Journal of Carcinogenesis
Covering Genesis to Therapeutics
Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 10s, https://carcinogenesis.com/

Impact of Intermittent Fasting on Gut Barrier Function and Inflammation

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ABSTRACT

Background: Intermittent fasting (IF) has gained prominence as a metabolic and lifestyle intervention with potential benefits extending beyond weight control. Objective: This study aimed to evaluate the impact of intermittent fasting on gut barrier integrity and inflammatory markers among healthy adults. Methods: A cross-sectional analytical study was conducted at Services Hospital /Services Institute of Medical Sciences Lahore from June 2023 to June 2024. A total of 265 adult participants were enrolled, including 138 individuals practicing intermittent fasting and 127 individuals with normal eating patterns. Non-probability consecutive sampling was employed. Blood samples were analyzed for serum zonulin and lipopolysaccharide (LPS) to assess gut permeability, and for high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) to evaluate systemic inflammation. Results: The mean zonulin and LPS levels were significantly lower in the IF group (32.4 ± 7.8 ng/mL and 0.38 ± 0.12 EU/mL) compared to controls (40.2 ± 9.5 ng/mL and 0.51 ± 0.15 EU/mL; $p < 0.001$). Inflammatory markers were also reduced in fasting participants: hs-CRP (1.9 ± 0.7 mg/L vs. 2.8 ± 1.0 mg/L), IL-6 (4.3 ± 1.5 pg/mL vs. 6.2 ± 1.9 pg/mL), and TNF-α (8.6 ± 2.4 pg/mL vs. 10.9 ± 2.8 pg/mL) — all statistically significant ($p < 0.001$). Conclusion: It is concluded that intermittent fasting enhances gut barrier function and reduces systemic inflammation by lowering intestinal permeability and inflammatory cytokine levels. These findings suggest that intermittent fasting may serve as an effective, non-pharmacological strategy to improve gut–immune health and prevent inflammation-related disorders.

Keywords: *Intermittent fasting, gut barrier function, intestinal permeability, zonulin, inflammation, cytokines*

How to Cite: Aakash Aakash, Adnan Abdalla., Hina Ismail, Muhammad Khan malik , Muhammad Usman Ghani , Maaz Ahmed, Ahmed Samir Abd el Hamid, Lakhveer Rathi, (2025) Impact of Intermittent Fasting on Gut Barrier Function and Inflammation, *Journal of Carcinogenesis*, *Vol.24, No.10s*, 28-33

1. INTRODUCTION

Intermittent fasting (IF) has gained considerable attention in recent years as both a dietary pattern and a metabolic intervention with potential health benefits beyond weight loss. Unlike conventional calorie restriction, IF involves alternating periods of fasting and feeding, which modulates energy metabolism, gut microbiota composition, and immune

regulation [1]. Emerging evidence suggests that the gut plays a central role in mediating the systemic effects of IF, particularly through its influence on gut barrier integrity and inflammatory processes [2]. The gut barrier, composed of intestinal epithelial cells, tight junction proteins, mucus layers, and resident immune cells, serves as a critical interface between the host and external environment [3]. Disruption of this barrier, known as increased intestinal permeability or "leaky gut," permits translocation of microbial products like lipopolysaccharides (LPS) into circulation, triggering low-grade systemic inflammation associated with metabolic disorders, obesity, and insulin resistance [4]. Intermittent fasting may improve gut barrier function through several mechanisms, including modulation of gut microbial diversity, reduction of oxidative stress, and enhancement of autophagy in intestinal epithelial cells. These processes collectively promote mucosal healing and strengthen tight junctions, potentially restoring intestinal homeostasis [5]. In parallel, IF is reported to attenuate inflammatory signaling by downregulating pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β while enhancing anti-inflammatory mediators like IL-10. Animal models demonstrate that intermittent fasting regimens such as alternate-day fasting and time-restricted feeding can suppress endotoxemia, improve intestinal morphology, and recalibrate immune responses [6]. The human gut is a complex ecosystem, hosting trillions of microorganisms that play essential roles in nutrient absorption, immune education, and barrier maintenance. Disruption of this ecosystem, known as dysbiosis, has been linked to a wide spectrum of diseases, including metabolic syndrome,

inflammatory bowel disease, and autoimmune conditions. IF appears to restore microbial balance by increasing the abundance of beneficial bacteria such as *Akkermansia muciniphila* and *Lactobacillus*, which contribute to mucin production and reinforce intestinal tight junctions [7]. This restructuring of the microbiota not only strengthens the barrier but also modulates the production of short-chain fatty acids (SCFAs) like butyrate, propionate, and acetate key metabolites that nourish colonocytes and exert potent anti-inflammatory effects. Thus, fasting-induced microbial remodeling can serve as a bridge linking dietary rhythms to improved mucosal integrity and reduced systemic inflammation [8]. Moreover, intermittent fasting triggers metabolic adaptations that have downstream effects on gut physiology. During fasting, glycogen stores are depleted, and the body shifts toward fatty acid oxidation and ketone body production. Ketone bodies, particularly β-hydroxybutyrate, exhibit anti-inflammatory properties and act as signaling molecules that suppress the activation of the NLRP3 inflammasome, a critical driver of intestinal and systemic inflammation [9]. This metabolic switch also induces mild cellular stress, activating protective pathways such as autophagy, which helps clear damaged proteins and organelles in gut epithelial cells [10]. By promoting cellular renewal and reducing oxidative damage, IF contributes to the maintenance of a resilient and functional gut barrier. The influence of intermittent fasting extends to the immune system as well [11]. Periods of fasting are associated with a transient reduction in circulating leukocytes, followed by a surge in hematopoietic stem cell proliferation upon refeeding. This cyclical suppression and regeneration of immune cells may contribute to a more balanced and less inflammatory immune profile [12]. Additionally, fasting modulates the hypothalamic-pituitary-adrenal (HPA) axis and the release of glucocorticoids, which can exert regulatory effects on gut permeability and immune tolerance. Through these intertwined metabolic and neuroendocrine pathways, IF orchestrates a systemic anti-inflammatory state that complements its local effects on intestinal barrier function [13].

2. OBJECTIVE

This study aimed to evaluate the impact of intermittent fasting on gut barrier integrity and inflammatory markers among healthy adults.

3. METHODOLOGY

A cross-sectional analytical study was conducted at Services Hospital /Services Institute of Medical Sciences Lahore from June 2023 to June 2024. A total of 265 adult participants were included in the study. Non-probability consecutive sampling was used to recruit eligible participants.

4. INCLUSION CRITERIA:

Adults aged 20–60 years.

Individuals practicing intermittent fasting for at least 8 weeks (including time-restricted feeding or alternate-day fasting).

Healthy volunteers with no major chronic illness.

5. EXCLUSION CRITERIA:

Individuals with gastrointestinal disorders, autoimmune diseases, or metabolic syndrome.

Participants taking probiotics, corticosteroids, or anti-inflammatory medications.

Pregnant or lactating women.

Individuals who had recently undergone antibiotic therapy (within the last month).

6. DATA COLLECTION PROCEDURE:

After obtaining ethical approval and informed consent, participants were divided into two groups: those following intermittent fasting (IF group) and those with normal eating habits (control group). A structured questionnaire was used to collect demographic data, dietary habits, and fasting duration. Blood samples were obtained after overnight fasting to assess inflammatory and intestinal barrier markers. Anthropometric data, including weight, height, and BMI, were recorded using standardized methods. Gut barrier function was evaluated by measuring serum zonulin and lipopolysaccharide (LPS) levels using enzyme-linked immunosorbent assay (ELISA). Systemic inflammation was assessed through high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) levels. These markers were selected to represent both localized gut permeability and systemic inflammatory activity. Dietary intake during feeding windows was also assessed using a 24-hour dietary recall to ensure that both groups maintained comparable nutrient intake profiles. Venous blood samples of 5 mL were drawn under aseptic precautions and centrifuged to separate serum, which was stored at −80°C until analysis. All biochemical assays were performed in duplicate to ensure accuracy and reproducibility, following manufacturer-recommended ELISA protocols. Laboratory personnel conducting the assays were blinded to participant grouping to eliminate bias.

7. DATA ANALYSIS

Data analysis was conducted using SPSS version 26. Continuous variables were expressed as mean ± standard deviation, while categorical variables were reported as frequencies and percentages. Between-group comparisons for continuous variables were made using the independent sample t-test, and categorical variables were compared using the chi-square test. Correlations between fasting duration and inflammatory markers were determined using Pearson correlation analysis. A p-value of <0.05 was considered statistically significant.

8. RESULTS

Data were collected from 265 patients, both groups were similar in age (36.4 ± 8.7 vs. 37.2 ± 9.1 years; p = 0.48) and gender distribution (53.6% vs. 54.3% males; p = 0.92). However, BMI was significantly lower in the intermittent fasting (IF) group (24.6 ± 3.2 kg/m²) compared to controls (26.1 ± 3.6 kg/m²; p = 0.01). Most participants were non-smokers (88.4% vs. 85.8%) and physically active (73.2% vs. 69.3%), with no significant differences (p > 0.05).

Table 1. Baseline Demographic and Clinical Characteristics of Participants (N = 265)

Variable	IF Group (n = 138)	Control Group (n = 127)	p-value
Age (years), mean ± SD	36.4 ± 8.7	37.2 ± 9.1	0.48
Gender (Male), n (%)	74 (53.6)	69 (54.3)	0.92
BMI (kg/m²), mean ± SD	24.6 ± 3.2	26.1 ± 3.6	0.01
Smoking status (Non-smoker), n (%)	122 (88.4)	109 (85.8)	0.52
Physical activity (Moderate/High), n (%)	101 (73.2)	88 (69.3)	0.46

IF participants had markedly lower zonulin (32.4 ± 7.8 vs. 40.2 ± 9.5 ng/mL; p < 0.001) and LPS levels (0.38 ± 0.12 vs. 0.51 ± 0.15 EU/mL; p < 0.001), indicating improved gut integrity. Inflammatory markers were also significantly reduced—hs-CRP (1.9 ± 0.7 vs. 2.8 ± 1.0 mg/L), IL-6 (4.3 ± 1.5 vs. 6.2 ± 1.9 pg/mL), and TNF-α (8.6 ± 2.4 vs. 10.9 ± 2.8 pg/mL), all with p < 0.001—suggesting reduced systemic inflammation in the fasting group.

Table 2. Gut Barrier Function Markers Among Study Participants (N = 265)

Parameter	IF Group (n = 138)	Control Group (n = 127)	p-value
Zonulin (ng/mL), mean ± SD	32.4 ± 7.8	40.2 ± 9.5	<0.001
Lipopolysaccharide (LPS) (EU/mL), mean ± SD	0.38 ± 0.12	0.51 ± 0.15	<0.001
hs-CRP (mg/L), mean ± SD	1.9 ± 0.7	2.8 ± 1.0	<0.001
IL-6 (pg/mL), mean ± SD	4.3 ± 1.5	6.2 ± 1.9	<0.001

TNF-α (pg/mL), mean ± SD	8.6 ± 2.4	10.9 ± 2.8	<0.001

Table 3 reveals strong negative correlations between fasting duration and zonulin (r = -0.56), LPS (r = -0.48), hs-CRP (r = -0.48), IL-6 (r = -0.44), and TNF-α (r = -0.39), all statistically significant ($p < 0.001$). BMI correlated positively with zonulin (r = 0.39; p = 0.004), indicating that higher BMI was linked to poorer gut barrier function.

Table 3. Correlation Between Fasting Duration, BMI, and Biochemical Markers (N = 138, IF Group)

Variable	Zonulin (r)	LPS (r)	hs-CRP (r)	IL-6 (r)	TNF-α (r)	p-value
Fasting Duration (weeks)	-0.56	-0.48	-0.48	-0.44	-0.39	<0.001
BMI (kg/m²)	0.39	0.32	0.35	0.31	0.29	0.004

It shows that time-restricted feeding (TRF) produced better outcomes than alternate-day fasting (ADF). Zonulin was lower in TRF (30.8 ± 6.9 vs. 34.5 ± 8.2 ng/mL; p = 0.02), as were hs-CRP (1.7 ± 0.6 vs. 2.2 ± 0.8 mg/L; p = 0.03) and IL-6 (4.1 ± 1.3 vs. 4.6 ± 1.6 pg/mL; p = 0.04).

Table 4. Subgroup Analysis by Type of Fasting (N = 138, IF Group Only)

Parameter	Time-Restricted Feeding (n = 82)	Alternate-Day Fasting (n = 56)	p-value
Zonulin (ng/mL), mean ± SD	30.8 ± 6.9	34.5 ± 8.2	0.02
hs-CRP (mg/L), mean ± SD	1.7 ± 0.6	2.2 ± 0.8	0.03
IL-6 (pg/mL), mean ± SD	4.1 ± 1.3	4.6 ± 1.6	0.04

9. DISCUSSION

The present study evaluated the impact of intermittent fasting on gut barrier function and systemic inflammation among 265 adult participants. The results demonstrated that individuals practicing intermittent fasting exhibited significantly lower levels of serum zonulin and lipopolysaccharide (LPS), reflecting improved intestinal barrier integrity. Additionally, inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) were markedly reduced in the fasting group compared to the control group. These findings strongly support the hypothesis that intermittent fasting enhances gut barrier function and exerts anti-inflammatory effects, likely through interconnected metabolic and microbial mechanisms. The gut barrier serves as a selective interface, permitting nutrient absorption while preventing microbial translocation and toxin entry [14]. Increased permeability or "leaky gut" has been implicated in systemic inflammation and metabolic dysfunction. The lower zonulin and LPS levels observed in fasting participants suggest that intermittent fasting stabilizes tight junction proteins and reduces endotoxin leakage. This aligns with experimental evidence that fasting promotes epithelial regeneration, enhances mucosal defense, and reduces intestinal oxidative stress. The metabolic switch that occurs during fasting, shifting from glucose to fatty acid and ketone metabolism, may also play a key role in strengthening the barrier by inducing autophagy and suppressing oxidative injury in intestinal epithelial cells [15]. Furthermore, the significant decrease in inflammatory markers highlights the systemic benefits of fasting beyond gut physiology. Chronic low-grade inflammation is a major contributing factor in metabolic syndrome, insulin resistance, and cardiovascular diseases. The observed reduction in hs-CRP, IL-6, and TNF-α levels suggests that intermittent fasting modulates immune activity toward a less inflammatory profile [16]. This anti-inflammatory effect can be partially attributed to decreased LPS-induced immune activation due to improved gut permeability, as well as to direct cellular effects of fasting, such as reduced NF-κB pathway activation and enhanced antioxidant capacity. Interestingly, correlation analysis revealed that longer fasting duration was associated with greater improvement in both gut barrier integrity and inflammatory status [17]. This suggests that sustained adherence to intermittent fasting may yield cumulative physiological benefits. The inverse association between fasting duration and zonulin or inflammatory cytokines underscores the potential of fasting as a long-term health-promoting behavior. Conversely, the positive correlation between BMI and zonulin reinforces the well-established link between obesity, intestinal permeability, and systemic inflammation. It also suggests that the beneficial effects of intermittent fasting on gut integrity may be partially mediated by weight reduction and improved metabolic control. When comparing fasting types, time-restricted feeding demonstrated more pronounced benefits than alternate-day fasting [18]. This could be attributed to better synchronization of feeding windows with circadian rhythms, which regulate intestinal epithelial turnover and immune activity. Aligning food intake with the body's natural metabolic cycles may enhance gut microbiota diversity and promote efficient energy utilization. Time-restricted eating may also be more sustainable and physiologically stable, reducing stress responses that can accompany

longer fasting intervals [19,20]. However, despite its promising outcomes, this study has some limitations. Being cross-sectional, it cannot establish causality, and potential confounding factors such as unreported dietary variations, hydration status, or physical activity may have influenced biochemical results. Furthermore, gut microbiome profiling was not performed, which could have provided mechanistic insight into the observed changes. Longitudinal and interventional studies incorporating microbiome sequencing and metabolomic analysis would be valuable for understanding the temporal and molecular dynamics of fasting-induced gut and immune adaptations.

10. CONCLUSION

It is concluded that intermittent fasting exerts a beneficial influence on gut barrier function and systemic inflammation. The findings of this study reveal that individuals practicing intermittent fasting had significantly lower serum zonulin and lipopolysaccharide levels, indicating enhanced intestinal integrity and reduced permeability. Moreover, the decline in inflammatory biomarkers, including hs-CRP, IL-6, and TNF-α, demonstrates that fasting contributes to a marked reduction in chronic low-grade inflammation. These outcomes suggest that intermittent fasting plays a regulatory role in maintaining gut–immune balance by strengthening the intestinal barrier and suppressing inflammatory signaling pathways. The observed correlation between longer fasting duration and improved biochemical profiles further supports the notion that consistent adherence amplifies these physiological benefits..

REFERENCES

[1] Fu R, Zhang P, Zhang JW, Hong Y, Chen B, Cao GD. Intermittent fasting exacerbates colon inflammation by promoting Th17 cell differentiation through inhibition of gut microbiota-derived indoleacrylic acid. World J Gastroenterol. 2025 Jun 14;31(22):108815. doi: 10.3748/wjg.v31.i22.108815. PMID: 40539205; PMCID: PMC12175853.

[2] Paukkonen I, Törrönen EN, Lok J, Schwab U, El-Nezami H. The impact of intermittent fasting on gut microbiota: a systematic review of human studies. Front Nutr. 2024 Feb 12;11:1342787. doi: 10.3389/fnut.2024.1342787. PMID: 38410639; PMCID: PMC10894978.

[3] Haasis, E., Bettenburg, A., & Lorentz, A. (2024). Effect of Intermittent Fasting on Immune Parameters and Intestinal Inflammation. Nutrients, 16(22), 3956. https://doi.org/10.3390/nu16223956

[4] Yin W, Sun L, Liang Y, Luo C, Feng T, Zhang Y, et al. Maternal intermittent fasting deteriorates offspring metabolism via suppression of hepatic mTORC1 signaling. FASEB J. 2023;37:e22831. doi:10.1096/fj.202201907R.

[5] Dje Kouadio DK, Wieringa F, Greffeuille V, Humblot C. Bacteria from the gut influence the host micronutrient status. Crit Rev Food Sci Nutr. 2024;64:10714–29. doi:10.1080/10408398.2023.2227888.

[6] Varady KA, Cienfuegos S, Ezpeleta M, Gabel K. Clinical application of intermittent fasting for weight loss: progress and future directions. Nat Rev Endocrinol. 2022;18:309–21. doi:10.1038/s41574-022-00638-x.

[7] Yuan X, Wang J, Yang S, Gao M, Cao L, Li X, et al. Effect of intermittent fasting diet on glucose and lipid metabolism and insulin resistance in patients with impaired glucose and lipid metabolism: a systematic review and meta-analysis. Int J Endocrinol. 2022;2022:6999907. doi:10.1155/2022/6999907.

[8] Mendonça MLM, Carvalho MR, Romanenghi RB, Santos DSD, Filiú WFO, Pagan LU, et al. Impact of combined intermittent fasting and high-intensity interval training on apoptosis and atrophy signaling in rat fast- and slow-twitch muscles. Physiol Rep. 2024;12:e16181. doi:10.14814/phy2.16181.

[9] Li C, Zhang H, Wu H, Li R, Wen D, Tang Y, et al. Intermittent fasting reverses the declining quality of aged oocytes. Free Radic Biol Med. 2023;195:74–88. doi:10.1016/j.freeradbiomed.2022.12.084.

[10] Antarianto RD, Kadharusman MM, Wijaya S, Hardiny NS. The impact of prolonged and intermittent fasting on PGC-1α, Oct-4, and CK-19 liver gene expression. Curr Aging Sci. 2023;16:49–55. doi:10.2174/1874609815666220627155337.

[11] Gallage S, Ali A, Barragan Avila JE, Seymen N, Ramadori P, Joerke V, et al. A 5:2 intermittent fasting regimen ameliorates NASH and fibrosis and blunts HCC development via hepatic PPARα and PCK1. Cell Metab. 2024;36:1371–93.e7. doi:10.1016/j.cmet.2024.04.015.

[12] Di Vincenzo F, Del Gaudio A, Petito V, Lopetuso LR, Scaldaferri F. Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. Intern Emerg Med. 2024;19:275–93. doi:10.1007/s11739-023-03374-w.

[13] Liu A, Liang X, Wang W, Wang C, Song J, Guo J, et al. Human umbilical cord mesenchymal stem cells ameliorate colon inflammation via modulation of gut microbiota–SCFAs–immune axis. Stem Cell Res Ther. 2023;14:271. doi:10.1186/s13287-023-03471-9.

[14] Palenca I, Seguella L, Del Re A, Franzin SB, Corpetti C, Pesce M, et al. N-palmitoyl-D-glucosamine inhibits

TLR-4/NLRP3 and improves DNBS-induced colon inflammation through a PPAR-α-dependent mechanism. Biomolecules. 2022;12:1163. doi:10.3390/biom12081163.

[15] Cai J, Liu J, Fan P, Dong X, Zhu K, Liu X, et al. Dioscin prevents DSS-induced colitis in mice by enhancing intestinal barrier function and reducing colon inflammation. Int Immunopharmacol. 2021;99:108015. doi:10.1016/j.intimp.2021.108015.

[16] Aldars-García L, Chaparro M, Gisbert JP. Systematic review: the gut microbiome and its potential clinical application in inflammatory bowel disease. Microorganisms. 2021;9:977. doi:10.3390/microorganisms9050977.

[17] Martín-Hernández D, Gutiérrez IL, González-Prieto M, MacDowell KS, Robledo-Montaña J, Tendilla-Beltrán H, et al. Sphk2 deletion is involved in structural abnormalities and Th17 response but does not aggravate colon inflammation induced by sub-chronic stress. Sci Rep. 2022;12:4073. doi:10.1038/s41598-022-08011-8.

[18] Pan H, Chen X, Wang P, Peng J, Li J, Ding K. Effects of Nemacystus decipiens polysaccharide on mice with antibiotic-associated diarrhea and colon inflammation. Food Funct. 2023;14:1627–35. doi:10.1039/d1fo02813h.

[19] Guo Y, Luo S, Ye Y, Yin S, Fan J, Xia M. Intermittent fasting improves cardiometabolic risk factors and alters gut microbiota in metabolic syndrome patients. J Clin Endocrinol Metab. 2021;106:64–79. doi:10.1210/clinem/dgaa644.

[20] Akhtar AM, Ghouri N, Chahal CAA, Patel R, Ricci F, Sattar N, et al. Ramadan fasting: recommendations for patients with cardiovascular disease. Heart. 2022;108:258–65. doi:10.1136/heartjnl-2021-319273