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INTERMITTENT FASTING: A COMPREHENSIVE REVIEW OF MECHANISMS, METABOLIC EFFECTS, AND CLINICAL APPLICATIONS

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ABSTRACT

Intermittent fasting (IF) has become increasingly popular due to its potential to enhance metabolic health and to reduce the risk of chronic disease. Unlike traditional calorie restriction, IF alternates between periods of eating and fasting. The transition between feeding and fasting results in a metabolic switch from using glucose for energy to using fatty acids and producing ketones from fat. The transition from glucose utilization to fatty acid oxidation activates a number of cellular pathways, such as AMPK, inhibition of mTOR, and stimulation of autophagy. Activation of these pathways improves cellular repair and reduces oxidative stress. A growing body of clinical and laboratory evidence supports the use of IF to reduce body weight, increase insulin sensitivity and improve both cardiovascular and neurological health. Furthermore, IF also may have a role in regulating circadian rhythms and modulating gut microbiome composition. There are still some concerns regarding the long-term

adherence of individuals to IF, as well as variability related to fasting protocols and the potential for adverse effects on specific populations. Despite these limitations, IF is an emerging and adaptable approach for improving metabolic health and more studies are required to determine the long-term safety and efficacy of IF.

Keywords: Autophagy; AMPK; circadian rhythm; mTOR; insulin sensitivity; Intermittent fasting; Metabolic switching; oxidative stress; obesity

INTRODUCTION

Intermittent fasting (IF) is gaining popularity among people who want to lose weight, regulate their metabolism, and possibly live longer. IF is focused on when you eat rather than how much you eat; it consists of alternating periods of eating and not eating. IF works by activating the body's adaptive response to a change in the fuel source used for energy production (the transition from using sugar [glucose] as a primary fuel source to using fat [fatty acids] as a primary fuel source) through a process called metabolic switching **[1-3]**.

During the time a person is fed, he/she is primarily using sugar (glucose). Some of the surplus energy (calories) consumed will be stored as glycogen (the storage form of sugar in the liver] or triglycerides (the storage form of fat in adipose or fatty tissue) **[4]**. Once glycogen stores are depleted (typically after about 10–12 hours of fasting), the body will switch from using sugar to utilizing fatty acids from stored body fat (adipose [fat] tissue) as the primary fuel source **[5]**. While fatty acids are being utilized by the body for fuel, the liver will produce ketone bodies (from the fatty acids), which can also be used by the brain and other tissues of the body for energy.

Changes in hormones impact this type of metabolic adaptation, such as reduced insulin levels and increased glucagon secretion leading to the release of fats and energy mobilization through lipolysis **[6]**. Additionally, intermittent fasting stimulates AMPK and inhibits mTOR, activating various cellular signaling pathways that result in improved mitochondrial function and activation of cellular repair processes including autophagy **[7]**. All of these responses to metabolic adaptations will lead to improved cellular resilience, metabolic flexibility, and decreased oxidative stress **[8]**.

The prevalence of obesity, type 2 diabetes mellitus, cardiovascular disease and other metabolic disorders has driven the search for effective and sustainable dietary interventions for managing the effects of these diseases **[9]**. Due to its ease of application, flexibility, and ability to affect multiple body systems, such as circadian rhythms and gut microbiota, intermittent fasting has gained popularity in the diet

community as an effective and sustainable method for maintaining metabolic health **[10, 11]**.

This review aims to provide a comprehensive overview of the different types of intermittent fasting, the underlying mechanistic pathways, its clinical applications, as well as its limitations and potential adverse effects.

Mechanistic Factors Linking Intermittent Fasting with Health

Intermittent fasting exerts its beneficial effects through multiple interconnected metabolic and cellular mechanisms **[12]**. These mechanisms include metabolic switching, activation of cellular signaling pathways, hormonal regulation, and modulation of oxidative stress, inflammation, circadian rhythm, and gut microbiota, **[13]** which together contribute to improved metabolic health and longevity.

Metabolic Switching

Understanding the basic physiological processes involved in glucose metabolism (the breakdown of sugar) and lipids (the breakdown of fats), and the concept of 'metabolic switching', is necessary for understanding why fasting may affect health **[14]**. The glucose-fatty acid cycle refers to competition for oxidation between glucose (sugar) and fatty acids, and the fed-fast cycle consists of 4 stages: the fed, post-absorptive, fasting, and starvation state.

During the fed state there is usually a high level of circulating glucose in the blood (higher than normal), thus providing the primary source of energy. When we are in a fed state and consume more energy than our body requires to support our current activity, this excess energy is stored in our fat cells (as triglycerides) **[15]**. On the other hand, as your body continues to be in a fasted state (i.e. no food consumed), over a longer period of time your body begins to utilize triglycerides (stored fat) by breaking them down into fatty acids and glycerol to provide energy **[16]**. The liver converts these free fatty acids into ketone bodies (metabolically) so they can be used as the primary source of energy for the body, particularly the brain **[17]**.

Metabolic switching is the process by which your body utilizes glucose as its primary fuel source, and when your glycogen stores in your liver are depleted (generally occurred after approximately 12 hours of fasting), you initiate a transition to using ketone bodies produced from the breakdown of fatty acids as your primary energy source **[17]**. The switch from glucose utilization to ketone body (from fatty acids) utilization has an adaptive (evolutionary) advantage for facilitating the mobilization of fat tissue while protecting the integrity of muscle and function **[18]**. This metabolic switching promotes greater metabolic flexibility and better body composition.

Cellular Signaling Pathways (AMPK, mTOR, Sirtuins)

Intermittent fasting (IF) causes the body's metabolism to switch to respond differently than normal. IF improves the body's metabolism, health span, and the length of time we live by activating multiple cellular pathways.

After fasting, you will notice an increase in AMP and decrease in ATP; the change in the amounts of; AMP and ATP activate AMP-activated protein kinase (AMPK). When AMPK is activated, it inhibits anabolic pathways and promotes catabolic processes, which include autophagy and therefore eliminating damaged proteins improving how well your mitochondria work.

Simultaneously fasting by reducing circulating amino acids and glucose will inhibit mTOR; hence decreasing protein synthesis and increasing autophagy. Fasting will stimulate NAD+-dependent deacetylases (known as sirtuins) to promote mitochondrial biogenesis; reduce oxidative stress on the cell, and promote cellular survival.

Together these pathways affect how the body changes from a growing/energy-storing state to a repairing/maintaining state and building your body's resistance to stress; thus improving the overall health of your metabolism.

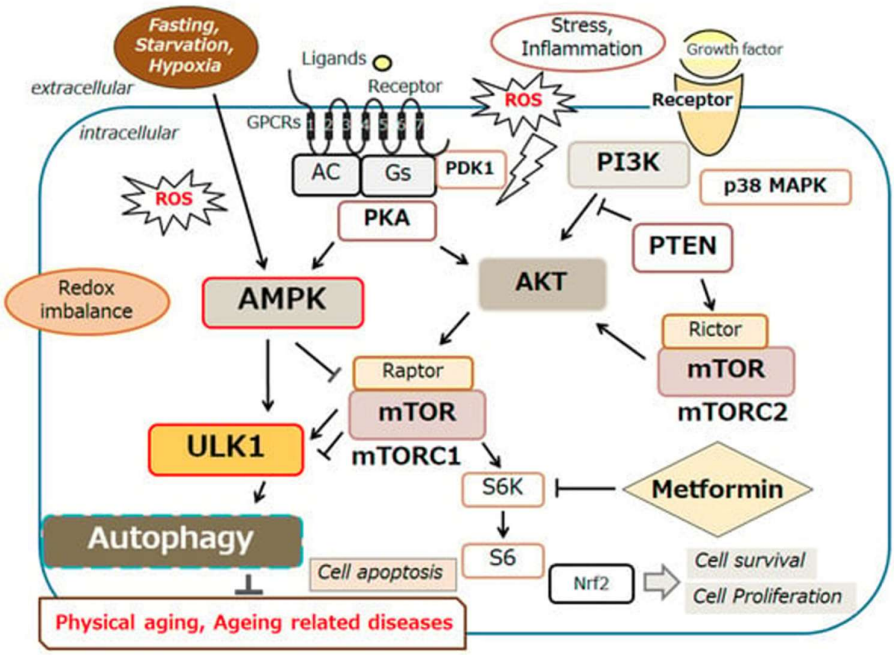

Figure 1: Intracellular signalling pathway to Autophagy

Autophagy

Autophagy is a critical cellular process enhanced during intermittent fasting. It involves the degradation and recycling of damaged cellular components, including proteins and organelles. This process helps in maintaining cellular integrity and function by removing dysfunctional structures.

Activation of autophagy during fasting plays a significant role in preventing the accumulation of damaged molecules, thereby reducing the risk of various diseases, including neurodegenerative disorders and cancer **[20]**. It also supports cellular adaptation during nutrient deprivation by providing substrates for energy production.

An overview of the intracellular signaling pathway relevant to autophagy. With several key molecules, such as AMPK, PI3K, AKT, mTOR, and ULK1, the autophagy signaling might be involved in the regulation of physical aging and/or aging-related diseases. Inflammation, starvation, fasting, and/or hypoxia are known to initiate the autophagy signaling pathway. Arrowhead indicates stimulation, whereas hammerhead shows inhibition. Note that several signaling pathways such as cytokine-induction and/or inflammatory responses have been omitted for clarity. Abbreviation: mTOR, mammalian/mechanistic target of rapamycin; PI3K, phosphoinositide-3 kinase; AKT, protein kinase B; ROS, reactive oxygen species; AMPK, adenosine

monophosphate-activated protein kinase; ULK1, autophagy activating kinase 1; mTORC1, mTOR complex 1.

Hormonal Regulation

Insulin is the primary hormone during the fed state, where glucose is used as the main energy source, whereas during fasting, glucagon becomes the dominant hormone, promoting glycogen breakdown and energy mobilization.

Adipokines are also affected by intermittent fasting (IF), particularly leptin and adiponectin. Leptin helps to control body weight by reducing appetite and increasing the amount of energy expended, while adiponectin increases the oxidation of fatty acids and uptake of glucose. The changes in body composition from IF promote improved sensitivity to both leptin and adiponectin, aiding in appetite control and the regulation of metabolism.

Mitochondrial Function

Intermittent fasting improves mitochondrial function by enhancing mitochondrial biogenesis and efficiency. It promotes better utilization of energy substrates and reduces mitochondrial oxidative damage. Improved mitochondrial function contributes to increased energy production, better metabolic performance, and reduced risk of age-related diseases.

Oxidative Stress

The generation of reactive oxygen species (ROS) is a natural part of cellular metabolism; however, excessive ROS production leads to oxidative stress, which contributes to metabolic disorders and atherosclerosis **[14]**.

Intermittent fasting reduces oxidative stress by improving mitochondrial efficiency and activating antioxidant defence mechanisms. Studies have shown reductions in oxidative stress markers such as 8-isoprostane in individuals following time-restricted eating patterns. These effects contribute to improved cellular function and reduced disease risk.

Inflammation

Chronic inflammation is a key factor in the development of metabolic diseases. Intermittent fasting reduces inflammation by decreasing pro-inflammatory cytokines and improving immune function **[15]**.

Changes in adipokine secretion, including increased adiponectin and improved leptin sensitivity, also contribute to the anti-inflammatory effects of intermittent fasting. These mechanisms help reduce the risk of obesity, cardiovascular disease, and insulin resistance **[12]**.

Circadian Rhythm

Regulating circadian rhythms is one of the key functions of intermittent fasting. Many of the body's functions - for example, the metabolism of food, the secretion of hormones by the body, and the function of the gastrointestinal tract - are regulated by circadian rhythms.

Eating restrictedly over a specific time period can cause these functions to align better with our biological clock, which increases metabolic activity. Disrupted circadian rhythms have been linked to metabolic dysfunction, and intermittent fasting helps to restore both nutrient usage and hormone response by regulating the use of nutrients by the body.

Gut Microbiota

The gut microbiome composition and function are influenced by intermittent fasting.18 The gut microbiome is important for energy metabolism, immune function, and inflammatory responses. Changes in how often we eat during intermittent fasting might influence the diversity and function of our gut microbiome, positively impacting metabolic health. People with dysbiosis experience obesity and metabolic disease; it's possible that intermittent fasting promotes the growth of a healthy gut microbiome and subsequently supports overall health improvement.

Clinical Applications of Intermittent Fasting

Research has shown that intermittent fasting (IF) may be beneficial for preventing and treating a variety of chronic diseases/metabolic diseases. Researchers attribute a good deal of IF's clinical benefits to metabolic switching, increased insulin sensitivity, decreased inflammation and stimulation of bodily repair processes.

Obesity and Weight Management

Intermittent fasting plays a significant role in weight loss and obesity management **[19]**. Visceral adipose tissue functions as an endocrine organ by secreting adipokines such as leptin and adiponectin. Leptin regulates appetite and energy expenditure, while adiponectin enhances fatty acid oxidation and glucose uptake.

During intermittent fasting, the shift from glucose metabolism to fatty acid utilization leads to reduction in adiposity, particularly visceral fat. This reduction improves leptin and adiponectin sensitivity, resulting in better appetite control and metabolic regulation.

Trepanowski *et al*., 2017, looked at how effective alternate-day fasting is compared to daily Caloric restriction when it comes to weight loss, Maintenance as well as several Risk factors associated with Cardiovascular Disease in a Clinical Trial. The study took place over one year in an academic hospital located in the City of Chicago with Adult participants ages 18-64 years old (average Body Mass Index). After the completion of the 1-Year period, subjects were split into three groups and then from there they consisted of: Alternate Day Fasting (calories were reduced by either 25% or 125%) (no added Weight Change to the Normal Diet), Daily Caloric Reduction (reduced amount daily by 75%), and No Treatment (treated like the normal Diets have been treated

before). The primary outcome was Body Weight change and secondary outcomes included Condom Usage and/or Number of (<there should be another variable). At the end of 12 months, there were no differences (at baseline) between the two groups that lost the most weight due to whether or Not they were either in either or group from their 12 month outcomes (Control vs Alternate Day Fasting were also not compared before the 12 Month time point). Furthermore, there was a significantly greater than 38% dropout rate of individuals in the Alternate Day group of subjects to their "Normal" Diet to what would normally be considered a "Normal Weight" to an average of 4.5% away from their initial baseline value. In addition, the dropout rates for each of the No Treatment and Daily Caloric Restriction groups (Compounded by non-Eating Meals) were lower to the No Treatment Group (25% compared to 29.5% and 29% compared to 31% respectively) than the mean across both groups over the Estimated Period of Each Group's Diet. 98% of Individuals were then classified as having been on their current "Traditional" Diet upon completion of the Third Stage Diet. Overall, the authors concluded that alternate-day fasting did not improve health beyond calorie restriction.

Diabetes Mellitus

Intermittent fasting plays an important role in the management of type 2 diabetes mellitus by improving insulin sensitivity and overall metabolic regulation. One of the primary mechanisms underlying these benefits is weight reduction, which has been shown to decrease fasting plasma insulin levels, improve cardiovascular risk factors, and reduce systemic inflammation.

Fasting promotes a variety of beneficial effects at the molecular level. The mechanisms behind these effects can be attributed to the regulation of several key metabolic signaling pathways (e.g., FoxO, mTOR, AMPK). In the context of the fed state, mTOR is activated by hormone-mediated nutrient sensing, thus promoting cellular proliferation and the use of stored energy. In contrast, during the fasting condition, AMPK and FoxO are activated to promote cellular protection against oxidative stress, and inhibit excessive cellular replication.

In addition, the metabolic switch that occurs between the fed and fasting conditions is critical to understanding the positive impact of repeated fasting on an individual's metabolism. Evidence suggests that with repeated fasting, an individual transitions from the primary use of glucose as their energy source to the use of fatty acids and ketone bodies. This transition leads to improved metabolic flexibility (which may be altered or diminished in individuals with diabetes or obesity).

Fasting enhances mitochondrial function, activates autophagy, stimulates cellular defense systems against oxidative/metabolic stress, and reduces the level of inflammation. Together, these adaptations positively affect glucose homeostasis and insulin sensitivity **[22]**.

In addition, fasting-induced depletion of both glucose and amino acids activates AMPK and inhibits mTOR signaling, which enhances the body's ability to repair damaged tissues. Overall, the metabolic/molecular changes that occur from intermittent fasting mediate the beneficial role of intermittent fasting as a dietary strategy in the management of diabetes mellitus

Cardiovascular Diseases

Intermittent fasting has beneficial effects on cardiovascular health by improving lipid profiles, reducing blood pressure, and decreasing inflammation. It has been associated with reductions in total cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol.

At the molecular level, IF reduces oxidative stress and improves endothelial function, thereby lowering the risk of atherosclerosis and other cardiovascular diseases. Additionally, activation of AMPK and inhibition of mTOR contribute to improved cardiac metabolism and function.

Mechanistically, a key regulator of autophagy and cellular metabolism is the mammalian target of rapamycin (mTOR). Reducing the activity of mTOR diverts cellular resources from non-essential anabolic reactions toward catabolic processes, including the activation of complexes involved in autophagy. In addition, 5' adenosine monophosphate-activated protein kinase (AMPK), which is activated by high AMP to adenosine triphosphate ratio (that occurs in energy-deprived states such as fasting), is a cellular nutrient-sensing control mechanism that instigates a coordinated response to promote energy production, meanwhile restricting energy consumption. When activated, AMPK promotes autophagy partly by inhibiting mTOR, but also directly activating autophagosome formation.

Inhibition of mTOR activates microphthalmia-associated transcription factors EB (TFEB) and E3, which are master regulators of autophagy and lysosomal biogenesis. In fasting conditions, TFEB translocate to the nucleus, where it induces the expression of genes involved in autophagy and lysosomal biogenesis. These lysosomal degradative processes generate nutrients that provide energy to support cellular metabolic functions. Another major upstream regulator of mTOR activity is the growth hormone/insulin-like growth factor-1 (IGF-1) signalling pathway. Fasting is associated with a significant reduction in the circulating levels of IGF-1 in humans. Such

reduction in IGF-1 signalling leads to mTOR inhibition and subsequent activation of autophagy. These pathways promote a shift in cellular metabolism toward a more catabolic state, fostering the maintenance of essential functions, instead of growth and energy storage.

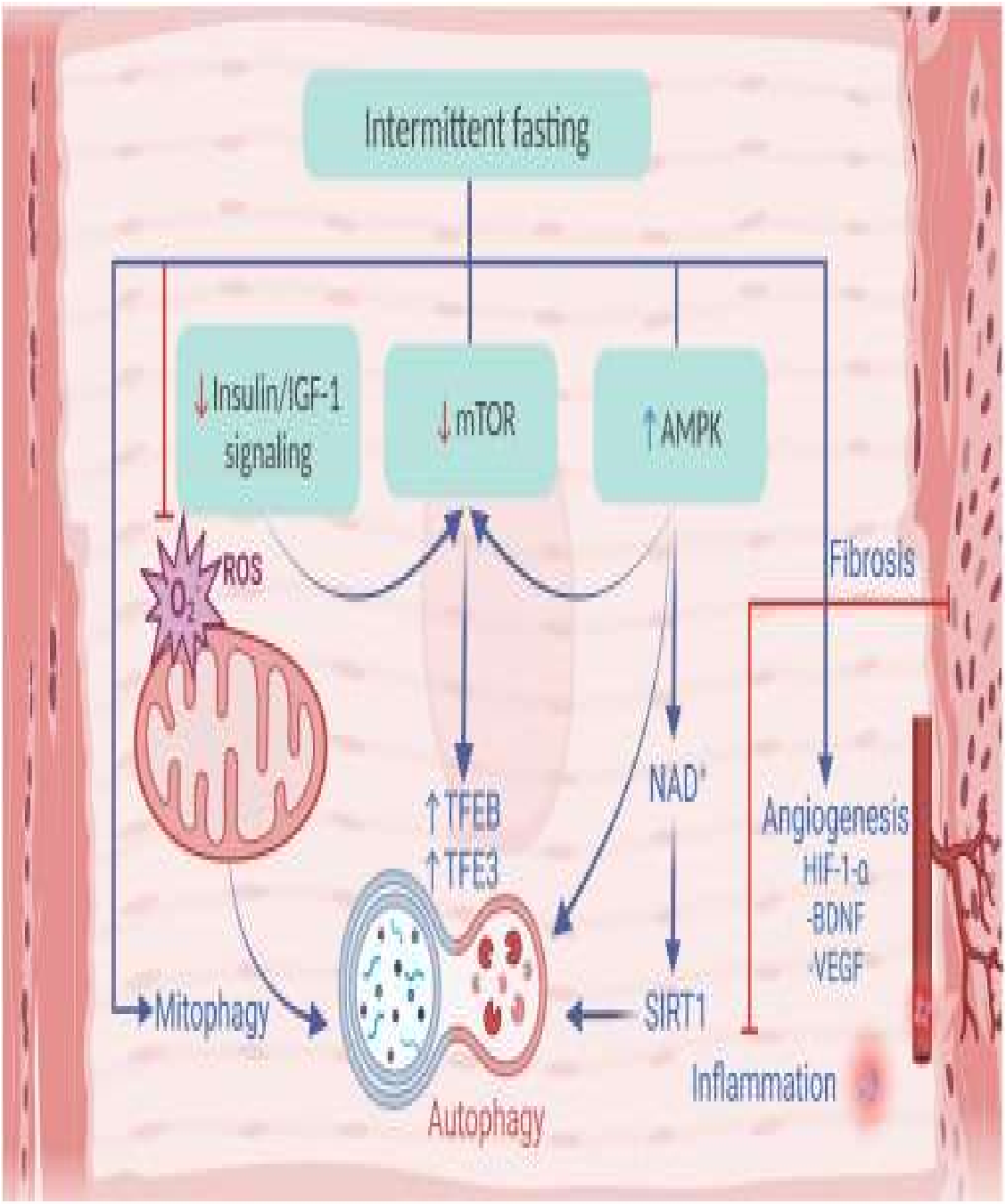

Figure 2: Illustration of the Metabolic Shift from Glucose Utilization to Lipid Oxidation During Intermittent Fasting

The molecular effects of intermittent fasting are numerous. Intermittent fasting decreases the signalling of mTOR and IGF-1 while increasing that of AMPK and SIRT1, and also increases the expression of the genes of autophagy in the heart. Additionally, intermittent fasting promotes proangiogenic molecules as well as inhibiting fibrosis and inflammation. AMPK (5' adenosine monophosphate-activated protein kinase), BDNF (brain-derived neurotrophic factor), HIF-1-α (hypoxic inducible factor 1-alpha), NAD (nicotinamide adenine dinucleotide), ROS (reactive oxygen species), and VEGF (vascular endothelial growth factor) are some of the key molecules that illustrate these effects of intermittent fasting.

Cancer

Intermittent fasting has shown potential as an adjuvant therapy in cancer treatment. Fasting reduces circulating levels of glucose, insulin, and insulin-like growth factor-1 (IGF-1), which are essential for tumor growth and proliferation.

It also enhances autophagy and promotes metabolic stress in cancer cells, making them more susceptible to chemotherapy. At the same time, fasting protects normal cells from treatment-induced damage by improving cellular stress resistance.

Fasting or fasting-mimicking diets have been shown to inhibit tumor progression and improve treatment outcomes in certain cancers, although more clinical studies are required to establish its efficacy and safety.

Total health depends on dietary practices and nutritional patterns. There are growing concerns about high-calorie diets (defined by their caloric density and nutritional composition) possibly contributing to the formation of existing tumors, including lung, liver, colorectal, sarcoma and many other cancerous diseases. Caloric restriction and fasting are effective in inhibiting tumor cell proliferation and may help improve inflammatory and autoimmune diseases by modulating a decrease in peripheral pro-inflammatory cells, as well as improving the features associated with inflammation. Most cancer patients tolerate fasting well and can use it to help prevent or lessen the effects of chemotherapy on red blood cell and platelet counts; moreover, it may help protect normal cells from damage to DNA. Studies have provided substantial evidence for the protective, adaptive effects associated with CR and IF in patients with liver, breast, colorectal and pancreatic cancers.

The tumor suppressive benefits of fasting arise mainly from activating metabolic re-programming in the organism and changing the signalling pathways of a wide variety of metabolic processes, changing the genetic make-up of the tumour and increasing the use of autophagy. There are also effects on circadian rhythms, sleep and activity patterns and hormone secretion during

fasting. In addition to decreasing the production of insulin and providing an alternative source of energy (ketone bodies), fasting also has the potential for a more broad protective role for the body by providing energy to maintain physiological levels of blood glucose from the breakdown of lipids, proteins and carbohydrates. Furthermore, during fasting, due to the influence of fasting on autophagy, cells will begin the process of eating themselves by removing foreign material and decreasing tumour growth by doing so.

Mechanisms by which fasting or fasting-mimicking diets kill cancer cells in solid tumors:

Preclinical and early clinical research indicates that fasting or using fasting-mimicking diets (FMDs) lowers specific nutrients and factors that stimulate tumor development (such as glucose, IGF1 and insulin) as well as enhances autophagy. Fasting has a metabolic influence on the TCA cycle by generating lactate from glucose transport/glucose utilization (GLUT)/aerobic glycolysis and generating carbon dioxide, which is important for mitochondrial function, from the TCA cycle. Decreasing glucose availability and pushing cancer cells to increase oxidative phosphorylation, generate reactive oxygen species (ROS), lose mitochondrial membrane potential ($\Delta\Psi m$) and have increased ratios of ADP to ATP through fasting can create an anti-Warburg effect that can produce oxidative DNA damage and activate p53, induce further DNA damage and apoptosis predominantly during the administration of chemotherapy agents. Fasting or FMDs activate the autophagic cellular (i.e. organismal) program via the AMPK signaling pathway through IGF1 and promote the organismal autophagy program through P62 and LC3II. Both fasting and FMDs can dramatically reduce the amount of CD73 in certain types of cancer cells by promoting the process of autophagy leading to decreased production of adenosine in the extracellular environment and inhibiting the advancement of macrophages to the immunosuppressive M2 activation phenotype. Importantly, both fasting or FMDs may produce very different or even opposite results in some cancer cell types or even in the same type of cancer **[26]**.

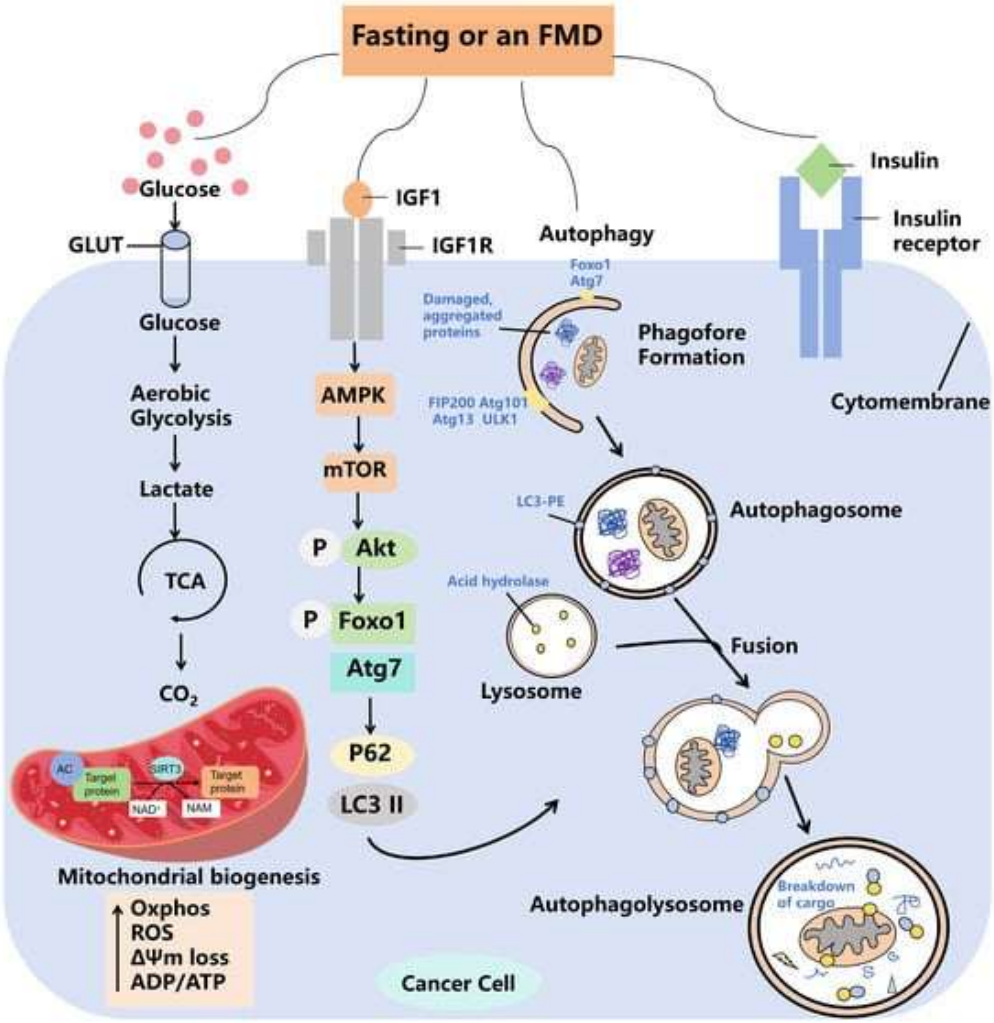

Figure 3: Mechanisms by which fasting or fasting-mimicking diets kill cancer cells in solid tumors

Oxidative Stress and Inflammation

Intermittent fasting reduces oxidative stress and inflammation, which are key contributors to many chronic diseases. It decreases the production of reactive oxygen species and enhances antioxidant defense mechanisms **[13]**.

Additionally, IF reduces pro-inflammatory cytokines and improves immune function, thereby lowering the risk of metabolic disorders such as obesity, diabetes, and cardiovascular diseases.

Aerobic life naturally generates molecular oxygen through the formation of reactive oxygen species (ROS). Basal levels of ROS are crucial for carrying out diverse cellular functions, including signal transduction pathways, the protection of host cells against microorganisms, regulation of gene expression, and the promotion of cellular proliferation or death. Oxidative stress is defined as an imbalance in the production of ROS and the inability of the body to adequately detoxify these reactive oxidation

products. Accumulation of ROS may lead to metabolic syndrome development, as well as the advancement of atherosclerosis disease, if production of ROS is not regulated and circulating amounts rise. Results from laboratory short-term studies indicate that TRE may lead to consistent decreases in oxidative stress markers in certain populations. For example, in a 6-hour TRE study involving obese adults with prediabetes, the average plasma level of 8-isoprostane (lipid peroxidation indicator) showed a 14% decrease. There also was a change in 8-isoprostane plasma at week 8 among groups that adhered to 4- and 6-hour TRE, with percentage decreases of 37% and 43%, respectively, compared to a control group with no meal time limitations. On the whole, there were no differences in the levels of inflammatory markers (e.g., tumor necrosis factor-alpha (TNF-alpha) and extracellular interleukin-6 (IL-6)) due to any of these interventions. We have also shown that TRE is protective against oxidative stress due to its alignment with circadian time and the regulatory function it plays in the production of different signalling molecules as well as its role in maintaining mitochondrial homeostasis and decreasing oxidative stress. The process of intermittent fasting activates adaptive cellular responses that evolved over time and are integrated into the body; they improve glucose regulation, increase resistance to stress and suppress inflammation by activating cellular signalling pathways that enhance innate defences against oxidative and metabolic stresses and clearing out and repairing damaged molecules. These encouraging preliminary studies suggest that TRE could provide some assistance in regulating human ROS production.

Circadian Rhythm and Metabolic Health

Intermittent fasting plays an important role in aligning metabolic processes with circadian rhythms. Time-restricted eating helps regulate hormone secretion, glucose metabolism, and lipid utilization.

Disruption of circadian rhythms is associated with metabolic disorders, and IF helps restore this balance, thereby improving overall metabolic health.

As organisms adapted to the light-dark cycles that are part of a 24-hour day, the distribution of essential life-sustaining activities such as eating and sleeping has become modulated over time with respect to daily cycles of light and dark. Multiple physiological mechanisms exhibit similar cyclic behaviours and are referred to as circadian rhythms. The daily variation in behaviour and metabolism is controlled by molecular circadian clocks that correspond with the outside day-night cycle.25 Changes or disruptions to circadian rhythms are generally accompanied by disruptions in metabolic function, which can manifest as any of a range of pathological conditions,

including obesity and type 2 diabetes, both of which are symptoms of a broader metabolic syndrome. One of the major dietary trends of contemporary society is the shift from an average of three to four meals a day to 45% of the total daily energy intake being consumed during the evening meal and at night **[26]**. The consumption of a greater proportion of total daily energy intake in the evening adds to the misalignment of the body's circadian rhythms and disrupts metabolic processes. This combination results in the excessive ingestion of energy and a disturbance in overall metabolic health. When food intake times are matched to the central circadian clock, the metabolism of fats, proteins, and carbohydrates is changed. Intermittent fasting (IF) has potential as a means of realigning disrupted circadian rhythms and treating or preventing obesity and metabolic disease **[27]**.

Time-restricted eating (TRE) is a good option for achieving this since it places food intake into a defined period (usually 8-12 hours) that is consistent with the circadian rhythm, allowing for optimal nutrient use to support health. Melatonin production is also an important factor in glucose regulation because it decreases the amount of glucose ultimately converted to insulin in response to food ingestion during late-night hours (typically 2 - 3 hours prior to bedtime) and increases this response after waking in the morning. Additionally, there is a decrease in insulin release by the pancreas as the body approaches its period of rest, leading to increased lengths of time where blood glucose levels are above normal due to consumption of food late at night resulting in storage of triglycerides (TG) within the body's fat reserve. A study on overweight/obese females who followed a time-restrictive eating (TRE) approach with a feed time of less than 11 hours and initiated their fast 2 hours prior to sleep, demonstrated a reduction in energy intake, glycemic load and frequency of eating frequency **[28. 29]**. The results indicate that early time-restricted feeding (eTRF) is believed to lower mean glucose levels over a 24 hour period, alter lipid metabolism and oxidation and gene expression of the circadian clock, stimulate autophagy and have anti-aging benefits **[30]**. **(Table 2)**.

Another study involving prediabetic individuals (n = 119) showed that longer feeding intervals (>12 hours) were related to higher % body fat. Additionally, females (n = 146) participating in another TRE research comparing between an eating time frame of <12 hours with >12 hours showed a significant reduction in caloric intake during the shorter eating time frame; these results are consistent with prior TRE findings and indicate additional health benefits can result from calorie consumption being restricted to certain time frames with breaks separating

those intervals by several hours from the night sleep interval **[31]**.

Intermittent Fasting and Exercise

Combining intermittent fasting with regular exercise might help maximize potential metabolic benefits from that approach.32 In addition, exercising while fasting may also increase fat oxidation and improve insulin sensitivity and also preserve lean body mass **[33]**. Therefore, it is possible that using a combination of these two methods may also provide the greatest benefit in terms of managing one's body weight and improving metabolic health, but this should be taken into account along with how each person tolerates this combination and their method of obtaining proper nutritional support **[34]**.

Modifiable Lifestyle Behaviour

Intermittent fasting influences several modifiable lifestyle behaviour, including energy intake, energy expenditure, sleep patterns, and adherence to dietary practices, which collectively contribute to its metabolic effects.

Energy Intake:

Energy intake has been shown to be lower with alternate-day and modified fasting in the metabolic research studies identified so far. While many studies examining fasting regimens' impact on free-living adults rely upon self-reported food intake data which tend to have a poor correlation with objective measures of food intake, the weight reduction seen in most studies can be used as a surrogate measure for intermittent fasting; most trials show a significant reduction in weight with a majority reporting drops greater than baseline value(s).

Because most fasting regimens limit meals to fewer total hours of availability to eat, overall energy consumption decreases and the potential for obesity decreases. In addition to changes in total caloric intake, there are also reported changes to appetite regulating hormones (leptin, ghrelin and xenin), especially among night and shift workers, which can affect hunger and/or total caloric intake.

Energy Expenditure

It has been shown through the use of animal studies that the circadian timing system maintains the functions of physical activity and expenditure of energy. In mice experiment with time-restricted isocaloric feeding regimens, muscle coordination and physical activity were improved, especially during the last portion of the feeding period. However, there are still limited data in humans, and therefore we cannot draw any firm conclusions regarding the effect, if any, that intermittent fasting has on total daily energy expenditure in free-living adults. More research will be needed to determine the actual effects of intermittent fasting on metabolic rate and physical activity.

Sleep

Numerous observational studies have reported that night time eating is associated with reduced sleep duration and poor sleep quality **[35]**. These disturbances can contribute to insulin resistance and increase the risk of obesity, diabetes, cardiovascular diseases, and cancer.

Eating at abnormal circadian times, particularly late at night, may lead to circadian desynchronization and disruption of normal sleep patterns. Although intermittent fasting may help improve circadian alignment, there is limited direct evidence examining its effects on sleep in free-living adults **[36]**.

Adherence and Sustainability

Following an intermittent fasting schedule plays a critical role in the effectiveness of this eating approach in the long run. Although intermittent fasting yields positive impacts on metabolism, long-term adherence to fasting will likely be difficult for many people due to social, cultural and work-related reasons **[37]**.

Other symptoms that can occur from intermittent fasting are hunger, irritability and fatigue; some of these may deter the individual from adhering to their intention to fast, and overeating while eating could negatively affect some individuals' workout performance, thus reducing the overall benefits associated with intermittent fasting. Therefore, one should take into consideration how things such as long-term sustainability and the individual's ability to adapt will be addressed when developing a long-term plan for implementing an intermittent fasting lifestyle change.

Limitations of Intermittent Fasting

Intermittent fasting has several limitations that must be considered prior to being used in clinical practice despite its numerous benefits.

The greatest limitation, however, is that there are no long-term, clinical studies examining both the safety and efficacy of intermittent fasting. Energy restriction has been studied over shorter, less extended time frames; thus, long-term impacts on different groups of people are uncertain. Variability between different fasting regimens (protocols, or durations) and methods of study design (protocol and/or design) make it challenging to establish clinical guidelines that are common across sites.

Another major limitation associated with intermittent fasting is adherence to intermittent fasting regimens over time is often difficult for many individuals. If a person is fasting for an extended period of time, they may become very hungry and irritable; this will lead to decreased adherence over time. Therefore, sustaining the diet over time, and therefore successfully implementing it into a person's lifestyle and diet, is likely to be more challenging.

The individual differences that can occur with each person's response to intermittent fasting is another limitation. Some of these include age, gender, metabolic health, and lifestyle factors. Because of this variability among individuals, it is challenging to generalize the benefits of intermittent fasting to all people; therefore, it can be concluded that intermittent fasting has many barriers that must be overcome.

In addition, it is possible to experience some negative effects, such as fatigue, decreased physical performance, and difficulty of maintaining a proper ratio of nutrients during the eating window.

Precautions:

If you're thinking about trying intermittent fasting, be careful. Not everyone can do it; people will have different side effects from intermittent fasting,38 such as low blood sugar levels, especially if they're on insulin or other medications that lower glucose levels. Medical supervision is a must when someone has diabetes and is trying intermittent fasting.

Some common side effects of intermittent fasting, especially during the initial adjustment phase, include dizziness, weakness and headaches, dehydration, and difficulty concentrating. While these side effects usually don't last forever, they could affect your daily life **[39]**.

In general, pregnant women, nursing mothers, children, older adults, and people with a history of eating disorders and chronic diseases should not do intermittent fasting. Using intermittent fasting could create nutritional deficits and poor health in these groups.

If a person eats improperly during eating times while following intermittent fasting, they might also suffer from not eating enough nutrients, resulting in losing muscle, getting inadequate amounts of essential vitamins and minerals, and suffering decreased overall health. It is important to eat a balanced diet when using intermittent fasting **[40]**.

CONCLUSION

Intermittent fasting is an effective dietary approach that offers multiple health benefits through metabolic switching, hormonal regulation, and activation of cellular repair mechanisms such as autophagy. It plays a significant role in improving metabolic health, promoting weight loss, and reducing the risk of chronic diseases including diabetes, cardiovascular disorders, and cancer.

Intermittent fasting has many clinical uses because of the physiological processes that are believed to underlie it; these include an increase in mitochondrial performance, a decrease in oxidative stress, and influences on what are known as inflammation and circadian rhythm patterns in various systems. In addition, research explores how intermittent fasting alters gut microbiota,

hence supporting its extension into an overall health-promoting effect.

Despite these benefits, there are certain limitations to intermittent fasting which may impede use. Some of the most pertinent limitations include a lack of longitudinal data, challenges associated with adherence to the diet, variability among individuals regarding the response to the diet, and potential lack of appropriateness of intermittent fasting for all populations. Furthermore, care must be taken in delivery methods when implementing intermittent fasting for at-risk individuals or those with pre-existing health issues.

Overall, intermittent fasting is considered a promising and adaptable nutrition intervention that may improve metabolic function and help to prevent diseases. More large-scale and long-term trials are needed to provide suitable guidelines for intermittent fasting and further evaluate its long-term safety and effect.

To optimize health performance and benefit from intermittent fasting, future research needs to include longer-term (clinical) studies, personalisation of fasting models, and the relationship(s) between intermittent fasting with dietary quality and physical exercise.

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