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Intermittent Fasting in Weight Management and Systemic Health: Mechanisms, Clinical Efficacy, and Biological Barriers - A Narrative Review

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ABSTRACT

Introduction. While most weight management approaches are difficult to maintain and focusing only on reducing calorie intake, intermittent fasting (IF) has gained popularity as an affordable and drug-free lifestyle option. However, its effects at both the cellular and systemic levels are still being discovered and are not yet fully understood.

Aim: To present the role, strategies, and mechanisms of intermittent fasting in the body over time, both in the context of weight management and its broader health impacts.

Materials and methods. Narrative, non-systematic review. We searched PubMed/MEDLINE and Google Scholar for English-language studies published between 2015 and 2026. Forty-nine studies were included.

Results. Intermittent fasting promotes ketone body production in the liver by breaking down fat and increasing cellular cleanup processes, rather than using glucose as the primary fuel source. It promotes clinically significant reductions in liver fat accumulation, improved peripheral insulin sensitivity, lowered blood pressure, and favourable restructuring of lipid profiles. Clinical trials show effects similar to continuous calorie restriction, including weight loss and improved cardiometabolic health in the first 1 to 6 months. These changes occur through pathways such as AMPK activation, mTORC1 suppression, sirtuin signalling, and changes in the gut microbiome. However, changes in fat tissue, hormone responses, and the body's adaptations make it hard to keep the weight off long term.

Conclusions. Intermittent fasting improves cardiometabolic and cellular health, with its most robust benefits driven by circadian timing rather than caloric restriction alone. Long-term weight loss matches continuous caloric restriction rather than exceeding it, as adipose tissue's persistent biological memory favors regain, so intermittent fasting should be recommended as a scalable lifestyle strategy rather than a guaranteed cure for obesity.

Key words: intermittent fasting; time-restricted eating; autophagic flux; metabolic flexibility; weight regain; gut-brain axis; cardiometabolic health

1. Introduction.

The modern environment has rapidly become obesogenic, disrupting human metabolic physiology and behavioural patterns [1, 2, 3]. World Health Organization (WHO) classify excessive adipose accumulation using Body Mass Index (BMI) into standard thresholds for underweight (BMI < 18.50 kg/m²), normal weight (18.50–24.99 kg/m²), overweight (25.00–29.99 kg/m²), and obesity (≥ 30.00 kg/m²) [2, 3, 4]. Population-level variances in body composition and cardiometabolic risk are reflected in regional lower BMI levels. This is especially true in Asia, where obesity is defined as BMI ≥ 27.00 kg/m² [2], while broader Southeast Asian guidelines define obesity as ≥ 23.00 kg/m² [3].

Across these categories, the global impact of metabolic disease has grown rapidly. Since 1990, adult obesity rates have more than doubled, with over 1 billion people affected in 2022 (890 million adults and 160 million children and teens) [3]. This results in 18.5% of women and 14.0% of men worldwide being obese in 2022, which simultaneously shifts the main problem from underweight to obesity. Projections suggest that more than 4 billion people could be affected by 2035 [6], and adult cases may reach 3.8 billion by 2050 [6]. This rise in adults is linked to a growing crisis among children, with obesity rates in youth aged 5-19 quadrupling between 1990 and 2022 to 160 million, and possibly reaching 254 million by 2030 [3, 7]. This growth in adolescence, a particularly sensitive period, is driven by a mix of genetics, socioeconomic factors, and behavioural changes that lead to poor diet, lack of exercise, and excessive screen time [8].

This rise in obesity leads to both more health problems and economic challenges [9, 10]. Too much body fat causes many chronic diseases, including heart disease, insulin resistance, hormone problems [11, 12], and certain cancers like colorectal, breast, liver, pancreatic, ovarian, and kidney cancers [3, 13]. When obesity starts in childhood, it can cause sleep apnea [14, 15], fatty liver disease [15], mental health issues [15], and early-onset type 2 diabetes with rapid blood vessel damage [15]. Obesity early in life also increases the risk of staying overweight as an adult [15], developing PCOS [15], and facing early disease and death from non-communicable diseases [14, 15]. The economic impact is substantial, with obesity-related health costs accounting for 5.8% of public health budgets and 0.6% of GDP in some European countries [16]. Worldwide, these costs are about 2.19% of global GDP [10], and could rise to 3.29% by 2060 [10] or cause a 2.9% drop in global GDP as soon as 2035 [6]. To tackle this

crisis, we need both broad policy changes and practical lifestyle solutions that are easy for individuals to use [9, 16].

Research Objective. To present the role, strategies, and mechanisms of intermittent fasting in the body over time, both in the context of weight management and its broader health impacts, especially in the context of the most common health problems.
Four questions are addressed:

1. What changes occur during different fasting durations?
2. Are different intermittent fasting protocols more effective than continuous caloric restriction?
3. What are the cellular mechanisms through which intermittent fasting exerts systemic health benefits?
4. What's contributing to weight regain after diet-induced weight loss?

2. Materials and methods

This narrative review was conducted to collect and synthesize evidence on the biological mechanisms, clinical efficacy, and weight-regain barriers associated with intermittent fasting. Literature searches were performed in the PubMed/MEDLINE and Google Scholar databases. The search covered publications from January 2015 to August 2026 to capture recent clinical trials and mechanistic studies published since intermittent fasting rose as a mainstream weight-management strategy. The review was restricted to English-language publications. Reference lists of retrieved articles were hand-searched for additional primary sources.
The keywords included combinations of: "intermittent fasting", "time-restricted eating", "alternate-day fasting", "caloric restriction", "autophagy", "AMPK", "mTORC1", "ketogenesis", "beta-hydroxybutyrate", "gut microbiota", "gut-brain axis", "metabolic flexibility", "weight regain", "adipose tissue remodelling", and "cardiometabolic health". Boolean operators AND and OR were used to refine the search results.
The review included randomized controlled trials, prospective cohort studies, systematic reviews, and meta-analyses as primary evidence for clinical efficacy outcomes, alongside key experimental, mechanistic, and physiological studies - including relevant preclinical (rodent and cell-culture) models - used to characterize the cellular and molecular pathways underlying fasting adaptation. Narrative and scoping reviews were retained separately for contextual and

mechanistic synthesis, particularly for pathways not yet addressed by systematic reviews or primary studies, and are identified as such wherever cited rather than treated as primary evidence for the review's clinical efficacy conclusions. Case reports and non-English publications were excluded.

The selection process involved screening titles and abstracts, followed by full-text assessment of eligible articles against the criteria described above. Searches across both databases returned an initial pool of candidate records, which was narrowed by removing duplicates and applying these criteria. Forty-nine studies met the inclusion criteria and were retained for the final synthesis.

3. Clinical Intermittent Fasting Protocols

Long-term weight management relies heavily on dietary interventions inducing energy restriction [17]. Modest weight loss brings profound cardiometabolic improvements, including increased insulin sensitivity, reduced hepatic steatosis, and improved glycemic control [11, 12, 18]. However, traditional continuous energy restriction (CER) is often difficult to sustain, and most people regain lost weight over time because biological mechanisms actively defend fat mass, such as altered gut hormones, reduced energy expenditure, and adaptive adipose physiology. [19, 20, 21]. GLP-1 receptor agonists offer effective pharmacological glycemic control and weight reduction [19, 17, 22]. In comparison, intermittent fasting (IF) is an expandable, low-cost, non-pharmacological alternative for cardiometabolic restoration [19, 23, 24, 25].

Historically, various cultures practiced IF worldwide for spiritual and health reasons [24]. It is grounded in the biological feast-and-fast cycle embedded in human evolutionary physiology [26]. Rather than continuous calorie tracking, IF structures regular transitions between extended fasting periods and normal eating windows [19, 23, 24]. Modern clinical protocols standardize IF into three main regimens:

- Time-Restricted Eating (TRE) - Restricts daily food intake to a specific window (e.g., 16:8) without requiring caloric counting [19, 24]
- Alternate-Day Fasting (ADF / mADF) - Alternates between complete or modified fasting days (allowing 20%–25% of energy needs, or ~400–600 kcal) and ad libitum eating days [19, 23, 24]

- Whole-Day Fasting (WDF) - Incorporates 1 to 2 non-consecutive fasting days per week (e.g., the 5:2 diet) [19, 23, 24].

In a clinical comparison, both 16:8 time-restricted eating and alternate-day fasting (specifically the 5:2 protocol) showed statistically similar short-term changes in body weight, body mass index, and relative body fat. Both schedules are equally suitable for structured weight-loss programs [27].

4. Systemic Efficacy and Health Outcomes

At the systemic level, extended food deprivation triggers a metabolic switch. As liver glycogen depletes, substrate utilization shifts away from glucose oxidation and lipogenesis toward adipose tissue fat mobilization, fatty acid beta-oxidation, and hepatic ketogenesis [23, 24, 26]. Fasting enhances adaptive cellular responses that suppress systemic inflammation, alter gut microbiota composition and downstream circulating metabolites, and activate autophagy [23, 24, 26, 28]. In adults with overweight, obesity, or metabolic syndrome, syntheses of reviews and network meta-analyses of RCTs put IF's benefits across a fairly wide range: smaller waist circumference and fat mass, lower visceral adiposity, reduced blood pressure, and improvements in total cholesterol, LDL-C, triglycerides, and fasting insulin [18, 19, 23]. Several independent systematic reviews report the same pattern [24, 25].

ADF has a modest edge over CER in short-term weight loss, but that gap closes in longer trials - by 24 weeks or more, the two approaches produce similar reductions in weight and cardiometabolic risk [19]. Much of this comes down to timing: summaries of systematic reviews find that weight loss tends to plateau within the first 1 to 6 months as the body adapts metabolically [23]. HbA1c responses are less consistent and depend heavily on who's fasting. In people with Type 2 Diabetes, glycemic improvement varies with how well the condition is managed and how closely the protocol is followed [19, 24], whereas non-diabetic individuals see more predictable gains mainly in weight loss, better insulin sensitivity, and lower blood pressure [23, 24, 25].

5. Chronological Dynamics of Intermittent Fasting (0–72+ Hours)

As a fast progresses, the body shifts from storing energy to breaking it down and protecting cells at the molecular level [31, 32, 33]. This progression is time-dependent: how long someone fasts determines which fuels are used, how hormone levels shift, and when cleanup processes like autophagy switch on [23, 32, 34].

In the early postprandial period (0–6 h), a mixed meal drives insulin and blood glucose to spike within the first hour, settling back to baseline by 2–4 h [29]. Insulin remains high through this window, which in turn suppresses both lipolysis and glucagon release [32]. The liver starts drawing down glycogen almost immediately [32, 33], while plasma triglycerides stay elevated well past 6 h, keeping the body in a lipogenic state [30, 32]. With insulin and nutrients abundant, macroautophagy stays switched off [33, 35]. However, glycophagy initiates early, breaking down glycogen to meet initial glucose demand [35]. The clinical signature of this phase is the postprandial glucose peak [29], clearance of serum amino acids [32], and elevated plasma triglycerides, a pattern that can persist 12–16 h daily in people who eat frequently [30].

Early ketogenesis and autophagy start by 6–12 h, as the body has left the postprandial state behind [32, 33]. Insulin keeps falling [31, 32, 33] and the glucagon-to-insulin ratio starts to climb [32]. Around the 8-hour mark, metabolism pivots from burning glucose to burning fat [31, 37], and the liver begins producing the first ketone bodies [31, 37]. Hepatic lipophagy, the autophagic breakdown of lipid droplets, initiates to sustain mitochondrial beta-oxidation [34, 38]. By 6 hours, double-membrane autophagosomes are already visible under electron microscopy [34]. Beta-hydroxybutyrate (BHB) levels start rising [31, 37, 39], while skeletal muscle releases more amino acids to support gluconeogenesis [33, 36].

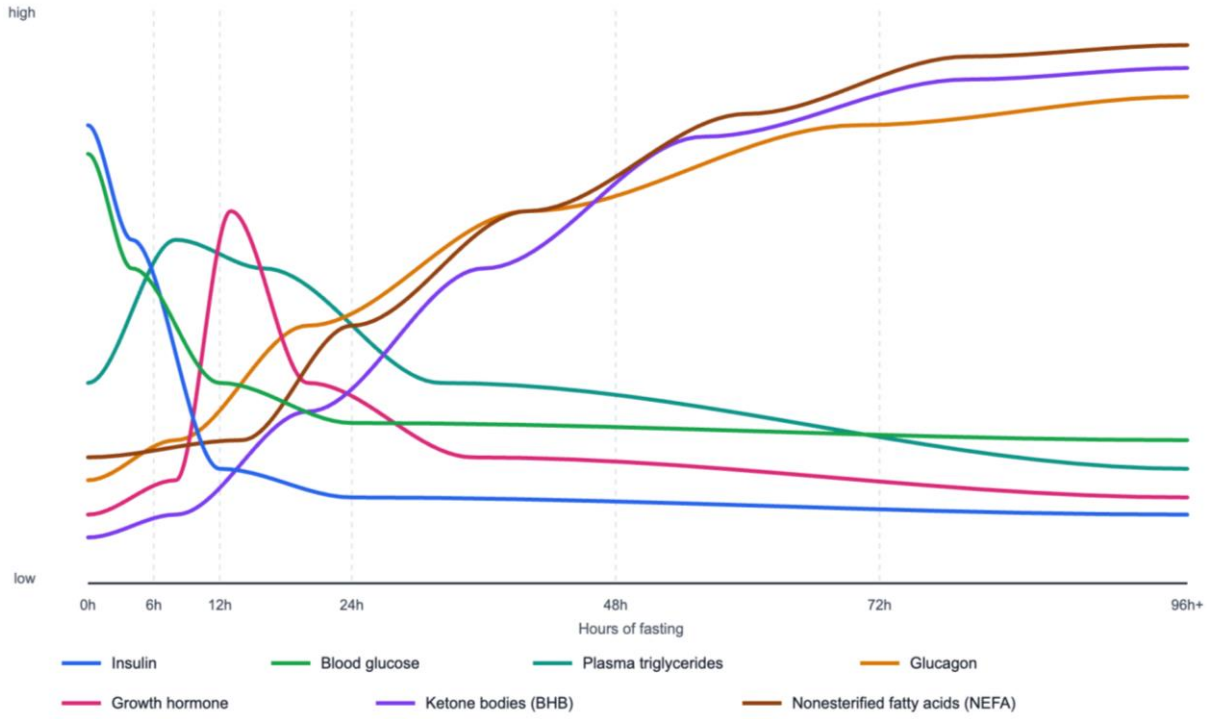
Between 12 and 14 h, three hormonal axes reset at once. Hepatic glycogen stores are largely depleted by then [32, 33], marking the start of metabolic adaptations that no longer depend on immediate energy availability [31, 33]. The pancreas elevates the glucagon-to-insulin ratio and suppresses baseline hyperinsulinemia [31, 32, 33]. Growth hormone surges alongside IGFBP-1, which binds up free IGF-1 [26, 31], and the thyroid axis dials down bioactive T3 while keeping TSH steady, serving as an energy-sparing adjustment [31, 32, 40]. As insulin's inhibition of mTORC1 diminishes, autophagic flux accelerates across the body [30, 33]. IGFBP-1 peaks here while free IGF-1 drops [26, 31], and TSH holds steady even as peripheral T3 declines [31, 32, 40].

The gluconeogenic shift (16-48h) demonstrates a sharp drop in glucose oxidation between 16 and 22 h [31, 32], while insulin stays low throughout [31, 32]. Endogenous glucose production shifts almost entirely to gluconeogenesis over this window. By 22 h, 67% , over 90% by 40–42 h [32], until it is essentially the sole glucose source by 48 h [32, 33]. After 48 h, peripheral tissues develop temporary insulin resistance to reserve glucose for the brain and other CNS tissues that cannot run on anything else [31, 33]. Selective protein breakdown also

accelerates, as amino acids are recycled to fuel hepatic gluconeogenesis, while structural proteins are largely spared [32, 36]. Hepatic gluconeogenic output peaks here [32], alongside a temporary dip in insulin-stimulated glucose uptake in skeletal muscle and adipose tissue [32, 33].

Systemic lipolysis (18–96 h) picks up in white adipose tissue between 18 and 24 h [31, 33] and roughly doubles by 72–96 h [32], with hormone-sensitive lipase essentially fully active once insulin is suppressed [32]. Around day 4, the brain switches to ketone bodies as its main fuel, letting hepatic gluconeogenesis ease off [32]. Adipose tissue also downregulates local renin-angiotensin activity, as angiotensinogen secretion falls to about a third of baseline after three days to alter local blood flow and lipid release [31]. Lipophagy and cytosolic lipases work in tandem here, maximizing the rate of fatty acid mobilization from lipid droplets [34, 38, 41]. Circulating nonesterified fatty acids surge [26, 42], while BHB levels settle into a steady-state plateau [31, 39].

From roughly 24 to 72+h, extended proteostasis and autophagy dominate. At this stage, both liver and peripheral tissues undergo substantial catabolic and cytoprotective remodelling [33, 36], as the body completes its shift to protein-sparing ketone oxidation [26, 32]. Sustained high glucagon paired with low insulin now drives organ-level quality-control processes [33, 39]. Lysosomal cathepsin D and chaperone-mediated autophagy both become active [34, 38, 43]; perilipin coat proteins (PLIN2/PLIN3) on lipid droplets are selectively broken down, helping prevent hepatic steatosis [34, 38, 41], and double-membrane autophagosome formation continues steadily throughout [33, 34]. Accordingly, PLIN2 and PLIN3 levels fall [34, 38], and the NLRP3 inflammasome is suppressed, reducing pro-inflammatory cytokines such as IL-1β and TNF-α [33, 37, 39].



Source: own elaboration. Figure 1. Relative Changes in Circulating Fuels and Hormones Across a Section 5. Curves show relative direction and timing of change, not measured concentrations. Dashed lines mark 6h / 12h / 24h / 72h.

6. Molecular and Cellular Mechanisms of Intermittent Fasting

The lack of nutrients inside cells, due to the changes described above, starts a molecular chain of events that changes energy use, improves quality control, and strengthens tissues [23, 31, 33, 39].

6.1 The Core Nutrient-Sensing Network (AMPK, mTORC1, and Sirtuins)

Changes happening in cells as a result of fasting are conducted by three primary mechanisms translating energy depletion into transcriptional and enzymatic reprogramming [31, 39]:

Energy Stress Sensing via AMPK: Declining intracellular ATP levels elevate the AMP-to-ATP ratio, directly activating 5'-AMP-activated protein kinase (AMPK) [35, 39]. Active AMPK, to maintain cellular ATP levels, suppresses energy-consuming anabolic processes (such as de novo lipogenesis) and activates catabolic processes (such as fatty acid beta-oxidation) [31, 33].

mTORC1 Deactivation and ULK1 Uncapping: AMPK directly phosphorylates and inhibits mechanistic target of rapamycin complex 1 (mTORC1) [31, 33]. Fasting-induced hypoinsulinemia and decreased circulating growth factors also inhibit mTORC1. It removes the tonic inhibitory block on the Unc-51-like autophagy activating kinase 1 (ULK1) initiation complex and fully launches autophagic flux [31, 33, 39]

NAD$^+$-Dependent Sirtuin Signalling (SIRT1/SIRT3): Metabolic stress increases intracellular NAD$^+$ availability, driving the activity of sirtuin deacetylases [31, 39]. SIRT1 works synergistically with AMPK to deacetylate nuclear Forkhead Box O (FoxO1/FoxO3) transcription factors, inducing master antioxidant and autophagic gene programs [31, 39]. Mitochondrially localised SIRT3 deacetylates key enzymatic targets, such as HMGCS2. It is associated with increased PDK4 expression, which inhibits the pyruvate dehydrogenase complex and shifts oxidation away from pyruvate toward fatty acid derivatives and ketone bodies [39].

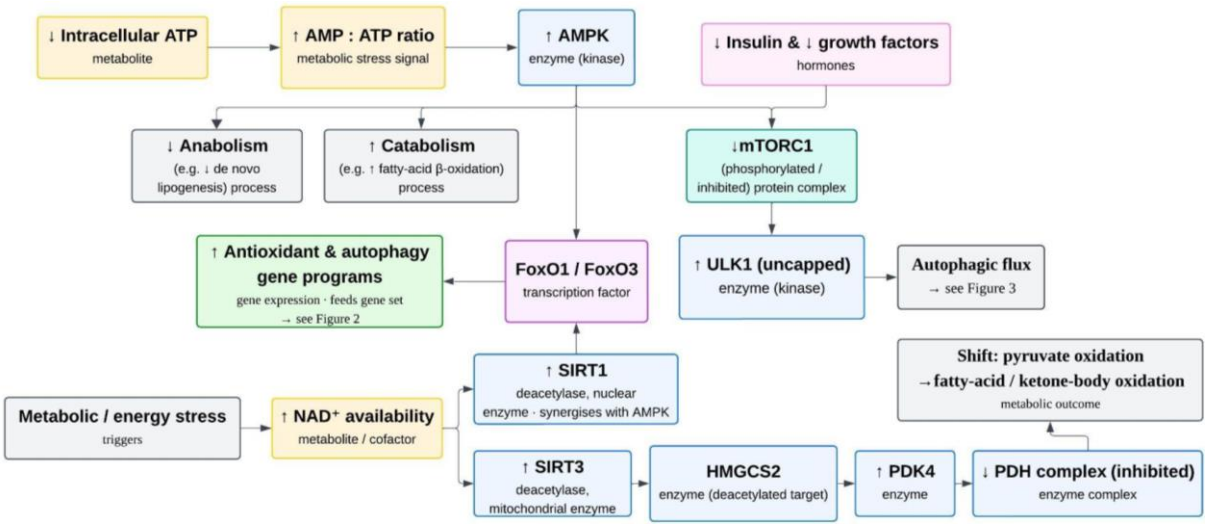


Figure 2. The Core Nutrient-Sensing Network. Arrows = activation / leads to. ↑ / ↓ = up-/down-regulation

6.2 Autophagic Execution and Selective Organellar Clearance

Activation of AMPK and suppression of mTORC1 follow macroautophagy execution and targeted organellar degradation [35, 38, 43]:

Initiation and Nucleation: The active ULK1 complex engages the class III phosphatidylinositol 3-kinase (PI3KC3/VPS34) nucleation complex (containing Beclin-1, VPS34, and ATG14) to generate local phosphatidylinositol-3-phosphate (PI3P) pools and initiate autophagosome membrane assembly [38, 43]. In parallel, hypoinsulinemia suppresses Akt signalling what permits FoxO1/3 nuclear translocation, which subsequently upregulates

core autophagic machinery including ATG7, ATG14, ULK1/2, NBR1, WDR45, and GABARAPL1 [35, 43].

Selective Organellar Degradation:

Glycophagy is an early lysosomal degradation of intracellular glycogen by specialized autophagosomes that releases glucose during initial postabsorptive stress [35].

Lipophagy and Direct Acid Lipolysis: Lipo-autophagosomes separate cytosolic lipid droplets or engage in contact-dependent lysosomal degradation to release free fatty acids [38, 41]. In rodent knockout models, genetic disruption of core autophagic machinery (ATG5 or ATG7) blocks lipid droplet delivery to mitochondria, severely impairing starvation-induced hepatic ketogenesis [34, 36, 38]. This causal mechanism has not been directly demonstrated in human tissue and is inferred in humans indirectly from circulating ketone and lipid biomarkers.

Chaperone-Mediated Autophagy (CMA): Extended fasting induces CMA to degrade perilipin proteins (PLIN2 and PLIN3) on the lipid droplet surface, enabling cytosolic lipases and lipophagic machinery to access stored neutral lipids while preventing hepatic steatosis [34, 38]. This pathway has been characterized primarily in rodent hepatocyte models.

Mitophagy and Inflammasome Restriction: Damaged mitochondria are targeted for lysosomal degradation through the accumulation of PTEN-induced kinase 1 (PINK1) and recruitment of the E3 ubiquitin ligase Parkin [38, 43]. Removal of ROS-generating mitochondria prevents cytosolic release of mitochondrial DNA (mtDNA) and damage-associated molecular patterns (DAMPs, AMPs), with resulting suppressing NLRP3 inflammasome assembly and dampening systemic inflammation [33, 39]. The PINK1/Parkin mechanism is established largely in cell culture and rodent models [38, 41, 43]; human circulating cytokine data support the downstream anti-inflammatory outcome [26, 29, 33, 39].

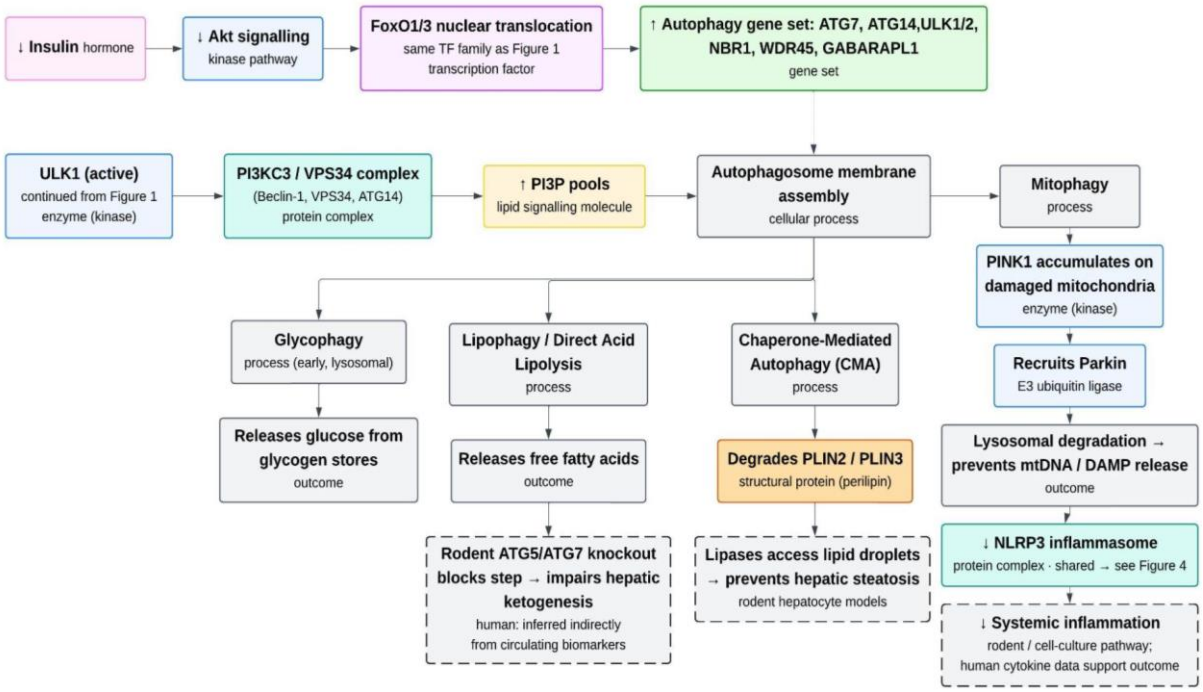


Figure 3. Autophagic Execution and Selective Organellar Clearance. Arrows = activation / leads to. ↑ / ↓ = up-/down-regulation. Dashed border = mechanism established primarily in rodent or cell-culture models, not yet confirmed in human tissue

6.3. Mitochondrial Biogenesis, Circadian Coherence, and Cytoprotection

Following the autophagic clearance of damaged cellular components, cells initiate structural regeneration in coordination with circadian rhythms [30, 31, 39].

- Coupled Mitochondrial Biogenesis: AMPK and SIRT1 work together to activate PGC-1α, a master regulator of mitochondrial gene expression [31, 39].Once switched on, PGC-1α drives de novo mitochondrial biogenesis, assembles the oxidative phosphorylation machinery, and measurably increases mitochondrial DNA replication under fasting conditions [31, 39].
- Circadian Clock Alignment: Fasting does not just affect metabolism in isolation — it also resets the body's peripheral clocks, the BMAL1/CLOCK and PER/CRY feedback loops that keep tissues synchronised [3, 30]. When eating is confined to a restricted window, this shows up as sharper morning surges in clock genes like BMAL1, CRY1, and RORA, which in turn keep mitochondrial activity, lipid handling, and inflammatory control running in step with the body's natural rhythm [29, 30, 31]. These findings come from human trial data, not animal models.
- BHB-Mediated Cytoprotection and Anti-Inflammatory Signalling*:* Beta-hydroxybutyrate (BHB) does more than supply energy during a fast — it also functions as a signal in its

own right [31, 39]. It blocks NLRP3 inflammasome assembly, limiting the release of the inflammatory cytokines IL-1β and IL-18 and dampening inflammation downstream [39]. At the same time, sirtuins activate FoxO transcription factors, which switch on superoxide dismutase — an antioxidant enzyme that helps protect cells against ischemic, oxidative, and apoptotic damage [30, 39].

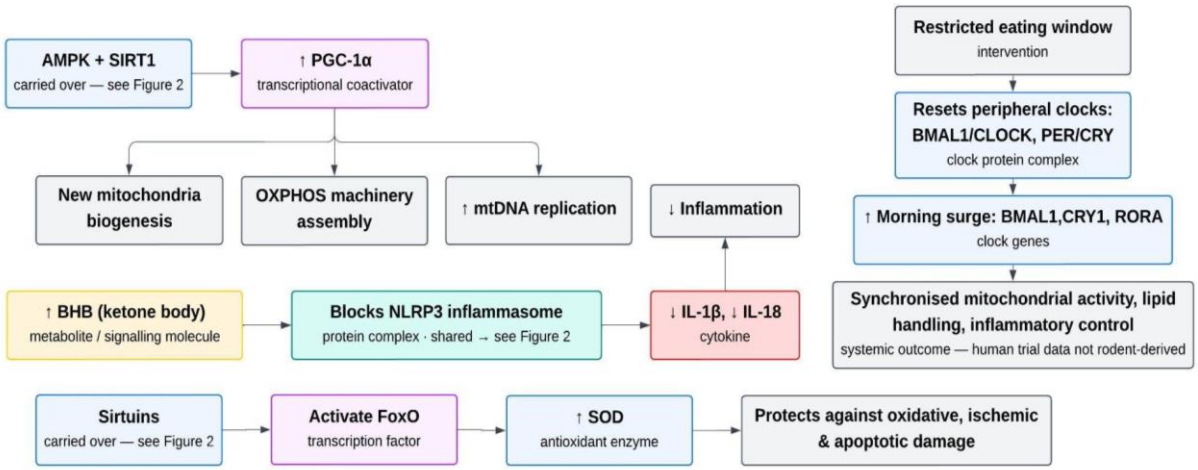


Figure 4. Mitochondrial Biogenesis, Circadian Coherence, and Cytoprotection. Arrows = activation / leads to. ↑ / ↓ = up-/down-regulation

7. Systemic Crosstalk: The Liver-Macrophage Axis, Gut Microbiome, and Neuroprotection

Fasting does not merely alter intracellular processes, but fundamentally alters intercellular communication [37, 44]. In the liver, hepatocytes cannot switch on ketogenesis alone. They require an initial signal from resident immune cells, and this metabolic cross-talk is what activates ketogenesis during a fast [37, 44]

A different version of the same idea plays out over a much longer distance, between the gut microbiome and the brain: as fasting reshapes which bacteria dominate the gut, the downstream effects seem to reach neurons directly, showing up as measurable neuroprotection and, in some studies, eased psychological strain [28, 44, 45].

7.1. The Macrophage-Hepatocyte Glucocorticoid Axis in Fasting Ketogenesis

Hepatocytes do not manage the liver's transcriptional response to fasting alone [37]. Single-cell genomic studies in mice show that hepatocytes and the liver's resident immune cells (Kupffer cell macrophages) must communicate for fasting-induced ketogenesis to occur [37]. As fasting progresses, rising glucocorticoid levels activate the glucocorticoid receptor (GR) in both cell types [37]. In macrophages, GR acts almost like a checkpoint: once activated, it

suppresses pro-inflammatory signaling, chiefly TNF, while boosting anti-inflammatory factors like Cd163 and Pla2g7 [37]. As long as local TNF stays suppressed, hepatocyte GR is free to move into the nucleus [37], where it partners with PPARα at fasting-responsive gene sites to switch on the core fat-oxidation and ketogenic genes: Hmgcs2, Acad11, Cyp4a10, Cyp4a14, and Hadhb [37].

If macrophage GR is not working properly, the opposite happens: TNF keeps circulating locally, hepatocytes become resistant to glucocorticoid signalling, GR cannot get into the nucleus, and fat mobilisation stalls [37]. This circuit was mapped in mice with macrophage- and hepatocyte-specific gene knockouts, but whether the same gatekeeping mechanism plays out identically in the human liver has not been directly tested [37].

7.2. Ecological Reassembly of the Gut Microbiome and Host Metabolome

Because fasting removes dietary nutrients from the gut almost entirely, it offers a rare natural experiment for studying how gut bacteria interact directly with their host once their usual food supply disappears [28]. During multi-day water fasting or time-restricted eating, the microbiome undergoes structural reorganization rather than simple contraction, with measurable shifts in dominant species [28, 46, 47]. Bacteria that specialise in breaking down dietary carbohydrates like starch, sucrose, and pectin lose ground quickly [28], while species equipped to digest the host's own mucus lining take over [28]. *Akkermansia muciniphila* is the clearest example: this mucinolytic bacterium has a documented survival advantage once other carbohydrate sources run out [46, 47], and members of the *Lachnospiraceae* family use a similar mucin-fermenting strategy to hold their ground through extended fasts [47].

Fasting also raises oxidative stress in the gut, and surviving bacteria respond by upregulating the pentose phosphate pathway to generate NADPH, providing the reducing power needed for antioxidant defense [28]. This may explain why overall microbial diversity tends to hold steady or even increase during human fasting and time-restricted eating, rather than collapsing under stress [46, 47].

This produces a distinct division into two functional groups [28]:

Fasting-Resistant Bacteria (FRBs): around 130 species, mostly from the *Bacteroidetes, Proteobacteria,* and *Fusobacteria phyla*, that get by on host-derived molecules — amino acids, glycoproteins, short-chain fatty acids — once dietary carbohydrates disappear [28]. When some food intake continues, as in time-restricted eating or Ramadan fasting, this group

notably includes a beneficial expansion of *Faecalibacterium prausnitzii*, an anti-inflammatory species that helps maintain gut barrier function [46, 47].

Fasting-Sensitive Bacteria (FSBs): around 140 species, mostly from the *Firmicutes phylum*, that decline once complex dietary carbohydrates disappear [28]. The drop is far steeper during prolonged water-only fasting — even *Faecalibacterium prausnitzii*, normally considered beneficial, falls off sharply, alongside pro-inflammatory groups like *Veillonellaceae* and *Negativicutes* [28, 47].

These shifts in the gut community do not stay contained to the gut — they ripple into the bloodstream. Multi-omics data show that more than half of the compounds detectable in blood and urine change measurably during fasting, largely reflecting metabolic byproducts from this shifting bacterial population [28]. Once refeeding begins, these levels return to baseline, which says something notable about how adaptable and reversible the human microbiome-host system really is [28].

7.3. The Gut-Brain-Microbiota Axis and Neuroprotective Signalling

The gut-brain-microbiota axis (GBA) is the bidirectional signalling pathway through which fasting-induced substrate switching, ketosis, and microbial restructuring exert downstream effects on the central nervous system [44, 45]. When this pathway is disrupted, the mechanism is well characterised: a compromised intestinal barrier permits translocation of bacterial endotoxins such as lipopolysaccharide into systemic circulation, and the resulting peripheral inflammation compromises blood-brain barrier integrity and precipitates neuroinflammation [44, 45].

Fasting counteracts this cascade primarily by enriching protective bacterial taxa, which reinforces epithelial tight junctions and thereby limits inflammatory signalling to the brain, reducing microglial activation and neuroinflammation downstream [44, 45, 47]. In parallel, fasting-adapted microbial short-chain fatty acids (acetate, propionate, butyrate) and tryptophan-derived metabolites enter systemic circulation [48, 49]. Notably, these SCFAs stimulate intestinal enterochromaffin cells to convert dietary L-tryptophan to serotonin via tryptophan hydroxylase 1 (TPH1), the rate-limiting step in serotonin biosynthesis, thereby supporting central serotonin availability, systemic neuroimmune regulation, and reduced neuronal oxidative stress [49].

Ketone bodies act as an independent neuroprotective substrate rather than merely a vehicle for microbial metabolites [26, 31]. Beta-hydroxybutyrate and SCFAs cross the blood-brain barrier via monocarboxylate transporters, enhancing mitochondrial bioenergetic efficiency, BDNF expression, and neuronal ATP generation [26, 49]. This evidence base is predominantly preclinical: the hippocampal-level detail derives from rodent models of dietary restriction and probiotic supplementation, while human data rely on peripheral biomarkers and behavioural outcomes rather than direct central tissue measurement. In these animal models, the combined effect of substrate switching and reduced inflammatory tone activates three discrete quality-control pathways in the hippocampus [44, 45, 49]:

- **Autophagy and Proteostasis:** Fasting and probiotics switch on macroautophagy in the brain, which helps clear toxic protein aggregates via a p62-dependent pathway and keeps neurons from triggering their own pro-apoptotic cascades under stress [44, 49].
- **Mitochondrial Homeostasis and Stress Resistance:** Prolonging a fast or pairing it with probiotics alters mitochondrial function in brain cells, making oxidation more efficient and activating antioxidant gene expression in response [44]. The net effect is improved mitochondrial resilience under stress [44].
- **BDNF and Synaptic Plasticity:** Both fasting and targeted probiotics raise BDNF levels, which supports new neuron growth, restores synaptic markers like PSD-95 and synaptophysin, and is linked to better cognitive performance and memory [44, 49].

These mechanisms have real translational weight — across several major neurological conditions, both animal and human evidence point to meaningful therapeutic benefit [44, 48, 49]:

- **Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI):** AD patients tend to show a dysbiotic gut profile — more pro-inflammatory phyla like *Pseudomonadota* and *Actinomycetota*, fewer SCFA producers like *Faecalibacterium* and *Roseburia* [45]. In animal models, correcting this balance through probiotics (*Agathobacter rectalis, Akkermansia muciniphila*) or direct SCFA administration reduces amyloid-beta and tau buildup, calms microglial activity via the Akt/NF-kB and ERK/JNK/NF-kB pathways, and slows cognitive decline [44, 45, 49]. In humans, though, the evidence is still observational — we can see the correlation, but the causal mechanism hasn't been established in the same way [44, 45, 49].

- **Multiple Sclerosis (MS):** A similar pattern shows up in MS — butyrate-producing genera like *Faecalibacterium* and *Roseburia* are consistently depleted, tipping the immune balance toward inflammatory Th17 responses and away from regulatory T cells [48]. Fasting and probiotic therapies (*Lactobacillus casei Shirota, Bifidobacterium infantis*) appear to help by restoring that Treg/Th17 balance, raising IL-10, and reinforcing the gut-brain barrier [48].
- **Parkinson's Disease (PD) and Mood Disorders:** In PD models, adding butyrate-producing bacteria (or butyrate itself) calms microglial overactivation through the RAS-ERK-NF-kB pathway, which protects dopamine neurons and improves motor symptoms; this evidence is mostly from rodents so far [44]. The human data points in a related but distinct direction: restoring *Faecalibacterium* specifically tracks improvements in anxiety and depression [44, 46, 47].

8. Adipose Tissue Plasticity, Epigenetic Memory, and the Biology of Weight Regain

Intermittent fasting is genuinely effective at reducing body weight and restoring cardiometabolic function [19, 24], but keeping that weight off long-term is a different problem entirely [20, 21]. Beating weight regain means tackling three things at once: the neuroendocrine feedback loops that push back against weight loss, an immune system that seems to "remember" a person's prior obesity, and structural stress responses happening inside white adipose tissue (WAT) itself [20, 21, 42].

8.1. Adipose Tissue Immune Remodelling and the Adipocyte p53 Control Loop

In obesity, WAT does not just store more fat — it physically deteriorates, becoming hypertrophic, oxygen-starved, and mechanically strained [21, 42]. When someone loses weight through dieting, adipocytes shrink, but they do so within a dense, fibrotic extracellular matrix. This mismatch generates mechanical and oxidative stress, enough to trigger localised cell death and form crown-like structures — clusters where macrophages surround and clear dying adipocytes [20, 21, 42]. Interestingly, these fasting-recruited macrophages do not fit the usual M1/M2 classification at all. Instead, they are a distinct population called Lipid-Associated Macrophages (LAMs), identifiable by a specific set of markers: Cd11c, Trem2, Gpnmb, Mmp12, and Lipa [42]. This was all characterised in mouse adipose tissue; whether human WAT shows the same LAM phenotype and marker profile remains an open question.

Adipocyte p53 signalling appears to drive this remodelling [42]. When nutrients become scarce, p53 activates in mature fat cells and sets off a cascade of pro-inflammatory and apoptotic signalling [42]. Researchers tested this directly in mice, knocking out p53 specifically in adipocytes (using an AdipoQ-CreERT2 x p53-lox/lox model), and found that doing so prevented the excess macrophage buildup and apoptotic stress that normally accompanies fasting [42]. The same knockout mice also showed better whole-body metabolic flexibility, improved lipid mobilisation, and sharper insulin sensitivity [42]. Human data present a related but less pronounced results— this time correlational rather than causal: diabetic patients on periodic fasting show metabolic responses that track with their p53 status, and people who regain weight after bariatric surgery tend to have lower TREM2 and TP53 expression in their visceral fat [21, 42]. Together, this points to a kind of persistent "obesity memory" — epigenetic and immunological — that resists remodelling and primes the tissue to re-accumulate fat quickly once refeeding starts [21, 42]. That said, it is important not to conflate these evidence types: the mouse-knockout data establishes causation, while the human findings are still correlational.

8.2 Physiological and Neuroendocrine Barriers to Weight Loss Maintenance

The body tightly defends its energy stores: weight loss activates powerful, evolutionarily conserved compensatory mechanisms designed to resist weight reduction and restore lost fat mass [20, 21]. Foremost among them is metabolic adaptation, wherein resting energy expenditure drops by more than body-mass changes alone would predict, meaning the body becomes disproportionately more energy-efficient than expected [20, 21]. On top of that, losing too much fat-free mass reduces the amount of metabolically active tissue a person has left, which in turn drives compensatory overeating and pushes fasting ghrelin levels up even under restricted intake [21].

This also has a neuroendocrine layer. Energy restriction lowers circulating neurotensin, a hormone that normally suppresses appetite [20, 21]. The brain picks up on this deficit and responds by ramping up hypothalamic hunger signals — specifically NPY and AgRP — which together push individuals to eat more [3, 21]. People who are especially prone to regaining weight also tend to show an exaggerated neurotensin spike after eating, compared to those who maintain their loss [21]. This hormonal pressure is reinforced by memory at the cellular level, through three distinct mechanisms:

- **Chromatin Accessibility:** Adipocytes that were once part of an obese phenotype do not fully reset — they retain altered chromatin structure and histone marks from before, which primes fat-storage genes to reactivate quickly once food becomes available again [21].
- **Adipose T Cell Retention:** T cells "primed" during the original obese state persist in adipose tissue even after weight loss, maintaining low-grade inflammation that promotes weight regain [21].
- **Adaptive Thermogenesis:** Not every adaptation works against weight maintenance, though. Weight fluctuation also recruits a specific immune cell population from bone marrow that secretes FGL2, which acts on beige adipocytes via TMEM120A receptors to boost thermogenesis — functioning as a built-in counterweight that helps limit regain [21].

9. Clinical Translation, Pharmacological Comparisons, and Future Directions

9.1. Long-Term Clinical Efficacy and Circadian Alignment

Pooling 99 randomised trials and 6,582 adults gives a fairly clear picture: ADF, TRE, and WDF all outperform ad-libitum eating in the short term [19, 23]. Push the timeline to 24 weeks, though, and fasting stops looking special — CER catches up completely, and the two approaches end up producing roughly the same amount of weight loss [19, 23]. Most people plateau somewhere in that first six months, once resting energy expenditure drops and the daily discipline fasting requires gets harder to sustain [19, 23].

What seems to matter just as much is when someone eats. In supervised trials, people assigned to early time-restricted feeding — a morning-aligned window with dinner finished before 3 PM — saw their blood pressure drop and their insulin sensitivity improve regardless of whether they actually lost weight [19, 24, 29]. Beta-cell function improved too, and lipid peroxidation measurably declined [29, 30]. Shift that same eating window later in the day, and the pattern reverses: late time-restricted eating leaves people with worse post-meal glucose control and slower lipid clearance [29, 30].

9.2. Intermittent Fasting vs Pharmacotherapy and Macroeconomic Impact

GLP-1 receptor agonists produce weight reductions of 10–15%, a benchmark intermittent fasting does not come close to matching [17, 19, 25]. That efficacy comes at a cost, though: roughly half of patients discontinue treatment within two years, largely from GI side effects,

and a meaningful share of the weight lost is lean mass rather than fat [17, 19, 25]. Fasting sidesteps all of that simply by not requiring a prescription, a pharmacy, or ongoing drug costs — a large part of why it can scale to entire populations in a way a $1,000-a-month injection never will [17, 19, 25].

Obesity already drains roughly 2.19% of global GDP through healthcare spending and lost productivity [4, 10, 25]. A fasting protocol costs nothing to run and nothing to access, which puts it in a different category from every other intervention discussed in this review — not a replacement for medical treatment, but the one option that scales to a population without a health budget behind it [4, 10, 25]. What remains unanswered is whether pairing circadian-aligned fasting with newer pharmacotherapies could protect lean mass and slow the metabolic rebound that so often follows once someone stops taking the medication.

10. Discussion, Including Risks and Limitations

Several independent lines of evidence in this review converge on a shared explanatory framework. Nutrient depletion activates AMPK, suppresses mTORC1, and upregulates sirtuin signalling, and these three pathways jointly license autophagic flux, hepatic ketogenesis, and downstream anti-inflammatory signalling through BHB-mediated NLRP3 suppression [31, 39]. Distinct systems such as hepatocyte biology, adipose tissue immunology, and gut-brain signalling share this underlying mechanism, all converging on identical nutrient-sensing networks [37, 42, 44, 45]. That consistency strengthens confidence in the general model, even where tissue-specific details, such as the macrophage-hepatocyte glucocorticoid axis or the adipocyte p53 checkpoint, remain incompletely validated in humans, as discussed further below [37, 42].

The clinical literature supports two claims of differing strength. Intermittent fasting produces short-term weight loss and cardiometabolic improvement relative to ad-libitum eating, but this advantage over continuous energy restriction disappears after about 24 weeks [19, 23]. More robustly, early time-restricted feeding improves blood pressure and insulin sensitivity independent of weight change, pointing to a circadian rather than purely caloric mechanism of benefit [19, 29]. This second finding carries more clinical weight than the first, since it does not depend on sustained weight loss, which is the outcome hardest to maintain over time. Neuroprotective outcomes constitute a third class, set apart from the previous domains by the

relatively nascent state of supporting evidence. Fasting-induced microbial and ketogenic changes correlate with improvements in mitochondrial function, BDNF signalling, and synaptic markers, with downstream associations reported in Alzheimer's disease, multiple sclerosis, and Parkinson's disease [26, 44, 45, 48, 49]. However, that evidence base relies heavily on rodent models and correlative human biomarker data rather than direct causal testing in human subjects.

Three recurring weaknesses limit how far these clinical findings can be generalised. Trial duration and sample size are systematically inadequate, as most randomised controlled trials and meta-analyses on intermittent fasting efficacy cluster at or below the 24-week mark. This window corresponds to the period when advantages over continuous energy restriction wane, meaning the literature has largely not observed long-term outcomes after intervention convergence [19, 23]. Methodological underpowering further compounds this issue. For instance, in one of the more rigorous early time-restricted feeding protocols, the expected decrease in serum insulin-like growth factor 1 failed to reach statistical significance ($p = .11$), plausibly indicating an inadequate sample size rather than the absence of a physiological response [30]. Evidence regarding microbiome and gut-brain signaling faces even more substantial methodological challenges. Key confounders, including baseline body mass index, age, and dietary fibre intake, are inconsistently controlled across cohorts [46, 47]. Furthermore, marked shifts in microbial diversity reported in small, single-arm studies often fail to replicate in larger pooled analyses [19, 23, 47]. This inconsistency suggests that these discrepancies stem from statistical underpowering and study design heterogeneity rather than a lack of true physiological impact. Most structurally significant is that much of the mechanistic evidence synthesised in this review derives from rodent knockout models rather than human tissue, including the ATG5/ATG7-dependent route to hepatic ketogenesis, the macrophage-hepatocyte glucocorticoid axis, and the adipocyte p53 control loop [34, 37, 42]. Corresponding human evidence remains strictly correlative, as seen in clinical observations tracking p53 status against fasting responses in patients with diabetes, or TREM2 expression against post-bariatric weight regain [21, 42]. Associations of this nature demonstrate that a pathway is detectable in humans rather than confirming that it executes the identical causal role observed in the corresponding knockout model. This distinction should properly govern the degree of confidence with which the mechanistic claims synthesised throughout this review are evaluated against its clinical findings.

Across both intermittent fasting and pharmacotherapy, adverse effects are documented with considerably higher precision than long-term clinical benefits. Glucagon-like peptide-1 receptor agonists demonstrate a two-year discontinuation rate approaching 50 per cent, driven primarily by gastrointestinal intolerance [22, 25], with lean tissue accounting for 20 to 40 per cent of total mass loss under these therapeutic agents [17, 25]. Intermittent fasting carries its own distinct clinical risk profile, with most participants reporting mild adverse effects across studies [19]. Specifically, early time-restricted feeding has produced paradoxical increases in morning heart rate, cholesterol, and triglycerides among men with prediabetes [29], whereas 5:2 fasting elevates the risk of hypoglycemia in patients with type 2 diabetes and occasionally induces electrolyte imbalances [19, 24]. In both cases, the imbalance between well-quantified risk and less certain long-term benefit calls for caution in how either intervention is recommended for extended use.

Addressing these gaps will require several specific developments. Long-term RCTs of at least 52 weeks, tracking hard clinical endpoints such as cardiovascular events and mortality, would clarify whether IF's short-term advantages translate into meaningful long-term outcomes [19, 23]. Causal methods such as faecal microbiota transplantation and metabolomics-driven modelling would move microbiome research beyond descriptive taxonomic shifts toward genuine mechanistic understanding [44, 47]. Targeted human tissue studies, particularly adipose or hepatic biopsy cohorts, are needed to test directly whether the rodent-derived mechanisms discussed throughout this review hold up in human physiology. Finally, interventional trials combining early time-restricted feeding with low-dose GLP-1 therapy, together with standardised definitions for metabolic syndrome and a core outcome set for microbiome research, would address both the treatment-combination question raised above and the heterogeneity problem underlying much of the current literature [25, 45, 46, 47].

11. Conclusions

This review points to a consistent asymmetry that should guide how its findings are used. The cellular and mechanistic evidence is coherent across multiple tissue systems, but that coherence is strongest in preclinical models and weakens considerably once tested against direct human data. The clinical evidence follows a related pattern: intermittent fasting performs well on short-term, weight-independent measures such as blood pressure and insulin

sensitivity, yet loses its distinctiveness on long-term weight outcomes, where it converges with continuous caloric restriction rather than surpassing it.

This asymmetry has a practical implication. Intermittent fasting is best supported as a circadian-aligned strategy for improving cardiometabolic and cellular health, a claim that rests on comparatively strong human evidence. It is not well supported as a long-term solution to obesity or weight regain on its own, since the biological barriers to sustained weight loss described earlier in this review operate largely independently of which dietary strategy produced the initial loss.

The same caution extends to comparisons with pharmacotherapy. Neither intervention has a clean advantage: one offers greater short-term efficacy at the cost of higher discontinuation and lean-mass loss, the other offers greater accessibility without matching that efficacy. Positioning the two interventions as competitors misrepresents both the scientific evidence and the clinical need, whereas the more productive framing and urgent research priority centers on how they might be combined effectively rather than which one should be selected.

Taken as a whole, intermittent fasting warrants recommendation as a scalable, low-cost, circadian-aligned lifestyle strategy for cardiometabolic and cellular health, offered with the explicit understanding that it is neither a substitute for indicated pharmacotherapy nor a guaranteed resolution to obesity or weight regain.

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