The Effects of Meal Timing and Frequency, Caloric Restriction, and Fasting on Cardiovascular Health: an Overview

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ABSTRACT

Cardiovascular disease (CVD), which is the leading cause of death worldwide, is strongly affected by diet. Diet can affect CVD directly by modulating the composition of vascular plaques, and indirectly by affecting the rate of aging. This review summarizes research on the relationships of fasting, meal timing, and meal frequency with CVD incidence and progression. Relevant basic research studies, epidemiological studies, and clinical studies are highlighted. In particular, we discuss both intermittent and periodic fasting interventions with the potential to prevent and treat CVD.

Keywords: Fasting; Fasting mimicking diet; Caloric restriction; Blood pressure; Cardiovascular disease

INTRODUCTION

Human aging and age-related diseases are now considered the greatest challenges and financial burdens faced by all countries, developing or developed.1 In particular, aging has remarkable effects on the heart and arterial system, increasing the risk for cardiovascular disease (CVD), including atherosclerosis, hypertension, myocardial infarction, and stroke.2,3 Increases in the average lifespan of humans have made CVD the top cause of death globally, with more than 17.9 million deaths in 2016.4 Most cases of CVD could be prevented by addressing behavioral risk factors (e.g., tobacco use, unhealthy diet, obesity, sedentary behavior, and harmful use of alcohol) using population-wide strategies.5 Although major strides have been made in the reduction of CVD mortality and morbidity through behavioral interventions and population-based surveillance programs,4 the majority of industrialized countries still have the highest CVD rates in the world.7 Thus, there is an increasing need to detect and manage people who suffer from CVD and those who are at an elevated risk.

In the last decades, mounting evidence began to suggest relationships between eating behaviors—in terms of timing and frequency—and CVD and cardiometabolic health markers.8 Another concept that has attracted significant interest and debate among researchers is calorie restriction (CR), which involves a reduced daily caloric intake...
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(approximately by 20%–40%) with no changes in meal frequency. Previous reviews of in vivo and human studies have consistently demonstrated that chronic CR can extend longevity and decrease the risk for multiple age-related diseases, including tumors, CVD, and neurodegeneration.9,12 Results from experimental studies have also indicated that CR with adequate nutrient intake may be a suitable intervention for preventing CVD and slowing the accumulation of molecular damage.13

More recently, findings from well-controlled investigations in experimental animal models and emerging human studies have indicated that fasting may provide an effective strategy to reduce weight, delay aging, and optimize health.14,15 Fasting is achieved by ingesting no food or caloric beverages for periods that typically range from 12 hours to 3 weeks. It is well known that fasting results in ketogenesis and promotes potent changes in metabolic pathways and cellular processes, such as stress resistance, lipolysis, and autophagy.16,17

Despite these benefits, both the duration and severity of fasting and CR regimens reduce compliance and make them unfeasible for most people, a perception that may also exist due to undesirable side effects. For this reason, experts have started to gather consensus opinions on less drastic dietary interventions and drugs that mimic the effects of fasting and CR, but that are practical, realistic, and safe.18

Among these, the intermittent fasting (IF) is considered to be less restrictive than traditional approaches for CR, since it consists in an adequate daily caloric intake with the use of short and strict CR.18 In this review article, we trace the path that led researchers to hypothesize that fasting has health benefits, with a particular focus on cardiovascular health. We first summarize evidence from epidemiological studies on the effects of meal timing and frequency on CVD and its risk factors. Next, we describe the benefits of CR on cardiovascular and metabolic factors. Finally, we describe 2 types of fasting regimens—IF and a fasting-mimicking diet (FMD)—and their potential protective effects on cardiovascular health.

HOW MEAL TIMING AND FREQUENCY AFFECT CARDIOVASCULAR HEALTH

The implications of meal timing and frequency for cardiovascular health were recently illustrated in a scientific statement from the American Heart Association (AHA).19 Specifically, the AHA stated that the state-of-art knowledge is scarce and inconclusive, and that more studies are warranted to understand the effect of meal frequency on CVD.19

In the last 40 years, the prevalence of eating breakfast and lunch consistently declined,20 and many studies have provided support that total energy intake at breakfast is inversely associated with weight gain and CVD risk factors, such as elevated serum low-density lipoprotein (LDL) cholesterol, low serum high-density lipoprotein (HDL) cholesterol, and hypertension.21,22 Interestingly, we have recently shown that skipping breakfast is a risk factor for poor cardiovascular health,8 in accordance with the definition of the AHA.24 Our findings, together with previous data, guided the design of several clinical interventional studies analyzing the impact of breakfast consumption on multiple CVD risk factors. However, most of those studies were 1-day interventions or had a very short duration, thus providing limited evidence.25 The role of meal timing in regulating the circadian patterns of metabolism has been chiefly investigated in observational studies.25-26 At the molecular/
cellular level, circadian rhythms in gene expression synchronize metabolic processes with the external environment, allowing the organism to respond in a timely and effective way to physiological challenges.  

In mammals, this daily timekeeping is orchestrated by the biological clocks of the circadian timing system, composed of master molecular oscillators within the suprachiasmatic nuclei of the hypothalamus, which pace self-sustained and cell-autonomous molecular oscillators in peripheral tissues through both neural and humoral signals.  

A recent study showed that skipping breakfast adversely affected the clock and clock-controlled gene expression and was correlated with an increased postprandial glycemic response in both healthy and diabetic individuals.  

Evidence has also been found regarding the effects of evening meals on body mass index (BMI) and weight control, but current knowledge is inconclusive and controversial regarding skipping dinner. A few observational studies have pointed towards a positive association between evening high-energy intake and BMI,  

with a higher risk for CVD in patients who ate late in the evening. However, other studies have found no relationship or an inverse relationship.  

We recently found that skipping dinner increased triglyceride levels and total cholesterol-to-HDL ratio, suggesting a potential influence on CVD risk. The concept of snacking is more closely related to the definition of meal frequency—a matter to be discussed in the following paragraph—but its association with CVD risk and health is also debated. Although we observed that the absence of snacking—with reduced meal frequency—might affect cardiovascular health, an analysis of data from the 2001-2008 National Health and Nutrition Examination Survey showed that snacking patterns were not linked to CVD risk factors.  

To the best of our knowledge, only a single prospective study has demonstrated that patients with a greater meal frequency had a lower risk of CVD than those with a lower meal frequency. Recently, our cross-sectional analysis of Czech individuals (the Kardiovize Brno 2030 study) demonstrated that eating more frequently may be an effective long-term preventive tool against weight gain and CVD risk. In turn, other studies have evaluated the effects of meal frequency on risk factors for CVD, such as obesity, cholesterol levels, fasting glucose or diabetes, and hypertension. Several epidemiological analyses have demonstrated an association between higher meal frequency and a lower risk of obesity.  

In contrast, a cross-sectional study of the Norfolk cohort of the European Prospective Investigation Into Cancer showed that greater meal frequency decreased total and LDL cholesterol levels, without alterations of HDL cholesterol levels. Other observational studies demonstrated that greater meal frequency reduced the risk of type 2 diabetes mellitus in men, but not in women.  

Several lines of evidence from clinical trials have raised questions on the impact of meal frequency on CVD risk. For instance, none of these trials confirmed the effect of meal frequency on body weight in the absence of CR. Several studies showed that greater meal frequency affected neither HDL cholesterol nor triglyceride concentrations.  

By contrast, a study by Stote et al showed that increasing meal frequency reduced cholesterol levels, whereas decreasing meal frequency had detrimental effects. That study also demonstrated that HDL cholesterol levels were higher in patients who ate only once per day.  

Evidence on the impact of meal frequency on blood pressure is also controversial and inconclusive. While most studies have shown no changes in blood pressure, the study by Stote et al reported that consuming 1 meal per day increased both systolic and diastolic blood pressure after an 8-week intervention. Interestingly, when participants transitioned to a regimen of 3 meals per day, both systolic and diastolic blood pressure decreased. With respect to fasting glucose and/or insulin levels, the current evidence is that either low or high meal frequency has no significant effects in the absence of weight loss.
CARDIOMETABOLIC BENEFITS OF CALORIE RESTRICTION

Previous reviews of studies on rhesus monkeys reported that CR without malnutrition extended the lifespan and reduced the risk for several diseases, including diabetes, cancer, sarcopenia, and neurodegenerative diseases. Moreover, chronic CR ameliorated the expected age-associated alterations in autonomic function and gene expression in skeletal muscle.

With respect to CVD, the monkey study of the Wisconsin National Primate Research Center reported that 20 years of CR reduced the incidence of CVD by 50%. In human beings, long-term CR has been found to lead to several metabolic and molecular changes that protected against age-related pathologies, including changes in markers for diabetes, hypertension, CVD, cancer, and dementia. Specifically, both observational and randomized clinical studies reported remarkable cardiometabolic adaptations mediated by CR. For instance, well-nourished individuals who restricted their total energy intake experienced beneficial effects on several CVD risk factors, such as LDL and HDL cholesterol, triglycerides, fasting glucose, and blood pressure. Moreover, long-term CR led to sustained improvements in intima–media thickness, left ventricular diastolic function, and heart-rate variability.

In the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy study, a phase 2, multicenter, randomized controlled trial conducted in young and middle-aged (21–50 years), healthy, non-obese (BMI, 22.0–27.9 kg/m²) men and women at 3 clinical centers in the USA, it was shown that 2 years of moderate CR significantly reduced multiple cardiometabolic risk factors.

THE IMPACT OF FASTING ON HEALTH: A FOCUS ON CARDIOVASCULAR DISEASE AND ITS RISK FACTORS

1. Intermittent fasting
The most potent and feasible forms of fasting include IF (including alternate-day fasting or fasting for 2 days a week, for example) and the FMD (a high-fat, low-calorie IF diet that may promote fat loss and reduce blood sugar, inflammation, and cholesterol, similar to other fasting methods). The most studied IF approaches so far are alternate days of energy restriction, with either a total fast or consumption of 25% of estimated requirements on alternate days, 2 non-consecutive days of energy restriction per week (the 5:2 approach), or time-restricted feeding, in which individuals fast for 16, 18, or 20 hours per day. Some of the health benefits of IF described in animals and humans are summarized in Table 1.

| Benefits of IF                                      | References                                  |
|-----------------------------------------------------|---------------------------------------------|
| Reduced insulin resistance and improved glucose homeostasis | Hoddy et al.\cite{83}; Carter et al.\cite{84}; Arnason et al.\cite{85}; Sutton et al.\cite{86} |
| Reduced blood lipids (including triglycerides and LDL cholesterol) | Malinowski et al.\cite{82}; Varady et al.\cite{87}; Catenacci et al.\cite{88} |
| Reduced markers of inflammation                      | Aksungar et al.\cite{89}                    |
| Reduced blood pressure                               | Sutton et al.\cite{83}; Malinowski et al.\cite{82} |
| Reduced oxidative stress                             | Faris et al.\cite{90}; Madkour et al.\cite{91} |
| Reduced risk of cancer                               | Zhu et al.\cite{92}                        |
| Increased cellular repair                            | Antunes et al.\cite{93}                     |
| Increased fat burning                                | Mattson et al.\cite{94}; Heilbronn et al.\cite{95} |
| Increased metabolic rate                             | Webber et al.\cite{96}                      |
| Improved memory and cognitive function               | Li et al.\cite{97}; Halagappa et al.\cite{98}; Brandhorst et al.\cite{99} |
| Reduced autoimmune diseases, protective patterns of gut flora | Cignarella et al.\cite{100}                 |

IF, intermittent fasting; LDL, low-density lipoprotein.
In vivo studies have demonstrated protective effects of IF against obesity, hypertension, glucose intolerance, insulin resistance and diabetes, inflammation, and the clinical progression of CVD in mice. Plausible mechanisms underpinning these beneficial effects include improved insulin sensitivity, increased levels of fibroblast growth factor 21, reduced inflammation and oxidative stress, and enhanced cellular and molecular adaptive stress responses (e.g., mitochondrial function, proteostasis, autophagy, and endogenous antioxidant enzymatic activity).

While in vivo models have been used extensively, the majority of epidemiological findings have been obtained through studies of patients who mostly fasted for religious reasons. For instance, a meta-analysis of 2 small studies within the Intermountain Heart Collaborative Study showed that participants who fasted routinely (1 time per month for 24 hours) had a lower risk of coronary artery disease and diabetes mellitus than those who did not. Beyond observational studies, several clinical trials have evaluated the effect of IF on health, especially cardiovascular health. Recently, it has been observed that 4 weeks of strict IF improved markers of health in middle-aged humans, including cardiovascular parameters, inflammatory markers, LDL levels, triiodothyronine levels, fat mass (in particular, trunk fat), and the fat-to-lean ratio. However, it is difficult to understand whether fasting directly affects cardiovascular markers or its benefits depend on weight loss. Indeed, it has been demonstrated that IF significantly reduced body weight after 3–24 weeks of an intervention. The greatest benefits were observed for interventions that provided a low-calorie meal on each fast day. Moreover, a comparison between alternate-day and periodic fasting demonstrated that the former strategy was more effective for reducing body weight. Interestingly, the positive effects of these strategies on body weight also resulted in reductions in triglyceride levels, which decreased after IF interventions, with more benefits in the studies that documented the greatest weight loss.

Several lines of evidence have shown that weight loss due to IF might be also useful for lowering both systolic and diastolic blood pressure. These studies also suggested that fasting might help prevent the progression from prehypertension to hypertension, but further research is needed to corroborate this finding.

With respect to cholesterol levels, current evidence is controversial. Although some studies have reported that IF reduced total cholesterol levels, no effect was observed in others. It is worth noting that the benefits of fasting were significant in patients with mildly elevated cholesterol levels. By contrast, no effect of fasting on HDL cholesterol was evident.

IF also appeared to reduce fasting glucose in patients with prediabetes, but not in healthy individuals. The greatest benefits were observed in patients who fasted on alternate days. Stronger evidence was reported in studies investigating the effect of fasting on insulin levels, which found that IF reduced fasting insulin levels independent of prediabetes status. Insulin concentration seemed to be associated with the degree of energy restriction, with the greatest reduction observed in the studies with the highest CR. More recently, Stekovic et al. demonstrated that alternate-day fasting improved cardiovascular health by reducing blood pressure, heart rate, arterial and pulse pressure, and pulse wave velocity. Interestingly, they proposed that these changes might reduce the risk for CVD, as measured by the Framingham Risk Score.
2. Fasting-mimicking diet

The FMD was recently created with the goal of replicating the benefits of fasting, while still providing the body with adequate nutrition. The modifications of the FMD avoid the calorie deprivation associated with other types of fasting, which should render it more feasible for patients and increase their compliance. A 5-day FMD consists of meals and snacks that are whole-food and plant–derived. The FMD is low in carbohydrates and protein, while being high in healthy fats such as olives and flaxseed. The first day of the FMD provides approximately 1,090 kcal (10% protein, 56% fat, and 34% carbohydrates), while days 2 through 5 provide only 725 kcal (9% protein, 44% fat, and 47% carbohydrates). This corresponds to 34%–54% of normal calorie intake. The low-calorie, high-fat, low-carbohydrate content of the meals causes the body to generate energy through gluconeogenesis from noncarbohydrate sources after glycogen stores are depleted. The creators and manufacturers of the FMD 5-day plan recommend following this regimen every 1–6 months, in order to mimic the body’s physiological response to traditional fasting methods, such as cell regeneration, decreased inflammation, and fat loss.

Some of the health benefits of FMD described in animals and humans are summarized in Table 2. In normal mice, 4 days of a FMD starting at middle age and administered bi-monthly yielded spectacular results. While FMD decreased the size of multiple organs/systems, this effect was followed upon re-feeding by an elevated number of progenitor and stem cells and regeneration. FMD cycles extended longevity, lowered visceral fat, reduced cancer incidence and skin lesions, rejuvenated the immune system, and retarded bone mineral density loss. In old mice, FMD cycles favored hippocampal neurogenesis and improved cognitive performance. A 4-day FMD was also shown to restore insulin secretion and glucose homeostasis in both type 2 and type 1 diabetes mouse models, as well as in pancreatic islets in humans with type 1 diabetes. These animal and ex vivo studies provide support for the use of the FMD to promote the health span.

As described for IF, the majority of findings on the benefits of FMD relate to weight loss. For instance, a previous study compared subjects who followed 3 months of an unrestricted diet to subjects who consumed the FMD for 5 consecutive days per month for 3 months. Three FMD cycles were able to reduce body weight and trunk fat, and to shrink total body fat. Moreover, FMD cycles also lowered blood pressure and decreased levels of insulin-like growth factor 1 (IGF-1), without serious adverse effects.

Strikingly, BMI, blood pressure, and fasting glucose, IGF-1, triglycerides, total and LDL cholesterol, and C-reactive protein levels were more beneficially affected in participants at risk for disease than in those who were not at risk. This benchmark study showed that cycles of a 5-day FMD were safe, feasible, and effective in reducing risk factors for aging and age-related diseases.

### Table 2. Health benefits of the FMD

| Benefits of FMD                                                                 | References                  |
|--------------------------------------------------------------------------------|-----------------------------|
| Modulates microbiota and promotes intestinal regeneration to reduce inflammatory bowel disease | Rangan et al.⁹⁹             |
| Neuroprotection in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–induced Parkinson disease mouse model | Zhou et al.¹⁰⁰              |
| Improving the efficacy of chemotherapy, while inhibiting side effects          | Lo Re et al.⁹⁹; Di Biase et al.¹⁰⁰; D’Aronzo et al.¹⁰¹; Safdie et al.¹⁰² |
| Inhibition of diabetes progression (type I and II), regeneration of β-islets | Wei et al.⁷⁶; Cheng et al.⁷⁶; Brandhorst et al.⁷⁶ |
| Decreased markers/risk factors for aging                                      | Wei et al.⁷⁶; Brandhorst et al.⁷⁶ |
| Reduced risk of cancer in humans                                              | Wei et al.⁷⁶; Brandhorst et al.⁷⁶ |
| Reduced risk of cardiovascular disease in humans                              | Wei et al.⁷⁶; Brandhorst et al.⁷⁶ |
| Reduced autoimmunity and symptoms of multiple sclerosis                       | Choi et al.⁷⁶               |
| Multi-system regeneration                                                     | Brandhorst et al.⁷⁶         |
| Improves cognition                                                            | Brandhorst et al.⁷⁶         |

FMD, fasting-mimicking diet.
Fasting has been practiced for centuries, if not for millennia, but only recently have molecular studies clarified its role in adaptive cellular responses that decrease inflammation and improve energy metabolism and cellular protection. In rodents, IF and the FMD protect against diabetes, cancer, CVD, and neurodegeneration, while in humans, fasting helps to reduce risk factors for developing these ailments. IF and the FMD have the potential to delay aging and CVD, while minimizing the side effects caused by chronic dietary interventions. Despite a wealth of proof obtained from model organisms and human pilot studies, solid randomized clinical trials and meta-analyses are still lacking. Moreover, only a few studies have documented adverse effects in response to fasting regimens, including hunger and feeling cold, irritable, or without strength. By contrast, they reported improvements in self-confidence and positive mood, and reductions in tension, anger, and fatigue. What is certain is that several classes of people need caution, such as children, pregnant women, those performing heavy physical work, patients with reactive hypoglycemia, and those who use antidiabetic drugs.

**CONCLUSION**

Although both IF and the FMD are promising, a cautious note is still needed. More efforts to understand the long-term effects of fasting on cardiovascular health and disease are warranted.

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