



International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
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ARTICLE TITLE	INTERMITTENT FASTING AND LIPID METABOLISM: MECHANISMS, CLINICAL EVIDENCE, AND THERAPEUTIC IMPLICATIONS
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DOI	https://doi.org/10.31435/ijitss.3(51).2026.5918
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RECEIVED	22 June 2026
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ACCEPTED	05 September 2026
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PUBLISHED	15 September 2026
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INTERMITTENT FASTING AND LIPID METABOLISM: MECHANISMS, CLINICAL EVIDENCE, AND THERAPEUTIC IMPLICATIONS

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ABSTRACT

Intermittent fasting (IF) is a way of eating that can help the body burn fat more efficiently and lower the risk of heart disease. It leads to helpful changes in blood composition and in metabolism. Still, there are questions about how safe, practical, and effective IF is over the long term. Because of these unknowns, it is important to have clear guidelines for IF and to continue research in this area.

Background & Aim: Common IF methods include alternate-day fasting (ADF), the 5:2 diet, time-restricted eating (TRE), and Ramadan fasting (RF). This review points out that we still do not fully understand how IF works in the body and highlights areas that need more study. The main aim is to show how dietary approaches can help manage metabolic diseases and support health, either on their own or alongside other treatments.

Summary: IF consistently improves lipid profiles, insulin sensitivity, body weight, and indirectly, due to the above cardiometabolic risk factors in people with obesity, metabolic syndrome (MeS), and type 2 diabetes (T2D). However, its effects on high-density lipoprotein cholesterol (HDL-C) are mixed. When compared directly to continuous energy restriction (CER) with concomitant energy deficits, both approaches are similarly effective for improving lipid and weight outcomes. IF may provide additional benefits for short-term fat loss and adherence. Additionally, it may be a profitable alternative to or support of pharmacological therapy.

KEYWORDS

Intermittent Fasting, Lipid Metabolism, Dyslipidemias, Metabolic Syndrome, Cardiometabolic Risk

CITATION

Gołacka, K., Szostak, P., Rynkowska, M., Maj, S., Sikorska, W., Sikorski, A., Kuźmiuk, D., Sidor, D., Gołacki, R., & Danio, J. (2026). Intermittent fasting and lipid metabolism: Mechanisms, clinical evidence, and therapeutic implications. *International Journal of Innovative Technologies in Social Science*, 3(51). [https://doi.org/10.31435/ijitss.3\(51\).2026.5918](https://doi.org/10.31435/ijitss.3(51).2026.5918)

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Introduction

Intermittent fasting (IF), which involves cycles of fasting and eating, is gaining attention for its ability to improve lipid metabolism, an important appertain of high cholesterol and heart disease prevention [Meng et al. (2020), Naous et al. (2023)].

The authors examined common IF protocols incorporating TRE, ADF, and the 5:2 diet - and their effects on lipid profiles in people with obesity, MetS, T2DM, and non-alcoholic fatty liver disease (NAFLD). ADF is based on fasting one day and eating normally the next day (alternately). The 5:2 diet relies on eating normally for five days a week and restricted daily calorie intake on two non-consecutive days. TRE is limiting the daily eating window. RF equals the dawn-to-sunset fasting and nocturnal eating time. Overall, most studies report improvements in lipid parameters, particularly reductions in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), while changes in HDL-C are less consistent. The above improvements could translate into a purposeful reduction in cardiovascular events, as an alternative to a few years of lipid-lowering therapy, although this relationship still needs to be confirmed in long-term outcome studies.

Control of TC, LDL-C, HDL-C, and TG is affected by diet, metabolic changes, and hormones [Meng et al. (2020), Yuan et al. (2022)]. This review brings together evidence from recent clinical trials, meta-analyses, and observational studies to survey IF and its way of affecting lipid profiles, along with the mechanisms behind these effects [Vo et al.(2024)], and how IF compares with CER across different groups and health conditions [Patikorn et al. (2021), Zhang et al. (2025)].

Research materials and methods

Authors performed a narrative review of available literature, published from January 2019 to April 2026, on the effects of intermittent fasting and its influence on lipid metabolism and cardiometabolic health. Several databases were searched comprehensively: PubMed, Scopus, Web of Science, Cochrane Library and additionally Google Scholar - to identify new records, hand-search reference lists of relevant studies and track citations.

Searching was based on using keywords and Medical Subject Headings (MeSH): (“intermittent fasting” OR “time-restricted eating” OR “time restricted feeding” OR “alternate-day fasting” OR “5:2 diet” OR “Ramadan fasting” OR “periodic fasting”) AND (“lipid metabolism” OR “lipid profile” OR “cholesterol” OR “triglycerides” OR “LDL” OR “HDL” OR “dyslipidemia” OR “cardiometabolic” OR “metabolic syndrome”).

Six reviewers independently selected titles and abstracts. They were following the assessment of only open-access articles. Final synthesis included 29 studies in total. No quantitative analysis was done due to the variety in protocols and populations.

Results

1. Effects on Lipid Profiles

The studies reviewed show that the previously mentioned IF methods, such as TRE, ADF, and the 5:2 diet protocol, can lead to modest yet clinically meaningful improvements in lipid profiles in people with obesity, MetS, and T2D [Ahmed et al. (2021)]. For example, Meng et al. (2020) come to, in their systematic review, that IF reduced TC, LDL-C, and TG levels but without a significant change in HDL-C levels. Likewise, Yuan et al. (2022) observed reductions in TC, LDL-C, and TG in patients with impaired glucose and lipid metabolism. Ahmed et al. (2021) also reported improvements in TC, LDL-C, and TG, with some increases in HDL-C in certain IF settings, in a quasi-randomized clinical trial. In the background of MetS, Almabruk et al. (2024) confirmed that, thanks to the IF, LDL-C and other cardiovascular risk factors decrease with only a limited change in HDL. Naous et al. (2023) showed that both ADF and TRE led to an improvement of serum lipids in overweight and obese adults. Batitucci et al. (2022) enlightened the fact that IF combined with high-intensity interval training (HIIT) greatly affects TG and LDL-C in obese women.

Recent open-access evidence published in 2025 further supports these findings. Recent open-access articles published in 2025 further support these findings. Lu at al. (2025) revealed in a GRADE-assessed meta-analysis of 8 RCTs featuring patients with MeS, that IF significantly reduces LDL-C (WMD = -6,42 mg/dl), simultaneously improving insulin resistance and Interleukin-6 (IL-6) levels. Song et al. (2025) performed a meta-analysis, showing that IF visibly changes LDL-C, fasting blood glucose levels, insulin levels, hence HOMA-IR index, hemoglobin A1c (HbA1c) (measurement of average glucose over past 3 month), and IL-6. It shows reinforcement of earlier observations about LDL-C and TG reductions with different IF protocols, while HDL-C and TC remain inconsistent.

2. Mechanisms of action

The organism is transforming from using glucose to using ketones as a source of energy, during IF, through enhancement of fatty acids oxidation and lowering fat accumulation and production [Feliipe et al. (2023)]. Kazmirczak et al. (2023) published that AMPK is activated by IF (increased AMP/ATP ratio during fasting activates AMPK), and it modifies both heart's lipid metabolism and TG accumulation. Vo et al. (2024) discovered that IF changes adipose tissue, lowers inappropriate lipid collection, boosts LPL activity, and helps eliminate TG from the blood. Zhang et al. (2020) reported on hepatic PLIN5 signaling and autophagy promotion via sirtuin 1 (SIRT1) (NAD⁺ levels rise during fasting, activating SIRT1, that deacetylates and activates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) and peroxisome proliferator-activated receptor alpha (PPAR α), further amplifying fatty acid oxidation while inhibiting lipogenesis), preventing lipid accumulation. Teker et al. (2024) suggested that a combination of IF and probiotics is successful with reduction of liver fat in elderly rats, which indicates possible translational potential in humans. Frank et al. (2021) endorsed the fact that IF modulated intestinal microbiome, which regulates bile acids metabolism and lipid homeostasis. Hasan et al. (2022) wrote about RF as a reducing PCSK9 level factor, which improves LDL-C clearance in metabolically healthy obese individuals.

3. Impact on specific groups

IF improved lipid metabolism in patients with T2D, even without accompanying body mass reduction. Mohamed et al. (2024) claimed that IF is reducing TG and LDL-C levels, while improving lipid metabolism in obese type 2 diabetics. Zaki et al. (2022) suggested that IF combined with ketogenic diet lowered LDL-C and TG levels in obese patients with T2D, with good compliance in most of them. Some studies about muscular lipid metabolism did not show relevant changes during the IF, even with PLIN5 level upgrowth, implying temporary fat storage adaptation [Zhang et al. (2020)]. Following emerging evidence shows decrease of TG and LDL-C in obese young adults and adolescents using IF. Jarrar et al. (2023) described lipid metabolism enhancement in type 2 diabetics during Ramadan fasting period, even when compliance varied.

4. Comparison with CER

IF and CER both offer valuable benefits for patients in improving lipid profiles [Meng et al. (2020)]. Siles-Guerrero et al. (2024) found that both IF and CER can achieve similar influence on weight loss and lipid profile improvements, though adherence to TRE may suit some patients better due to its flexible nature. Patikorn et al. (2021) claimed, employing 11 meta-analyses of RCTs, that IF, and especially modified alternate-day fasting (MADF) and 5:2 protocol, is related to body weight reduction (-1.67 kg) among other beneficial cardiometabolic outcomes with moderate to high-quality evidence [Mohamed et al. (2024)].

Discussion

Expanded evidence collection implicates that IF, specifically TRE and ADF, invariably lowers TC, LDL-C, and TG levels between different populations. Mentioned benefits presuppose embracing fatty acid oxidation, reducing VLDL production, and remodeling of adipose tissue. Changes in HDL-C are not as predictable, supposedly because of baseline lipid levels diversity, duration of studies, short intervention period, and health status of participants. Studies based on RF have limited outcomes due to its transient feature and observational advantage, however, providing culturally significant data. Available mechanistic studies show IF's effects on adipose tissue remodeling and alteration of intestinal microbiome, whereby most evidence originates from rodent models, notwithstanding, there is a conspicuous need to expand research and restrain these limitations [Jarrar et al. (2023)].

Heterogeneity in IF protocols, small groups of participants, and the lack of long-term safety data are key limitations in this matter. Results of the studies depend on initial lipid levels, gender, age, and duration of IF practice, as indicate subgroup analyses, revealing the need for personalized IF plans. Compliance of IF is high, in general, and may be more beneficial than CER, particularly with TRE, thanks to its flexibility. In diverse population groups ADF consequently reduces TC, TG and LDL-C levels [Cui et al. (2020)], likely because of elevated ketogenesis and fatty acid oxidation, fat tissue remodelling, and lowered VLDL production [Felipe et al. (2023)]. Differences in initial lipid levels, duration of IF intervention, miscellaneous health status, and protocol variance probably influence on alterations of HDL-C, which remain incoherent [Yuan et al. (2022)].

Results from mechanistic studies, mostly with animal models, show that IF upregulates PPAR-gamma, activates AMPK, maintains ketogenesis in liver, and regulates intestinal microbiome, yet still more human research is required [Felipe et al. (2023), Mohr et al. (2021)]. AMPK-phosphorylation is enhancing beta-oxidation, limiting accumulation of TG, and stabilizing cardiomyocytic microtubules. That process promotes catabolic pathways, inhibits lipogenesis, and supports biogenesis of cellular mitochondria [Vo et al. (2024)]. IF commence adipose tissue remodeling, via boosting lipoprotein lipase activity, enhancing lipolysis, and simultaneously narrowing the storage of lipids by browning the white adipose tissue (WAT). Inherently, it reduces ectopic fat deposition and clearance of circulating TG, which lead to intestinal barrier integrity improvement, endotoxemia reduction, bile acid metabolism modulation, thereby enhancement of lipid homeostasis and dampening of the body's inflammatory response [Mohr et al. (2021)]. IF also modulates the brain-gut-microbiome axis in obesity, affecting appetite regulation, hypothalamic inflammation, and peripheral insulin sensitivity via microbial metabolites and vagal signaling [Zaki et al. (2022)]. Combined IF with probiotics further reduces liver damage, fibrosis, and TG accumulation in aged models, suggesting synergistic effects on microbiome-mediated hepatic protection [Mohamed et al. (2024)]. IF via vagal signaling and microbial metabolites, modulates the brain-intestine-microbiome axis in obese individuals. It affects inflammation of the hypothalamus, change of appetite, sensitiveness of insulin in peripheral tissues [Zaki et al. (2022)]. The probiotics-IF combination additionally causes lower liver damage, fibrosis and TG collecting

in elderly models, implying microbiome-dependent probable synergistic protecting role in hepatic tissue [Mohamed et al. (2024)]. As an example of TRE, IF harmonizes eating regimen with circadian rhythms, influencing on embraced metabolic process flexibility, oxidation of fatty acids during physical activity and improved vascular function, resulting in enhanced endothelial integrity and energy metabolism [Hofstätter et al. (2025)].

Healy et al. (2021) highlighted how important it is to properly associate sleep, nutrition, and physical activity throughout the day. Systematic eating hours (e.g. via TRE) intensifies metabolic efficiency, by synergizing processes of the body's metabolism. Dietary fasting regimens such as IF's various protocols lead to beneficial gut microbiome transformations like increasing the number of bacteria that produce short-chain fatty acids (SCFA) (e.g. Akkermansia, Bifidobacterium), raised levels of propionate and butyrate, better intestinal barrier capacity, and anti-inflammatory outcomes. These alterations may be associated with improved glucose level control, lipid homeostasis, and protection from metabolic diseases, but human data stay highly associative [Mohr et al. (2021)].

Guo et al. (2022) showed in animal models that the alternate-day ketogenic diet maintains liver ketogenesis (by 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2) activity and beta-hydroxybutyrate production), prevents exaggerated lipid collection in the heart tissue, reduction of oxidative stress, slowing down heart failure progression, what suggest its plausible cardioprotective effects. Wang et al. (2024) revealed in an RCT that participants made greater weight loss than with standard dietary advice. The study population was 220 people over 6 months, with counted and ready calorie-deficient meals - they lost fat and maintained lean mass. Platform users lost more than 10% of their body mass more often than the control group.

Graham et al. (2025) showed from a different angle in a narrative review, that IF influences on vascular function and immunity system. It helps the endothelium, improving its flexibility and it evokes immunomodulation through better regulatory T lymphocyte activity, less concentration of proinflammatory cytokines in bloodstream, possibly mediated by metabolic switching and reduced oxidative stress. Zhang et al. (2020) revealed that fasting promotes autophagy by hepatic PLIN5 signaling via SIRT1 and prevents lipid droplets accumulation, conjointly reducing ectopic fat storage in the liver. Hofstätter et al. (2025) by RCT claimed that time-restricted feeding accompanied by 8-week exercise program adjusts using fat as source of energy during physical activity and regulates metabolic flexibility when comes to compare it with standard meal timing. Zhang et al. (2025) confirmed in a systematic review and metaanalysis that IF improves metabolic indicators connected to obesity, including TG level, body mass index (BMI), and other glucolipidic parameters - in comparison with CR.

Moon et al. (2020) reported that TRE significantly reduced TG - about 8-10% - in people suffering from metabolic conditions, with other benefits, like increased insulin sensitivity and healthier body composition. Siles-Guerrero et al. (2024) wrote that isocaloric IF protocols, in comparison to daily CR in some of the mentioned groups, achieve similar or hardly improved weight and lipid outcomes, but with better compliance thanks to their flexibility.

Research structure, population range, and measurement of final results are three main themes in the key limitations across available studies. Research structure includes protocol variety, predominance of short-term intervention profiles (<6-12 months), and small group sizes in mechanistic and early-phase trials. Elderly people and people with more comorbidities were not often participating in those trials, what is lowering population range. Outcome measures should rely on objective clinical endpoints - for example - cardiovascular events. Diverse effects in subgroups (initiatory lipid level, sex, age, diet duration) underline the necessity of personally fitted IF plans, idyllically integrated with some behavioral support or training plan to maximize advantages and their permanence [Patikorn et al. (2021), Dwaib et al. (2021)].

Conclusions

IF - more specifically - TRE, ADF, the 5:2 protocol, and RF regimen are potential and promising representation of non-pharmacological approach to gain cardiometabolic benefits and overall health improvement, as it is documented in numerous meta-analyses, RCTs, narrative reviews, and systematic reviews. The strongest and most replicable include:

- significant changes in TG level and insulin sensitivity improvements [Homeostatic Model Assessment for Insulin Resistance (HOMA-IR index), fasting insulin, HbA1c] among individuals with MeS, obesity, T2D, impaired glucose/lipid metabolism [Cui et al. (2020), Zaki et al. (2022), Lu et al. (2025), Song et al. (2025)]

- reduced TC and LDL-C levels (averagely by 12mg/dl and 8,5 mg/dL), with inconsistent or neutral changes in HDL-C [Yuan et al. (2022)].

- effective body weight loss, reduced BMI and fat mass (especially visceral fat), as well as waist circumference, often with better preservation of lean mass compared with CER, particularly when combined with physical activity [Patikorn et al. (2021)].

- improvements in MeS components, blood pressure, endothelial function, and inflammatory markers [Graham et al. (2025), Naous et al. (2023), Lu et al. (2025), Song et al. (2025)].

- Lipid and glycemic improvements during RF regimen are frequently temporary and tend to invert right after the fasting period ends, although it is still safe and profitable [Jarrar et al. (2023)]. That strategy focuses on nocturnal eating, so it could affect metabolic outcomes differently. In contrast, CER shows comparable efficacy in weight loss, lipid profile improvement, and reducing cardiovascular risk factors, similar energy deficit, often demonstrating advantages in short-term fat mass loss, long-term adherence, and flexibility (especially TRE) [Siles-Guerrero et al. (2024)].

The biological mechanisms causing these effects are multifaceted and include:

- Activation of AMPK and changes in cardiac and adipose tissue lipid metabolism,
- Enhanced hepatic β -oxidation and ketogenesis - protection against NAFLD and cardiac lipid overload [Guo et al. (2022)].

- Adipose tissue remodeling, increased LPL activity, and transient adaptive inflammatory responses that resolve over time [Vo et al. (2024)]

- The brain-intestine-microbiome axis and adjustment of gut microbiome through refining barrier function, increasing SCFA production, enhancing bile acid metabolism, and [Mohr et al. (2021)]

- Intensified fat oxidation, metabolic flexibility, and improved vascular function thanks to synchronization with circadian rhythms [Healy et al. (2021)].

Despite these promising findings, several important limitations persist. These include substantial variety of IF regimens, a predominance of short-term studies (less than 6 to 12 months), small group sizes in many mechanistic and early-phase trials, low-to-moderate quality of evidence for several lipid and glycemic measurements, a lack of long-term (at least longer than 12 months) randomized trials evaluating strong clinical endpoints (e.g. cardiovascular events and mortality), limited representation of older adults, ones with multimorbidity, and diversified ethnic groups. Results are associated with initial lipids, sex, age, duration of intervention, and lifestyle factors, highlighting the necessity for personalized IF protocols - especially ones integrating lifestyle and cultural factors may optimize clinical benefits.

Nevertheless, IF emerges as safe and effective dietary guidelines that can be use as a valuable alternative for or support of pharmacological therapy. The leverage of prospective cardiovascular consequences remains to be determined (addressing these limitations). It may establish the next frontier of evidence and sustain engagement within the medical community. Future high-quality, long-term clinical trials are needed to confirm the sustained cardiovascular benefits and objective strategies across different populations.

Proposition of Clinician Checklist:

- Has the patient been assessed for any contraindications to intermittent fasting?
- Does the patient currently take lipid-lowering medications, and how might IF complement or interact with them?
- Is the patient able to fit their fasting schedule into their lifestyle and cultural norms?
- Can a patient benefit from IF before or alongside pharmacological treatment?

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All authors have read and agreed to the published version of the manuscript.

Disclosure: The authors declare that there are no disclosures related to this article.

Supplementary Materials: No supplementary materials are available for this article.

Funding: This research received no external funding.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable.

Acknowledgements: No funding was received for this work.

Conflicts of Interest: The authors declare that there are no conflicts of interest

Use of Generative AI: During the preparation of this work, the authors used Grok and Grammarly for the purpose of language and readability improvement, text formatting, verification of bibliographic styles, and basic data analysis. After using these services, the authors reviewed and edited the content as needed and take full responsibility for the substantive content of the publication.

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