

Intermittent Fasting: Effects on Metabolism and Weight Management

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ABSTRACT:

Metabolic disorders and cardiovascular diseases have emerged as major global public health challenges due to their increasing prevalence and association with unhealthy dietary and lifestyle patterns. The major risk factors play a pivotal role in coronary heart and metabolic disorders and adiposity and high BMI. Intermittent fasting protocols, which alternate between calorie restriction and no calorie intake, have shown more positive effects on metabolic syndrome. Eating habits, including inadequate intake of fruits and vegetables and high salt intake, contribute to chronic diseases. Intermittent fasting has become a viable substitute for calorie restriction. Intermittent fasting enhances blood pressure, insulin sensitivity, and weight reduction, particularly when done early, whereas being active physically enhances the overall well-being of life and physiological and psychological aspects.

KEYWORDS:

Metabolic syndrome, calorie restriction, feeding periods, intermittent fasting, non-communicable diseases.

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INTRODUCTION

The major risk factors that play a pivotal role in coronary heart and metabolic disorders like type 2 diabetes are adiposity and high BMI. Adiposity and weight are linked to nervous issues and play a part in the development of cardiometabolic illness, such as inflammation, insulin resistance, high blood pressure, endothelial dysfunction, and dyslipidemia (Jiang and others, 2016). Dietary methods that alternate feeding periods with either calorie restriction or no calorie intake during the fasting period are part of the IF protocols. variable IF protocols, including the diet, alternate-day fasting, and time-restricted feeding, have variable scheduling for the fasting and feeding periods. Five days of unrestricted eating are followed by two days a week when people follow a very-low-calorie diet (less than 800 calories per day) as part of the fasting diet (Daly and Langdon, 2022). Over the last 5 decades, the occurrence of metabolic factors, which are a major reason for metabolic syndrome (MetS), has spread globally, creating major public health concerns (Blüher, 2019). According to The American Heart Association (AHA) metabolic syndrome MetS refers to the co-existence of three or more factors that commonly includes: increased abdominal waist (>102 cm for men

and >88 cm for women), lower levels of high-density lipoprotein cholesterol (HDL-C) (<40 mg/dL for men and <50 mg/dL for women) high blood pressure (>135/85 mmHg), hypertriglyceridemia (>150 mg/dL), and insulin resistance (IR), which is indicated by fasting glucose levels >100 mg/dL. The presence of these abnormalities that results in (METS) significantly contributes to the development of atherosclerotic cardiovascular disease (ASCVD).

Treating obesity and overweight, which have become worldwide public health concerns, with traditional dietary calorie restriction (DCR) is not a sustainable approach. Most patients lose weight during the first few months of treatment but often gain it back when they stop doing what is advised. The dropout rate might be anywhere between 20 and 40 percent, which makes it challenging to cure obesity with nutrition. Although its effectiveness is still up for debate, intermittent fasting (IF) has been suggested as a therapy to fight obesity in place of DCR. Nevertheless, other studies demonstrate that IF has more positive effects than DCR on metabolic syndrome and its constituents, such as non-alcoholic fatty liver disease (NAFLD) (Panda 2016).

Although Food and nutrition are widely recognized as an important factor in human health however limited research has fully explained how the quantity, quality and timing of food intake influence the progression of diseases. Dietary behavior is considered a major contributor to chronic health conditions. Several nutritional factors associated with disease risk include low consumption of fruits, vegetables, whole grains, and healthy fats, together with excessive intake of processed foods, sugary beverages, salt, and sweets (Mozaarian, 2017).

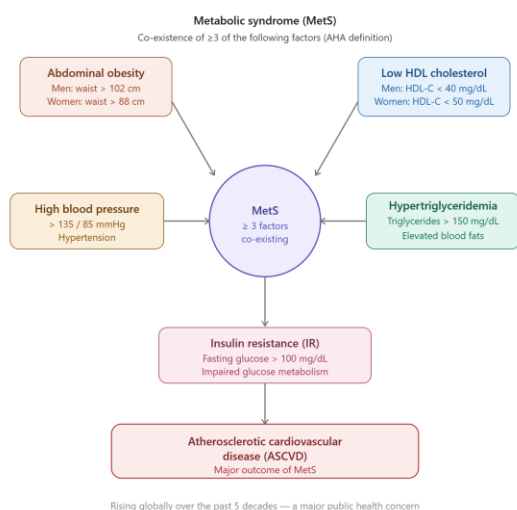


Figure 1: Diagnostic Criteria of Metabolic Syndrome (MetS) and Its Association with Atherosclerotic Cardiovascular Disease (ASCVD)

The DM is a complex illness brought on by a confluence of environmental, genetic, and epigenetic variables. Increased life expectancy and unhealthy lifestyle choices, like eating more foods high in added sugars and saturated fats and leading a sedentary lifestyle, are risk factors for obesity and related comorbidities, like metabolic syndrome, also known as insulin resistance syndrome. This situation is thought to be a DM predictor. Actually, there is a concerning increase in "diabesity," the term for the cohabitation of diabetes and obesity (Tuttle, 2022). Gene expression can be altered through epigenetic mechanisms without changes in the DNA (deoxyribonucleic acid)- which has nitrogen bases like guanine, adenine, thymine, and cytosine- sequence itself. Cellular characteristics and gene activity among cells sharing the same genetic background could be altered through these molecular changes. Enzymes that mediate these epigenetic mechanisms, including DNA methyltransferase, histone acetyltransferase, and histone deacetylase, mediate these events. One important outcome of epigenetic regulation is the formation of either relaxed chromatin (euchromatin), which supports transcriptional activity, or condensed chromatin (heterochromatin), which limits gene transcription (Tiffon, 2018). Numerous hormonal and metabolic background processes influence human behavior and determine day-to-day activities. Humans have adapted to the basic daily light/dark cycle on Earth, known as the circadian rhythm, which is the basis of the four wake-

sleep cycles, since the Stone Age until the twenty-first century. Our hormonal and metabolic well-being are significantly impacted by this extremely intricate cycle. As much as our food intake has shaped our lives throughout human evolution, so too have our wake/sleep cycles (Schott, 2019). Food availability variations during humans evolution played an important role in shaping metabolic adaptations and genetic development. During the hunter-gatherer era, humans gradually adapted to biological processes that improved survival under food scarcity and abundance. One such adaptation was the ability to efficiently store excess energy, which contributed to the development of metabolic characteristics observed in modern populations (Schott, 2019). Obesity epidemic, which has a major financial impact on health care systems is the main reason of the widespread public health issue of cardiometabolic diseases and disability is the. Over 1.9 billion people worldwide are overweight or obese, and the incidence of obesity is still rising despite the well-established negative effects of excess body weight. Obesity and body weight regulation are greatly impacted by a number of factors, including socioeconomic, physiological, and hereditary factors. For example, new research in recent years has suggested that timing of meal consumption may be a significant risk factor for obesity and cardiometabolic disorders (2019, Dashti). A high body mass index (BMI), which results from an excessive or aberrant buildup of fat, is a defining characteristic of obesity. According to the report, over 600 million people were obese globally in 2015. About 52.7% of people in the European Union were overweight in 2019, and the problem of excessive body weight continues to worsen. Obesity has been strongly linked to numerous chronic disorders, including cardiovascular disease, hypertension, type 2 diabetes, and obstructive sleep apnea (Spandidos, 2020). Additionally, it raises the risk of cancer in at least 13 body areas. Global research indicates that 4.7 million people died before their time due to obesity in 2017. Furthermore, the leading cause of increased death among patients infected with SARS-CoV-2 nowadays is obesity (Goumenou, 2020). The most successful non-pharmacological strategy to prolong health span is likely calorie restriction (CR), which involves a consistent decrease in energy intake while preserving ideal nutrition. Continuous daily CR, on the other hand, causes poor long-term adherence, which can be ascribed to environmental reasons such as the availability of high-caloric, tasty meals, behavioral variables such as social events, psychological factors such as heightened food reward, and biological ones such as increased appetite (Czajkowski, 2021). Intermittent fasting (IF) has become a viable substitute for continuous/traditional CR within the last ten or so years. Simply said, intermittent fasting (IF) alternates with periods of unrestricted eating, which may help with adherence (OConnor, 2021)

THE EFFECTS OF INTERMITTENT FASTING ON CENTRAL CLOCK HORMONES AND GENES

Intermittent fasting (IF) has been shown in recent human studies to enhance blood pressure and insulin sensitivity while reducing body weight and fat mass, especially when food intake is scheduled during the morning or midday hours (Sutton, 2018).

Hormonal Pathways and Intermittent Fasting

The link between the hormonal and neurological regulation of metabolism is formed by the hypothalamus, which is a component of both the endocrine and neurological systems. Peripheral circadian genes can independently regulate metabolic functions and interact with circadian clock genes, reflecting the reciprocal regulation involved in circadian rhythm control. The SCN helps regulate metabolism in different organs by sending timing signals through circadian clock genes. According to the review by Mazzocchi et al., disturbances in circadian rhythm may occur due to changes in metabolic activity in peripheral tissues or because of disruption of the body's central biological clock caused by irregular light and dark cycles (Marqueze, 2015).

Exercise as a Way of Life

Because of its multifaceted qualities, physical activity has gained significant recognition over time. It can be used to enhance overall well-being and physiological and behavioral aspects in almost any population, regardless of age. As a result of these advantages, medical professionals are increasingly using customized exercise programs as an additional form of therapy. In addition to its benefits for illness treatment, it has permeated healthy populations' daily lives (Eckstein, 2020).

Timing of Macronutrients

During physical exertion, the brain and muscles need carbohydrates, primarily glucose. Early carbohydrate intake appears to be more reasonable when the body is better able to manage blood glucose levels in the morning. Evidence from a crossover study involving ten healthy male participants showed that consuming carbohydrate-rich evening meals for three consecutive days could alter circadian rhythm patterns. The study further demonstrated reduced nighttime melatonin secretion along with an increase in the body's internal temperature lasting up to eight hours (Parasuraman, 2017).

Timing of Exercise

There is a wide range of viewpoints regarding whether their workout should be done in the morning or the evening. After a late sports unit, some people find that their training sessions are a terrific way to wind down, while others are unable to sleep at all. At first glance, this appears unexpected when considering the typical circadian cycle. Performance peaks in the afternoon and evening for both strength and endurance exercise. This is brought on by the core body temperature's (CBT) daily cycle (Bjorvatn, 2015)

Other Hormonal Pathways and Exercise

Numerous studies have examined the effects of exercise on hormonal and metabolic regulation. Physical activity can

stimulate GLUT4 activity in skeletal muscles through mechanisms that are not entirely dependent on insulin. GLUT4 functions as a glucose transport protein that helps move glucose into skeletal muscle, cardiac muscle, and adipose tissue cells. This process improves glucose utilization and enhances insulin sensitivity, highlighting the important role of exercise in the prevention and management of insulin resistance and diabetes (Tabarin and Duclos, 2016).

INTERMITTENT CALORIC RESTRICTION'S ROLE IN ALTERING METABOLIC PROCESSING OF LIPIDS AND CARBOHYDRATE COMPOUNDS

Rodent studies allow for a higher degree regulation of nutrient consumption and external factors, but results cannot be easily applied to human participants. The majority of IER rodent investigations have employed alternate-day complete fasting procedures. This type of IER can lower fasting glucose, insulin, and impaired insulin sensitivity (as assessed by HOMA-IR index) across research periods ranging from four weeks to a year. This, in turn, indicates enhanced hepatic insulin sensitivity (Heeren, 2015).

Modifications to the Distribution, Physiology, and Morphology of Adipose Tissue

The unhealthy proliferation of body fat tissue in predisposed individuals appears to be a significant contributor to metabolic disorders linked to obesity. This includes visceral adipose tissue accumulation, reduced insulin activity, disrupted fat storage, macrophage infiltration, which results in subclinical inflammation and disrupted adipokine release, and defective adipogenesis as well as excessive adipocyte hypertrophy in subcutaneous depots. As a result, an adverse hormonal and metabolic environment is created, which promotes the emergence of systemic insulin resistance and related metabolic diseases (Tinsley, 2016).

Time-restricted Feeding's Effects on Lipid and Glucose Metabolism

Mice are nocturnal creatures, and the dark/active period is when they expend the majority of their energy. It has been demonstrated that TRF (c12h), in which food consumption is confined to the dark phase, can both prevent and reverse the detrimental metabolic effects of a variety of nutritional challenges, such as high-fat and high-sugar obesogenic diets. When compared to mice given the same high-fat diet on an ad libitum basis, TRF mice exhibit decreased levels of fat deposition and steatosis liver changes, as well as enhanced glycemic tolerance and improved lipid profile; these changes may be due to improved homeostasis in various tissues. Crucially, these gains take place without alterations in energy intake (Bennion, 2015).

PERIODIC DIETARY PRACTICES

The three most extensively researched intermittent fasting plans are daily restricted eating window regimen (TRE), adjusted alternate-day fasting (MADF), which involves

fasting twice a week (5:2 periodic fasting), and alternating fasting schedule (ADF). A person on TRE limits their daily meal intake to 6 to 8 hours. This dietary approach might make it easier for people to stick to calorie restriction (Moresi, 2020).

research conducted during the 30-day Ramadan holiday, during which fasting is observed for 12 to 14 daylight hours (Memel, 2022).

Table 1: Summary of Major Intermittent Fasting Protocols

IF Protocol	Abbreviation	Description / Mechanism	Dietary Pattern	Key Feature / Benefit	Citation
Time-Restricted Eating	TRE	Daily eating is confined to a specific time window, typically 6–8 hours per day.	Daily restriction; eating allowed for 6–8 hours; fasting for the remaining 16–18 hours.	May enhance adherence to calorie restriction compared to conventional dieting approaches.	<i>Moresi, 2020</i>
Modified Alternate-Day Fasting	MADF	A modified form of ADF that incorporates two non-consecutive fasting days per week.	5:2 pattern — 5 regular eating days and 2 fasting/very low-calorie days per week.	Provides flexibility while maintaining metabolic benefits of periodic caloric restriction.	<i>Moresi, 2020</i>
Alternate-Day Fasting	ADF	Strict alternation between regular eating days and complete or near-complete fasting days.	Eating and fasting days alternate every 24 hours throughout the week.	One of the most extensively studied IF protocols; serves as a basis for MADF.	<i>Moresi, 2020</i>

CELLULAR REACTIONS TO THE METABOLIC SWITCH AND FASTING

Fasting has health benefits because it “flips the metabolic switch”. The body begins to use ketone bodies instead of glucose as a fuel source after at least 12 hours of fasting. This change is represented as the point of negative energy balance, when the liver’s glycogen reserves are depleted and free fatty acids are mobilized, leading to the formation of fatty acid-derived ketone bodies. At the cellular level, the pathways of mammalian target of rapamycin (mTOR) and AMP-activated protein kinase are enhanced by ketone bodies (Mainous, 2018).

Circadian Timing’s Effect on Adiposity

In order to ascertain the impacts of meal time variation, several groups have to find out how meal timing affects obesity and cardiometabolic health, various research groups have explored variations in meal timing across the day. Owing to the impact of meal schedule and the biological clock on obesity and cardiometabolic health. eTRE may be more beneficial than other types of TRE because the thermic effect of meals, insulin sensitivity, and circadian rhythm all peak in the morning (Poggiogalle, 2018).

Disease of the Nonalcoholic Fatty Liver

In cases of non-alcoholic fatty liver disease (NAFLD), both safety and benefits of time restricted eating (TRE) are observed. As previously mentioned, ketone bodies not only take over as the main energy source during extended fasting, but they also have a significant impact on cells, which enhances lipolysis. There are few human studies on NAFLD and TRE, and the majority of the data is derived from the

Temporary Fasting

Fasting can be broken down metabolically into three main phases: Stage 1: post-absorptive phase, which occurs approximately 6–24 hours after the start of fasting, during which glucose generated from breakdown of glycogen is preferentially consumed by the central nervous system (CNS) and numerous other systems. An increase is observed in ketogenesis, glucogenesis, and lipolysis, although a lesser increase is seen in the latter. Glycogenolysis falls off. Second Stage: Nutrients 2019, 11, 1192 5 of 16 The gluconeogenic phase is initiated approximately 1-10 days after the start of the fast. The central nervous system (CNS) receives glucose through protein catabolism, whereas other tissues consume fat and ketones (Enderle, 2015).

Extended Fasting: A Few Historical Instances

Francis Benedict’s 1915 preliminary research on the biochemical and physiological adaptations in a slender person who fasted for 31 days showed notable drops in body weight (12.4 kg at a rate of 0.84 kg/day on Day 1 to 0.32 kg/day on Day 31) . Blood pressure and body temperature were among the biological markers whose levels were maintained (Danielsson, 2019).

RAMADAN FASTING: A SHIFT FROM STANDARD EATING HABITS

The Ramadan fasting period represents a distinct shift from conventional dietary patterns. In most cultures, typical eating behavior consists of three main meals per day, often supplemented with additional snacks between meals. Any deviation from this usual pattern may significantly influence energy balance within the body. Commonly studied fasting

approaches include intermittent fasting (IF), periodic fasting (PF), and time-restricted feeding (TRF) (Longo, 2017).

Table 1: Average Daily Energy Intake During Non-Fasting Periods by Country and Sex

Country / Region		Average Energy (kcal)	Daily Intake (kcal)	Female (kcal)	Male (kcal)	Intake	Population Group	Citation
United Kingdom (UK)		2,250		2,000	2,500		Adults (non-fasting period)	Hamdy, 2016
United States of America (USA)		2,300		2,000	2,600		Adults (non-fasting period)	Hamdy, 2016
Australia		2,255		2,010	2,600		Adults (non-fasting period)	Hamdy, 2016

Note. All values represent estimated average daily energy intake for adults during non-fasting periods. kcal = kilocalories. Data sourced from Hamdy (2016).

The Diet for Ramadan

Maintaining a healthy weight is simply one aspect of maintaining a balanced diet; maintaining one's general nutritional well-being is as important. Energy consumption is crucial. However, it can be challenging to sustain a healthy, balanced diet over the long term due to a variety of factors that affect energy consumption, including cultural and lifestyle disparities. The average daily energy intake for adults during non-fasting periods is 2250 kcal (2000 kcal for females and 2500 kcal for males) in the UK, 2300 kilocalories (2000 kilo-calories for women and 2600 kilocalories for men) in the USA, and 2255 kilo-calories (2010 kilo-calories for women and 2600 kilo-calories for men) in Australia, according to recent statistics (Hamdy, 2016).

CONCLUSION

Adiposity and excess weight are crucial contributing factors to long-term health conditions like heart disease and metabolic disorders like type 2 diabetes. Intermittent fasting (IF) protocols, which alternate feeding periods with calorie restriction or no calorie intake during the fasting period, have shown more positive effects than traditional dietary calorie restriction (DCR) on metabolic syndrome and its constituents, such as non-alcoholic fatty liver disease (NAFLD). Eating habits, including inadequate consumption of fresh produce, plant-based foods, and grains, healthy dietary fats, and elevated consumption of sodium-rich foods, sweets, processed meats, and sugary drinks, are significant contributors to chronic diseases. Epigenomics characterizes reactions and processes that regulate gene functions without changing the nucleotide sequence of DNA. Intermittent fasting has become a viable substitute for continuous traditional calorie restriction (CR) in the last decade, alternating with periods of unrestricted eating to help with adherence.

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