Epigenetically Mediated Health Effects of Intermittent Fasting

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Abstract

Globally, the prevalence of chronic diseases such as obesity, cardiovascular disorders, diabetes, and cancer is rising. These conditions are influenced by both genetic and environmental factors, with nutrition being one of the most critical environmental determinants. Intermittent fasting (IF) is a dietary pattern that has gained attention for its potential health benefits and impact on metabolic regulation. Recent studies in the field of nutrition-epigenetics suggest that IF may exert these effects through epigenetic modifications, including DNA methylation, histone modifications, and regulation by non-coding RNAs. IF encompasses various approaches such as alternate-day fasting, time-restricted feeding, and whole-day fasting. Evidence indicates that IF can enhance lipid and glucose metabolism, support healthy aging, reduce inflammation, and improve mitochondrial and immune function by modulating gene expression epigenetically. It may also promote autophagy, stem cell renewal, and anti-cancer responses, suggesting its potential role in preventing or mitigating metabolic and neurodegenerative diseases. Despite these benefits, adverse effects of IF have also been reported. Particularly concerning are findings related to maternal IF, which may impair fetal development and metabolic health in offspring via epigenetic inheritance. Additionally, in other life stages, IF may lead to micronutrient deficiencies, hypoglycemia, hormonal imbalances, fatigue, and increased metabolic disease risk, especially in vulnerable populations or when fasting is prolonged or poorly planned. This review aims to summarize the current evidence on how IF influences health and disease through epigenetic mechanisms. Personalized recommendations considering age, health status, and nutritional needs are essential. More comprehensive human studies are needed to clarify IF's dual role and to optimize its application for health promotion.

Keywords: Fasting, circadian rhythm, diet therapy, epigenetic processes.

Aralıklı Açlık Diyetlerinin Epigenetik Aracılı Sağlık Etkileri

Öz

Dünya genelinde obezite, kardiyovasküler hastalıklar, diyabet ve kanser gibi kronik hastalıkların görülme sıklığı artmaktadır. Bu hastalıklar hem genetik hem de çevresel faktörlerden etkilenmektedir ve beslenme, en önemli çevresel belirleyicilerden biridir. Aralıklı açlık (AA), metabolik düzenleme üzerindeki potansiyel etkileri nedeniyle sağlık yararları açısından dikkat çeken bir beslenme modelidir. Beslenme-epigenetik alanındaki güncel çalışmalar, AA'nin bu etkilerini epigenetik değişiklikler yoluyla gösterebileceğini ortaya koymaktadır. Bu değişiklikler arasında DNA metilasyonu, histon modifikasyonları ve kodlamayan RNA'ların düzenlenmesi yer almaktadır. AA; gün aşırı oruç, zaman kısıtlı beslenme ve tam gün oruç gibi farklı uygulamaları içermektedir. Kanıtlar, AA'nin lipid ve glukoz metabolizmasını iyileştirebileceğini, sağlıklı yaşlanmayı destekleyebileceğini, inflamasyonu azaltabileceğini ve mitokondriyal ile bağışıklık fonksiyonlarını iyileştirebileceğini göstermektedir. Ayrıca, ototofajiyi, kök hücre yenilenmesini ve antikanser yanıtları teşvik ederek metabolik ve nörodejeneratif hastalıkların önlenmesinde potansiyel bir rol oynayabilir. Bu yararların yanı sıra, AA'nin olumsuz etkileri de bildirilmektedir. Özellikle gebelikte uygulanan AA'nin, epigenetik kalıtım yoluyla fetüsün gelişimi ve metabolik sağlığı üzerinde olumsuz etkileri olabileceği gösterilmiştir. Ayrıca, diğer yaşam dönemlerinde de mikrobesin eksiklikleri, hipoglisemi, hormonal dengesizlikler, yorgunluk ve artmış metabolik hastalık riski gibi olumsuzluklar görülebilmektedir, özellikle kırılgan bireylerde veya yetersiz planlanmış uzun süreli AA uygulamalarında. Bu derlemede, AA'nin epigenetik mekanizmalar yoluyla sağlık ve hastalık üzerindeki etkileri güncel literatür ışığında

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özetlenmektedir. AA uygulamalarında yaş, sağlık durumu ve bireysel beslenme ihtiyaçları göz önünde bulundurularak kişiye özel öneriler verilmesi önemlidir. Bu alandaki insan çalışmalarının artırılması, AA'nin çift yönlü etkilerinin netleştirilmesi açısından gereklidir.

Anahtar Sözcükler: Açlık, sirkadiyen ritm, diyet terapi, epigenetik süreçler.

Introduction

Intermittent Fasting

Following the Industrial Revolution, some changes have been observed in dietary habits due to the changing living conditions of human life. It is characterized by an increased frequency of meals during the day and irregular eating patterns with meals shifted to later hours of the day[1]. Along with these irregular eating habits developed over the process, the Western diet, which consists of highly processed foods, constitutes the main environmental factor in the current epidemic of metabolic diseases. Therefore, a transition to a healthy and nutritional diet can protect against the progression of chronic disease. Beyond this context, factors like side effects, patient adherence, tolerability, and shortcomings in disease management create obstacles to the practical use of pharmacological treatments in managing metabolic disorders. Hence, it is stated that dietary interventions can be used as a low-risk alternative or complementary treatment. Dietary interventions with adjusted meal timing or content show sustainable success in decreasing risk factors, revealing multiple favorable effects, and correcting disease conditions[2]. Among these dietary interventions, intermittent fasting (IF) has emerged in the last 10-15 years as a non-traditional approach to potentially reduce body weight and improve metabolic health, gaining popularity independently of calorie restriction. It encompasses various dietary interventions that include periodic intervals of fasting followed by eating[1,3]. Unlike other popular diets, it is suggested that IF could be an appealing alternative dietary intervention as it does not require calorie tracking and allows for unrestricted eating during specific hours of the day. There are various IF diets in terms of meal timing and energy intake cycles[3]. These can be grouped as alternate-day fasting, time-restricted feeding, and religious fasts[1,4,5].

Alternate Day Fasting: It is the most commonly preferred intermittent fasting diet intervention, except for religious fasting[4]. This dietary intervention is applied by alternating free eating days with fasting days. ADF has two main variations. In zero-calorie ADF, no caloric foods or beverages are consumed on fasting days, while MADF permits a meal, usually at lunchtime, covering around 25% of an individual's daily energy needs[6]. Additionally, alternate-day fasting can implement modified fasting with different durations. In this case, modified fasting periods with a small meal can extend up to 30-40 hours[4,5]. The 5:2 eating pattern represents an adjusted form of ADF, requiring two days per week with reduced calorie intake (500–1,000 kcal daily) while allowing unrestricted eating on the remaining five days. These lower-calorie days may be scheduled either consecutively or separately throughout the week[3].

Whole Day Fasting: Whole-day fasting involves completely avoiding food or severely restricting calories for only 1-2 days per week. These protocols can be as simple as a 24-hour fast once a week, but some include fasting multiple times per week or fasting periods longer than 24 hours[4].

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Time Restricted Feeding: Time-restricted eating protocols involve adhering to a daily routine in which a specific number of hours are fasted within 24 hours, and the remaining hours are allocated for eating. This method permits individuals to eat freely within a specific timeframe, typically ranging from 3–4 hours up to 10–12 hours, resulting in a fasting period of 12–21 hours daily. The most common form of time-restricted eating involves eating for eight hours and fasting for the remaining 16 hours. An essential aspect of IF is that while the timing of meals is regulated, total calorie consumption is generally not restricted[5,7].

Religious Fasting (Ramadan Fasting): Many religions, such as Islam, Christianity, Judaism include religious fasting[8]. These fasts, which vary in duration and dietary patterns, generally reduce the consumption of animal proteins, refined foods, and other worldly pleasures while increasing the intake of fruits and vegetables, social interaction, and religious practices such as prayer[9]. Therefore, the Ramadan fast in Islam can be examined within the context of intermittent fasting dietary interventions due to their similarities to secular intermittent fasting approaches. Ramadan fasting (RF) is a 30-day period during which Muslims abstain from food and drink from dawn to sunset during Ramadan[8,10]. Traditionally, it is common practice to wake up at the first light of dawn and have breakfast before dawn. Energy intake is limited to the evening, night, and very early morning hours[11,12].

Fasting Mimicking Diet: A nutritional regimen formulated to replicate the physiological effects of extended fasting while allowing limited nutrient consumption[13]. This dietary approach primarily consists of plant-based foods, including vegetables, nuts, seeds, and healthy fats such as olive oil[13,14]. It replaces regular meals with nutrient-dense bars, soups, and snacks, ensuring adequate micronutrient intake while inducing short-term calorie restriction. The diet is rich in complex carbohydrates and polyunsaturated fatty acids while being low in protein and sugar[14]. On the first day of a standard FMD protocol, approximately 1090 kcal is consumed, comprising 34% carbohydrate, 56% fat, and 10% protein. For the remaining days (days 2 through 5), the daily caloric intake is reduced to 725 kcal, with a macronutrient distribution of 47% carbohydrate, 44% fat and 9% protein[15].

Effects of Intermittent Fasting on Health

It is stated that various IF interventions in animal and human studies have great potential to delay adverse health conditions associated with aging, as well as reduce the potential for numerous health issues, with a focus on metabolic disorders, neurodegenerative diseases, and cancer[16-23]. Studies on animals have shown that IF has strong and persistent effects on biomarkers, lowering blood pressure, enhancing insulin sensitivity and glucose regulation, reducing body fat, and improving lipid metabolism[24,25]. In healthy individuals, IF has been found to improve systemic metabolic indicators and slow aging by enhancing the function of multiple organs[26,27]. IF helps address disorders in glucose and lipid metabolism, fosters the renewal of stem cells or organ tissues, and slows disease progression, particularly in those with obesity or metabolic syndrome[28-30]. Moreover, when applied in conjunction with chemotherapeutic agents, IF increases chemotherapeutic efficacy while reducing associated side effects[31]. IF stimulates the renewal and differentiation of various tissues and cells, while also

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enhancing antitumor immunity[32]. In addition, IF interventions affect the cellular autophagy, gut microbiome, and mitochondrial health[33-35]. A recent study demonstrated that intermittent fasting may promote weight loss by reducing fat accumulation without disrupting energy balance, thereby offering a protective effect against obesity[36].

Intermittent fasting (IF) has shown potential in delaying age-related diseases and reducing the risk of metabolic disorders like obesity, diabetes, and cancer. Animal and human studies indicate it improves metabolic health and may enhance chemotherapy outcomes.

Health Effects of Intermittent Fasting and Ramadan Fasting with Epigenetic Modifications

Despite extensive experimental evidence supporting the health benefits of IF dietary interventions, information on the underlying molecular mechanisms is insufficient and still under investigation[37,38]. However, with the increasing number of genetic-nutritional studies in recent years, dietary components or dietary interventions have been reported to be an environmental factor that can alter the expression of genes. Studies on the effects of these dietary interventions on humans are ongoing. The most widely accepted hypothesis in this area suggests that epigenetics is responsible for these processes. Epigenetics is defined as a field of science that examines the ability of environmental factors such as lifestyle, physical activity, exposure to toxins, and nutrition to modulate gene expression without changing our DNA sequence. Epigenetics utilizes epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs, to modulate and regulate gene expression[39]. At this point, IF interventions are seen as lifestyle interventions representing a potential environmental factor that can influence the epigenome through various epigenetic modifications[37]. Additionally, epigenetic modifications influenced by environmental factors are reported to be common in many diseases like obesity, metabolic syndrome, type 2 diabetes, insulin resistance, and cancer. Accordingly, the interactions between the environment and genetic structure are thought to be the underlying cause of the complex pathophysiology of chronic diseases[37,40].

N6-methyladenosine (m6A) methylation, a widespread and abundant epigenetic modification found in eukaryotic mRNA, is linked to obesity, lipid metabolism, and apoptosis, and plays a crucial role in both the physiological and pathological mechanisms underlying cardiovascular diseases[41,42]. In a study conducted by Zujie et al.[42], the favorable effects of IF on lipid accumulation, apoptosis, and m6A methylation in the heart tissue of obese mice were evaluated. Fifteen male C57BL/6J mice were divided into two groups: one group (n=15) was fed a high-carbohydrate (70%) normal diet, and the other group (n=30) was fed a high-fat diet (60%) for 13 weeks. At the end of 13 weeks, the obese mice on a high-fat diet were equally divided to form a third group. The third group of obese mice was subjected to 24:24 whole-day fasting for eight weeks, while the other two groups continued their previous diets. At the end of 21 weeks, IF intervention significantly reduced the mRNA expression of genes involved in fatty acid intake and synthesis (FATP1, FABP1, CD36, SREBF1, FAS, ACCα) and elevated the expression of genes involved in fatty acid breakdown (ATGL, HSL, LAL, LPL) in the hearts of mice with obesity induced by a high-fat diet. Moreover, IF attenuated apoptosis, indicated by a

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reduction in TUNEL-positive cells, a decline in the Bax/Bcl-2 ratio, and a decrease in Caspase 3 protein levels. Mechanistically, IF lowered m6A methylation levels by downregulating METTL3 and upregulating FTO. Therefore, it is suggested that IF may reduce lipid accumulation and apoptosis in the heart tissue through a mechanism associated with decreased m6A RNA methylation levels, thereby improving cardiac functional and structural impairment[42]. However, a 2015 study demonstrated that alternate-day fasting applied for six weeks protected mice from in vivo ischemia-reperfusion injury. Yet, in mice with impaired autophagy (heterozygous null for Lamp2, which encodes lysosomal-associated membrane protein 2), this protective effect was not observed; instead, a worsening effect was noted[43]. Another study conducted on rats subjected to alternate-day fasting for six months demonstrated an increase in myocardial fibrosis, a reduction in cardiac reserve, and an enlargement of the left atrial diameter compared to rats fed ad libitum. Therefore, it has been suggested that prolonged fasting may have detrimental effects, highlighting the need for greater caution in both fasting research and its practical applications[44].

Some studies conducted with dementia patients have shown that gene-environment interactions may underlie dementia[45,46]. It has been reported that IF is protective against age-related neurological diseases and physiologically regulates DNA methylation[46,47]. In a study investigating the effect of 16:8 time-restricted feeding on DNA methylation imaging in mice with vascular dementia (VaD) and its therapeutic effects in chronic cerebral hypoperfusion (CCH) associated with cognitive impairment, it has been shown that IF modulates DNA methylation and attenuates neuropathology and cognitive impairment. As a result, it was determined that slowing down the progression of vascular dementia is associated with an increase in DNA methylation due to hypermethylation observed in the IF group, compared to the control group with free access to food. In addition, in contrast to the control group, in the IF group, cognitive impairment and white matter lesions associated with neuropathology decreased; myelin basic protein activity and neuron numbers increased. These results offer insight into how IF could safeguard the brain from harm induced by CCH and indicate potential advantages in reducing neuropathological damage and cognitive impairments in VaD[46]. A study conducted on 5XFAD mice carrying genetic mutations associated with Alzheimer's disease (AD) reported contrasting findings. In this study, the mice were fed ad libitum (AL) until the age of two months. They were then randomly assigned to two different dietary groups: one receiving AL feeding daily and the other following an every-other-day (EOD) feeding regimen for a duration of four months. At the end of six months, tissue sample analyses revealed no significant differences in plaque accumulation between the two groups. However, the EOD-fed mice exhibited increased cortical inflammation and neuronal damage, along with a reduction in proteins associated with synaptic plasticity. These findings suggest that the EOD dietary pattern may exacerbate AD-like neurodegenerative and neuroinflammatory alterations. Therefore, based on the results of this study, it is emphasized that calorie restriction through fasting should be carefully considered in the early (prodromal) stages of neurodegenerative diseases[48,49].

Fasting can regulate histone methylation and consequent gene transcription. Jumonji-D3 (JMJD3/KDM6B), a histone demethylase from the KDM6 family, epigenetically

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activates genes by removing methyl groups from the H3K27-me3 histone. While JMJD3 is noted to have functions in differentiation and development, immunity, and tumor formation, and also plays a role in extending lifespan under mild mitochondrial stress, its metabolic functions have not been reported[50,51]. In a study conducted by Byun et al.[50], it was shown that the Fasting-Induced Fibroblast Growth Factor-21 (FGF21)/Protein Kinase A (PKA) signalling stimulates hepatic autophagy and lipid breakdown via the JMJD3 histone demethylase in mice. JMJD3 modulates gene activity epigenetically by demethylating the H3K27-me3 histone. Through the demethylation of the H3K27-me3 histone, it epigenetically activates genes that regulate the global autophagy network, including Atg7, Tfeb, Atgl, and Fgf21, leading to autophagy-mediated lipid degradation. Another study conducted by Seok et al.[51] demonstrated that the JMJD3 histone demethylase epigenetically activates mitochondrial fatty acid β-oxidation. Furthermore, it was found that JMJD3 forms a transcriptional complex with SIRT1 and PPARα, which epigenetically stimulates genes promoting β-oxidation, including Fgf21, Cpt1a, and Mcad. It was suggested that the JMJD3-SIRT1-PPARα complex creates a forward-feedback positive autoregulatory loop by automatically increasing the expression of its genes when stimulated by fasting. Therefore, the regulation of β-oxidation by this complex ensures the maintenance of energy balance in the liver during fasting[51]. Additionally, another animal study demonstrated that SIRT1 activates the PPARα signaling pathway under fasting conditions, thereby enhancing hepatic fatty acid β-oxidation. This mechanism was shown to contribute to metabolic health by preventing hepatic steatosis and inflammation, consistent with previous findings[52]. These studies demonstrate that fasting may positively influence the pathogenesis of non-alcoholic fatty liver disease (NAFLD) in mice by activating hepatic autophagy, lipid degradation, and fatty acid β-oxidation through the histone demethylation mechanism[50,51]. Moreover, previous studies have shown that fasting-induced FGF21 displays positive metabolic effects in mice, while these effects are not similar in humans. In mice, FGF21 levels rapidly increase within hours, while in humans, this increase is only observed after 7-10 days. This suggests that the function of FGF21 may have evolved differently in humans[53]. In addition to Jumonji-D3, a histone demethylase, SIRT1, a histone deacetylase, can also be cited as an example of histone modification. SIRT1 activates the expression of certain genes that regulate the body's biological clock and energy utilization through deacetylation. However, it has been noted that overexpression of SIRT1 in mice does not play a role in intensifying adaptations to intermittent fasting, suggesting that the contribution of SIRT1 to fasting-induced epigenetic modifications is controversial. Consequently, it has been demonstrated that SIRT1 may not be the sole mediator of dietary interventions related to fasting[54].

Non-coding RNAs (ncRNAs) have been shown to mediate the functions of IF. NcRNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are reported to be involved in a wide range of biological, physiological, and pathological processes[55,56]. Additionally, metabolic disorders such as metabolic syndrome and obesity, which tend to rise with age, are associated with irregular levels of circulating miRNAs[57]. The impact of time-restricted feeding, a form of IF dietary intervention, on the expression of circulating miRNAs, which act as intercellular signalling molecules and have the potential to regulate biological pathways for metabolic advantages, is under

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investigation[58]. In a study conducted by Saini et al.[58], a 4-week 16:8 time-restricted feeding intervention was applied to nine elderly participants aged 65 and over who were overweight, and the effects on overall circulating miRNA and the target genes of miRNAs that changed with the IF intervention were examined. A significant decrease in body weight was observed in all participants after IF (2.6 kg, $p < 0.01$). It was found that fourteen miRNAs were expressed differently before and after IF (eight were lower and six were higher). The low-level expressed miRNAs (miR-2467-3p, miR-4649-5p, miR-301a-3p, miR-543, miR-3132, miR-495-3p, miR-19a-5p, miR-4761-3p) were found to increase the expression of genes including PTEN, TSC1, and ULK1. This increase in gene expression was shown to inhibit protein synthesis/cell growth pathways related to these genes and activate cell survival and metabolic adaptation pathways, potentially promoting healthy aging[58].

Alongside miRNAs, lncRNAs could play a role in the impact of IF on glucose metabolism and metabolic stress. Some lncRNAs are thought to function as regulators of energy metabolism, which is linked to all major biological processes[6,59]. In a study conducted by Ruan et al.[59], it was determined that a type of long non-coding RNA, lncLGR, is induced in the liver of mice during fasting. The increased activity of lncLGR reduces glycogen storage by inhibiting hepatic glucokinase activity. lncLGR specifically binds to heterogeneous nuclear ribonucleoprotein L (hnRNPL) and facilitates hnRNPL's binding to hepatic glucokinase, thereby co-repressing the transcription of hepatic glucokinase. As a result, it has been shown that the lncRNA type lncLGR plays a functional role in glucose metabolism by reducing hepatic glucokinase enzyme activity. Another investigation by Brocker et al.[60] revealed that Gm15441, classified as a lncLGR, significantly contributes to mitigating inflammasome activation under fasting conditions. It was discovered that PPARα is activated by fatty acids released from adipose tissue during fasting, directly enhancing the expression of the long non-coding RNA gene Gm15441. The expression of Gm15441 represses the antisense transcript that codes for thioredoxin-interacting protein (TXNIP). This repression reduces the activation of the NLR family pyrin domain-containing 3 (NLRP3) inflammasome, caspase 1 (CASP1) cleavage, and pro-inflammatory interleukin 1β (IL1B) maturation, which are stimulated by TXNIP. Based on these studies, a mechanism has been proposed in which long non-coding RNAs (lncRNAs) attenuate hepatic inflammasome activation in response to metabolic stress induced by fasting[60]. In addition, a human study conducted on overweight/obese women evaluated the effects of intermittent fasting on inflammatory markers in adipose tissue and skeletal muscle. In an 8-week study, the IF group exhibited an increase in M1 macrophages (pro-inflammatory) in adipose tissue and M2 macrophages in skeletal muscle following a 24-hour fast. This rise in macrophage levels suggests that IF may trigger a transient inflammatory response associated with enhanced lipolysis[61]. As a result, these findings highlight the effects of fasting on genetic mechanisms that regulate both the inflammatory response and energy metabolism.

It is suggested that different IF approaches affect the expression of genes connected to human health and various diseases[62]. Although it is stated that there are insufficient studies examining the effect of Ramadan Fasting (RF) and related dietary and lifestyle changes on specific genes related to human health and diseases, it has been shown that

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RF has effects on the obesity gene (FTO)[62], antioxidant stress genes (TFAM, Nrf2, SOD2) and genes controlling metabolism (SIRT1, SIRT3)[63], circadian gene (CLOCK) and glucocorticoid-controlled genes (DUSP1, IL-1α)[64]. In a study conducted by Madkour et al.[62], the effects of RF on the FTO gene, which is associated with obesity and body fat accumulation, were investigated in overweight or obese fasting individuals. It was observed that the expression of the FTO gene significantly decreased at the end of Ramadan compared to before Ramadan in overweight or obese individuals. As a result, the reduction in FTO gene expression was noted to have positive effects on body weight and body fat percentage reduction, as well as the reduction in waist and hip circumference and other related metabolic events[62]. A human study investigated the beneficial effects of RF on antioxidant stress genes (TFAM, SOD2, Nrf2) and sirtuins (SIRT1, SIRT3), which are associated with aging and metabolism. The results showed an increase in antioxidant gene expression, including TFAM (90.4%), SOD2 (53.8%), and Nrf2 (411.8%), in overweight or obese individuals compared to those with normal body weight. However, at the end of Ramadan, there was a significant decrease in the SIRT3 gene (61.8%) that controls metabolism, while a decreasing trend was observed in the SIRT1 gene. Although the observed downregulation of SIRT1 and SIRT3 during fasting appears to contradict findings related to increased fatty acid oxidation and reduced visceral fat, this inconsistency is primarily attributed to the influence of other genetic and hormonal regulatory mechanisms rather than sirtuins themselves. In conclusion, based on the findings of this study, Ramadan fasting may be effective in reducing oxidative stress and inflammation in non-diabetic obese individuals through the activation of antioxidant genes (*TFAM*, *SOD2*, *Nrf2)*. Consequently, it may contribute to delaying the onset of diabetes and other metabolic disorders[63]. Conversely, there are also studies reporting the overexpression of SIRT1 and SIRT3 enzymes under conditions of prolonged fasting and caloric restriction[65,66]. In a double-blind randomized study in which intermittent fasting (IF) was applied to 12 healthy individuals for three weeks, a slight increase (2.7%) in SIRT3 expression was observed. However, despite this increase, no significant changes were found in the expression of other genes related to aging and metabolism, nor in oxidative stress markers. Furthermore, no adverse clinical findings or changes in body weight were reported[67]. In another study conducted by Ajabnoor et al.[64], it was found that RF caused significant changes in the circadian gene (CLOCK) and immune-regulating genes (DUSP1, IL-1α) in healthy individuals compared to before Ramadan. Accordingly, RF has been shown to be associated with improvements in certain cardiometabolic risk factors such as GGT, hsCRP, and IL 1 gene expression. However, it was also noted that the disruption of sleep patterns due to RF could lead to diurnal rhythm disturbances and a reduction in the mentioned benefits[64]. However, the effects of different intermittent fasting (IF) protocols on gene expression may not always result in metabolic benefits. In a study conducted on rats subjected to a long-term IF regimen—consisting of 3-day fasting and 3-day feeding cycles over 48 days—it was observed that lipid accumulation in white adipose tissue increased significantly. Notably, the expression of the Fsp27/Cidec gene, which is closely associated with lipid storage, was markedly upregulated. These findings suggest that certain IF patterns may exert adverse effects on lipid metabolism[68].

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Precautions to Consider/ Side Effects

Despite the promising effects of intermittent fasting, potential side effects should not be overlooked. Unfortunately, evidence highlighting these adverse outcomes remains scarce, likely due to the limited duration over which intermittent fasting is typically evaluated. Commonly noted symptoms include hypoglycemia, dizziness, and fatigue[69]. Hypoglycemia is the most significant side effect of intermittent fasting. A multi-country observational study by Beshyah et al. assessed the hypoglycemia risk during intermittent fasting in Ramadan. The study found that reduced caloric intake during fasting could lead to severe hypoglycemia[70]. Also, a study conducted on rats with ADF observed diastolic dysfunction and reduced cardiac reserve[71]. In the experiments conducted by Munhoz et al., IF demonstrated effectiveness in weight loss; however, its long-term safety has raised concerns[72].

In addition, the effects of long-term IF during pregnancy preparation and pregnancy on fetal metabolism remain unknown. However, appropriate nutrition before and during pregnancy is critical for both maternal health and fetal development[73]. During pregnancy, the placenta, fetal development, blood volume, and brain development have specific metabolic needs therefore, maternal nutrition plays a critical role in fetal health. Additionally, overnutrition, malnutrition, or obesity in pregnant mothers can increase the risk of metabolic diseases in their children during adulthood[74,75]. It is stated that maternal fasting during Ramadan can impair fetal growth and that maternal undernutrition during pregnancy can lead to epigenetic changes associated with impaired physiological functions in children[76-79]. In a study conducted by Yin et al.[76], the effects of IF applied to female mice before mating on the metabolism of their offspring were investigated. As a result, it was shown that maternal IF led to lower birth weight and impaired glucose metabolism in the offspring. Additionally, it was found that maternal IF applied before mating altered 2869 differentially methylated DNA regions in the liver of the offspring[76]. In another study that investigated the mechanism underlying the effects of long-term maternal IF on the metabolism of offspring in more detail, the effects of 24:24 IF applied to female mice for 12 weeks before mating were examined. The offspring of female mice that underwent long-term IF before pregnancy were found to have lower placental and birth weights compared to the offspring of mothers that were fed ad libitum. Over time, it was observed that the IF offspring caught up in weight to the control group offspring, closing the initial gap. Additionally, it was found that the IF offspring had increased adipose tissue and consequently impaired glucose tolerance. The presence of hepatic steatosis was observed with increased lipid and triglyceride levels in the liver. The underlying mechanism for these findings was shown to be the suppression of mTORC1 signalling, which is involved in cell growth and metabolism, due to decreased levels of DNA methyltransferases in the liver of IF offspring[78]. In a study conducted by Hussain et al.[79], 14 pregnant mice were divided into two groups, with half subjected to 16:8 nighttime IF for 21 days, while the other half were fed ad libitum. At the end of the 21 days, a significant decrease in the weight of the fetus, placenta, and yolk sac was observed in the IF group. Additionally, the tissues showed high levels of Folr1 gene expression and FRα protein. The findings indicated that maternal IF, despite hindering fetal growth, contributed to the transfer of folate from the

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mother to the fetus by increasing folate gene expression[79]. Consequently, women planning pregnancy are encouraged to steer clear of long-term intermittent fasting because of its negative effects on fetal health and the metabolic stability of the offspring[78].

Conclusions

Intermittent fasting (IF) encompasses various dietary patterns such as alternate-day fasting, whole-day fasting, time-restricted feeding, and Ramadan fasting. Accumulating evidence indicates that IF exerts both beneficial and adverse effects on health through epigenetic mechanisms. On the positive side, IF has been associated with enhanced lipid metabolism, apoptosis regulation, delayed cognitive decline, promotion of healthy aging, obesity prevention, and anti-inflammatory effects. These benefits are thought to be mediated via epigenetic modifications, including DNA methylation and demethylation, histone modifications, non-coding RNAs, and altered gene expression.

However, emerging findings also highlight potential adverse outcomes of IF. Notably, maternal intermittent fasting has been shown to negatively affect the offspring's development and metabolism through epigenetic inheritance. Furthermore, prolonged fasting or suboptimal nutrient intake during feeding windows may lead to micronutrient deficiencies, impaired glucose homeostasis, hormonal imbalances, and increased susceptibility to metabolic disorders—not only in individuals planning pregnancy but also across broader populations, particularly those with preexisting health vulnerabilities.

Therefore, health professionals should provide personalized guidance regarding IF practices, taking into account individual health status, age, lifestyle, and nutritional needs. It is essential to consider the duration and frequency of fasting, as well as diet quality during feeding periods. Overall, more comprehensive and longitudinal human studies are needed to clarify the dual role of IF - both protective and potentially harmful - on health via modifiable epigenetic mechanisms.

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