RESEARCH ARTICLE

Modified High-Fat High-Sucrose Diet Promotes Obesity and Alters Colonic Cytokines

Bernadette Dian Novita[1,*], I Gede Putu Adhi Wedharga[2], Yudy Tjahjono[3], Hendy Wijaya[3], Imelda Theodora[4], Martha Ervina[5], Yufita Ratnasari Wilianto[6], Sianty Dewi[7], Irene Lingkan Parengkuan[4], Herjunianto[8], Sabrina Maria Ghasani[2], Michael Christian Limantoro[2], Ferdinand Wiliam Jaya[2]

[1]Department of Pharmacology and Therapy, Faculty of Medicine, Universitas Katolik Widya Mandala, Jl. Kalisari Selatan No.1, Surabaya 60112, Indonesia
[2]Undergraduate Program, Faculty of Medicine, Universitas Katolik Widya Mandala, Jl. Kalisari Selatan No.1, Surabaya 60112, Indonesia
[3]Biomedical Laboratory, Faculty of Pharmacy, Universitas Katolik Widya Mandala, Jl. Kalisari Selatan No.1, Surabaya 60112, Indonesia
[4]Department of Anatomical Pathology, Faculty of Medicine, Universitas Katolik Widya Mandala, Jl. Kalisari Selatan No.1, Surabaya 60112, Indonesia
[5]Traditional Medicine Research Center, Faculty of Pharmacy, Universitas Katolik Widya Mandala, Jl. Kalisari Selatan No.1, Surabaya 60112, Indonesia
[6]Department of Clinical and Community Pharmacy, Faculty of Pharmacy, Universitas Katolik Widya Mandala, Jl. Kalisari Selatan No.1, Surabaya 60112, Indonesia
[7]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Katolik Widya Mandala, Jl. Kalisari Selatan No.1, Surabaya 60112, Indonesia
[8]Department of Internal Medicine, Faculty of Medicine, Universitas Katolik Widya Mandala, Jl. Kalisari Selatan No.1, Surabaya 60112, Indonesia

*Corresponding author. Email: novita@ukwms.ac.id

Received date: Aug 19, 2025; Revised date: Sep 19, 2025; Accepted date: Sep 23, 2025

Abstract

BACKGROUND: Western dietary patterns are often associated with increasing non-communicable diseases, including inflammatory bowel disease (IBD). In experimental models, a high-fat high-sucrose (HFHS) diet is used to mimic metabolic and inflammatory effects of such diets, however the data regarding colonic inflammation in Indonesia remain limited. Therefore, this study was conducted evaluated the impact of HFHS feeding on colonic interleukin (IL)-6, IL-10 expression, and the IL-6/IL-10 ratio.

METHODS: Six weeks old male C57BL/6 mice were randomly assigned to a normal fat diet (NFD) or HFHS diet group and fed *ad libitum* for 8 weeks. Colonic tissues were collected, and IL-6 and IL-10 expression was analyzed by immunohistochemistry.

RESULTS: HFHS-fed mice showed significant increases in body weight (increased by 22.44%, p=0.0047) and caloric intake (increased by 125.17%, p=0.0000), confirming obesity induction. Colitis was also evident, with higher histological colitis scores (p=0.0072). However, colonic IL-6 (increased by 9.12%, p=0.1236), IL-10 (increased by 1.49%, p=0.8013), and the IL-6/IL-10 ratio (increased by 7.38%, p=0.4000) showed no significant differences compared to NFD.

CONCLUSION: In C57BL/6 mice, an 8-week modified HFHS diet induced obesity, increased caloric intake, and mucosal injury, but did not significantly alter colonic IL-6, IL-10, or their ratio. This suggests preserved mucosal immune homeostasis consistent with an early compensatory phase rather than overt cytokine-driven inflammation. Longer or more intensive exposure may disrupt this balance, highlighting the need for further studies to define the temporal threshold and clarify immune microbiome interactions in colitis progression.

KEYWORDS: high-fat high-sucrose diet, colon inflammation, IL-6, IL-10, obesity mice

Indones Biomed J. 2025; 17(5): 456-64

Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are among the most prevalent colonic non-communicable diseases (NCDs). Globally, the prevalence of IBD increased by 47.45% between 1990 and 2019.(1) This rising trend has been associated with the adoption of a Westernized diet, characterized by high intakes of fat, sugar, and salt, and low fiber consumption.(2) In addition to its direct impact on the colon, the Western diet also contributes indirectly through obesity-related low-grade chronic inflammation, a recognized factor in IBD pathogenesis. Approximately, 15–40% of IBD patients are obese, suggesting a significant role of obesity as a modifiable risk factor for IBD.(3)

Animal models of diet-induced obesity (DIO) are commonly employed to investigate the mechanisms linking obesity and colitis. Among these, mice are widely used due to their relatively rapid metabolism and short lifespan, which allow for the accelerated modeling of disease processes corresponding to long-term dietary exposure in humans. (4) The inbred C57BL/6 mouse strain is the most widely applied in DIO studies due to its susceptibility to obesity and metabolic syndrome, unlike more resistant strains such as SWR/J, A/J, and CAST/Ei.(5)

Various DIO models incorporate different formulations of high-fat, high-cholesterol, or high-sugar diets. Short-term exposure (three weeks) to a high-fat diet (HFD) has been shown to induce colonic atrophy and inflammation in mice. (6) Among sugar types, a high-sucrose diet appears to elicit greater obesity and metabolic disturbances than diets rich in glucose or fructose.(7) Moreover, the mode of sugar ingestion influences disease outcomes liquid sucrose intake results in greater adiposity and insulin resistance compared to solid intake.(8) Based on these observations, a combination of solid high-fat and liquid high-sucrose (HFHS) diets may offer a more robust model of obesity and associated colitis than HFD or high-sugar diets alone. This model also mirrors common human eating habits, which often involve high-fat foods consumed alongside sugar-sweetened beverages.

Sugar-sweetened beverages are known to exacerbate HFD-induced colonic mucosal inflammation by upregulating pro-inflammatory cytokines and chemokines.(9) Among these, interleukin (IL)-6 and IL-10 play central roles in the colonic immune response to obesogenic diets.(10,11) IL-6, a pro-inflammatory cytokine, may worsen intestinal inflammation in IBD via activation of transcription factors such as nuclear factor-kappaB (NF-κB) and CCAAT/enhancer-binding protein beta (C/EBPβ).(12,13) In contrast, IL-10 serves as an anti-inflammatory cytokine that protects the intestinal mucosa from inflammation associated with gut dysbiosis.(14) The ratio of IL-6 to IL-10 is considered a critical marker of immune balance, reflecting the interplay between pro- and anti-inflammatory responses. Although the IL-6/IL-10 ratio has been extensively studied in systemic inflammatory conditions, such as COVID-19, its role in colonic inflammation remains inadequately understood. (15,16) By evaluating the IL-6/IL-10 balance in the context of diet-induced obesity, the current study was conducted to address this gap and provide a more integrative perspective on mucosal immune regulation, with potential implications for understanding disease progression and therapeutic responsiveness.

Western-style diets are rising globally and are linked to IBD, yet experimental HFHS models rarely report local colonic cytokine balance, particularly IL-6/IL-10, leaving a gap in understanding early mucosal inflammation under diet-induced obesity. To address this urgent gap, we investigated the detrimental effects of a modified HFHS diet on obesity and colitis in C57BL/6 mice, specifically evaluating body weight, caloric intake, colonic IL-6 and IL-10 expression, and the IL-6/IL-10 ratio. The HFHS regimen comprised a solid pellet diet with 45% kilocalories from fat plus 20% (w/v) sucrose in drinking water. This design aimed to characterize the colonic inflammatory response accompanying excessive Western diet intake, with emphasis on cytokine profiles and their implications for colitis development.

Methods

Animals, Diet, and Experimental Design

Age-matched six-week-old male C57BL/6 mice (18–22 g, n=10) were obtained from Kemuning Laboratory Animal Supplier (Karanganyar, Indonesia). Required sample size was calculated using an a priori analysis (Means: difference between two independent means) in G*Power 3.1 software (Düsseldorf, Germany) with an effect size d=3.43, α=0.05, and a target power of 0.95 according to a previous study. (11) Ten weeks of high-fat and high-sugar diets in mice significantly altered cytokine expression along the gut–brain axis in a sex-dependent manner, highlighting the profound systemic and neuroimmune consequences of dietary interventions.(11) All animals were housed under controlled conditions with a 12-hour light/dark cycle, ambient temperature of 22–25°C, and relative humidity

of 50–60%. Following one week of acclimatization with *ad libitum* access to a normal fat diet (NFD), mice were randomly assigned using a random computer-generated number (n=5 per group) to either the NFD group or the HFHS diet group and treated for 8 weeks (Figure 1).

The NFD pellet contained 69.5% kilocalories (kcal) from carbohydrates, 21% kcal from protein, and 16.5% kcal from fat. In contrast, the modified HFHS pellet was formulated with 39% kcal from carbohydrates, 16% kcal from protein, and 45% kcal from fat. Detailed dietary formulation was listed in Table 1. The high-sucrose solution was prepared by dissolving finely ground sucrose in distilled water to a concentration of 20% (w/v) and provided as drinking water. Both food and drinking solutions were offered *ad libitum* to simulate natural feeding behavior. Intake was monitored daily by weighing and replacing food and water.

At the end of the 8 weeks intervention, mice were weighed and euthanized via intraperitoneal injection of 90 mg/kgBW ketamine and10 mg/kgBW xylazine. The entire colon was then excised, weighed, and processed for paraffin embedding for subsequent histological and immunohistochemical analysis. All animal procedures followed the guidelines of the Institutional Animal Care and Use Committee (IACUC) and were approved by the Health Research Ethics Committee, Universitas Hang Tuah, Surabaya, Indonesia (Approval No. E/017/UHT.KEPK.03/IV/2024).

Colonic Histology Analysis

Colon tissue specimens were preserved using a 10% neutral-buffered formalin solution, then embedded in paraffin and sliced into 5 µm thick sections. These sections underwent hematoxylin and eosin (H&E) staining to facilitate histological evaluation of the mucosa, submucosal layer, and muscularis propria. H&E-stained slides were visualized using a microscope (Olympus CX-31; Olympus, Tokyo, Japan) with a digital camera (Olympus DP21). The histology slides were analyzed by measuring the colitis score based on a previous study.(17) Colonic inflammation was evaluated based on three major categories: immune cell infiltration, mucosal damage, and architectural alterations. Immune infiltration was scored semi-quantitatively across the lamina propria (0–3), submucosa (0–2), and muscularis (0–1), with leukocyte presence reflecting the severity of inflammation. Mucosal damage was graded from 0 (no damage) to 3 (severe), with intraepithelial lymphocytosis, erosions/crypt abscesses, and ulcerations representing progressive stages. Finally, architectural changes were assessed from 0 (normal mucosa) to 3 (invasive carcinoma), with intermediate stages including hyperplasia and low- to high-grade dysplasia. This scoring system allowed for a structured evaluation of colonic

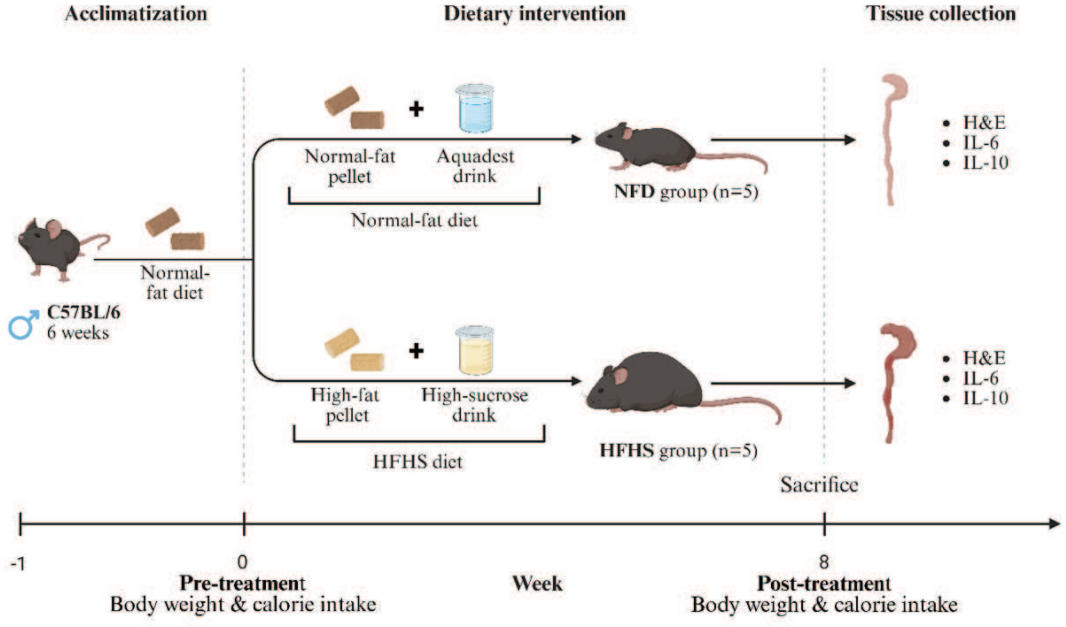

Figure 1. Experimental design to evaluate the detrimental effects of a modified HFHS diet on the C57BL/6 Mice's colon. Following one week of acclimatization, mice were randomly assigned to either NFD group, receiving standard chow and distilled water, or the modified HFHS group, receiving a high-fat diet (45% kcal from fat) and 20% (w/v) sucrose solution as drinking water. Both diets were administered *ad libitum* for 8 weeks.

Table 1. Experimental diet composition.

Composition	Quantity (% w/w)	
	NFD	HFHS
Carbohydrate		
Cornstarch	38.3	22.8
Sucrose	13	14
Maltodextrin	15	12
Cellulose	5	1.5
Fat		
Palm oil	4	7
Lard	4	18
Protein		
Casein	20	20
Minor Elements		
Vitamin & mineral mix*	4	4
L-Methionine	0.5	0.5
Choline chloride	0.2	0.2

*Super Fat (Tamasindo Veterinary Animal & Plant Health Care, Semarang, Indonesia; formulated by Otsuda, Japan).

inflammatory and neoplastic changes. The pathologist was blinded to the treatment groups to minimize bias.

Colonic Immunohistochemistry Analysis

Colon tissue samples were fixed in 10% neutral-buffered formalin, embedded in paraffin, and sectioned at a thickness of 5 µm. Sections were deparaffinized with xylene (three washes) and rehydrated through a graded ethanol series. Endogenous peroxidase activity was blocked using hydrogen peroxide, followed by two phosphate-buffered saline (PBS) washes. Antigen retrieval was performed by immersing the slides in citrate buffer solution (10 mM sodium citrate, 0.05% Tween-20, pH 6.0, adjusted with 1 N HCl), followed by a PBS rinse. Sections were incubated overnight at 4°C with either anti-IL-6 or anti-IL-10 polyclonal antibodies (Elabscience Biotechnology, Houston, TX, USA) at a dilution of 1:200. After incubation, the slides were washed twice with PBS and treated with Impact DAB chromogen substrate to visualize antibody binding, followed by another two PBS washes. Counterstaining was performed using Mayer's modified haematoxylin solution.

Immunostained sections were examined under a light microscope (Olympus CX-31, Olympus, Tokyo, Japan) equipped with a digital camera (Olympus DP21) at 400× magnification. A minimum of five randomly selected high-power fields (HPFs) per section were analysed. Quantification of IL-6 and IL-10 expression was performed using FIJI (ImageJ) software by measuring the mean gray value to determine relative staining intensity. In brief, deconvoluted DAB-stained images were selected, subjected to automatic thresholding for binarization, and subsequently inverted to generate black-and-white outputs. Staining intensity was quantified as the mean gray value (range 0–255). No constraints on object size or circularity were applied, since the analysis focused on overall signal intensity rather than discrete cellular elements. While this approach may incorporate minor artifacts, the use of consistent thresholding across all groups reduced bias, and the uniform application of the method ensured comparability between samples. Each analyzed image had a resolution of 1600 × 1200 pixels.

Statistical Analysis

All data were analysed using GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA) and expressed as mean±standard error of the mean (SEM). Time-wise changes in body weight and calorie intake were analyzed using two-way repeated measures ANOVA to evaluate effects due to time (week-0 *vs.* week-8), diet (NFD *vs.* HFHS), and the time × diet interactive effect. Bonferroni post-hoc test was applied to assess the difference among diet groups. Independent group comparisons were conducted using an unpaired two-tailed Student's t-test for normally distributed and homogenous data. When assumptions of normality or homogeneity were violated, the non-parametric Mann–Whitney U test was applied. Normality of data distribution was assessed using the Shapiro–Wilk test, while homogeneity of variances was evaluated using the Brown–Forsythe test. A $p<0.05$ was considered statistically significant.

Results

Diet Induced Obesity and Increased Caloric Intake

Body weight was measured at the beginning and end of the 8 weeks intervention period (Figure 2A). Mice in the HFHS group exhibited a significantly higher final body weight (42.02±2.28 g) compared to those in the normal fat diet (NFD) group (34.32±1.04 g; $p=0.0047$). Body weight increased substantially over time, with the majority of variation attributed to the time factor (Table 2). Diet also contributed to differences in body weight, with higher values observed in the HFHS group. Additionally, a significant interaction between time and diet indicated that weight changes over time differed between the diet groups. Daily caloric intake per mouse was also recorded at week-0 and week-8 of the study (Figure 2B).

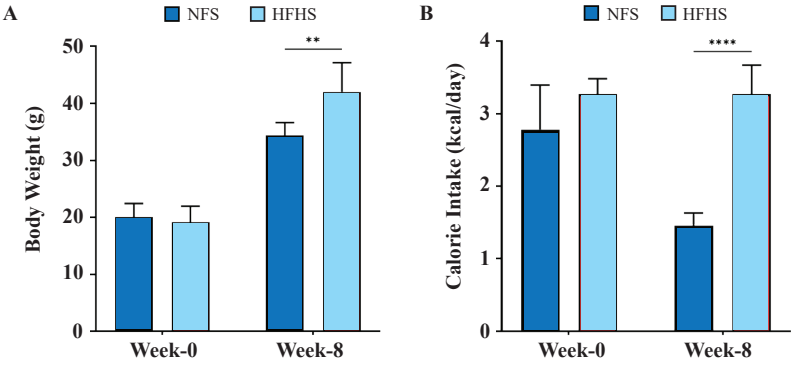

Figure 2. HFHS diet increases body weight and caloric intake in mice. A: Pre- and post-treatment body weight in both groups. B: Average daily caloric intake in both group. Data are presented as mean±SEM (n=5 per group). Statistical significance was determined by two-way ANOVA followed by Bonferroni post-hoc. **p<0.01, ****p<0.0001. NFD: normal fat diet; HFHS: high-fat high-sucrose diet.

The HFHS group demonstrated significantly higher final average calorie consumption (3.27±1.18 kcal) compared to the NFD group (1.45±0.08 kcal; p<0.0001). Calorie intake changed significantly over time, with diet being the main contributor to the observed variation (Table 2). The HFHS group consistently consumed more calories than the NFD group, and the pattern of change over time differed between the two diets. Among the two parameters (body weight and calorie intake), the subject factors were negligible, suggesting minimal inter-mouse variability. These findings indicate that the HFHS diet effectively induces obesity and hypercaloric intake in C57BL/6 mice.

The Modified High-Fat High-Sucrose Diet Mildly Increased Colonic IL-6 Expression While Maintaining IL-6/IL-10 Ratio Balance

The histopathological colonic responses were assessed following the extraction of the colon at the end of the eighth week of intervention (Figure 3). The HFHS group exhibited a significant increase in the colitis score (6.60±0.93; p=0.0072) compared to the NFD group (Figure 3B; 1.80±0.97). A more detailed analysis of the colitis subscore revealed that the HFHS group displayed greater microscopic alterations in the mucosa, epithelial integrity, and mucosal architecture (Figure 3C). Although these indicators did not reach statistical significance individually, except epithelial damage (HFHS: 1.60±0.24 *vs.* NFD: 0.40±0.24; p=0.0476), they showed a clear distinction when combined into the overall colitis score compared to the NFD group. This finding suggests that the HFHS diet induces early inflammation in the colon, as evidenced by histologic alterations.

The Modified High-Fat High-Sucrose Diet Mildly Increased Colonic IL-6 Expression While Maintaining IL-6/IL-10 Ratio Balance

Colonic protein expression levels of IL-6 and IL-10 were evaluated at week-8 using immunohistochemistry and quantified as mean gray values in arbitrary units (Figure 4A–B). Mice fed the HFHS diet showed a modest increase in IL-6 expression (136.4±3.44) compared to the NFD group (125.0±4.83), although the difference was not statistically significant (p=0.1256). Similarly, IL-10 expression levels in the HFHS group (136.2±4.75) were not significantly different from those in the NFD group (134.2±5.36; p=0.8013). The IL-6/IL-10 ratio, a marker of immune balance, was also calculated (Figure 4C). No significant difference was observed between the HFHS group (1.00±0.03) and the NFD group (0.93±0.06; p=0.4000). These results suggest that while HFHS diet exposure may initiate a mild pro-inflammatory response, indicated by a trend toward increased IL-6, it does not significantly disrupt the IL-6/IL-10 balance, implying preserved immune homeostasis in the colon at this early stage of dietary challenge.

Table 2. Summary of two-way repeated measures ANOVA for body weight and calorie intake.

Source of Variation	Body Weight (g)		Calorie Intake (kcal/day)	
	% Total Variation	p- value	% Total Variation	p- value
Time	83.87	0.0000	16.34	0.0018
Diet	2.79	0.0298	49.12	0.0004
Time x diet	4.51	0.0352	16.34	0.0018
Subject	3.21	0.7780	11.97	0.1873

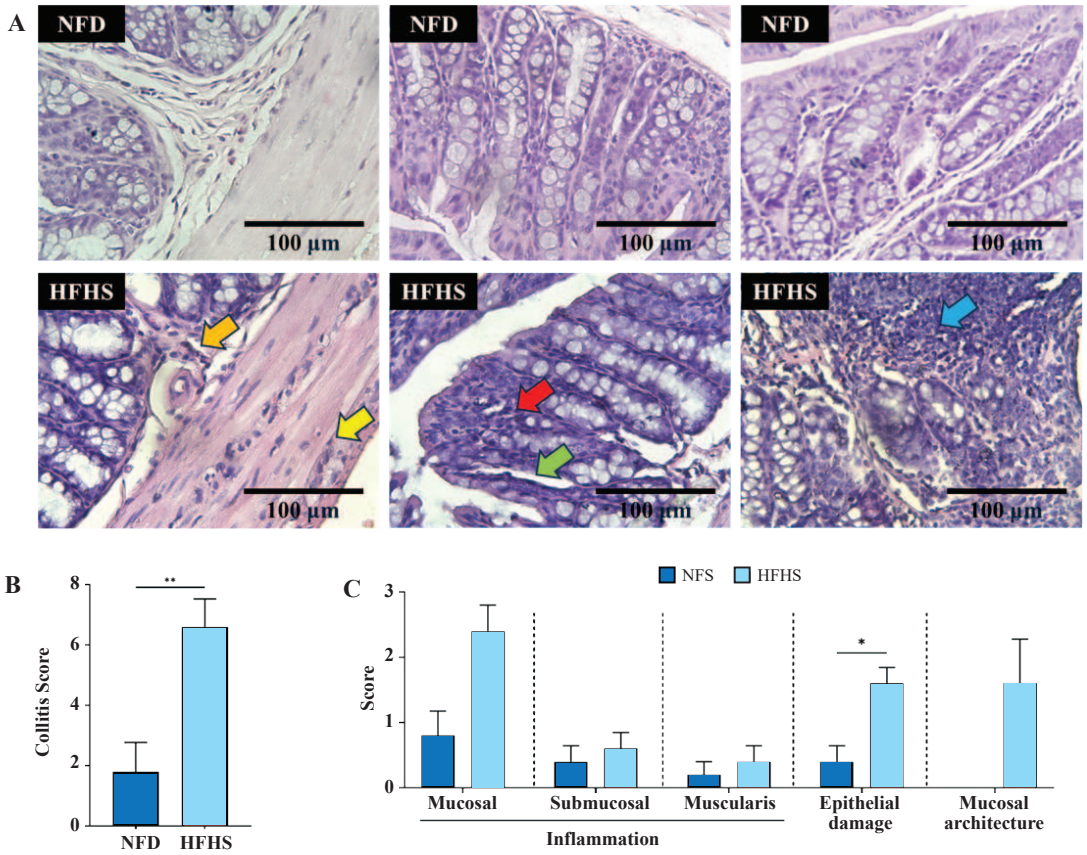

Figure 3. HFHS diet induces mild colitis. A: Representative histology samples of colon. The red arrow represents mucosal inflammation, the yellow arrow represents submucosal inflammation, the orange arrow represents muscularis inflammation, the green arrow represents mucosal damage, and the blue arrow represents mucosal architecture abnormality. B: Colitis score between the two groups. C: Colitis subscore between the two groups. Data are presented as mean±SEM of mice (n=5) in each group. *p<0.05.

Discussion

Sub-chronic consumption of a HFHS diet has been implicated in the development of colitis, primarily through mechanisms involving oxidative stress and immune dysregulation.(17,18) The present study demonstrates that 8 weeks of HFHS feeding in C57BL/6 mice leads to the development of obesity, accompanied by increased caloric intake, but does not induce a significant pro-inflammatory response in the colon. These findings suggest that the colon may engage in a compensatory immunological mechanism during the early phase of HFHS-induced obesity.

Consistent with previous studies, the HFHS diet successfully induced obesity, as evidenced by a 26.89% higher body weight in HFHS-fed mice compared to the NFD group (Figure 2A–B). It is generally accepted that rodents are considered obese when their body weight exceeds that of the control group by more than 15%.(19) In addition, the significant increase in calorie intake observed in the HFHS group further supports the hypercaloric and obesogenic nature of the diet. These findings are in agreement with earlier studies reporting similar outcomes in the week-8 HFHS-fed C57BL/6 mice.(7,20)

IL-6 is a key early-response pro-inflammatory cytokine, often upregulated in the initial stages of colitis.(21) In this study, IL-6 expression in the colon of HFHS-fed mice increased by 9.12% compared to controls, though this change was not statistically significant (Figure 3A–B). IL-10 expression also showed no significant differences (Figure 3A–B), and the IL-6/IL-10 ratio remained unaltered (Figure 3C), suggesting intact compensatory mechanisms that maintain immune balance. Given its central role in driving low-grade inflammation associated with both colitis and obesity-related cardiometabolic disease progression, IL-6 and IL-10 has emerged as a promising therapeutic target.(22) This is supported by evidence that phytotherapeutic approaches using various medicinal leaves have demonstrated beneficial effects in experimental models of colitis or low-grade inflammation, largely mediated by suppression of IL-6 expression and upregulation of IL-10 expression.(23,24,25) Similarly, modulation of intestinal

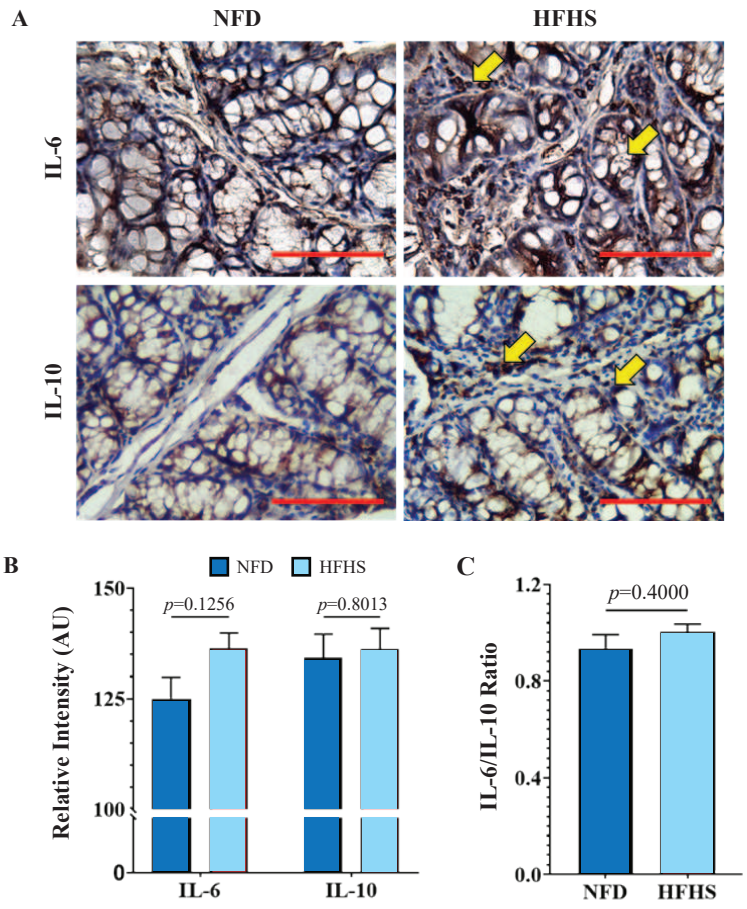

Figure 4. HFHS diet induces mild colonic IL-6 upregulation while maintaining IL-6/IL-10 balance. A: Representative images of colon IHC staining (400× magnification, red bar represents 100 µm). The yellow arrow represents IL-6 or IL-10 positive cells. B: Colonic IL-6 and IL-10 expression. C: IL-6/IL-10 expression ratio. Data are presented as mean±SEM of mice (n=3) in each group.

inflammation through probiotics such as *Lactococcus lactis* D4 can attenuate colitis partly via IL-6 regulation, while interventions like Vitamin D3 supplementation also improve outcomes by suppressing IL-6 activity.(26,27)

These observations are in line with previous research showing modest increases in IL-6 and slight reductions in IL-10 in the colon following HFD or high-sucrose diets in C57BL/6 mice.(11) However, a key limitation of this study is the relatively short duration of dietary intervention, which may have limited the detection of statistically significant changes in cytokine expression. Longer feeding durations may be required to observe robust and sustained inflammatory responses. A plausible explanation for the absence of significant cytokine changes despite histological colitis is that the 8-weeks time point captures an early adaptive phase in which compensatory mechanisms maintain mucosal immune balance. Potential mechanisms include enhanced activity of regulatory T cells, B cell development, and M2-polarized macrophages; induction of negative feedback regulators such as suppressor of cytokine signaling 3 (SOCS3), and microbiota-derived metabolites (*e.g.*, short-chain fatty acids) that suppress excessive IL-6 release.(28,29,30) Together, these processes may explain why IL-6/IL-10 ratios remained stable at this stage, while also pointing to the need for longitudinal and mechanistic studies to determine when and how this compensatory balance is lost.

Importantly, the lack of significant changes in colonic IL-6 and IL-10 expression despite clear evidence of obesity and histological colitis represents a negative but informative finding. This suggests that early-stage mucosal immune responses to obesogenic diets may be buffered by compensatory mechanisms that maintain cytokine balance. (31) Such an observation is novel because most prior studies emphasize overt inflammatory activation, whereas documenting preserved IL-6/IL-10 equilibrium provides new insight into the temporal dynamics of diet-induced inflammation.

The implications of this finding are twofold. First, it highlights the need for longitudinal studies to identify the precise time point at which compensatory immune control is lost and overt cytokine imbalance emerges. Second, it underscores the importance of expanding the cytokine panel beyond IL-6 and IL-10, as other mediators may show earlier dysregulation and contribute to the transition toward chronic inflammation. Moreover, integration with microbiota

profiling may further clarify the pathways linking dietary fat and sucrose overload to mucosal immune adaptation.

Several limitations should be acknowledged. Beyond the relatively short feeding duration, the study was limited by its focus on a restricted set of cytokines, the modest sample size, and the use of a single mouse strain, which may constrain generalizability. Addressing these factors in future work will strengthen the understanding of how obesogenic diets modulate early colonic immune responses.

Conclusion

In summary, sub-chronic HFHS feeding for 8 weeks induced obesity and hypercaloric intake in C57BL/6 mice with mucosal damage but did not significantly disrupt colonic cytokine balance. The preserved IL-6/IL-10 ratio suggests a compensatory immune response during the early phase of dietary challenge. These findings indicate that diet-induced obesity can trigger epithelial injury without immediate overt inflammation, implying initial protective pathways in the colon. However, prolonged or more severe dietary exposure may overwhelm these mechanisms and predispose to colitis. Therefore, future investigations employing longitudinal and dose response approaches, combined with detailed immune, epithelial, microbiome, and metabolic profiling, are warranted to identify the temporal threshold at which compensation fails and to elucidate the mechanistic pathways linking obesogenic diets with epithelial injury and inflammatory progression.

Acknowledgments

This study was granted by the Institute for Research and Community Services (LPPM) at Widya Mandala Surabaya Catholic University, Indonesia.

Authors Contribution

BDN was involved in writing-original draft preparation, formal analysis, conceptualization, methodology, validation, writing-review & editing, supervision, as well as project administration. IAW was involved in the study investigation, data curation, visualization, writing-original draft preparation, and formal analysis. YT was involved in the conceptualization, methodology, validation, supervision, and project administration. HW was involved in the conceptualization, methodology, validation, supervision, and project administration. IT, ME, YRW, SD, ILP, and H were supervising the study. SMG and MCL were involved in the study investigation. FWJ assisted in the visualization. All authors took part in a critical revision of the manuscript.

Conflict of Interest

The authors declare no conflict of interests

References

1. Wang R, Li Z, Liu S, Zhang D. Global, regional and national burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019: A systematic analysis based on the Global Burden of Disease Study 2019. BMJ Open. 2023; 13: e065186. doi: 10.1136/bmjopen-2022-065186.
2. Qiao J, Lin X, Wu Y, Huang X, Pan X, Xu J, *et al.* Global burden of non-communicable diseases attributable to dietary risks in 1990-2019. J Hum Nutr Diet. 2022; 35(1): 202–13.
3. Singh S, Dulai PS, Zarrinpar A, Ramamoorthy S, Sandborn WJ. Obesity in IBD: Epidemiology, pathogenesis, disease course and treatment outcomes. Nat Rev Gastroenterol Hepatol. 2017; 14(2): 110–21.
4. Rydell-Törmänen K, Johnson JR. The applicability of mouse models to the study of human disease. Methods Mol Biol. 2019; 1940: 3–22.
5. Martins T, Castro-Ribeiro C, Lemos S, Ferreira T, Nascimento-Gonçalves E, Rosa E, *et al.* Murine models of obesity. Obesities. 2022; 2(2): 127–47.
6. Tanaka S, Nemoto Y, Takei Y, Morikawa R, Oshima S, Nagaishi T, *et al.* High-fat diet-derived free fatty acids impair the intestinal immune system and increase sensitivity to intestinal epithelial damage. Biochem Biophys Res Commun 2020; 522(4): 971–7.
7. Simoes ICM, Karkucinska-wieckowska A, Janikiewicz J, Szymanska S, Pronicki M, Dobrzyn P, *et al.* Western diet causes obesity-induced nonalcoholic fatty liver disease development by differentially compromising the autophagic response. Antioxidants 2020; 9(10): 995. doi: 10.3390/antiox9100995.
8. Togo J, Hu S, Li M, Niu C, Speakman JR. Impact of dietary sucrose on adiposity and glucose homeostasis in C57BL/6J mice depends on mode of ingestion: Liquid or solid. Mol Metab. 2019; 27: 22–32.
9. Shon WJ, Jung MH, Kim Y, Kang GH, Choi EY, Shin DM. Sugar-sweetened beverages exacerbate high-fat diet-induced inflammatory bowel disease by altering the gut microbiome. J Nutr Biochem. 2023; 113: 109254. doi: 10.1016/j.jnutbio.2022.109254.
10. Ye M, Joosse ME, Liu L, Sun Y, Dong Y, Cai C, *et al.* Deletion of IL-6 exacerbates colitis and induces systemic inflammation in IL-10-deficient mice. J Crohns Colitis. 2020; 14(6): 831–40.
11. Church JS, Renzelman ML, Schwartzer JJ. Ten-week high fat and high sugar diets in mice alter gut-brain axis cytokines in a sex-dependent manner. J Nutr Biochem. 2022; 100: 108903. doi: 10.1016/j.jnutbio.2021.108903.
12. Alhendi A, Naser SA. The dual role of interleukin-6 in Crohn's disease pathophysiology. Front Immunol. 2023; 14: 1295230. doi: 10.3389/fimmu.2023.1295230.
13. Pawłowska-Kamieniak A, Krawiec P, Pac-Kożuchowska E. Interleukin 6: Biological significance and role in inflammatory bowel diseases. Adv Clin Exp Med. 2021; 30(4): 465–9.

14. Wei HX, Wang B, Li B. IL-10 and IL-22 in Mucosal Immunity: Driving Protection and Pathology. Front Immunol. 2020; 11: 1315. doi: 10.3389/fimmu.2020.01315.
15. Jafrin S, Aziz MA, Islam MS. Elevated levels of pleiotropic interleukin-6 (IL-6) and interleukin-10 (IL-10) are critically involved with the severity and mortality of COVID-19: An updated longitudinal meta-analysis and systematic review on 147 studies. Biomark Insights. 2022; 17: 11772719221106600. doi: 10.1177/11772719221106600.
16. McElvaney OJ, Hobbs BD, Qiao D, McElvaney OF, Moll M, McEvoy NL, *et al.* A linear prognostic score based on the ratio of interleukin-6 to interleukin-10 predicts outcomes in COVID-19. EBioMedicine 2020; 61: :103026. doi: 10.1016/j.ebiom.2020.103026.
17. Li X, Wei X, Sun Y, Du J, Li X, Xun Z, *et al.* High-fat diet promotes experimental colitis by inducing oxidative stress in the colon. Am J Physiol Gastrointest Liver Physiol. 2019; 317(4): 453–62.
18. Yamamoto K, Harada N, Yasuda T, Hatoko T, Wada N, Lu X, *et al.* Intestinal Morphology and Glucose Transporter Gene Expression under a Chronic Intake of High Sucrose. Nutrients. 2024; 16(2): 196. doi: 10.3390/nu16020196.
19. de Moura e Dias M, dos Reis SA, da Conceição LL, Sediyama CMN de O, Pereira SS, de Oliveira LL, *et al.* Diet-induced obesity in animal models: points to consider and influence on metabolic markers. Diabetol Metab Syndr 2021; 13(1): 32. doi: 10.1186/s13098-021-00647-2.
20. Régnier M, Rastelli M, Morissette A, Suriano F, Le Roy T, Pilon G, *et al.* Rhubarb supplementation prevents diet-induced obesity and diabetes in association with increased akkermansia muciniphila in mice. Nutrients. 2020; 12(10): 2932. doi: 10.3390/nu12102932.
21. Nakase H, Sato N, Mizuno N, Ikawa Y. The influence of cytokines on the complex pathology of ulcerative colitis. Autoimmun Rev 2022; 21(3): 103017. doi: 10.1016/j.autrev.2021.103017.
22. Meiliana A, Wijaya A. Update on obesity: Induced inflammation to cause cardiometabolic diseases. Indones Biomed J. 2022; 14(2): 116–38.
23. Andari D, Khan FI, Jakfar SI. Methanol extract of katuk (Sauropus androgynus) leaves as an anti-inflammatory agent: Animal study in carrageenan-induced rat models of inflammation. Mol Cell Biomed Sci. 2022; 6(3): 129–34.
24. Puspitaningrum I, Ikawati M, Fakhrudin N, Nurrochmad A. Immunomodulatory effect of dioscorea esculenta L. on NF-κB, TLR-4, TNF-α, and IL-10 expressions in LPS-stimulated RAW 264.7 mouse macrophages. Indones Biomed J. 2025; 17(3): 307–16.
25. Rahardhian MRR, Ardiansyah F, Susilawati Y, Wilar G, Sumiwi SA, Levita J, *et al.* Immunomodulatory and acute toxicity studies of peronema canescens jack leaves: in vivo hematological analysis and in vitro IL-6 gene expression inhibition. Indones Biomed J. 2025; 17(2): 295–306.
26. Monica E, Hasanah PD, Fadillah A, Aulia R, Sulistijono E, Wibowo S. Administration of vitamin D3 improves hemoglobin level by regulating TNF-α and IL-6 in DSS-induced colitis mice. Indones Biomed J. 2020; 12(2): 130–5.
27. Suswita R, Alvarino, Darwin E, Jamsari. Lactococcus lactis D4 has potential effect to alleviate inflammation and reverse dysbiosis in colitis rat model. Indones Biomed J. 2024; 16(2): 199–207.
28. Fu XL, Duan W, Su CY, Mao FY, Lv YP, Teng YS, *et al.* Interleukin 6 induces M2 macrophage differentiation by STAT3 activation that correlates with gastric cancer progression. Cancer Immunol Immunother. 2017; 66(12): 1597–608.
29. Sa'adah NAM, Ardiansyah E, Fadlilah DN, Izati R, Al-Faizah BN, Kavitarna SA, *et al.* Green tea yogurt supplemented with L. paracasei E1 microcapsules increases erythrocyte counts and B cell development in high-fat fructose diet mice. Mol Cell Biomed Sci. 2025; 9(1): 58–68.
30. Zhou D, Li Y. Gut microbiota and tumor-associated macrophages: potential in tumor diagnosis and treatment. Gut Microbes. 2023; 15(2): 2276314. doi: 10.1080/19490976.2023.2276314.
31. Febriza A, Ridwan R, As'ad S, Kasim VN, Idrus HH. Adiponectin and its role in inflammatory process of obesity. Mol Cell Biomed Sci. 2019; 3(2): 60–6.