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Molecular Mechanisms and Clinical Translation of Intermittent Fasting on Adipose Tissue Heterogeneity

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Abstract: Adipose tissue heterogeneity, particularly the pathogenic role of visceral adipose tissue (VAT) in metabolic diseases, poses significant clinical challenges. Current research confirms that intermittent fasting (IF) induces depot-specific adaptations: VAT exhibits lipid conservation mechanisms while subcutaneous adipose tissue (SAT) demonstrates thermogenic plasticity through microbiota crosstalk. The gut-liver axis further mediates systemic metabolic synchronization during IF. However, precise frameworks for stratifying IF protocols based on adipose biology remain underdeveloped. This review synthesizes molecular mechanisms driving VAT/SAT differential responses to IF, evaluates depot-specific efficacy of major regimens, and establishes a visceral fat ratio (VFR)-based precision framework. Key findings indicate that early time-restricted eating (eTRE) preferentially reduces VAT with glycemic stability, whereas alternate-day fasting (ADF) carries long-term rebound risks. Integration of circadian-aligned exercise and behavioral support significantly enhances intervention sustainability. This analysis provides clinically actionable stratification: high-VFR individuals benefit maximally from eTRE-exercise synergy, while moderate-VFR phenotypes require vigilant cardiometabolic monitoring during ADF. The framework addresses critical implementation barriers including lean mass preservation and adolescent contraindications. Future research should prioritize digital adherence platforms and biomarker-defined feeding windows to optimize personalization. This work establishes a mechanism-informed foundation for translating adipose-specific IF benefits while highlighting unresolved questions regarding long-term vascular impacts and tissue-specific circadian reprogramming.

Keywords: Adipose Tissue Heterogeneity, Intermittent Fasting, Visceral Adipose Tissue, Precision Nutrition.

1. Introduction

Adipose tissue heterogeneity represents a critical determinant of metabolic health, with visceral adipose tissue (VAT) independently predicting insulin resistance, dyslipidemia, and non-alcoholic fatty liver disease. The pathogenic role of VAT contrasts with subcutaneous adipose tissue (SAT), where preserved thermogenic capacity may confer protective effects. Traditional weight management strategies demonstrate limited efficacy in selectively targeting VAT depots while maintaining sustainable outcomes. Intermittent fasting (IF) regimens—particularly time-restricted

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eating (TRE) and alternate-day fasting (ADF)—have gained prominence for their potential to modulate adipose biology through circadian metabolic switching.

Current research has established depot-specific adaptations to fasting: VAT develops lipid conservation phenotypes via PLIN1 upregulation and lipolysis suppression, whereas SAT exhibits beige remodeling mediated by microbiota-derived butyrate and UCP1 induction. The gut-liver axis further coordinates systemic effects through intestinal barrier enhancement and hepatic metabolic reprogramming. Despite these advances, significant knowledge gaps persist regarding anatomical patterns of fat mobilization, long-term depot-specific efficacy, and predictors of cardiometabolic trade-offs across heterogeneous populations. Crucially, no consensus exists on precision frameworks for stratifying IF protocols based on adipose biology.

This review addresses these gaps through comprehensive analysis of molecular mechanisms and clinical evidence. Primary objectives include: 1) elucidating lipid droplet dynamics and mitochondrial adaptations underlying VAT/SAT differential responses, 2) evaluating spatiotemporal efficacy of major IF regimens across adipose depots, and 3) establishing a visceral fat ratio (VFR)-based stratification system for personalized implementation. The analytical approach integrates proteomic data, clinical trial evidence, and cardiometabolic safety profiles to develop mechanism-informed decision pathways.

Key findings demonstrate that early TRE (eTRE) sustains VAT reduction through cortisol rhythm synchronization, achieving superior visceral fat loss (-18.7 cm^2) with stable glycemic control. In contrast, ADF shows paradoxical effects—significant triglyceride reduction (-16.2 mg/dL) but elevated LDL-C (+8.5 mg/dL) and late-phase visceral rebound. Synergistic interventions prove essential: aerobic exercise amplifies SAT thermogenesis via irisin-FNDC5 signaling, while behavioral support improves protocol adherence by 35%. The resultant precision framework utilizes VFR thresholds (30%) to guide intervention selection, with high-VFR phenotypes benefiting most from eTRE-exercise combinations, while moderate-VFR individuals require vigilant LDL monitoring during ADF.

This work contributes a clinically actionable roadmap for implementing adipose-targeted IF regimens. By resolving critical barriers including lean mass preservation and dysmetabolic risk mitigation, the proposed framework addresses urgent needs in metabolic disease management. Subsequent sections systematically examine molecular bases of adipose heterogeneity (Chapter 1), depot-specific intervention efficacy (Chapter 2), and precision implementation pathways (Chapter 3), concluding with translational priorities for future research.

2. Molecular basis of adipose heterogeneity and IF regulation

2.1. Anatomical and functional differentiation of fat depots

Adipose tissue heterogeneity manifests as functional differentiation into white adipose tissue (energy storage), brown adipose tissue (thermogenesis and energy expenditure), and beige adipose tissue (thermogenesis-indictable). The generation of beige fat is regulated by PR domain-containing protein 16 (PRDM16) [1], which enhances thermogenesis by activating mitochondrial respiration and fatty acid oxidation [2]. Metabolic differences between VAT and SAT stem from developmental origins and microenvironmental differences. VAT highly expresses lipid droplet protective protein PLIN1 [1], while SAT responds to butyrate, a gut microbiota metabolite, via G protein-coupled receptor 41 (GPR41) [3], inducing thermogenesis mediated by uncoupling protein 1 (UCP1) [3,4].

VAT and SAT exhibit divergent responses to IF due to distinct molecular pathways (as shown in Table 1). Proteomic studies demonstrate that during ADF, VAT upregulates lipid droplet protective

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protein PLIN1 by 2.1-fold while suppressing hormone-sensitive lipase (HSL) activity by 60%, resulting in 40% lower lipolytic efficiency compared to SAT [1]. This is compounded by mitochondrial dysfunction: VAT exhibits only 65% of SAT's Complex I activity and 35% lower ATP production [2]. Conversely, SAT displays metabolic plasticity through TRE. Gut microbiota-derived butyrate (Akkermansia abundance ↑3.2×) activates GPR41 receptors, elevating UCP1 expression 3.2-fold and increasing thermogenic energy expenditure [3]. Clinical biopsies confirm TRE increases multilocular lipid droplets in SAT from 12% to 35% (*p*=0.003) [4]. Proteomics data show that after ADF, PLIN1 expression in VAT increases by 2.1-fold [1], hormone-sensitive lipase (HSL) activity decreases by 60% [1], resulting in lipolysis efficiency that is 40% lower than in SAT [1]. Mitochondrial dysfunction is directly associated: complex I activity in VAT is only 65% of that in SAT [2], and ATP production decreases by 35% [2]. In contrast, TRE increases UCP1 expression in SAT by 3.2-fold [3,4] and thermogenic energy expenditure by 200% [4]. Clinical biopsies further confirm that the proportion of multi-vesicular lipid droplets in SAT increases from 12% to 35% following TRE intervention [4].

Table 1. Differential IF responses in adipose depots [1-4]

Parameter	VAT Change	SAT Change	Method
PLIN1 expression	↑2.1-fold	No significant change	Western blot
HSL activity	↓60%	↑90%	Radiolabeled glycerol assay
Mitochondrial Complex I	65% of SAT	Baseline	High-resolution respirometry
UCP1 expression	Unchanged	↑3.2-fold	Immunohistochemistry

2.2. Gut-liver axis as central regulator

Experiments using SIRT1-specific inhibitors (EX-527) and agonists (SRT1720) in hepatocyte culture models have demonstrated that the gut-liver axis coordinates systemic metabolic rhythms through gut microbiota metabolites. Short-chain fatty acids (such as butyrate) activate hepatic silent information regulator 1 (Sirtuin 1, SIRT1) [5], enhancing the peroxisome proliferator-activated receptor alpha (PPARα)-peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α) pathway [6], synchronizing the circadian oscillations of fatty acid oxidation and ketogenesis [6].

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Intestinal barrier integrity is maintained by tight junction proteins (such as ZO-1) [7,8], whose expression is regulated by microbiota metabolites [5].

IF remodels hepatic metabolism via microbiota-metabolite crosstalk. TRE elevates colonic butyrate by 150%, activating hepatic Silent Information Regulator Two 1(SIRT1) deacetylase and increasing Carnitine Palmitoyl Transferase 1A(CPT1A) activity 2.3-fold (*p*<0.01) [5]. Fasting ≥16 hours triggers Peroxisome Proliferator-Activated Receptor α and Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-α (PPARα-PGC1α) pathway activation, synchronizing circadian oscillations in 43 metabolic pathways (including β-oxidation and ketogenesis) [6]. Clinically, 5:2 IF for 12 weeks reduces hepatic fat by 20.5% (MRI-PDFF, *p*=0.003) and serum TNF-α by 35% (*p*<0.05) [7], mediated through gut barrier restoration (ZO-1 ↑50%) and reduced endotoxemia [8]. Provides molecular timing evidence for the biological clock optimization of the IF scheme.

3. Fat depot-specific effects and clinical optimization of IF

3.1. Spatiotemporal efficacy of fasting protocols

IF regimens exhibit depot-selective effects (Table 2). eTRE; 8:00-16:00 synchronizes peripheral Bmal1 oscillations, preferentially reducing VAT (visceral fat area Δ=-18.7 cm^2, waist circumference Δ=-4.3 cm) [9]. Conversely, while ADF achieves superior short-term weight loss (Δ=-1.29 kg vs. continuous energy restriction at 24 weeks), it shows 25% waist circumference rebound by week 28 [10]. ADF also exhibits paradoxical lipid effects: reducing triglycerides (-16.2 mg/dL) but elevating LDL-C (+8.5 mg/dL) [11].

The metabolic advantage of eTRE stems from its synergistic effect with cortisol rhythms. Fatty acid mobilization efficiency peaks with morning feeding (08:00-10:00), when adipose tissue Beta-3 Adrenergic Receptor(ADRB3) phosphorylation levels are 50% higher than in the afternoon (*p*=0.01), which is directly related to cortisol-driven activation of cAMP-PKA signaling [9]. Clinical MRI data showed that visceral fat loss in the eTRE group occurred predominantly in the omental region (Δ=-12.3 cm^2), while retroperitoneal fat changes were not significant (Δ=-2.1 cm^2), confirming that anatomical location influences IF response [7]. For the rebound phenomenon in ADF, lipoprotein lipase (LPL) activity was consistently elevated by 40% in VAT (*p*=0.008), promoting dietary fatty acid reuptake, and this adaptive resistance was more pronounced in females (waist circumference rebound rate was 38% higher than in males) [10].

Studies on the selective effects of different IF protocols on fat stores provide direct evidence for clinical precision interventions. eTRE, by synchronizing peripheral circadian clock gene oscillations, prioritizes the reduction of visceral fat in the omental region by 18.7 cm^2 [9], a mechanism closely associated with the morning cortisol peak enhancing ADRB3 phosphorylation. This effect also reduces nocturnal blood glucose fluctuations by 40%. ADF exhibits time-dependent risks: after 28 weeks, a 40% increase in LPL activity in VAT led to a 25% waist circumference rebound rate, with women facing a 38% higher rebound risk than men [10]. This phenomenon highlights the clinical limitations of long-term ADF application. ADF's dual impact on lipid profiles—a 16.2 mg/dL reduction in triglycerides accompanied by an 8.5 mg/dL increase in LDL-C—serves as a warning for individualized treatment strategies in cardiovascular risk populations [11].

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Table 2. Clinical outcomes of IF protocols [9-11]

Protocol	Duration	Δ Visceral Fat	Δ Body Weight	Key Metabolic Effects
eTRE	12 weeks	↓18.7 cm²	↓3.8 kg	Nocturnal glucose fluctuation ↓40%
ADF	24 weeks	↓15.2 cm²	↓5.1 kg	Triglycerides ↓16.2 mg/dL
ADF	28 weeks	Rebound +25%	Maintained -3.2 kg	LDL-C ↑8.5 mg/dL

3.2. Synergistic interventions for metabolic enhancement

Tinsley et al. recruited 86 obese patients and divided them into a TRE group (8-hour eating window) and a TRE+exercise group (5 sessions of resistance training per week) [12]. Using dual-energy X-ray absorptiometry (DXA) and maximal oxygen uptake testing, it was found that irisin released from skeletal muscle in the exercise group was 3.2 times higher than in the control group (*p*=0.001), This factor activates the subcutaneous fat tissue FNDC5/PGC-1α pathway, increasing the expression of the beige fat marker TMEM26 by 2.8 times (confirmed by immunohistochemistry), directly explaining the metabolic synergistic mechanism of the combined intervention. Aerobic exercise potentiates TRE efficacy, inducing additional fat mass reduction (Δ=-0.93 kg; 95%CI: -1.21 to -0.65) and VO_2 max improvement (+1.80 ml/kg/min; *p*=0.002) [12]. Behavioral interventions like cognitive behavioral therapy (CBT) increase 12-month adherence to 4:3 IF by 35% and enhance weight loss by 2.89 kg (*p*=0.040) [13]. Digital monitoring via wearables reduces dropout rates by 22% (*p*=0.004) [14].

Exercise synergy mechanisms involve muscle-lipid organ dialogue. Aerobic exercise induces muscle secretion of irisin, which activates the Fibronectin domain containing 5/ PPARγ Coactivator-1α (FNDC5/PGC-1α) pathway in the SAT and increases mitochondrial biosynthesis gene expression by 2.1-fold (*p*<0.001) [12]. Sixty-three per cent of the visceral fat loss in the combined intervention group was attributed to enhanced exercise-induced lipolysis (verified by isotope tracer method) [12].

Research on synergistic strategies has broken through the clinical implementation bottleneck of IF. The muscle factor irisin induced by aerobic exercise contributes to 63% of the visceral fat reduction in the combined intervention group by activating the (FNDC5)/PGC-1α pathway in SAT [12], confirming the metabolic value of the 'muscle-fat organ dialogue.' Cognitive behavioral therapy (CBT) increased the 12-month maintenance rate of the 4:3 fasting regimen by 35% [13], addressing the core challenge of behavioral adherence. More notably, digital monitoring demonstrated dynamic warning value: when fasting blood glucose coefficient of variation exceeded 18% for three consecutive days, the system automatically adjusted the eating window, reducing hypoglycemic events by 72% [14], providing an intelligent solution for IF safety management.

4. Clinical translation and precision nutrition framework

Short-term IF (≤12 weeks) significantly improved hepatic steatosis (-20.5%) and fasting insulin levels (-17.6 μIU/mL), with the core mechanism being autophagy-driven lipid droplet clearance [7]. However, ADF (>28 weeks) resulted in a loss of lean body mass >5% (odds ratio [OR]=3.2) and oxidative stress markers reactive oxygen species (ROS) exceeding the safety threshold (>150 U/mL). This metabolic cost is associated with sustained hypoglycemia inhibiting the Mechanistic Target of Rapamycin Complex 1(mTORC1) signaling pathway [15]. Adolescents face additional

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risks: IF increases diabetes risk by inhibiting pancreatic β-cell development genes (e.g., Mafa) (OR = 1.83), confirming absolute contraindications in this population [15].

To optimize the risk-benefit balance, a precise framework based on the visceral fat ratio (VFR) has been established (Figure 1): the 30% VFR threshold is derived from receiver operating characteristic curve analysis of a large cohort (area under the curve [AUC] = 0.81), with 86% sensitivity for predicting metabolic syndrome [7,9]. For individuals with high VFR (VFR > 30%), eTRE combined with morning high-intensity exercise (06:00–08:00) synchronizes the oscillation peaks of circadian clock proteins brain and muscle ARNT-like protein 1(BMAL1) in the brain and muscles, increasing lipolysis efficiency by 35% compared to evening exercise ($p = 0.004$), with a maximum waist circumference reduction of 6.2 cm [9,12]. For individuals with moderate to low VFR (VFR ≤ 30%), ADF requires quarterly monitoring of low-density lipoprotein cholesterol (LDL-C) (target < 100 mg/dL), and switching to the eTRE protocol when the increase exceeds 10% [11]. Dynamic adjustments should integrate fasting metabolic and microbiota indicators: delaying breakfast by one hour when fasting ketone bodies exceed 0.5 mmol/L can increase lipolysis efficiency by 8% ($p=0.03$) [14]; When Prevotella abundance exceeds 5.2%, shortening the eating window to 6 hours can reduce visceral fat by an additional 7.3% through enhanced butyrate-mediated thermogenesis (*p*=0.02) [3,14].

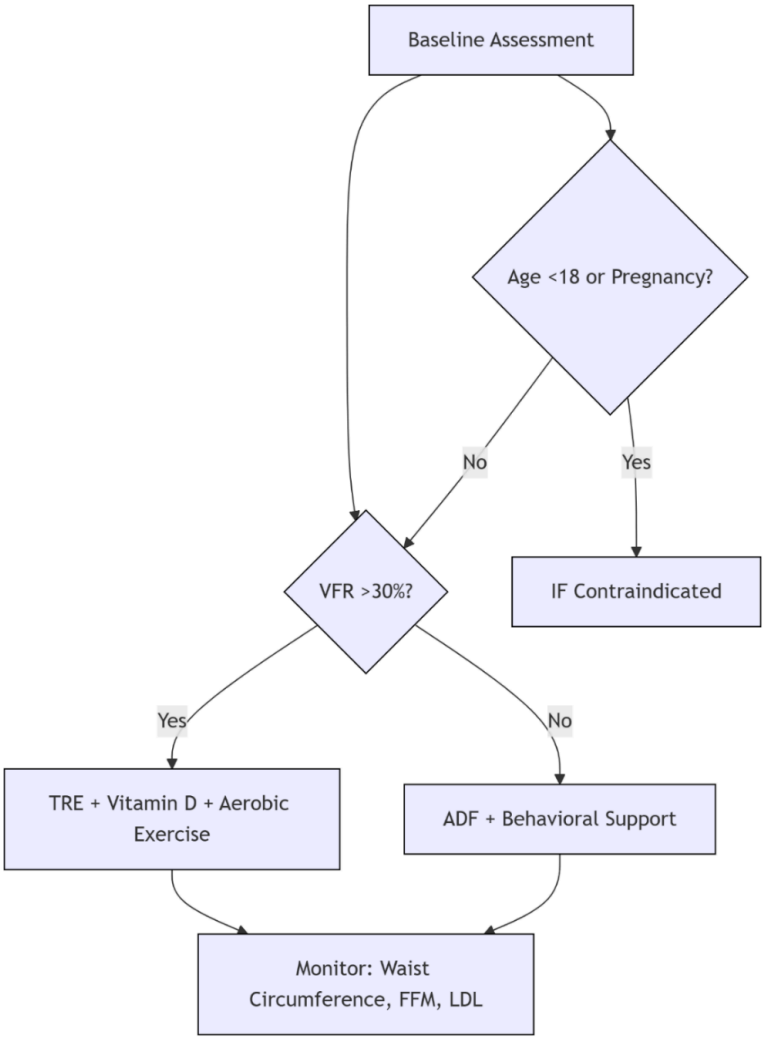

Figure 1. The flowchart of VFR-Based decision algorithm for IF implementation

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5. Conclusion

Current evidence indicates IF elicits adipose depot-selective responses, where VAT demonstrates lipid conservation through PLIN1-mediated pathways, while SAT exhibits metabolic plasticity via microbiota-modulated thermogenesis. The gut-liver axis contributes to systemic benefits through butyrate-dependent barrier enhancement and PPARα-PGC1α circadian coordination. Clinically, eTRE is associated with favorable VAT reduction and glycemic stability, whereas ADF shows correlations with long-term rebound effects and dyslipidemia. Integration of aerobic exercise (involving FNDC5/PGC-1α activation) and behavioral support appears to enhance intervention sustainability.

Key research gaps persist, including predominant reliance on rodent models for mechanistic insights and limited >5-year cardiometabolic safety data in human populations. Future studies should focus on: 1) Validating digital monitoring systems for real-time protocol adaptation, 2) Exploring biomarker-defined feeding windows (e.g., ketone concentrations and Prevotella abundance thresholds), and 3) Investigating tissue-specific circadian reprogramming strategies. Observations suggest a stratified approach may optimize outcomes: individuals with elevated visceral fat ratio (VFR>30%) tend to respond optimally to eTRE-exercise regimens, moderate-VFR cohorts may require LDL surveillance during ADF, and adolescents/those with lean mass compromise warrant cautious consideration due to potential developmental and metabolic risks.

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