

RESEARCH ARTICLE

Comparative Study of Intermittent Fasting and High Fat Diet in Preventing Amnesia in an In Vivo Model

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Abstract

The increase prevalence of Alzheimer's disease has intensified the search for non-pharmacological interventions, with dietary regimens like intermittent fasting (IF) and high-fat diets (HFD) showing promise yet possessing paradoxical metabolic effects. A direct comparison of their efficacy in a controlled model is lacking. This study aimed to directly compare the prophylactic potential of IF and HFD against metabolic and inflammatory markers associated with cognitive decline in a zebrafish larvae model. Zebrafish larvae were allocated to four groups for 12 weeks based on their diet variation. Survival, biometric data (weight), lipid profiles (cholesterol, triglycerides), and gene expression of metabolic (srebf1c and pparab) and pro-inflammatory (tnf- α and il1b) markers were analyzed. The HFD group exhibited significantly reduced survival, increased weight, dyslipidemia, and upregulated expression of both metabolic and pro-inflammatory genes. In contrast, HFD+IF2 regimen completely mitigated the HFD-induced lethality, normalized lipid levels and weight, and potently suppressed the pro-inflammatory cytokine expression to baseline levels. The HFD+IF1 group showed intermediate benefits, indicating that late intervention was less effective than a proactive strategy. Intermittent fasting, when implemented concurrently with a high-fat diet, is a powerful intervention that fully counteracts the detrimental metabolic and inflammatory effects of the diet. The potent anti-inflammatory effect of IF provides a compelling mechanistic rationale for its potential in preventing diet-associated amnesia, highlighting the critical importance of dietary timing in maintaining brain health.

1. Introduction

Alzheimer's disease (AD) is characterized pathologically by the accumulation of amyloid-beta plaques and neurofibrillary tau tangles, leading to synaptic dysfunction, neuronal death, and the progressive erosion of memory (Khan et al. 2025). In recent years, the focus has shifted from purely pharmacological interventions towards modifiable lifestyle factors, with diet emerging as a potent non-invasive modulator of brain health and disease risk. Among various dietary regimens, intermittent fasting (IF) and high-fat diets (HFDs) represent two seemingly paradoxical approaches

that have both demonstrated significant, albeit distinct, impacts on brain physiology and cognitive function. The central premise of this investigation is rooted in the intricate relationship between metabolic health and brain function. The brain, despite constituting only 2% of body weight, consumes approximately 20% of the body's energy, making it exquisitely sensitive to metabolic perturbations (Engl and Attwell 2015). Energy metabolism in the brain is tightly coupled to synaptic activity, neurotransmitter synthesis, and cellular repair mechanisms (Li and Sheng 2022). Dysregulation of this metabolic harmony, as seen in

conditions like insulin resistance and type 2 diabetes, is a well-established risk factor for cognitive decline and AD, a connection so strong that AD has been controversially termed "Type 3 Diabetes" (de la Monte 2014; Arnold et al. 2018). This metabolic-cognitive axis provides a compelling rationale for exploring dietary interventions that fundamentally alter systemic and cerebral energy metabolism.

IF primarily focuses on the timing of food consumption. Protocols such as alternate-day fasting or time-restricted feeding (e.g., 16:8, fasting for 16 hours and eating within an 8-hour window) have been shown to induce a metabolic switch from glucose-based to ketone-based energy metabolism (Soliman 2022). Ketone bodies, particularly beta-hydroxybutyrate, are not merely an alternative fuel source for neurons; they are potent signaling molecules that can inhibit histone deacetylases, leading to increased expression of neurotrophic factors like brain-derived neurotrophic factor (BDNF) (Jang et al. 2023). Conversely, the role of high-fat diets in brain health is complex and context-dependent. Chronic consumption of a typical processed diet, high in saturated fats and refined sugars, is strongly associated with metabolic syndrome, neuroinflammation, and impaired cognitive function (Martínez Leo and Segura Campos 2020). By drastically reducing carbohydrate intake, the ketogenic diet forces the liver to produce ketone bodies from dietary fats (Watanabe et al. 2020), inducing a state of nutritional ketosis similar to that achieved with IF. The therapeutic potential of the ketogenic diet has long been established for drug-resistant epilepsy, and growing evidence suggests benefits for other neurological conditions.

Despite the promising data for both IF and HFD, a direct, controlled comparison of their efficacy in preventing amnesia within the same experimental system is lacking. Most studies investigate each diet in isolation, against a standard control diet, making cross-comparisons difficult due to variations in species, disease models, and dietary compositions. To address these studies, we

used the zebrafish as a model organism. The zebrafish offers a unique and powerful platform for neuroscience research. Its brain, while simpler than that of mammals, possesses a high degree of conservation in terms of major neuroanatomical structures, neurotransmitter systems, and genes relevant to learning, memory, and neurodegeneration (Paduraru et al. 2023). Their rapid development, optical transparency during early stages, and genetic tractability are added advantages (Tan et al. 2022). Furthermore, the ability to induce amnesia through well-established chemical agents, such as scopolamine or aluminum toxicity, provides a controlled and reproducible model of cognitive dysfunction. Therefore, this study is designed to directly compare the prophylactic potential of intermittent fasting and a high-fat, ketogenic diet against amnesia in a zebrafish model.

2. Materials and Methods

2.1. Zebrafish Larvae Husbandry and Experimental Setup

Wild-type AB strain zebrafish (*Danio rerio*) larvae at 3 days post-fertilization (dpf) were randomly distributed into four experimental groups with distinct dietary regimens for a total study duration of 12 weeks. Group 1 (Control) received a standard diet for the entire 12-week period. Group 2 HFD for 12 weeks. Group 3 (HFD + IF1) underwent a 8-week HFD feeding period, followed by a 4-week combined intervention of HFD and IF. Group 4 (HFD + IF2) was subjected to a concurrent regimen of HFD and IF for the full 12 weeks. The HFD was prepared by supplementing a standard diet with 20% (w/w) coconut oil. The IF protocol consisted of a 16-hour fast followed by an 8-hour feeding window daily (Figure 1). Larvae were maintained in a controlled recirculating system, and the medium was changed regularly to ensure optimal water quality.

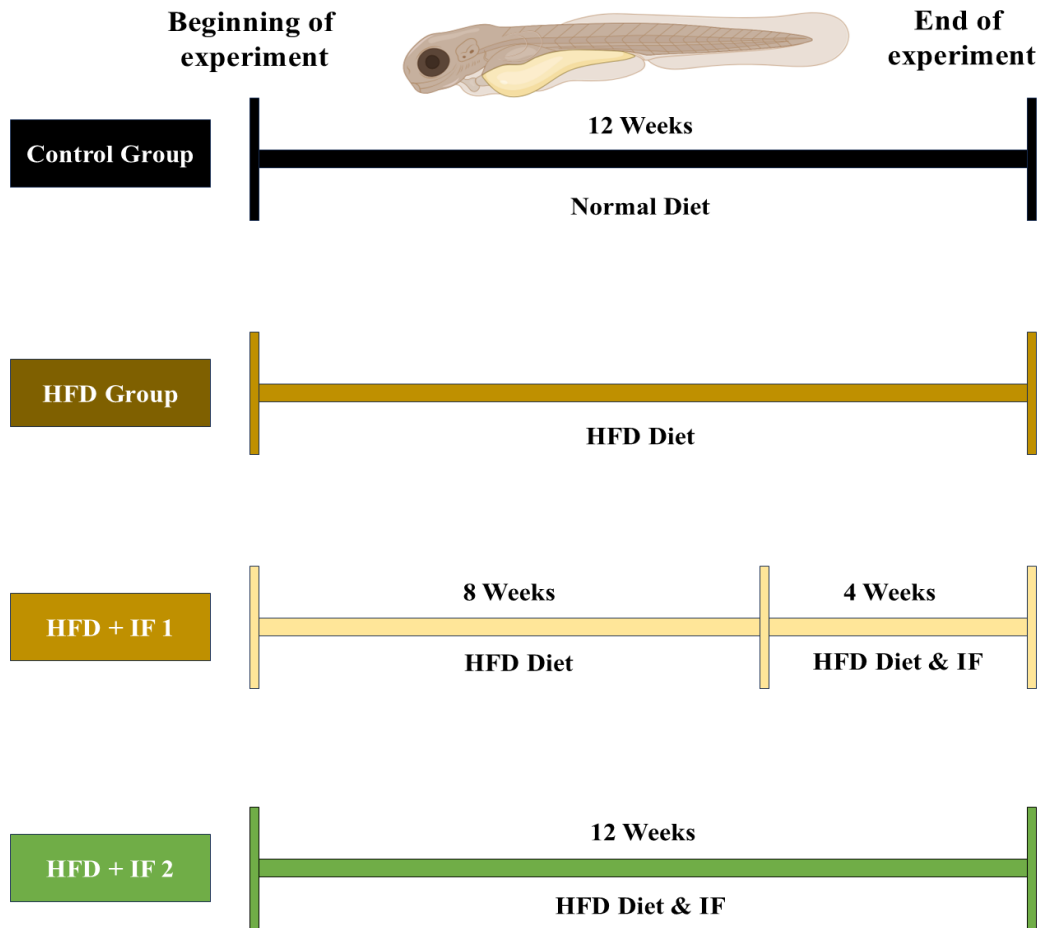


Figure 1: Schematic of the experimental design and dietary regimens. Zebrafish larvae (3 days post-fertilization) were allocated into four groups: Control (standard diet for 12 weeks), HFD (high-fat diet for 12 weeks), HFD+IF1 (HFD for 8 weeks followed by HFD combined with Intermittent Fasting for 4 weeks), and HFD+IF2 (concurrent HFD and IF for 12 weeks). IF was implemented as a 16-hour fast/8-hour feed daily cycle.

2.2. Survival Rate Analysis

Larval survival was monitored daily throughout the 12-week experimental period. The number of deceased larvae in each group was recorded every 24 hours, identified by the absence of a heartbeat and lack of movement. The cumulative survival rate for each of the four experimental groups was calculated at the end of the study period and expressed as a percentage of the initial population (Dai et al. 2015).

2.3. Larval Biometric and Biochemical Analyses

At the endpoint (12 weeks), larvae from each group (n=30 larvae per group) were anesthetized and pooled for analysis. The total wet weight of each pooled sample was measured using a precision microbalance to assess growth differences. For biochemical analysis, lipids were extracted from larval homogenates using a chloroform-methanol mixture. The concentrations of total cholesterol, free cholesterol, and triglycerides in the extracts were quantified using specific enzymatic colorimetric assay kits, with

absorbance measured via a microplate reader (Zhang et al. 2024). All biochemical values were normalized to the total protein content of the sample, determined by a Bradford assay, to account for variations in biomass.

2.4. Gene Expression Studies

Total RNA was isolated from the different groups of zebrafish larvae (n=20/group) using a commercial RNA extraction kit. RNA purity and concentration were determined spectrophotometrically. Following DNase treatment, cDNA was synthesized from 1 µg of total RNA using a reverse transcription kit. The mRNA expression levels of genes relevant to proinflammatory and lipid metabolism (srebf1c, pparab, tnf-α, and il1b) were analyzed by quantitative real-time PCR (qRT-PCR) using gene-specific primers (Table 1). The expression of the target genes was normalized to a stable reference gene (β-actin), and the relative fold change in expression was calculated using the $2^{-\Delta\Delta Ct}$ method, comparing each treatment group to the control group (Shihana et al. 2023).

Table 1: Primers used in Gene expression studies

Gene	Forward Primer	Reverse Primer	Reference
srebf1c	CATCCACATGGCTCTGAGTG	CTCATCCACAAAGAAGCGGT	(Li et al. 2018)
pparab	CGTCGTCAGGTGTTTACGGT	AGGCACTTCTGGAATCGACA	(Li et al. 2018)
tnf- α	AAGGAGAGTTGCCTTTACCG	ATTGCCCTGGGTCTTATGG	(Silva et al. 2024)
il-1 β	TGG CGA ACG TCA TCC AAG	GGA GCA CTG GGC GAC GCA TA	(Silva et al. 2024)
beta-actin	CTGTTCCAGCCATCCTTCTT	TGTTGGCATAACAGGTCCTTAC	(Silva et al. 2024)

2.5. Statistical analysis

All data are presented as the mean $\pm$ SEM from at least three independent replicates. For comparisons across the four experimental groups, a one-way analysis of variance (ANOVA) was performed. If the ANOVA indicated a significant overall effect ($p < 0.05$), post-hoc comparisons between individual groups were conducted using Tukey's Honestly Significant Difference test to control for multiple comparisons.

3. Result

3.1. Effect of dietary interventions on larval survival rate

The survival rate data reveals a critical finding regarding the toxicity of a chronic HFD and the protective

effect of IF. The group maintained on a continuous HFD for 12 weeks exhibited the lowest survival rate reduced to 45%, indicating that a sustained high-fat regimen is detrimental to the overall health and viability of zebrafish larvae. In stark contrast, the group subjected to a concurrent regimen of HFD and IF for the full 12 weeks demonstrated a survival rate (85%) comparable to the control group. This suggests that IF, when implemented early and consistently, can completely mitigate the lethal effects of the HFD. The intermediate group, which received HFD for 8 weeks before introducing IF, showed a partial rescue (65%) (Figure 2), implying that while late intervention is beneficial, it is not as effective as a prophylactic strategy in counteracting the cumulative toxicity of the high-fat diet.

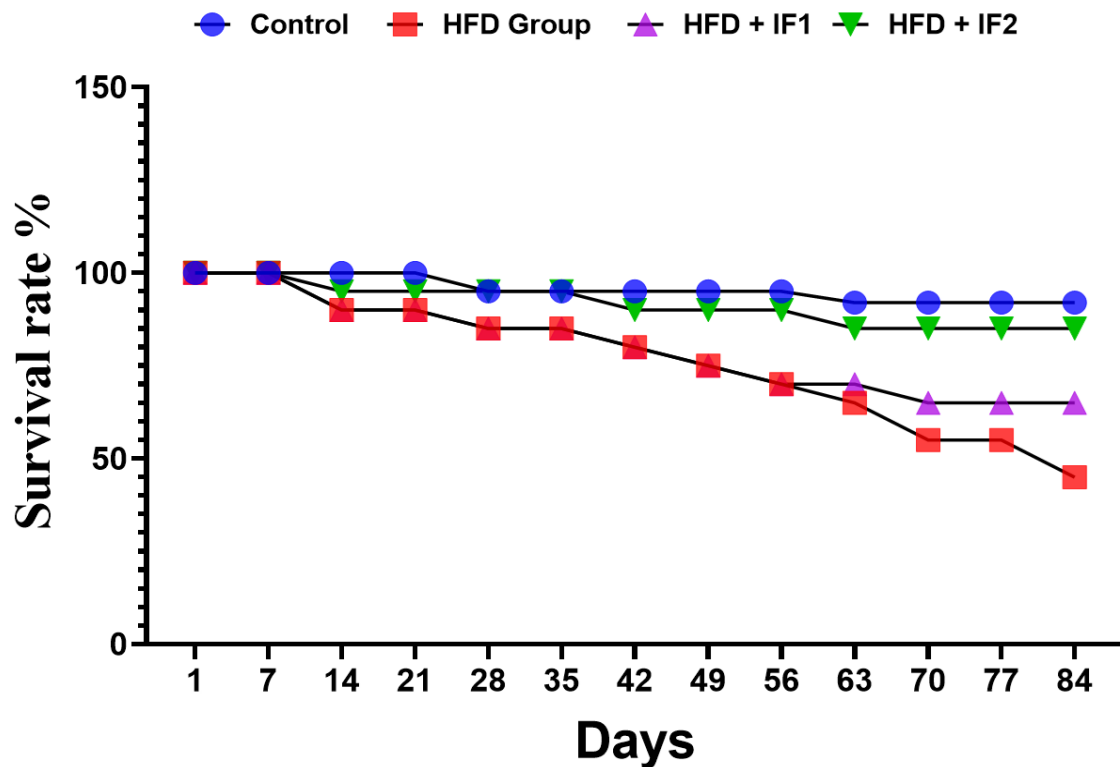


Figure 2: The survival percentage of zebrafish larvae over the 12-week experimental period. The HFD-only group showed a significant reduction in survival compared to the Control. The HFD+IF2 group (concurrent diet) demonstrated a survival rate comparable to the Control, while the HFD+IF1 group (late intervention) showed a partial rescue. Data are presented as mean $\pm$ SEM.

3.2. Impact of diets on larval growth and lipid metabolism

The biochemical results provide insights into the metabolic state induced by the different diets. The final larval weight was significantly highest in the HFD group (9 mg), indicating that the high-fat diet promotes growth or adiposity. Notably, the two IF-intervention groups of HFD+IF1 (8 mg) and HFD+IF2 (6 mg) showed a reduction in weight compared to the HFD-only group, suggesting that IF can counterbalance the weight-gain effect of the high-fat diet. This pattern is mirrored perfectly in the lipid profiles.

The HFD group displayed markedly elevated levels of total cholesterol (0.045 nmol/g of protein), free cholesterol (0.047 nmol/g of protein), and triglycerides (0.037 nmol/g of protein), confirming the diet's success in inducing a hyperlipidemic state. The introduction of IF, particularly the concurrent regimen of HFD+IF2, effectively normalized these levels, bringing them down to near-control values in total cholesterol (0.035 nmol/g of protein), free cholesterol (0.033 nmol/g of protein), and triglycerides (0.026 nmol/g of protein) (Figure 3). This demonstrates that IF potently counteracts the dyslipidemia caused by a high-fat diet.

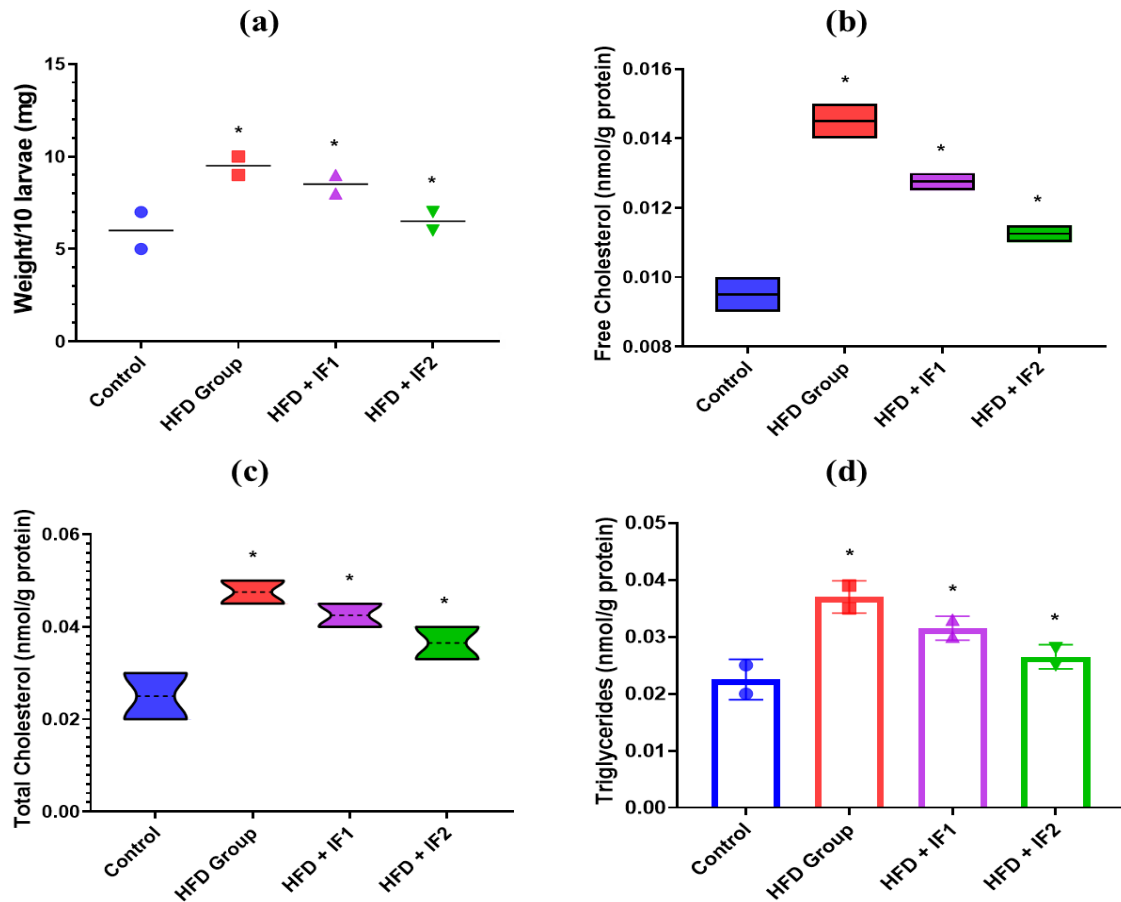


Figure 3. Figure 3: (A) Final wet weight of Zebrafish larvae, (B) Free Cholesterol, (C) Total Cholesterol, and (D) Triglyceride levels normalized to total protein. The HFD group resulted in significantly increased weight and dyslipidemia. Intermittent Fasting interventions (HFD+IF1 and HFD+IF2) counteracted these effects, normalizing metabolic parameters.

3.3. Gene expression analysis of metabolic and inflammatory markers

The gene expression data elucidates the molecular mechanisms underlying the observed physiological changes. The expression of key metabolic genes, *sreb1c* (4.3 fold) and *pparab* (2.4 fold), was significantly upregulated in the HFD group. This reflects a metabolic adaptation to the high-fat intake, promoting both lipid storage and utilization. The application of IF2 in HFD larvae, suppressed this upregulation in *sreb1c* (2.6 fold) and *pparab* (1.3 fold), normalizing the expression towards control levels. More importantly, the HFD

triggered a pronounced pro-inflammatory response, with a substantial increase in the expression of the inflammatory cytokines *tnf-α* (2.1 fold) and *il1b* (1.7 fold) (Figure 4). This indicates that the HFD induces neuroinflammation, a key driver of cognitive decline. Crucially, both IF protocols completely abolished this inflammatory response in *tnf-α* (1.5 fold) and *il1b* (1.2 fold), reducing cytokine expression to baseline levels. This powerful anti-inflammatory effect is a likely mechanism through which IF could prevent amnesia in this model.

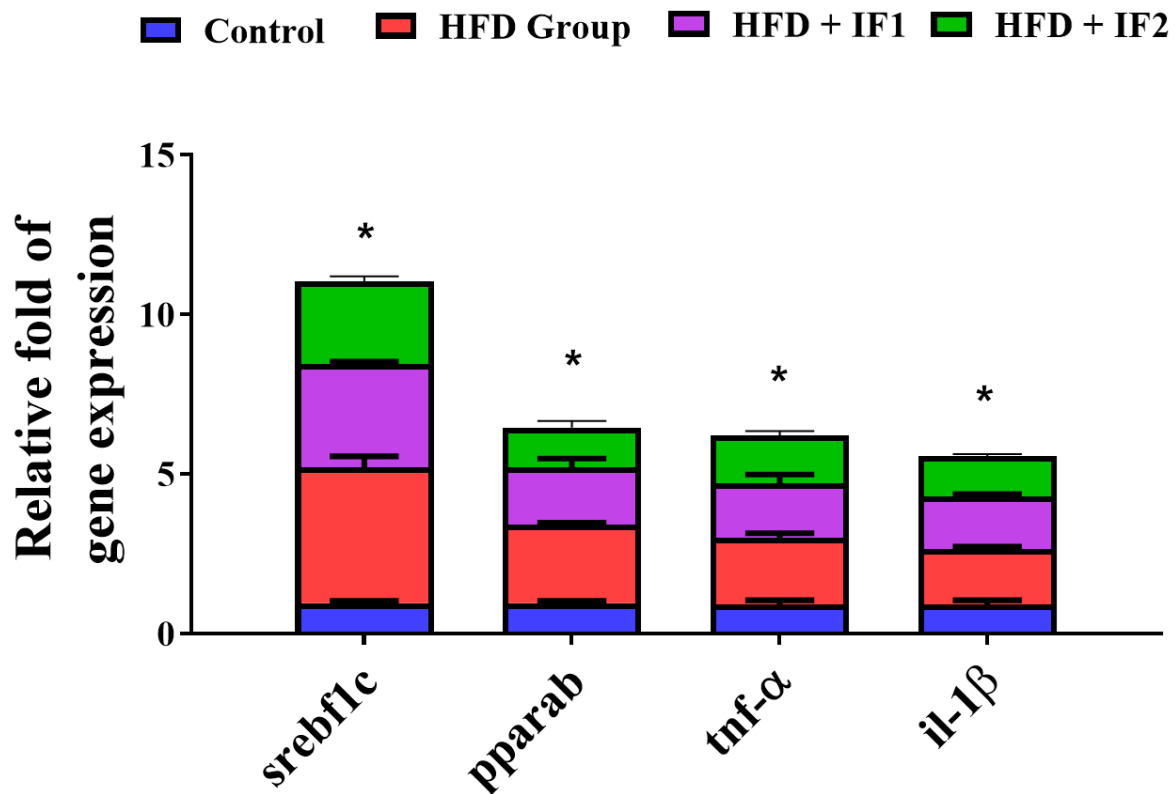


Figure 4: Relative mRNA expression levels of (A) *sreb1c*, (B) *pparab*, (C) *tnf- α* , and (D) *il1b* were quantified by qRT-PCR and normalized to β -actin. The HFD group showed significant upregulation of both lipid metabolism genes and pro-inflammatory cytokines. Both IF regimens (HFD+IF1 and HFD+IF2) effectively suppressed the HFD-induced inflammatory response and modulated metabolic gene expression.

4. Discussion

This study provides compelling evidence that IF is a potent intervention capable of mitigating the detrimental effects of a chronic HFD in a zebrafish model, with the timing of the intervention being a critical determinant of efficacy. Our findings demonstrate that a continuous HFD leads to significant mortality, dyslipidemia, and a pro-inflammatory state, all of which are profoundly ameliorated by the concurrent implementation of IF. These results have significant implications for understanding how dietary patterns can modulate metabolic health and neuroinflammation, a key driver of cognitive decline. The markedly reduced survival rate in the HFD-only group underscores the systemic toxicity of a sustained lipid-rich diet. This finding aligns with studies in mammalian models where long-term HFD consumption leads to organ dysfunction, metabolic syndrome, and reduced lifespan (Leonardi et al. 2020). The most significant finding was the complete rescue of survival in the HFD+IF2 group, which maintained a survival rate statistically indistinguishable from the control. This suggests that the metabolic stress induced by the HFD is not solely due to the fat content itself, but rather to the constant metabolic burden of processing it. IF, by imposing a daily fasting period, likely allows critical

recovery processes to occur (Longo et al. 2021). This could include enhanced autophagy, a cellular "housekeeping" process that clears damaged organelles and proteins, which is known to be upregulated during fasting states (van Niekerk et al. 2016). The partial rescue in the HFD+IF1 group indicates that while late intervention is beneficial, some of the HFD-induced damage may become irreversible over time, highlighting the importance of early and proactive dietary management.

The biometric and biochemical data offer a clear metabolic narrative. The increased larval weight and elevated levels of total cholesterol, free cholesterol, and triglycerides in the HFD group are classic hallmarks of diet-induced obesity and metabolic dysfunction. The effectiveness of IF, particularly the concurrent regimen, in normalizing both weight and lipid profiles is consistent with the established physiological effects of fasting (Yuan et al. 2022). During the fasting window, insulin levels drop, prompting a shift from lipid storage to lipid mobilization and fatty acid oxidation to meet energy demands (Marko et al. 2024). This metabolic switch prevents the continuous lipid accumulation seen in the HFD-only group. Our results correlate with human and animal studies showing that time-restricted feeding improves insulin sensitivity

and reduces hepatic steatosis, even without a reduction in overall caloric intake. The normalization of lipid levels by IF is a crucial finding, as dyslipidemia is a well-established risk factor for cardiovascular disease and has been strongly linked to the pathogenesis of Alzheimer's disease through mechanisms that compromise cerebrovascular integrity and promote amyloid-beta accumulation (Apátiga-Pérez et al. 2022; Naous et al. 2023). The HFD-induced upregulation of the pro-inflammatory cytokines *tnf- α* and *il1b* is a canonical response to metabolic stress and is consistently observed in the brains of animals fed a processed diet, where it drives neuroinflammation and synaptic impairment (Tan and Norhaizan 2019). The complete suppression of this inflammatory response in both IF intervention groups provide a compelling molecular mechanism for the protective effects of IF. The likely mediator of this effect is the elevation of ketone bodies, such as BHB, during the fasting state. BHB is not merely an alternative fuel; it is a signaling molecule that has been shown to inhibit the NLRP3 inflammasome, a key activator of the inflammatory cascade leading to the production of *IL-1 β* and other cytokines (Youm et al. 2015). By preventing the HFD-induced neuroinflammation, IF directly targets a key pathway implicated in amnesia and neurodegenerative diseases. Furthermore, the modulation of *srebf1c* and *pparab* by IF indicates a restoration of metabolic homeostasis. The downregulation of *srebf1c* suggests reduced lipogenic drive, while the normalization of *pparab* reflects a balanced state of fatty acid oxidation, both contributing to the improved metabolic phenotype.

5. Conclusion

In conclusion, our data demonstrate that Intermittent Fasting is not merely a tool for weight management but a powerful metabolic and anti-inflammatory strategy that can completely counteract the deleterious effects of a high-fat diet on survival, lipid metabolism, and neuroinflammation. The superiority of the concurrent (HFD+IF2) regimen over the late-intervention (HFD+IF1) model underscores the concept of "metabolic resilience" that proactively maintaining metabolic flexibility can prevent the onset of damage, rather than just treating it after the fact. Given the established link between neuroinflammation and cognitive decline, the observed suppression of *tnf- α* and *il1b* provides a strong mechanistic rationale for the hypothesis that IF could effectively prevent HFD-induced amnesia. Future work will directly link these molecular and metabolic improvements to cognitive performance in the scopolamine-induced amnesia model, further solidifying the role of IF as a non-pharmacological strategy for promoting brain health.

Declarations

Ethics approval statement

Not applicable

Consent to participate

Not applicable

Consent to publish

Not applicable

Data Availability Statement

The data are available from the corresponding author upon reasonable request

Competing Interests

The authors declare that they have no conflict of interest

Funding

Not Applicable

Author contribution

L.K: Conceptualization, Data curation, Investigation, Writing, Editing, & Formal analysis.

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