

The effects of intermittent fasting on markers of health: A narrative review

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Abstract

Background: Intermittent fasting (IF) has gained significant popularity in recent years, both in medical and sports fields, primarily due to its potential improvements in various systems of the human body, including the metabolic, cardiovascular, and immune systems.

Aim: This narrative review aims to explore the health effects of intermittent fasting (IF) in both healthy and unhealthy subjects, as well as mice. It aims to shed light on the diverse physiological mechanisms through which IF may influence health outcomes.

Materials and Method: A comprehensive search for English-language manuscripts related to IF was conducted on PubMed and Google Scholar. The reviewed manuscripts focused on the effects of intermittent fasting on the immune system and lipid profiles.

Results: The data analysis revealed that intermittent fasting had a positive impact on the mentioned indicators. The findings suggest that IF could be an effective strategy for achieving better overall health.

Conclusion: Intermittent fasting appears to offer potential health benefits, showing positive effects on the immune system and lipid profiles. Further research is warranted to fully understand the mechanisms underlying these effects and to explore its suitability as a health intervention.

Keywords: aging, hematological parameters, intermittent fasting, immune system, lipid profile.

Introduction

Intermittent Fasting (IF) has emerged as a popular dietary intervention that has attracted significant attention from researchers and health enthusiasts. As one of the most studied strategies for human health improvement, IF involves alternating

periods of eating and fasting, leading to reduced caloric intake without compromising essential nutrients. With various forms of IF, such as periodic day fasting, religious fasting, alternate day fasting, modified fasting, and time-restricted eating see Table 1, researchers have explored its

potential health benefits extensively [1]. Diet and exercise have long been studied as crucial factors influencing human health. IF emerges as a promising strategy due to its flexible nature and potential to be integrated into different lifestyles [2]. This paper explores the concept of Intermittent Fasting, its various forms, and the existing scientific evidence supporting its positive effects on human health.

IF is a dietary approach that involves alternating periods of eating and fasting [3]. Unlike traditional diets that focus solely on restricting caloric intake, IF allows individuals to reduce their calorie consumption while maintaining essential nutrient intake, preventing malnutrition [3]. The different types of IF, such as periodic day fasting, religious fasting, alternate day fasting, modified fasting, and time-restricted eating, offer various approaches that can be tailored to individual preferences and

Table 1. The different types of intermittent fasting

Types of intermittent fasting regimens	Description
Periodic Fasting	This involves alternating fasting and eating days where participants fast one or two days a week and eat unlimited food and fluids on other days [7].
Religious Fasting	This is fasting that occurs at specific times or occasions, such as Islamic fasting and during Ramadan month. Researchers consider it as a form of intermittent fasting, where Muslims can only eat at night [8]. There is also the Daniel fast, which lasts for 21 days. Animal products, refined carbs, food additives, preservatives, sweeteners, flavorings, caffeine, and alcohol are all prohibited on the Biblical-based Daniel Fast [9].
Alternate Day Fasting	Fasting days (no energy-containing meals or beverages ingested) are alternated with eating days (foods and beverages consumed as desired) [10].
Modified Fasting Regimens	On planned fasting days, modified regimens allow for ingesting 20-25% of energy demands. Among these Modified Fasting Regimens is the famous 5:2 diet, which entails extreme energy restriction on two non-consecutive days each week and ad libitum eating on the remaining five days [11].
Time-restricted Eating/Feeding	TRE (in the human model)/TRF (in the animal model) is a type of intermittent fasting that focuses on feeding timing rather than specific food choices or calorie restriction [12].

MATERIAL AND METHODS

Experimental studies and clinical trials published on IF were collated using keywords from PubMed and Google

goals [4].

Numerous studies have investigated the potential health benefits of IF, and their findings have been encouraging [5]. Research has suggested that IF may contribute to a decreased risk of chronic diseases, aid in weight management, and even play a role in anti-aging effects [5]. However, despite the growing body of evidence supporting these claims, the precise biological mechanisms through which IF influences health markers, such as lipid profile and immunological parameters, remain to be fully elucidated [6].

This overview aims to summarize the extensive literature on IF in studies conducted on human subjects and animal models to shed light on its effects and potential mechanisms of action. By understanding the physiological changes induced by IF, we can gain valuable insights into its impact on overall health and longevity.

Scholar. Studies were searched using the terms “intermittent fasting”, “alternate day fasting”, “5:2 diet”, “Ramadan Fasting”, “Daniel Fasting”, “Periodic Fasting”,

“Time Restricted Eating”, or “Time-Restricted Feeding” in combination with “immune system” or “hematological parameters” or “lipid profile”. Manuscripts were assessed if they included results of preclinical studies in animal models or clinical trial studies in healthy and unhealthy subjects. Studies in another language than English were excluded. A total of 43 studies were found and categorized by their effect on lipid profile and immunological parameters.

RESULT AND DISCUSSION

1 Effects of intermittent fasting on immunological parameters.

Understanding immunological parameters is critical for measuring immune system function. These parameters provide insights into the immune response, inflammation levels, and overall immune health. In contrast, most studies investigated the effect of IF on weight and metabolism. A developing collection of proof proposes that this nutritional intervention may also affect immunological parameters. In one study conducted by American researchers, a diet mimicking fasting for 3 days enhanced the immune system and reduced pro-inflammatory cytokines in an experimental autoimmune encephalomyelitis model using mice [13]. This study demonstrated that a fasting-mimicking diet can decrease autoimmunity by promoting lymphocyte apoptosis. Similarly, Bloomer et al. (2011) observed a reduction in markers of oxidative stress during a 21-day Daniel Fast [14]. However, the literature provides contradictory findings regarding the impact of IF on immune cell levels. Siadat et al. (2014) reported that Ramadan fasting had no significant effect on lymphocyte cell levels and did not alter the CD4⁺/CD8⁺

ratios in a group of healthy young and adult participants [15].

On the other hand, Develioglu et al. (2013) observed an increase in immune cells, specifically lymphocytes, during the IF period in healthy men aged 20 to 59 years, accompanied by a reduction in the humoral response [16]. Additionally, Cignarella et al. (2018) found that intermittent fasting-induced shifts in the gut microbial community, characterized by an increase in the abundance of Lactobacillaceae and Bacteroidetes, as well as a reduction in segmented filamentous bacteria (SFB) [17]. These alterations were shown to increase the number of regulatory T cells and improve their responses in a mouse model of Multiple Sclerosis (MS) with immunological dysregulation and central nervous system (CNS) inflammation.

Other intervention studies have explored the effects of IF on the inflammatory system [18, 19]. Fann et al (2014) reported a reduction in interleukin-IL1 β and IL-18 levels in C57BL6/J mice during IF. A study was designed to evaluate the effect of the combination of intermittent fasting and physical activity on the expression of inflammation markers in diabetic rats. The study reported that IF, exercise, and honey administration were all found to improve antioxidant capacity and decrease oxidative stress and inflammation, according to biochemical analysis of liver tissue samples in diabetic rats [19]. Time-restricted eating for 12 weeks reduced NK (natural killer) cells and attenuated the pro-inflammatory status in older people [20]. Lastly, fasting cycles in combination with chemotherapy helped to protect healthy cells from chemotherapy without reducing its effectiveness on tumor cells [21].

Numerous animal studies have demonstrated the potential positive effects of intermittent fasting (IF) on immunological parameters in animal models [20-23], and there is also emerging evidence from human studies [15-20]. Moreover, IF has been linked to reduced levels of inflammatory cytokines and markers [18-20,27], suggesting potential anti-inflammatory properties. Nevertheless, more controlled human trials are essential to establish and comprehend these findings fully. Further research is warranted to unravel the underlying mechanisms behind IF's influence on immunological parameters and inflammation in human subjects, accounting for diverse fasting patterns and populations. Long-term studies are pivotal in assessing the sustained benefits and potential risks associated with IF. Addressing these research gaps will provide a more comprehensive understanding of IF's impact on immune system function and inflammation, ultimately contributing to evidence-based recommendations for its therapeutic potential.

2 Effect of intermittent fasting on hematological parameters.

Hematological parameters play a crucial role in assessing overall health and diagnosing various diseases. Given the potential physiological adaptations and health benefits associated with fasting, the effect of Intermittent Fasting (IF) on hematological parameters has been a subject of great interest. However, studies investigating this effect have yielded conflicting results. Some research has reported a decrease in hematological parameters, including white blood cell

count, platelet count, reticulocyte count, red blood cells, and hemoglobin levels, in response to intermittent fasting [20-23]. Conversely, other studies have found no significant changes in these parameters, particularly in unhealthy participants such as those with metabolic syndrome and chronic myeloid leukemia [24-26]. These discrepancies underscore the potential influence of individual health conditions and underlying factors on hematological parameters during intermittent fasting.

Several factors need to be considered to understand the discrepancies observed in these studies. One significant aspect is the timing of blood sampling, as dehydration is more likely to occur later in the day compared to the early morning. The varying results from previous studies could, in part, be attributed to the time of day when blood samples were collected (e.g., afternoon versus morning). Intermittent fasting encompasses different methods, each with a unique approach and timing. Importantly, most intermittent fasting regimens do not restrict water intake during fasting periods, ensuring individuals maintain adequate hydration [7, 10-11]. However, a notable exception is observed during the holy month of Ramadan, where Muslims fast from sunrise to sunset, abstaining from food and water [8]. In addition to sampling time, other factors such as climate, temperature, and physical activity levels may also influence study outcomes. The variations in fasting protocols, including differences in duration and timing, as well as participant characteristics and sample sizes, can further contribute to the heterogeneity of results.

Future studies should carefully consider these factors and strive for standardized

methodologies to understand the impact of intermittent fasting on hematological parameters. Only with a more systematic and standardized approach can we

elucidate the true effects of intermittent fasting on hematological markers and their potential implications for human health.

Table 2. Effects of different types of IF on immunological parameters and hematological parameters.

Author (Year)	Participants	Type of IF and duration	Changes
Bloomer et al. (2011)[9]	43 Unhealthy participants 13 males; 30 females Age: 20-62 years No control group	21-day Daniel Fast Duration: 21 days	- improvement in biomarkers of antioxidant status and oxidative stress
Choi <i>et al.</i> (2016)[13]	Murine experimental autoimmune encephalomyelitis (EAE) model. Normal diet groups vs. diet mimicking fasting group	diet mimicking fasting duration: 3 days	-↓ pro-inflammatory cytokines. -↓ autoimmunity
Siadat <i>et al.</i> (2014)[15]	38 healthy participants: 9 females and 29 males Age: 17 to 51 years No control groups	Ramadan Fasting 2 years (1999-2000)	-↔ lymphocyte cell levels. -↔ the percentages of CD4+/CD8+ ratios
Develioglu et al. (2013)[16]	35 healthy male participants Age: 20–59 years No control group	Ramadan Fasting Duration: 30 days	-↓Serum IgG/ salivary IgA concentrations -↔ Serum IgM levels -↑lymphocyte numbers
Fann, et al (2014) [18]	Murine model, Male C57BL6/J mice Age: ten weeks Control Group vs. Intermittent Fasting Group	Intermittent fasting (16 h of fasting daily) Duration: 4 months	↓the activation of NF-κB and MAPK signaling pathways, the expression of NLRP1 and NLRP3 inflammasome proteins. ↓ IL-1β and IL-18 in the ischemic brain tissue.
Agbonifo-Chijiokwu, et al (2023) [19].	Murine model, Diabetic rats. IF group vs control group	IF and exercise Duration: 4weeks	↓ liver transcription factor (resistin, SREBP-1c) ↓inflammatory cytokines/enzyme (TNF-α, IL-6, IL-1β, MPO)

Gasmi <i>et al</i> 2018 [20]	40 healthy male participants Age of young participants: 24-26 Age of adult participants: 51-57 Experimental group vs control group	Time-restricted eating Duration: 12 weeks	↓ NKCD16+, NKCD56+ ↔ CD3, CD4+, and CD8+ levels ↓ hematocrit, total white blood cells, lymphocytes, and neutrophils
Lee <i>et al.</i> (2012)[21]	Murine models of neuroblastoma	Fasting cycles in combination with chemotherapy	-↑ phosphorylation of the stress-sensitizing Akt. -↑ oxidative stress, caspase-3 cleavage, DNA damage, and apoptosis - retarded growth of tumors -sensitized a range of cancer cell types to chemotherapy
Nasiri, <i>et al</i> (2016) [22]	59 healthy participants: 34 males/25males Age range: 15-24 Female faster group vs. male faster group	Ramadan fasting Duration: 30 days	↑Platelet ↓White Blood Cell ↑ Hemoglobin and hematocrit
Ahmed <i>et al.</i> (2023) [23]	52 participants with sickle cell disease: 27males and 25 females Age: 31.1±9.2 No control groups	Ramadan Fasting Duration: 30 days	↓ platelet count ↔ White blood cell, hemoglobin
Yassin, <i>et al</i> (2021)[24]	49 participants with chronic myeloid leukemia: 36 males and 13 females. Age: 46.8 + 14.51 years No control groups	Ramadan Fasting Duration: 3 years	↔ white blood cell, haemoglobin, platelet count, haematocrit
Roy, A. S., & Bandyopadhyay, A. (2017) [25]	77 healthy participants, untrained males Age experimental group: 22.73±1.56 years. Age Control group: 22.92±1.36 years Experimental group vs control	Ramadan fasting Duration: 30 days	↔haemoglobin, red blood cells, white blood cells

	group		
Wilkinson <i>et al</i> (2020) [26]	19 participants with metabolic syndrome 13 males and 6 females Age: 59 ± 11.14 No control groups	Time-restricted eating (daily eating window from ≥ 14 h) Duration: 12 weeks	↔ White blood cell, haemoglobin, haematocrit, platelet count
Moro <i>et al</i> (2020)[27]	16 participants, elite male cyclists Age: 19.3 ± 0.1 years TRE group vs control group	Time-restricted eating (8-h feeding window) Duration: 28 days	↓ IGF-1 in TRE group ↓ neutrophils-to-lymphocytes ratio in TRE group.
Allen <i>et al</i> (2020) [28]	25 healthy participants: 12 males and 13 females Age: 21-58 years. IF group vs control group	Combination of IF and physical activity (8-h eating window and 16-h fasting window) Duration: 3 months	↓ Glutathione and Interleukin-1β

Abbreviations: IF: intermittent fasting; SOD: superoxide dismutase; Akt: Protein kinase B; DNA: Deoxyribonucleic Acid; CD4+: CD4 T helper cells; CD8+: CD8 T Cell; IgG: Immunoglobulin G ; IgA: Immunoglobulin A; IgM: Immunoglobulin M ; TNFα: Tumor Necrosis Factor-alpha NK: Natural killer cells.

↑: increase; ↓: decrease; ↔: no change

3 Effects of intermittent fasting on lipid profile.

A lipid profile consists of a set of blood tests that assess the levels of fats (lipids) in the bloodstream, including total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG). Numerous studies have investigated the impact of Intermittent Fasting (IF) on lipid profiles, yielding mixed results. For instance, alternate-day

fasting has been found to induce alterations in lipid profiles in both healthy and obese participants [29-32]. Additionally, other IF approaches, such as fasting calorie restriction and Daniel Fast, have improved lipid profiles among young and adult participants [33, 34]. However, certain studies have reported no significant lipid profile changes for healthy and unhealthy individuals [35, 36]. These divergent findings underscore the complexity of the relationship between IF and lipid profiles,

warranting further research to elucidate the contributing factors and mechanisms behind these differences.

Among the limited studies focusing on elderly individuals, one investigation involving participants with cardiovascular risk factors, who followed IF for four weeks, found no significant changes in total cholesterol (TC) and low-density lipoprotein (LDL) levels. However, they did observe a decrease in high-density lipoprotein (HDL) levels and an increase in triglyceride (TG) levels [37]. In contrast, a 12-week study exploring fasting calorie restriction in healthy older adult men (aged 50-70 years) reported improvements in metabolic parameters [33].

Bhutani et al. (2013) examined the effects of alternate-day fasting (ADF) with exercise on the lipid profile of obese participants. The results demonstrated that the ADF with exercise group experienced favorable alterations in weight loss, reduced LDL cholesterol levels, and increased HDL cholesterol levels. These findings suggest that combining ADF with exercise can effectively manage obesity and its associated metabolic complications. In another study by Cai et al. (2019), the potential of two interventions, ADF and time-restricted eating (TRE), were

compared in patients with non-alcoholic fatty liver disease (NAFLD). After 12 weeks, the TRE group exhibited a decrease in total cholesterol (TC), while the ADF group showed a reduction in triglyceride (TG) levels. In contrast, no significant changes were observed in the lipid profile of the control group. These findings highlight the potential benefits of both ADF and TRE interventions in improving lipid profiles, with ADF specifically targeting TG reduction and TRE associated with TC decrease, thus holding promise for managing NAFLD and its associated metabolic complications.

Several factors may contribute to the discrepancies observed in these studies. Differences in nutritional behavior and lifestyles between populations (e.g., young versus elderly), variations in blood sampling times (morning versus evening), diverse diets across different countries (e.g., USA, India, Iran), and changes in physical activity levels during intermittent fasting are all potentially confounding variables that should be carefully considered when interpreting the results of IF studies, especially in elderly populations. Future research should strive for standardized methodologies and larger sample sizes to improve the understanding of IF's impact on lipid profiles in different age groups and populations

Table 3. Effects of intermittent fasting on lipid profile.

Author (Year)	Participants	Type of IF and duration	Changes
Wilkinson <i>et al</i> (2020) [26]	19 participants with metabolic syndrome: 13 males and 6 females	Time-restricted eating (10 hours eating window) Duration: 12	↓LDL, TC ↔TG, HDL

	Age: 59 ± 11.14 No control groups	weeks	
Hoddy <i>et al.</i> (2014)[29]	59 obese participants: 50 females and 9 males. Age: 25-65 years Groups: - ADF-L: lunch - ADF-D: dinner - ADF-SM: small meals	Alternate Fasting Duration: 8 weeks	Day ↔ Plasma lipids ↑ LDL in all groups
Stekovic <i>et al.</i> (2019)[30]	57 participants, healthy males or females ADF group vs control group	Alternate fasting Duration: 4 weeks	day -↓ levels of cholesterol, LDL
Baccouche <i>et al.</i> (2014)[37]	87 elderly participants with cardiovascular risk factors: 45 females and 42 males. Age: 71.6 ± 5.5 years No control groups	Ramadan Fasting Duration: 3 years	-↔ TC and LDL -↓ HDL -↑ TG
Bhutani <i>et al.</i> (2013)[38].	64 obese participants Age: 25-65 years 4 groups: -Combination group -ADF group -Exercise group -Control group	Alternate fasting endurance exercise combine Duration: 12 weeks	day and -↓ LDL, ↑ HDL in the combination group.
Cai <i>et al.</i> (2019)[39]	264 participants, adults with non-alcoholic fatty liver disease : 87 males and 177 females Age: 18-65 years 3 groups: ADF group TRF group	Alternate fasting Time-restricted feeding Duration: 12 weeks	day -↓ TC in ADF, TRF, control groups -↓ triglycerides in ADF, TRF groups -↔ HDL, LDL in ADF, TRF, control groups

	Control group		
Varady <i>et al</i> (2013)[31]	30 participants, healthy and overweight : 8 males and 22 females. Age:35 to 65 years Groups: ADF group vs control group	Alternate day fasting Duration: 12 weeks	↓TG, TC in ADF group ↑ LDL in ADF group ↔ HDL in ADF group
Trepanowski, <i>et al</i> (2017)[32]	100 participants: obese 86 females and 14 males Age: 18 to 64 years Groups: -alternate-day fasting group -daily calorie restriction group -control group	-Alternate-day fasting -daily calorie restriction Duration: 1 year	↔ TG in all the groups ↑ HDL in ADF group, ↑ LDL in ADF group
Teng <i>et al.</i> (2013)[33]	56 participants, healthy males Age: 50–70 years Fasting calorie restriction group vs control group	Fasting calorie restriction Duration: 12 weeks	- improvements in metabolic parameters
Alleman <i>et al.</i> (2013)[34]	29 healthy participants Age: 18 to 66 years Group modified Daniel Fast diet vs group traditional Daniel Fast diet.	the modified Daniel Fast diet vs the traditional Daniel Fast diet Duration: 21 days	- Improvements in lipid parameters in both groups.
Johari <i>et al.</i> (2019) [35]	43 participants who had non-alcoholic fatty liver disease : 10 females and 33 males. Age: 18 to 70 years Control group vs modified alternate caloric restriction group	Modified alternate-day calorie restriction Duration: 8 weeks	- ↔ lipid parameters (TC, LDL, HDL and TG)
Parvaresh <i>et al.</i> (2019)[36]	-70 participants with metabolic syndrome.	-Calorie restriction modified	-↔ triglyceride, TC, LDL, HDL in both groups.

	Age: 25-60 years Group calorie restriction vs group modified alternate day fasting diet	alternate-day fasting diet Duration: 8 weeks.	
Varady <i>et al.</i> (2015)[40]	29 participants, healthy females Age: 25–65 years Group ADF-High Fat diet vs group ADF-Low Fat	- Alternate-day fasting diet high fat (45% fat). - alternate-day fasting diet low fat (25% fat) Duration: 8 weeks	- ↓ TC, LDL and TG in both groups. ↔ HDL in both groups.
Mohammadzade <i>et al.</i> (2017) [41]	30 participants, healthy males Age: 20-35 years no control group	Ramadan fasting Duration: 30 days	↓ TG, ↑HDL ↔ TC, LDL
Sutton <i>et al.</i> (2018) [42]	8 participants, overweight males with prediabetes. Age: 56 ± 9 years Control group vs eTRF group	Early Time-Restricted Feeding (6 h of eating window) Duration: 5 weeks	↔ LDL, HDL in eTRF group ↑ TG, TC in eTRF group
Jamshed <i>et al.</i> (2019) [43]	11 participants, overweight male or female Age: 20-45 years Control group vs eTRF group.	Early Time-Restricted Feeding Duration: 4 days	↑ TC, Ketones

Abbreviations: LDL: Low-density lipoprotein; HDL: high-density lipoprotein; TC: total cholesterol, TG: Triglyceride , ADF: Alternate day fasting; eTRF: early time restricted feeding; TRE: Time restricted eating.

↑: increase; ↓: decrease; ↔: no change

Conclusion:

This is a summary of the most prominent scientific studies published on the impact of IF, in all its forms, on human health and the physiological mechanisms by which

this intervention might change health outcomes. Despite the contradictory results found in the literature, most of the data showed that IF positively impacts the immune system and hematological

parameters; moreover, it improves lipid profiles. This intervention appears to be an effective strategy for a healthy lifestyle.

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Author contribution

All Authors contributed equally to this review

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