asthma showed lower levels of inflammation such as tumor necrosis factor-alpha and brain-derived neurotrophic factors as well as oxidative stress including nitrotyrosine, 8-isoprostane, protein carbonyls, and 4-hydroxynoneal adducts. Moreover, they had higher levels of the antioxidant uric acid.[8]

Circadian Rhythm Theory

The circadian rhythm theory assumes that physiologic processes occur at the most advantageous time as dictated by evolution.[9] Fasting properly may allow optimization with our organs' peripheral clocks such as those in the liver, adipose, and skeletal tissues. Dysregulation of this system increases the risk for chronic diseases, as evidenced by higher rate of cardiometabolic diseases in shift workers.[10] One circadian example relevant to intermittent fasting is decreasing insulin levels later in the day.[11] Late dinners are associated with higher postprandial glucose levels than daytime meals, increasing the risk of diabetes. In humans, circadian misalignment increases insulin resistance after only 3 days.[10] Nighttime eating decrease both quality and quantity of sleep, which also leads to increased insulin resistance, obesity, and cardiovascular disease. [12,13] Different time-restricted fast regimens have demonstrated variable results based on the timing of the fast, which emphasizes the role of circadian system in this

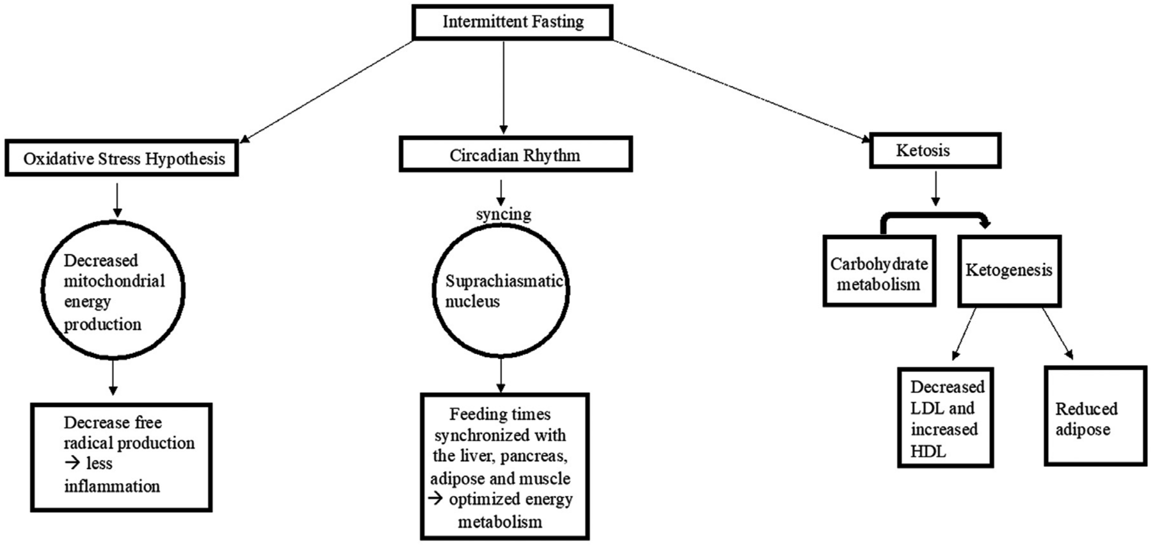

Figure 1 Mechanisms of intermittent fasting: Proposed mechanisms of how intermittent fasting reduces cardiovascular risk factors. There are three main theories: oxidative stress hypothesis, circadian rhythm, and ketogenic state. The oxidative stress hypothesis postulates that fasting reduces stress, leading to fewer free radical with less mitochondrial energy production, ultimately lowering the body's oxidative stress. The circadian rhythm component focuses on syncing eating periods to the organ's circadian rhythm, optimizing glucose and fat utilization. The third mechanism, ketogenic state, recognizes that intermittent fasting induces ketogenesis, which decreases blood pressure and adipose tissue. HDL= high-density lipoprotein; LDL= low-density lipoprotein.

dietary pattern. Subjects who were allowed to eat during the middle of the day had better weight loss with less adipose, glucose control, lipid levels, and inflammation.[14] In contrast, those on a time-restricted fast regimen that allowed late afternoon or evening intake defined as beyond 4:00 pm had no improvement and even worsening of glucose control, blood pressure, and lipid levels.[15,16] Thus, intermittent fasting when timed properly, may sync with one's circadian rhythm and, thus, improve cardiac health.

Ketogenic State

Intermittent fasting induces a ketogenic state, as evidenced by the rise in β-hydroxybutyrate levels in overweight individuals who fast.[8] After 6-8 hours of fasting, ketone levels become detectable, which signals a switch from fat storage to fat use with a decrease in low-density lipoproteins (LDLs) and an increase in high-density lipoproteins (HDLs) levels.[17,18] This change from using glucose as energy to using fatty acids and ketones for energy is called "intermittent metabolic switching." Furthermore, the ketogenic diet promotes weight loss because processing ketones requires greater energy.[19] Intermittent fasting contains elements of the ketogenic diet, benefitting from increased adipose metabolism leading to improvement in weight and lipids. Importantly, intermittent fasting may be more beneficial than the ketogenic diet, as the latter involves high consumption of animal fats. Excessive fat intake can be detrimental because it is associated with higher levels of trimethylamine N-oxide, a metabolite associated with increased cardiovascular risk that has been found to be higher in a ketogenic diet.[20]

THE EFFECT OF INTERMITTENT FASTING ON CARDIOVASCULAR RISK FACTORS

Obesity

In a study of men who were overweight with type II diabetes, subjects in both caloric restriction and intermittent fasting regimens experienced weight loss, with intermittent fasting subjects losing 1.1% of body fat with a mean 6.5% weight loss after 12 weeks.[21] (Table 1) Similar findings were observed in both premenopausal females who were overweight or obese and were randomized to intermittent fasting and caloric restriction for 6 months. The intermittent fasting and caloric restriction groups had comparable results with the intermittent fasting group losing 6.4 kg (95% confidence interval [CI] 4.8-7.9 kg) and the caloric restriction group losing 5.6 kg (95% CI 4.4-6.9 kg).[22] A study with 16 men and women who were not obese and underwent alternative day fasting for 22 days did lose 2.5 $\pm$ 0.5% of initial body weight (P <0.001) and 4 $\pm$ 1% of their fat mass (P <0.001).[23] Interestingly, subjects who were obese and were randomized to fasting except for lunch or dinner for 8 weeks had similar weight loss with the lunch group losing 3.5 $\pm$ 0.4 kg (P <0.001) and the dinner group 4.1 $\pm$ 0.5 kg (P <0.001).[24] Despite not adhering to the circadian rhythm, weight loss likely occurred because of the limited calorie consumption. The change in weight may also be related to the use of fatty acids for energy, which is consistent with a ketogenic state.

Blood Pressure

Human studies have shown reductions in both systolic and diastolic blood pressure with intermittent fasting. A small study of men with prediabetes had an average reduction of systolic blood pressure of 11 $\pm$ 4 mm Hg and a diastolic blood pressure reduction of 10 $\pm$ 4 mm Hg after 5-weeks of fasting for 18-hour periods.[25] Similarly, a prospective observational study of 82 Muslims who celebrated Ramadan, a month-long religious holiday involving daytime fasting, showed a 3-point reduction in systolic blood pressure although diastolic change was not significant.[26] One potential explanation for this is a decrease in sympathetic tone and increase in parasympathetic tone. Using power spectral analysis of heart rate and arterial pressure, rats placed on intermittent fasting have a lower frequency component in diastolic blood pressure variability, a marker for sympathetic tone. Additionally, these rats have a higher frequency component of the heart rate variability spectra, a marker for parasympathetic tone.[4] Higher vagal activity has been associated with decreased levels of inflammatory cytokines, including tumor necrosis factor-alpha, interleukin-1b, interleukin-6, and interleukin-8, which are implicated in the pathogenesis of atherosclerosis.[27] Thus, intermittent fasting appears to have the ability to lower blood pressure, which thus could improve mortality from cardiovascular disease.

Dyslipidemia

In addition to blood pressure, intermittent fasting seems to have a positive impact on lipid values. In a study with 60 adults who were overweight or obese, the alternative day fasting group who underwent a 75% caloric restriction every other day had a reduction in LDL by 10 $\pm$ 4% and reduction in triglycerides 17 $\pm$ 5% after 12 weeks.[28] However, these changes could be explained by weight loss observed. Muslims celebrating Ramadan had better HDL, LDL, triglycerides, and very low-density lipoprotein levels, resulting in an decrease in average Framingham risk score 13.8 to 10.8.[26] Similar to this study, another study with 83 participants who were obese also showed improvement in HDL and LDL after 12 weeks of alternative day fasting combined with exercise.[29] It is unclear why discrepancies among these studies regarding HDL exist. One explanation could be the difference in timing in relation to circadian rhythms because the first study involved fasting every other day, while Ramadan involves fasting from sunrise to sundown. In mice models, intermittent fasting does appear to be more beneficial when food intake occurs during times of activity as compared to more dormant times, as measured by hepatic production of circadian genes such as mPER and mClock.[30]

Table 1 Effects of Intermittent Fasting on Cardiovascular Risk Factors

Study Title	Duration (weeks)	Subjects	Intervention	Results
Obesity				
Ash (2003)	12	n = 51, M only Mean age 54 yo Overweight DM 2	ADF	Mean weight loss of 6.4 ± 4.6 kg Reduction in waist circumference 8.1 ± 4.6 cm Loss of body fat 1.9 ± 1.5%
Harvie (2011)	24	n = 107, F only Mean age 40 yo overweight and obese premenopausal	2 day a week fast (75% caloric restriction)	Lost 6.4 kg (CI 4.8-7.8)
Heilbronn (2005)	3	n = 16, M and F Male mean age 34 yo; Female mean age 30 yo nonobese	ADF	Decrease in body fat 2.5 + 0.5% of initial body weight 4 + 1% of their fat mass (*P* <0.001)
Hoddy (2014)	8	n = 74, M and F Mean age 45 yo obese	ADF for either lunch, dinner or small meals	ADF-lunch 3.5 ± 0.4 kg ADF-dinner for 4.1 ± 0.5 kg ADF-small meals 4.0 ± 0.5 kg
Wilkinson (2019)	12	n = 19, M and F Mean age 59 yo Metabolic Syndrome	10-h fast	Weight reduction 3.3 ± 3.2 kg BMI reduction 1.1 ± 0.97 kg/m^2 Waist circumference 4.5 ± 6.7 cm
Hypertension				
Eshghina (2013)	6	n = 15, F only Mean age 34 Overweight and obese	3 d/wk fast (75% caloric restriction)	SBP ↓ 115 + 9 mm Hg to 105 + 10 mm Hg DBP ↓ 83 + 11 mm Hg to 75 + 11 mm Hg)
Nematy (2012)	4	n = 82, M and F Mean age 54 yo ≥1 Cardiovascular risk factor	Ramadan	SBP ↓ 133 ±6 mm Hg to 130 ± 7 mm Hg NS DBP
Sutton (2018)	5	n = 8, M only Mean age 56 yo Prediabetic	18-h daily fasts	SBP ↓ 11 ± 4 mm Hg DBP ↓ 10 ± 4 mm Hg
Wilkinson (2019)	12	n = 19, M and F Mean age 59 yo Metabolic Syndrome	10-h fast	SBP ↓ 5 ± 10 mm Hg DBP ↓ 7 ± 8 mm Hg
Dyslipidemia				
Bhutani (2013)	12	n = 83, M and F Mean age 42 yo obese	ADF (75% caloric reduction) ADF combined with exercise	LDL ↓ 12 ± 5% NS TG HDL ↑ 18 ± 9%
Nematy (2012)	4	n = 82, M and F Mean age 54 yo ≥1 Cardiovascular risk factor	Ramadan	LDL ↓ 13 (110 ± 46 to 97 ± 35) TG ↓ 41 (225 ± 129 to 183 ± 112) HDL ↑ 4 (43 ± 9 to 48 ± 8)
Varady (2011)	12	n = 60, M and F Mean age 47 yo overweight and obese	ADF (75% caloric reduction)	LDL ↓ 10 ± 4% TG ↓ 17 ± 5% HDL ↑ 16 ± 5%
Diabetes Mellitus				
Bhutani (2013)	12	n = 83, M and F Mean age 42 yo obese	ADF (75% caloric reduction) ADF combined with exercise	NS fasting glucose NS insulin

Table 1 (*Continued*)

Study Title	Duration (weeks)	Subjects	Intervention	Results
Catenacci (2016)	8	n = 14, M and F Mean age 40 yo obese	ADF (100% calorie reduction)	Fasting glucose ↓6.0 + 2.1 mg/dL NS insulin
Klempel (2012)	8	n = 54, F only Mean age 48 yo Prediabetic, obese	Total fast 24-h then 6 d of 70% liquid intake Total fast 24-h then 6 day of 70% food intake	Insulin ↓ 3.0 ± 3.0 uIU/ml Glucose ↓ 4.0 ± 3.0 mg/dL
Sutton (2018)	5	n = 8, M only Mean age 56 yo Prediabetic	18-h daily fasts	Fasting insulin ↓3.4 ± 1.6 mU/L Insulinogenic Index ↑14 ± 7 U/mg

ADF = alternative day fast; BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; DM 2 = diabetes mellitus type II; F = female; HDL = high-density lipoprotein; LDL = low-density lipoprotein; M = male; NS = not significant; SBP = systolic blood pressure; TG = triglyceride; YO = years old.

Diabetes

In contrast to blood pressure and dyslipidemia, the relationship between intermittent fasting and diabetes is not as straightforward. Males who were not obese and fasted for 20-hour intervals and then ate without restriction on alternative days showed increased insulin-mediated glucose uptake after 2 weeks.[31] Another small study of men with prediabetes had better insulin sensitivity and increased beta cell responsiveness, as measured by a higher insulinogenic index calculated by the change in insulin divided by change in glucose within the first 30 minutes of an oral glucose tolerance test.[25] However, the data does not consistently support improvements in fasting glucose levels, which may be the result of a latency period or missed glucose fluctuations during the day.[25,31] In a study with individuals who were obese on alternative day fasting, insulin sensitivity did not appear to change after the 8-week intervention.[5] The difference in the outcomes of these studies may be explained by the different populations studied (obese vs non-obese), suggesting distinct impacts based on subgroups.

THE EFFECT OF INTERMITTENT FASTING AFTER A CARDIOVASCULAR EVENT

Even after a cardiovascular event, intermittent fasting may confer cardiac protection. In observational studies, Muslims with a history of ischemic cardiomyopathy have a decreased incidence of acute decompensated heart failure during Ramadan compared with other parts of the year.[32] The Intermountain Heart Collaborative Study Group performed a meta-analysis of 2 studies involving Latter Day Saints that combined about 648 patients. They compared the incidence of coronary heart disease defined as at least 1 coronary artery with ≥70% stenosis in those who underwent a monthly 1-day religious fast with those who did not. The subjects who followed the fast had a lower risk for coronary heart disease with odds ratio 0.65 (CI 0.46-0.94).[33] Although human data is sparse regarding intermittent fasting after a cardiovascular event, these observational studies suggest a positive impact.

INTERMITTENT FASTING AND LONGEVITY

Currently, there are no randomized controlled trials with humans regarding longevity and intermittent fasting. On the cellular level, human skin fibroblasts in vitro conditions simulating intermittent fasting had longer life spans than controls. In addition, this group retained their youthful morphology whereas the controls developed a senescent morphology, which is associated with a smaller, thinner appearance. Thus, this ex vivo study in human fibroblasts suggests that intermittent fasting could delay aging at the cellular level.[34]

INTERMITTENT FASTING VERSUS CALORIC RESTRICTION

Although intermittent fasting and caloric restriction are similar, it is important to make the distinction between these 2 dietary patterns (Figure 2) because they may lead to different biologic outcomes. One important distinction is that intermittent fasting does not necessarily involve limiting calories as caloric restriction does. In humans, the impact of intermittent fasting on cardiovascular risk factors (ie, blood pressure, fasting glucose, and lipid profile) can be still seen during Ramadan without decreasing caloric intake. On average, they have lower blood pressures during this month.[26] In adults who were obese, intermittent fasting and caloric restriction appear to have similar effects on improving lipid panels, whereas alternative day fasting groups had a significantly better impact on fasting glucose.[5]

In terms of practicality, it may be easier for an individual to adhere to intermittent fasting rather than caloric restriction because caloric restriction has poor long-term compliance rates with 1 study citing a dropout rate of 21% after 2 months and a 42% dropout after 1 year.[35-37] Thus far, long-term trials of 1 year show either similar or worse compliance rates with intermittent fasting compared to caloric restriction.[38,39] However, both these trials involved alternative day fasting regimens with 2 days of fasting interspersed within 1 week. Time-restricted fast regimens such as

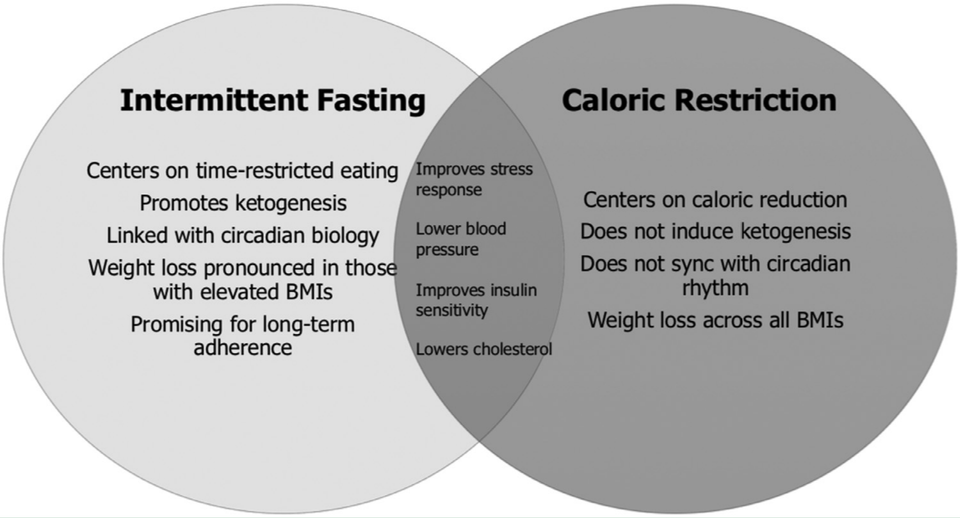

Figure 2 Similarities and differences between intermittent fasting and caloric restriction. Intermittent fasting shares commonalities as well as differences with caloric restriction. Both have been shown to reduce cardiovascular risk factors, including improving blood pressure, insulin sensitivity, and dyslipidemia. In addition, it shares the common pathway of reducing stress response. Intermittent fasting revolves around defined periods of fasting syncing with the circadian rhythm, whereas caloric restriction focuses on restricting overall calories. Thus far, intermittent fasting appears promising for individuals who are overweight and obese, and it remains to be seen if adherence is easier with intermittent fasting regimens.

16-hours of fasting and 8-hours of eating may have better adherence rates when compared to caloric restriction.

Although intermittent fasting is distinct from caloric restriction, this type of dietary regimen may also lead to better cardiovascular outcomes because the literature demonstrates fasting improves various cardiovascular risk factors such as diabetes, hypertension, and cholesterol. Despite the limited number of studies, the ability of intermittent fasting to improve cardiac health appears promising.

FUTURE DIRECTIONS AND LIMITATIONS

More studies are needed to evaluate mechanisms, efficacy in humans, target populations, and safety of intermittent fasting. There are numerous intermittent fasting regimens ranging from 12- to 16-hour daily fasts to 5:2 strategy, and it remains uncertain which strategy is the best for cardiovascular health, especially with evidence suggesting that intermittent fasting regimens should follow circadian rhythms.[14] Certain regimens may be easier to adhere to than others. Future studies should also investigate the safety of each intermittent fasting strategy as well.

In addition to finding effective intermittent fasting regimens tailored to different patient populations, future studies should establish the duration of intermittent fasting needed before cardiovascular benefits occurred. For humans, benefits appeared within a month during observational Ramadan studies. Extending intermittent fasting for longer may lead to continued improvement in both cardiovascular risk factors and events. Furthermore, it should be established if these benefits extend beyond the duration of intermittent fasting. Rats that were placed initially on intermittent fasting with subsequent improvement of blood pressure had reversal of this improvement 3-4 weeks after returning to an ad libitum diet.[4] However, for adults who were obese and were on intermittent fasting for 8 weeks then transitioned back to their regular diet for 24 weeks still maintained their lower cholesterol and glucose levels.[5] Although intermittent fasting was effective for this population of patients, it is unclear if intermittent fasting affects all populations similarly.

CONCLUSIONS

Human studies show promise for cardiovascular benefit in intermittent fasting. Although the exact mechanisms remain to be elucidated, intermittent fasting appears to positively impact multiple cardiovascular risk factors, including obesity, hypertension, dyslipidemia, and diabetes. Furthermore, intermittent fasting has been associated with improved outcome after a cardiac event. These results should encourage future studies to optimize the potential of intermittent fasting to improve cardiovascular outcomes.

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