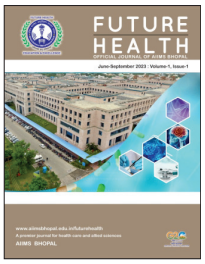
ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://futurehealthjournal.com

Future Health



Review Article

Intermittent fasting & cardiometabolic diseases

Nalini Mishra[1], Vishnu Narayan Mishra[2]

[1]L N Medical College Bhopal, [2]Department of General Medicine, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India

***Corresponding author:**
Prof. Nalini Mishra, Dean,
L N Medical College Bhopal,
Bhopal, Madhya Pradesh, India.

drmishranalini@gmail.com

Received: 09 December 2024
Accepted: 30 December 2024
Published: 14 February 2025

DOI:
10.25259/FH_77_2024

Quick Response Code

ABSTRACT

Medically speaking fasting could be defined as the ability of the body to meet its macro and micro nutrients requirements during either shortage or absence of food during a limited period of time. In human beings Intermittent Fasting (IF) regimens are most widely studied fasting methods with significant medical benefits. IF in humans ameliorates multiple metabolic & hormonal factors that are implicated in the pathogenesis of atherosclerosis, type II DM, obesity, cardiovascular diseases, neuro- degenerative & cancerous illnesses, which are the leading causes of morbidity, disability and mortality in human beings. These health benefits of intermittent fasting are not just the result of weight loss or reduced free radical production. Instead intermittent fasting triggers evolutionarily developed and preserved adaptive cellular responses that evolved billions of years ago in prokaryotes and allows mammals including humans in preventing and treating diseases and having favorable effects on aging, as IF improves glucose regulation, increases stress resistance, suppresses inflammation, promotes cellular autophagy and leads to cells engage in tissue specific processes of growth, repair and plasticity. G-K switch is supposed to play a major role in this process. Overall evidence suggests that IF regimens are not harmful in healthy normal weight, overweight, or obese adults.

Keywords: Intermittent fasting, Diabetes Mellitus, Dyslipidemia, Coronary artery disease, Obesity

INTRODUCTION

Fasting has been practiced for many centuries all over the globe in some form or the other. Almost all religious groups, including Hindus, Christians, Jews, Buddhists, Sikhs, Jains and many others, incorporate periods of fasting into their rituals. A method of fasting is to do it on designated days of the week or year, or on various religious occasions. At this juncture, it is important to emphasize that this review focuses on Intermittent Fasting (IF) & its role in cardiometabolic diseases.

The beneficial roles of fasting for human health were known by as early as the 5th century BC, when Greek physician Hippocrates recommended abstinence from eating or drinking for certain illnesses. Positive physiological effects of fasting were noticed in the latter part of the 19th century, when some organized studies on fasting were carried out in animals and humans. At the beginning of the 20th century, knowledge about nutrition and nutritional requirements of the human body became available, leading to a wide array of approaches where fasting was used in the prevention and treatment of diseases. But, the mechanism behind the beneficial effects of fasting on human health remained unclear. It is only in the last few decades that the favorable role of IF on adaptive cellular responses leading to reduced oxidative damage and inflammation has been demonstrated, leading to cellular protection by optimizing energy metabolism.[1]

HOW FASTING COULD BE DEFINED

Medically speaking, fasting could be defined as the ability to meet the body's macro and micronutrient requirements during a limited period of either shortage or absence of food by using the energy reserves of the body without affecting health. The fasting process may be complete or partial, lengthy or short or intermittent. Fasting is distinct from caloric restriction (CR), in which the daily caloric intake is reduced by 20-40%, but meal frequency is maintained. Starvation, is a state of chronic nutritional insufficiency, but is also used to define extreme forms of fasting, which can result in degeneration and even death.

TYPES OF INTERMITTENT FASTING

In human beings, IF regimens are the most widely studied fasting methods with significant medical benefits. Commonly prevalent intermittent fasting methods are as follows–

The Circadian rhythm fasting - The circadian rhythm diet, also known as the body clock diet, is basically a form of a time-restricted eating plan where one eats in synchronization with the body's internal clock. Food is consumed during the day, within a window of 12 hours or less, and the remaining 12 hours or more are dedicated to fasting. The fast may begin at 7, 8 or 9 pm and end at 7, 8 or 9 am. To get maximum benefits from this type of an eating pattern, one should finish their last meal before sunset or a little after sunset, i.e. dinner by 6.30 or, maximum by 7 pm. This dietary pattern is followed by the Jain community. Circadian misalignment a condition that is highly prevalent in shift workers, resulting in a decrease in leptin, an increase in glucose and insulin, an increase in mean arterial blood pressure, and reduced sleep efficiency.[2] If one is not hungry after the completion of the 12 hours fast, then they can extend their fasting period to 13, 14, 15 or 16 hours, according to what suits their body. Later on, this method could be clubbed with the 16:8 fasting method for one or two days of the week.

Time Restricted Feeding (TRF) - Also known as 16:8 Fasting, it is a type of IF that focuses on eating within a particular window of time. TRF involves limiting food intake to fixed hours. In most studies, an 8 hour window has been suggested. In this method of Intermittent Fasting 16 hours of the day are dedicated to fasting, and food consumption is restricted to an eight-hour window. There are no food restrictions during this eight-hour window. Time restriction may vary according to individual preferences and lifestyle; people may choose one of the following 8 hour eating windows (1) 9 a.m. to 5 p.m. (2)10 a.m. to 6 p.m. or (3) 12 p.m. to 8 p.m. within this food window three healthy meals should be consumed.[3] This method has become popular in recent years, and it shows promise as a possible new paradigm in the approach to weight loss and other potential long-term health benefits in "Cardio metabolic Diseases".

Alternate day fasting (ADF) - For the more advanced IF participants, fasting every alternate day for a full 24-hour period is an option. ADF consists of alternating the days in which the calorie consumption limit is 75% of normal. The so called "fast day" and "feeding day", during which food is eaten ad libitum (at one's pleasure). IF helps reduce the body weight and is cardio protective, probably because of the reduction of visceral fat due to increased adiponectin concentration and decreased leptin and LDL concentration.

5:2 intermittent fasting (fasting 2 days each week)- In this type of IF, participants spend five days of the week eating regularly while restricting intake to 500 calories only two days of the week. One could spread this out over the week, for example, restriction calories on In Periodic Fasting (PF), fasting cycles last two or more days and are at least a week apart, while in IF, cycles usually last 24 hours and are one to few days apart. It is advisable that the five regular eating days include healthy food. Reducing caloric intake to just 25% on fasting days could be achieved by eating three smaller meals, breakfast and late lunch, or one single meal. One should consume foods high in fiber and protein in order to stay satiiated on fasting days.[4] In a recently published study by Templeman *et al.*[5], it was found that alternate-day fasting is less effective in reducing body fat than a matched degree of daily energy restriction.

MECHANISM OF BENEFICIAL EFFECTS OF INTERMITTENT FASTING (INTERMITTENT METABOLIC SWITCHING)

Every time we consume food, the glycogen stores in our liver are replenished; liver glycogen provides about 700-900 calories of energy through glucose, an amount that lasts about 10 to14 hrs in individuals who are not exercising. This period is sufficient to cause depletion of liver glycogen stores and trigger a metabolic switch so that adipose cells release fatty acids, which are converted to ketone bodies β-hydroxybutyrate and acetoacetate in the liver. In humans, ketone levels start rising 10 to 12 hours after the onset of fasting. This transition from the utilization of carbohydrates and glucose to fatty acids and ketones as the major cellular fuel source is referred to as the 'G-to-K switch'.[6] As exercise accelerates the depletion of liver glycogen stores, it hastens the onset of the G-to-K switch, for example, this metabolic switching may occur 4 hours after a recent meal in someone who exercises or runs for 1 hour (during which time he uses approximately 600 calories). While one is restricting calories for a period of time, cells modulate their working to resist

stress. This is achieved by a reduction in insulin signaling and overall protein synthesis. Ketone bodies, act as potent signaling molecules with positive effects on cell and organ functions by altering major cellular pathways that are known to influence health and aging.

On recovery from fasting, the cells switch back to glucose for their energy ('K-to-G switch'). This causes an increase in glucose levels; ketone levels fall, cells increase protein synthesis and undergo repair by up-regulating autophagy to remove damaged molecules and recycling their components. Studies in animals and humans have shown that many of the health benefits of IF are not simply the result of weight loss or reduced free radical production.[7,8] IF triggers the old evolutionarily developed and conserved adaptive cellular responses, between and within organs, such that they improve glucose regulation and increase stress resistance, leading to engagement of cells in tissue-specific processes of growth, plasticity and suppression of inflammation.[9] These cellular and molecular mechanisms responsible for the protective effects of calorie restriction evolved billions of years ago in prokaryotes when they were attempting to survive in very hostile environments largely devoid of energy sources. This process has been passed over the generations.[10] In experimental conditions, food reduction has been shown to extend Drosophila longevity. Similarly in various animal experiments on mice and rats, the positive effects of 20-40% CR on ageing and diseases have been observed. It seems that a similar alternate metabolic program that evolved billions of years ago in microorganisms allows mammals, including humans, to prevent and treat diseases and has a favorable effect on ageing.[11]

IF activates stress-induced pathways and increases the transcription of stress-induced proteins such as Heat Shock Protein (HSP). They get attached to unfolded or misfolded proteins and restore normal configurations. They have anti-inflammatory and anti-apoptotic properties. Elevations in HSPs mitigate insulin resistance, glucose intolerance, & hyperglycemia in animal studies as well.[12] Cellular senescence is associated with an accumulation of malfunctioning constituents inside the cell due to reduced autophagy, a process by which distorted molecules and impaired organelles are eliminated. IF promotes cellular autophagy by stimulating sirtuin-1 activity, helps in reverting this process, and maintains cellular rejuvenation.[13] Another suggested mechanism for the beneficial effects of fasting is reduced levels of Advanced Glycation End products (AGEs) that result from non-enzymatic attachments of carbohydrate molecules to proteins, lipids, or nucleic acids during normal metabolism There is increased production or reduced excretion of AGEs in diabetes, where this can initiate several pathophysiological processes. In experimental studies mice exposed to a diet low in AGEs have extended mean and maximum life spans.[14] IF increases adiponectin levels in humans and laboratory animals; they are adipose-secreted proteins which are inversely related to body weight, adiposity, and insulin resistance. It modulates insulin activity and reduces beta-cell dysfunction. Diabetic patients are found to have lower levels of adiponectin. It is hypothesized that the propensity of adiponectin to shift metabolism from glucose to fat prevents oxidative stress and promotes longevity.[15]

ROLE OF INTERMITTENT FASTING IN CARDIOMETABOLIC DISEASES

Cardio-metabolic diseases, in general, are a group of common but often preventable conditions including, coronary artery disease, cerebrovascular diseases, hypertension, diabetes, dyslipidemia, non-alcoholic fatty liver disease (NAFLD) and insulin resistance - Which seems to be common to all of them. In recent times, there has been a definitive increase in the number of people experiencing one or more of the above conditions during their lifetime.

Obesity and Dyslipidemia- There have been multiple reports on the role of IF in decreasing body weight and improving glucose metabolism and dyslipedemia. IF has been shown to lower both overall fat mass & dangerous visceral fat. Under fasting conditions, the subcutaneous fat undergoes a change to become more like visceral fat, making it easier to access & use as energy. Populations on the island of Okinawa in Japan who maintain a regimen of IF have low rates of obesity, diabetes mellitus and they are found to have extreme longevity.[16] In a recently published meta-analysis of randomized controlled trials (RCTs) in the Chinese population, TRF eating was found to be the most adopted IF protocol followed by ADF. The IF intervention has been shown to reduce the body weight along with body fat mass, insulin resistance, low-density lipoprotein cholesterol and triglycerides levels in a significant manner when compared with control groups.[17] One more recent systematic review and meta-analysis found that participants who followed time restricted Eating demonstrated a reduction in body weight, body mass index, waist circumference and whole body fat mass (WBFM). Improvements in cardiometabolic risk factors, such as a decrease in insulin concentrations, total cholesterol and LDL concentrations, were also observed. It was therefore concluded that IF is useful for weight loss and improvements in cardiometabolic risk factors.[18]

Diabetes Mellitus- IF increases the sensitivity of tissues to insulin by increasing B-cells of the pancreatic islets. Members of the (Calorie restriction with optimal nutrition diet) CRON

Society who follow have low rates of diabetes mellitus.[19] In a few recent studies, daily caloric restrictions or 4:3 IF has been found to reverse insulin resistance in patients with type II diabetes and pre-diabetes even without weight loss.[20] In A recently published Annual Review of Nutrition, IF was found to be a safe diet therapy that can produce clinically significant weight loss in overweight or obese individuals. These regimens may also improve some aspects of cardiometabolic health, such as blood pressure, insulin resistance, and markers of oxidative stress. It was suggested by the authors that individuals should choose a fasting approach that they can most easily incorporate into their lifestyle to reap the long-term benefits of fasting.[21]

Cardiovascular disease - The IF diet positively affects many risk factors for the development of CV diseases; it decreases body mass and has a positive influence on lipid profile; it reduces the concentration of total cholesterol, triglycerides, and LDL cholesterol. IF inhibits the development of atherosclerotic plaque by reducing the concentration of inflammatory markers such as IL-6, homocysteine, and C-reactive protein (CRP), and by favorably altering levels of adipokines, such as an increase in adiponectin, decrease in leptin and resistin concentrations. It results in the lowering of resting heart rate and blood pressure; it limits cardiac hypertrophy and reduces the incidence of myocardial infarction.[22] Recent data from CALERIE-2 study has also shown that mild CR for 2 years had no negative effects on health related quality of life, based on assessments of vitality, mental health and bodily pain.[23]

Data from the CRON Society members shows that all cardiometabolic risk factors such as BP, Serum TNFα, IL6, fasting glucose, insulin, and insulin sensitivity are remarkably low in them; they had almost undetectable CR Pin their serum. Their intima media thickness of the common carotid arteries was significantly low, and they had better echocardiographic markers of left ventricular diastolic function and improved autonomic function. After nearly a century of research on CR in animals, the overall conclusion is that reduced food intake robustly increases their life span. In humans, IF ameliorates obesity, insulin resistance, dyslipidemia, hypertension and inflammation.[24]

Non alcoholic fatty liver disease- NAFLD is a growing concern globally owing to its rising prevalence and its association with various metabolic derangements. IF has been getting increased attention as a dietary modification to address weight management and to achieve improved metabolic wellbeing, and its potential beneficial effects on NAFLD. In a recent meta-analysis some studies suggested that IF may have benefits for NAFLD, but the evidence is still limited and inconclusive.[25] In animal studies by Lin X, IF has been found to be useful in reducing the impact of Non-alcoholic steatohepatitis in high fat and high cholesterol diet fed mice.[26]

CONCLUSION

IF triggers alternate metabolic programs that evolved billions of years ago in prokaryotes in energy scarce situations. The same mechanisms seem to operating in humans render a helping hand in preventing and treating diseases, and having favorable effects on aging. These evolutionarily developed and conserved adaptive cellular responses are integrated between and within organs in such a manner that it improves glucose regulation, increases stress resistance and promotes cellular autophagy. This leads to the engagement of cells in the processes of growth, repair and plasticity and suppresses inflammation. The G to K switch is supposed to play a major role in this process. CR with adequate nutrition in humans results in some of the same metabolic and molecular adaptations that have been shown to improve health and retard the accumulation of molecular damage in animal models of longevity. IF in humans ameliorates multiple metabolic & hormonal factors that are implicated in the pathogenesis of atherosclerosis, type II DM, obesity & cardiovascular diseases, leading to favorable effects on morbidity, disability and mortality in human beings. Overall evidence suggests that IFregimens are not harmful physically or mentally in healthy, normal weight, overweight, or obese adults.

Author contributions

NM: Design, conception, literature search & draft manuscript; VNM: Manuscript preparation and final draft. All authors approved the final version of manuscript.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patients' consent is not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Longo VD, Mattson MP. Fasting: Molecular mechanisms and clinical applications. Cell Metab 2014;19:181-92.
2. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci U S A 2009;106:4453-8.
3. Warwick KW.16:8 intermittent fasting: Benefits, how-to, and tips. MediLexicon International. Available from: https://www.medicalnewstoday.com/articles/327398 [Last accessed 2024 December 2].
4. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. N Engl J Med 2019;381:2541-51.
5. Templeman I, Smith HA, Chowdhury E, Chen YC, Carroll H, Johnson-Bonson D, *et al*. A randomized controlled trial to isolate the effects of fasting and energy restriction on weight loss and metabolic health in lean adults. Sci Transl Med 2021;13:eabd8034.
6. Courchesne-Loyer A, Croteau E, Castellano CA, St-Pierre V, Hennebelle M, Cunnane SC. Inverse relationship between brain glucose and ketone metabolism in adults during short-term moderate dietary ketosis: A dual tracer quantitative positron emission tomography study. J Cereb Blood Flow Metab 2017;37:2485-93.
7. Di Francesco A, Di Germanio C, Bernier M, de Cabo R. A time to fast. Science 2018;362:770-75.
8. Longo VD, Mattson MP. Fasting: Molecular mechanisms and clinical applications. Cell Metab 2014;19:181-92.
9. Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A. Intermittent metabolic switching, neuroplasticity and brain health. Nat Rev Neurosci 2018;19:63-80.
10. Gonidakis S, Finkel SE, Longo VD. Genome-wide screen identifies Escherichia coli TCA-cycle-related mutants with extended chronological lifespan dependent on acetate metabolism and the hypoxia-inducible transcription factor ArcA. Aging Cell 2010;9:868-81.
11. Fontana L, Partridge L, Longo VD. Extending healthy life span--from yeast to humans. Science 2010;328:321-6.
12. Speakman JR, Mitchell SE. Caloric restriction. Mol Aspects Med 2011;32:159-221.
13. Morselli E, Maiuri MC, Markaki M, Megalou E, Pasparaki A, Palikaras K, *et al*. Caloric restriction and resveratrol promote longevity through the Sirtuin-1-dependent induction of autophagy. Cell Death Dis 2010;1:e10.
14. Cai W, He JC, Zhu L, Chen X, Wallenstein S, Striker GE, *et al*. Reduced oxidant stress and extended lifespan in mice exposed to a low glycotoxin diet: Association with increased AGER1 expression. Am J Pathol 2007;170:1893-902.
15. Cui J, Panse S, Falkner B. The role of adiponectin in metabolic and vascular disease: A review. Clin Nephrol 2011;75:26-33.
16. Willcox DC, Willcox BJ, Todoriki H, Curb JD, Suzuki M. Caloric restriction and human longevity: What can we learn from the Okinawans? Biogerontology 2006;7:173-7.
17. Cheung K, Chan V, Chan S, Wong MMH, Chung GK, Cheng WY, *et al*. Effect of Intermittent fasting on cardiometabolic health in the Chinese population: A meta-analysis of randomized controlled trials. Nutrients 2024;16:357.
18. Panagiotou K, Stefanou G, Kourlaba G, Athanasopoulos D, Kassari P, Charmandari E. The effect of time-restricted eating on cardiometabolic risk factors: A systematic review and meta-analysis. Nutrients 2024;16:3700.
19. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: An update. Ageing Res Rev 2017;39:36-45.
20. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. Cell Metab 2018;27:1212-1221.e3.
21. Varady KA, Cienfuegos S, Ezpeleta M, Gabel K. Cardiometabolic benefits of intermittent fasting. Annu Rev Nutr 2021;41:333-61.
22. Most J, Gilmore LA, Smith SR, Han H, Ravussin E, Redman LM. Significant improvement in cardiometabolic health in healthy nonobese individuals during caloric restriction-induced weight loss and weight loss maintenance. Am J Physiol Endocrinol Metab 2018;314:E396-E405.
23. Martin CK, Bhapkar M, Pittas AG, Pieper CF, Das SK, Williamson DA, *et al*. Effect of calorie restriction on mood, quality of life, sleep, and sexual function in healthy nonobese adults: The CALERIE 2 randomized clinical trial. JAMA Intern Med 2016;176:743-52.
24. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, *et al*. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. Cell Metab 2018;27:805-815.e4.
25. Alorfi NM, Ashour AM. The impact of intermittent fasting on non-alcoholic fatty liver disease in older adults: A review of clinicaltrials.gov registry. Diabetes Metab Syndr Obes 2023;16:3115-21.
26. Lin X, Zhu X, Xin Y, Zhang P, Xiao Y, He T, *et al*. Intermittent fasting alleviates non-alcoholic steatohepatitis by regulating bile acid metabolism and promoting fecal bile acid excretion in high-fat and high-cholesterol diet fed mice. Mol Nutr Food Res 2023;67:e2200595.

How to cite this article: Mishra N, Mishra VN. Intermittent fasting & cardiometabolic diseases. Future Health. 2024;2:189-93. doi: 10.25259/FH_77_2024