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From Autophagy to Clinical Practice: Fasting and Caloric Restriction

Francesca Martinez-Nachon[1,2], Mariel Coronel[1,2], Luciana B. Sutanto[3], Joseph Varon[1,2,4]

Abstract

Fasting and caloric restriction (CR) are increasingly used to improve weight control and metabolic health, and they may also engage cellular maintenance pathways such as autophagy. Their clinical value, however, depends on whether patients can safely sustain the intervention. This narrative review synthesizes human evidence on practical factors that may improve fasting adherence or reduce ad libitum energy intake, including protein, hydration, dietary fiber, prebiotics, exogenous ketones, and caffeine. It also examines the relationship between fasting/CR and autophagy, disease-specific applications, measurement limitations, and clinical implementation.

Across human studies, protein, pre-meal water, viscous fiber, selected prebiotics, and replacement of caloric beverages show the most consistent potential to support satiety or reduce subsequent intake. Exogenous ketone esters may transiently reduce hunger when substantial ketonemia is achieved, whereas ketone salts and caffeine have less consistent behavioral effects. Fasting and CR activate nutrient-sensing pathways associated with autophagy, but direct evidence of tissue-specific autophagic flux in humans remains limited. The clinical meaning of autophagy is also context-dependent: enhancement may be favorable in some metabolic or neurodegenerative settings, while established tumors may use autophagy for survival.

Fasting and CR should therefore be viewed as selective therapeutic tools rather than universal prescriptions. Their responsible use requires a clear indication, individualized dosing, support for adherence, explicit contraindication screening, and ongoing monitoring of patient-centered outcomes.

Keywords: Fasting, caloric restriction, autophagy, time-restricted eating, appetite, energy intake, aging, metabolic health, autophagic flux

[1.] Universidad Popular Autónoma del Estado de Puebla, Puebla, Mexico
[2.] Dorrington Medical Associates, Houston, Texas, USA
[3.] Department of Nutrition, Faculty of Medicine and Health Sciences, Krida Wacana Christian University, Jakarta, Indonesia
[4.] Independent Medical Alliance, Washington, DC, USA

Corresponding author:
Joseph Varon, MD, FACP, FCCP, FCCM, FSRM
2219 Dorrington Street, Houston, Texas 77030, USA
Tel: +1 713-669-1670
Fax: +1 713-669-1671
Email: jvaron@imahealth.org

Introduction

Fasting and caloric restriction (CR) have long been studied as strategies to improve body weight, metabolic health, and biologic markers associated with healthy aging. Human trials demonstrate that sustained CR can improve body composition and cardiometabolic risk factors, while time-restricted eating (TRE) offers a schedule-based alternative that some patients find easier than continuous calorie counting. (1–4) These interventions are increasingly discussed in clinical practice, but their effectiveness depends on more than physiologic plausibility. The selected protocol must be tolerable, nutritionally adequate, compatible with the patient's daily life, and sustainable long enough to produce a meaningful therapeutic exposure.

Autophagy is one of the main biologic frameworks used to explain how nutrient restriction may influence cellular health. It is a conserved intracellular recycling process in which damaged proteins, organelles, and other cytoplasmic components are enclosed within autophagosomes and delivered to lysosomes for degradation and reuse. The molecular basis of this pathway was established largely through Yoshinori Ohsumi's yeast experiments, work recognized with the 2016 Nobel Prize in Physiology or Medicine. During nutrient deprivation, reduced insulin and amino-acid signaling suppresses mechanistic target of rapamycin complex 1 (mTORC1), while cellular energy stress activates AMP-activated protein kinase (AMPK). These changes permit Unc-51-like autophagy-activating kinase 1 (ULK1)-mediated initiation of autophagy and support lysosomal biogenesis through transcription factor EB (TFEB)-related programs. (5–9)

The clinical relevance of autophagy is not uniform. Impaired autophagy-lysosomal function is implicated in neurodegenerative disease, metabolic dysfunction, and aging biology, but established tumors may exploit the same pathway to survive nutrient deprivation or treatment stress. (10–17) Furthermore, the ability to induce autophagy cannot be inferred solely from weight loss, ketosis, or a change in a single biomarker. Autophagy is a dynamic flux process, and routine clinical assays capable of measuring tissue-specific flux are not yet available.

This review, therefore, addresses two connected questions: how fasting and CR can be implemented successfully in real-world patients, and how their potential autophagy-related effects should be interpreted clinically. The review synthesizes appetite-supporting strategies, disease-specific evidence, current and future measurement approaches, implementation methods, contraindications, and a practical roadmap for clinicians.

Methods: Narrative Evidence Selection

This manuscript was developed as a clinically oriented narrative review rather than a formal systematic review. The evidence synthesis was informed by six Elicit literature reports provided to the authors in January 2026. These reports were used as literature-discovery and evidence-organization tools for human studies addressing protein intake, exogenous ketones, hydration, dietary fiber, prebiotics, caffeine, hunger, satiety, and ad libitum energy intake.

Studies identified through the Elicit reports were reviewed alongside publications located through PubMed, journal websites, key review articles, and reference-list screening. Priority was given to randomized clinical trials, controlled feeding or crossover studies, systematic reviews, meta-analyses, and clinically relevant guidance documents. Mechanistic and preclinical publications were included when human evidence was limited or when they were needed to explain nutrient-sensing pathways, autophagic regulation, or disease-specific biology.

Because the original Elicit search strings, complete search history, and initial screening count were not available to the authors, no formal screening total or reproducible search algorithm is reported. The Elicit reports were used to identify candidate publications rather than as sources of primary evidence. Final references were selected according to relevance to the review objectives, emphasis on human data, methodological quality, and ability to inform clinical interpretation. The search was not intended to meet Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards or provide an exhaustive systematic evidence inventory.

Discussion

Fasting, Caloric Restriction, and Autophagy: A Clinician-Oriented Mechanistic Overview

Fasting and CR alter the balance between nutrient availability and cellular energy demand. Reduced insulin, growth-factor, and amino-acid signaling decreases mTORC1 activity, while energy stress activates AMPK. Together, these changes allow ULK1 to initiate autophagosome formation and promote TFEB-associated lysosomal biogenesis. Autophagosomes then fuse with lysosomes, where damaged proteins, dysfunctional organelles, and lipid substrates can be degraded and recycled. (5–9,16)

Cellular damage is generated continuously by normal metabolism and by environmental or disease-related stress. Reactive oxygen species, mitochondrial dysfunction, misfolded or aggregated proteins, lipid injury, DNA damage, inflammation, infection, toxins, and nutrient imbalance can all produce cellular components that must be repaired or removed. Basal autophagy functions as an intracellular quality-control system, while nutrient deprivation and other stressors can increase autophagic activity to mobilize substrates and remove damaged material. In this sense, autophagy links the metabolic signal created by fasting with cellular maintenance and adaptation. (7,8,16,18)

This relationship is dose- and context-dependent. A limited period of nutrient deprivation can act as an

adaptive metabolic stress, but prolonged or excessive fasting should not be assumed to produce progressively greater benefit. When energy and substrate depletion exceed physiologic reserve, especially in the presence of inadequate protein, micronutrient, fluid, or electrolyte intake, fasting can shift toward tissue catabolism and impaired repair rather than adaptive maintenance. The therapeutic objective is therefore not maximal fasting or maximal autophagy, but a tolerable stimulus that preserves nutritional and functional reserve. (7,9,19–21)

For clinicians, the central message is simpler than the full molecular pathway: fasting and CR may shift cells from nutrient-driven growth toward maintenance and recycling. This response may support proteostasis, mitochondrial quality control, and metabolic flexibility, but it does not guarantee clinical benefit in every organ or disease. The relationship is summarized schematically (**Figure 1**), while the limitations of inferring autophagic flux from static biomarkers are addressed separately below.

Practical Factors Associated with Fasting Success or Lower Ad Libitum Energy Intake

Fasting success is shaped by hunger, meal size, compensatory eating, food availability, social context, and the complexity of the prescribed protocol. The interventions below are best viewed as adherence-supporting tools. None replaces the need for an energy deficit when weight loss is the primary indication, and no single strategy consistently suppresses intake in every population.

Protein

The collective human evidence supports protein as the most consistent dietary factor for improving satiety and reducing subsequent energy intake. Acute preload studies commonly show lower intake at the next meal, while longer interventions suggest that higher-protein patterns can reduce spontaneous daily intake when protein replaces other macronutrients rather than simply adding calories. (22–31) Representative studies reported reductions of approximately 19% at a subsequent meal and sustained decreases of roughly 400–500 kcal/day in tightly controlled high-protein interventions. (22,23,25,26)

The magnitude of benefit varies with dose, source, age, and food environment. Effects often plateau around 20–30 g per eating occasion, and higher doses do not consistently produce additional satiety. Whey may generate a faster amino-acid and gut-hormone response than casein, but source-specific differences are less important clinically than total dose, energy substitution, and patient tolerance. (26–30) Older adults may show less appetite suppression, and highly palatable foods may override subjective fullness.

Clinical implication: protein can be used to make fasting or CR more tolerable, particularly when it is distributed across eating occasions and incorporated without increasing total energy intake. A pragmatic target is approximately 20–30 g per meal, adjusted for body size, renal function, age, and the need to preserve lean mass.

Exogenous Ketones

Evidence for exogenous ketones is less consistent and depends strongly on formulation. Ketone esters can raise beta-hydroxybutyrate to approximately 3–5 mmol/L and may transiently suppress ghrelin, hunger, and desire to eat for several hours. (32–35) Ketone salts generally produce lower ketonemia and have not demonstrated reliable appetite benefits during hypocaloric interventions. (36)

The main disagreement in the literature is not whether ketones alter appetite-related physiology, but whether these changes meaningfully reduce food intake. Several studies report lower hunger or ghrelin without a significant reduction in ad libitum energy intake. (32–39) Differences in metabolic health, exercise status, caloric content of the supplement, and timing of the test meal probably contribute to the heterogeneity.

Clinical implication: ketone esters may have a short-term appetite effect in selected individuals, but they should not be considered standard adherence tools. Their cost, caloric contribution, gastrointestinal tolerance, and uncertain effect on actual energy intake limit routine use.

Hydration

The human evidence indicates that water affects intake primarily through acute gastric distension and beverage substitution rather than through systemic hydration status. Water consumed immediately before a meal can reduce subsequent intake, particularly in older adults, whereas mild hypohydration does not reliably suppress eating when fluids are available during the meal. (40–44) Representative trials reported reductions of approximately 9–23% at the next meal, depending on age and timing.

The most clinically consistent strategy is replacing

caloric beverages with water. Unlike intentional dehydration, beverage substitution reduces energy exposure without requiring a physiologic stress state and is supported by randomized and observational evidence. (45–47)

Clinical implication: patients may be advised to consume approximately 300–500 mL of water close to a meal if tolerated and to replace sugar-sweetened or calorie-containing beverages with noncaloric fluids. Delayed water intake may be less effective because gastric emptying reduces the distension signal.

Dietary Fiber

Fiber cannot be treated as a single intervention. Its effects depend on viscosity, gel formation, fermentability, hydration, dose, and the surrounding food matrix. Across reviews, viscous or gel-forming fibers show the most consistent ability to increase fullness or reduce subsequent intake, but many studies demonstrate improved appetite ratings without measurable changes in calories consumed. (48–55)

This dissociation helps explain apparently conflicting findings. Subjective satiety reflects one component of eating behavior, while food reward, palatability, social setting, and habitual eating can override physiologic signals. Consequently, visual analogue scales should not be interpreted as substitutes for measured energy intake. (53)

Clinical implication: a gradual increase in well-hydrated viscous fiber may support adherence, particularly when it replaces lower-satiety foods. Dose escalation should be individualized because bloating, flatulence, diarrhea, or constipation may limit use. Fiber should be presented as an adjunct to dietary quality and energy control rather than as a standalone appetite treatment.

Prebiotics

Prebiotics overlap with the fiber literature but may additionally influence appetite through colonic fermentation, short-chain fatty acids, gut hormones, and microbiota composition. Acute and short-duration studies are generally more favorable than long-term trials. Polydextrose and targeted propionate delivery can reduce intake at a subsequent meal, while inulin-type fructans may improve satiety or modestly reduce intake in some participants. (52,56–62)

The evidence becomes less consistent when total daily intake, weight loss, or longer follow-up is considered. Baseline diet, fermentation capacity, gastrointestinal tolerance, study sponsorship, and compensation at later meals all influence results. This makes it difficult to recommend one universal prebiotic dose.

Clinical implication: selected prebiotics may be useful when they improve dietary quality or satiety and are well tolerated. A trial of polydextrose or inulin-type fructans can be considered, but clinicians should monitor symptoms and should not assume that short-term reductions at one meal will persist across the day.

Caffeine-Containing Beverages

Caffeine and coffee do not consistently reduce ad libitum energy intake. Controlled crossover studies and reviews show that any appetite effect is generally small, acute, and variable across sex, weight status, and habitual caffeine exposure. (63–70) Findings with decaffeinated coffee suggest that non-caffeine compounds may contribute to some observed responses.

Real-world behavior may offset any theoretical benefit. Sugar, cream, and other add-ins increase energy intake, and some populations may increase sweet-food consumption after caffeine exposure. (65,66) Habitual users also develop tolerance to several physiologic effects.

Clinical implication: unsweetened coffee or tea may fit within a fasting plan for patients who tolerate caffeine, but caffeine should not be prescribed as a dependable appetite suppressant. Sleep disruption, anxiety, palpitations, and caloric add-ins may outweigh a modest short-term effect.

Taken together, protein, pre-meal water, viscous fiber, selected prebiotics, and beverage substitution have the strongest practical potential to support adherence. Their value arises mainly from improving tolerability, reducing meal size, or replacing higher-energy alternatives. Exogenous ketones and caffeine remain optional, less predictable strategies.

Disease-Specific Relevance of an Autophagy-Compatible State

The clinical goal is not to maximize autophagy. The relevance of fasting and CR depends on the indication, disease stage, tissue, nutritional reserve, medication use, and the strength of human outcome data. The following sections distinguish established metabolic benefits from mechanistic or hypothesis-generating applications.

Obesity, Insulin Resistance, and Type 2 Diabetes

Obesity and insulin resistance represent the clearest indications for structured CR because the therapeutic target is an energy deficit and improvement in cardiometabolic risk. Both continuous CR and TRE can produce weight loss and metabolic improvement when adherence is maintained. (1–5) Exploratory peripheral blood mononuclear cell (PBMC) data suggest that intermittent TRE may alter measurable autophagic flux, but this does not establish equivalent activation in liver, adipose tissue, muscle, or pancreas. (5)

TRE does not consistently outperform energy-matched CR. Its value is therefore practical rather than inherently superior: some patients prefer a schedule-based rule, while others perform better with calorie targets or dietary substitution. In type 2 diabetes, medication review and glucose monitoring are essential because insulin and insulin secretagogues can create clinically significant hypoglycemia risk. (71)

Clinical implications: fasting or CR may be offered to appropriately selected patients with obesity, prediabetes, or type 2 diabetes when a sustainable energy deficit is the goal. Protocol choice should be driven by adherence, medication safety, preservation of lean mass, and measurable metabolic outcomes rather than by presumed autophagy activation.

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Hepatic Metabolic Disease

Autophagy and lipophagy are mechanistically involved in hepatic lipid handling, mitochondrial quality control, and inflammatory signaling. (15,16) However, the most reliable human pathway to improving MASLD remains sustained weight loss and metabolic improvement. There is currently no routine method for demonstrating that a fasting intervention has restored hepatic autophagic flux.

Clinical implications: CR, TRE, and exercise may be used as tools to achieve weight reduction and improve insulin sensitivity in MASLD. Monitoring should focus on weight, liver enzymes, fibrosis risk, and imaging when clinically indicated. Fasting should not be presented as a liver-specific autophagy therapy.

Cardiovascular Disease

Fasting and CR may improve cardiovascular risk indirectly through weight loss, blood-pressure reduction, glycemic improvement, and favorable lipid changes. Autophagy also has mechanistic roles in endothelial function, oxidative stress, macrophage biology, and plaque-cell survival. (1,2,72) These mechanisms are biologically relevant but have not established a separate clinical indication for fasting based on vascular autophagy.

Clinical implications: fasting-compatible strategies may be incorporated into comprehensive cardiovascular risk management when they improve weight or metabolic control. They should complement, not replace, evidence-based treatment of hypertension, dyslipidemia, diabetes, smoking, sleep, and physical inactivity. Patients with unstable cardiovascular disease require individualized assessment before fasting.

Neurodegenerative Disorders

Autophagy-lysosomal dysfunction is well described in Alzheimer disease and related neurodegeneration, where impaired clearance of protein aggregates and damaged organelles contributes to disease biology. (10,11) This creates a strong mechanistic rationale for studying nutrient-sensing and cellular maintenance pathways. Nevertheless, human trials have not established fasting or CR as disease-modifying therapy.

Clinical implications: fasting should not be recommended as treatment for Alzheimer disease, Parkinson disease, or other neurodegenerative disorders outside appropriately monitored research or broader lifestyle care. In older adults, potential mechanistic benefit must be balanced against weight loss, frailty, dehydration, medication complexity, and sarcopenia.

Oncology

Cancer demonstrates why autophagy cannot be labeled universally beneficial. Autophagy may reduce early cellular damage and suppress tumor initiation, yet established tumors can use autophagy to survive hypoxia, nutrient stress, and anticancer therapy. (12–14) Trials of hydroxychloroquine-based autophagy inhibition further demonstrate that the desired direction of modulation depends on the cancer and treatment regimen.

Clinical implications: patients receiving cancer therapy should not be given generalized advice to induce autophagy through fasting. Any fasting or nutritional intervention should be coordinated with oncology and nutrition teams, with attention to weight loss, cachexia, treatment toxicity, and the

goals of therapy.

Aging, Frailty, and Sarcopenia

Autophagy declines with age in several experimental models, and CR improves multiple markers associated with human health span. (1,2,9) However, evidence for extension of human lifespan is lacking. More importantly, aging populations are heterogeneous. A metabolically healthy, well-nourished adult and a frail older patient with involuntary weight loss do not have the same risk-benefit profile.

Clinical implications: healthy aging interventions should prioritize function, adequate protein, resistance exercise, sleep, and cardiometabolic risk reduction. In frailty, sarcopenia, or malnutrition risk, aggressive fasting is inappropriate; preservation of muscle and nutritional reserve takes priority over theoretical autophagy benefits. (19,20)

Chronic Inflammation and Immune Regulation

Autophagy interacts with innate immunity, inflammasome activity, mitochondrial damage, cytokine signaling, and intracellular pathogen handling. (18) CR may reduce inflammatory burden indirectly through weight loss and improved metabolic health, but chronic inflammation is a broad phenotype rather than a single indication.

Clinical implications: inflammatory or immune-mediated disease should be treated according to disease-specific evidence. Fasting may be considered only when it is otherwise clinically appropriate and safe, not as a general anti-inflammatory prescription.

Long COVID and Post-Viral Syndromes

Dysregulation of TFEB and the autophagy-lysosome pathway has been proposed as one possible contributor to persistent immune and metabolic abnormalities after coronavirus disease 2019 (COVID-19). (17,18) This literature is hypothesis-generating and does not establish that fasting restores autophagic function or improves post-viral fatigue.

Clinical implications: fasting should not currently be recommended as treatment for Long COVID or post-viral fatigue. Research should prioritize functional outcomes, symptom burden, nutritional status, and validated biologic measures before proposing therapeutic protocols.

Measuring Autophagy in Humans: From Static Biomarkers to Clinical Outcomes

Autophagy is a dynamic sequence that includes initiation, autophagosome formation, trafficking, lysosomal fusion, degradation, and recycling. Static markers capture only part of this process. Microtubule-associated protein 1 light chain 3-II (LC3-II) can increase because more autophagosomes are being formed or because lysosomal degradation is blocked. Sequestosome 1 (p62/SQSTM1) is also affected by transcription, synthesis, and degradation. For this reason, a single measurement cannot confirm increased autophagic flux.

Research approaches use multiple markers, repeated sampling, microscopy, or comparison before and after lysosomal inhibition. These methods are valuable experimentally but remain difficult to apply in routine practice. PBMC assays provide repeatable human samples and have been used in TRE research, yet they cannot automatically be extrapolated to the brain, liver, muscle, adipose tissue, or tumor microenvironment. (5)

Clinical measurements such as beta-hydroxybutyrate, glucose, insulin, triglycerides, liver fat, or body weight indicate that a metabolic intervention occurred; they do not directly measure autophagy. The distinction is clinically important because a patient may achieve ketosis or lose weight without demonstrable tissue-specific flux, and a change in an autophagy marker does not guarantee improved symptoms or disease outcomes.

For clinical adoption, perfect flux measurement may not be necessary. A more realistic approach is to validate reproducible, non-invasive proxies against tissue-level assays and patient-centered outcomes. Future frameworks may combine adherence measures, metabolic-state markers, accessible-cell signaling or PBMC flux, and disease-specific outcomes. The conceptual relationship between these levels of evidence is summarized schematically (**Figure 2**).

Clinical Implementation: Patient Selection, Dosing, and Follow-Up

The clinical value of fasting or CR depends on matching the intervention to a clear indication. Weight loss, insulin resistance, and cardiometabolic risk are the settings with the most established human benefit. Autophagy-related disease claims should not be used as the primary indication unless the patient is enrolled in an appropriate research protocol.

Before Starting

Baseline assessment should include weight history, body composition or sarcopenia risk when relevant, dietary intake, hydration, functional status, medications, glucose-lowering therapy, kidney and liver disease, pregnancy status, eating-disorder history, active cancer treatment, and the patient's work and family schedule. A fasting plan that conflicts with medication timing, overnight shifts, exercise, sleep, or family meals is unlikely to be sustained.

Selecting the Intervention

CR is the most direct intervention when weight loss is the primary goal. TRE can be selected when a schedule-based approach is easier for the patient, but it should not be described as inherently superior to calorie restriction. (73) A reasonable starting option is a consistent overnight fast or a 10–12-hour eating window, followed by gradual adjustment according to symptoms, adherence, weight trajectory, and metabolic response. More intensive or periodic fasting should be reserved for carefully selected and supervised patients.

Energy restriction does not selectively reduce adipose tissue; loss of fat-free and skeletal muscle mass can also occur. This concern becomes more important when restriction is severe or when patients have limited muscle reserve. In the TEMPO randomized clinical trial, severe energy restriction produced greater loss of whole-body lean mass and thigh muscle area than moderate energy restriction in postmenopausal women with obesity. (74) For clinical use, weight-loss strategies should therefore include adequate protein intake, resistance exercise when feasible, and monitoring for loss of strength, function, or lean mass in patients at risk for sarcopenia.

Supporting Adherence

The intervention should include practical strategies that reduce hunger without compromising nutritional adequacy. Adequate protein, water close to meals, replacement of caloric beverages, and gradual use of viscous fiber or selected prebiotics may improve tolerability. Exercise should be incorporated to support insulin sensitivity, cardiovascular health, and preservation of lean mass. Exogenous ketones and caffeine are optional and should not be represented as essential components.

Monitoring and Follow-Up

Follow-up should be linked to the indication. Weight, waist circumference, blood pressure, symptoms, adherence, and functional status are broadly useful. Glucose monitoring is necessary when diabetes medications create hypoglycemia risk. Lipids, hemoglobin A1c (HbA1c), liver enzymes, renal function, body composition, or imaging can be added when clinically relevant. Early follow-up may be needed within one to four weeks, followed by longer intervals once safety and adherence are established.

The intervention should be continued when it is safe, tolerable, and producing meaningful outcomes. It should be modified when hunger, scheduling, nutrition, or medication-related problems reduce adherence. It should be stopped when there is recurrent hypoglycemia, dehydration, excessive or unintended weight loss, functional decline, worsening eating-disorder symptoms, intolerance, or deterioration of the underlying disease (**Figure 3**).

Compliance, Accessibility, and Trackable Care

Compliance is a primary determinant of efficacy. A biologically plausible protocol produces little benefit when it is socially or physically unsustainable. Clinicians should therefore define the intervention in measurable terms: the eating window or calorie target, permitted beverages, minimum protein and fiber goals, medication instructions, monitoring plan, and symptoms that require stopping.

Accessibility also requires flexibility. Patient-selected windows, gradual progression, self-monitoring, and adaptation around work or family obligations may improve persistence. (75) The goal is not to enforce one ideal fasting schedule, but to identify the least burdensome protocol that produces the intended clinical outcome.

Contraindications and High-Risk Populations

Fasting and CR are not appropriate for every patient. The risk of reduced intake must be weighed against nutritional demand, metabolic reserve, medication use, and illness severity. A theoretical autophagy benefit should never override a clear risk of malnutrition, hypoglycemia, dehydration, functional decline, or treatment interference.

Pregnancy, Breastfeeding, Underweight, and Eating Disorders

Pregnancy and breastfeeding involve increased nutritional demands, and available Ramadan-fasting data do not justify prescribed fasting for weight loss or autophagy induction. (76) Patients who are un-

derweight, have active eating disorders, or demonstrate substantial disordered-eating risk should not be placed on restrictive fasting protocols and should receive appropriate specialist care. (77)

Frailty and Sarcopenia

Older adults with frailty, involuntary weight loss, sarcopenia, or malnutrition risk should prioritize adequate energy, protein, hydration, and resistance exercise. (19,20) Even modest weight loss may worsen function in vulnerable patients, and aggressive energy restriction can accelerate loss of lean tissue. (74) If an eating-window strategy is considered, it should not reduce protein distribution or total intake.

Diabetes and Advanced Chronic Disease

Insulin and insulin secretagogues increase the risk of hypoglycemia during fasting. Any protocol requires medication review, glucose monitoring, clear stopping rules, and clinician supervision. (71) Advanced chronic kidney disease (CKD) requires stage-specific energy, protein, fluid, and electrolyte management; unsupervised prolonged fasting is inappropriate. (21) Patients with unstable cardiovascular disease, severe liver disease, acute illness, or other advanced chronic conditions require individualized assessment.

Critical Illness

Critically ill and acutely hospitalized patients should not be included in generalized fasting recommendations. Critical illness is characterized by catabolism, variable organ function, and changing nutritional requirements. Nutrition decisions in this setting should follow disease- and intensive-care-specific guidance rather than outpatient fasting protocols.

Active Malignancy

Patients receiving active cancer therapy require oncology-specific decisions. Fasting may worsen weight loss or cachexia, while autophagy may either support or oppose treatment effects depending on tumor biology and regimen. (12–14) Generalized advice to induce autophagy should therefore be avoided.

Conclusion

Fasting and caloric restriction have demonstrated clinical value for weight management and cardiometabolic risk reduction, and they may engage nutrient-sensing pathways associated with autophagy and cellular maintenance. The evidence is strongest when the therapeutic objective is explicit and measurable. Additional disease-modifying effects through autophagy remain plausible in some settings but are not uniformly demonstrated in humans.

The main barrier is not a lack of biologic rationale; it is the challenge of translating that rationale into a safe and sustainable intervention. Protein, hydration, viscous fiber, selected prebiotics, beverage substitution, and behavioral structure can improve tolerability, but they do not replace an appropriate energy deficit or careful clinical follow-up. Likewise, ketosis or changes in static autophagy markers should not be assumed to represent tissue-specific flux or clinical benefit.

Fasting and CR should be viewed as therapeutic tools that require the same principles applied to other treatments: a clear indication, individualized dosing, attention to contraindications, measurable outcomes, and readiness to modify or discontinue the intervention. In selected patients, a structured protocol may improve metabolic health and support long-term behavioral change. In vulnerable populations, the same intervention may increase the risks of malnutrition, sarcopenia, hypoglycemia, dehydration, or clinical deterioration. Responsible clinical adoption therefore depends on careful patient selection, practical implementation, and ongoing monitoring rather than universal recommendations.

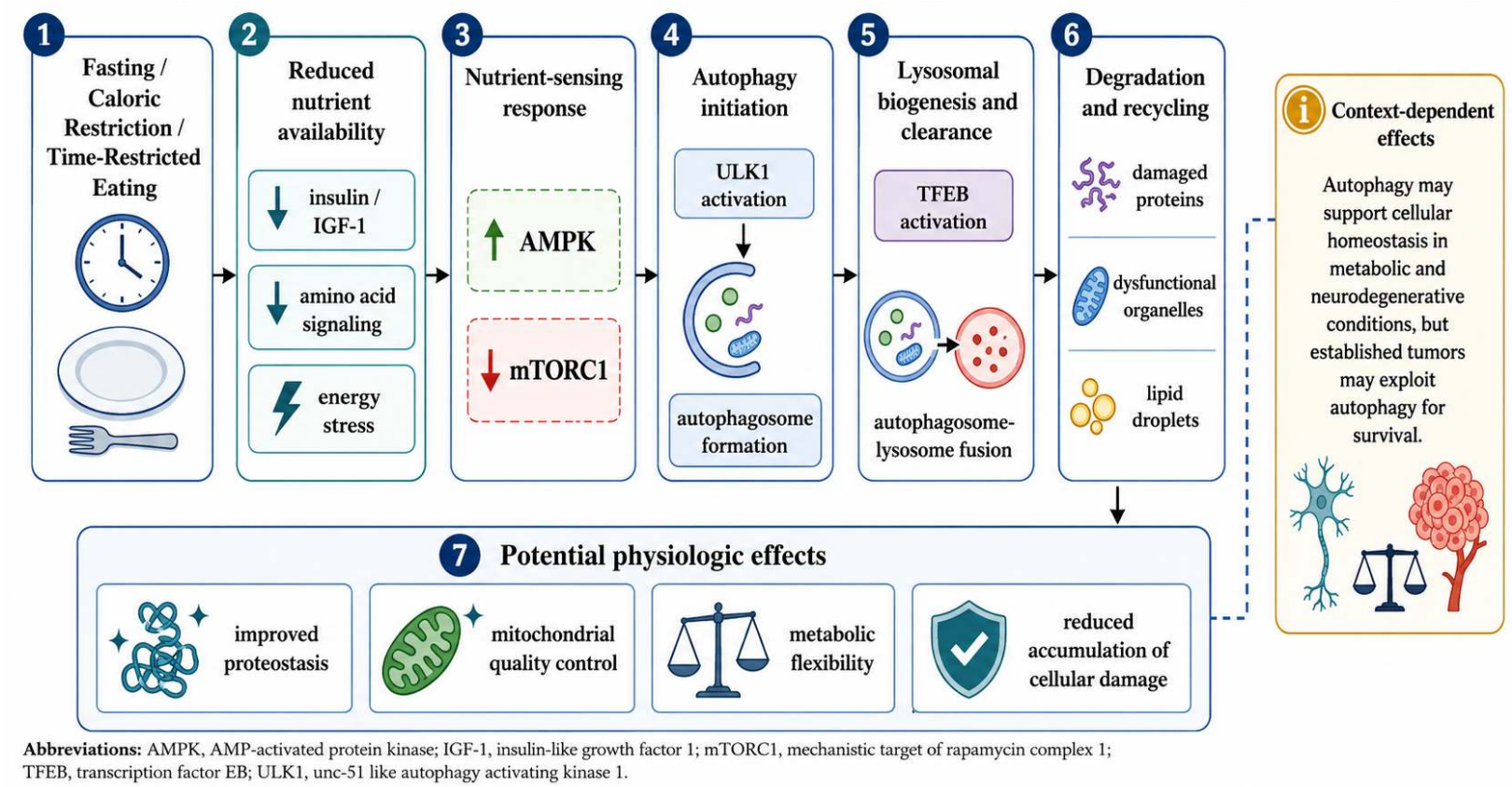
Table 1. Human-Focused Clinical Framing of Fasting/CR and Autophagy

Condition	Clinical objective	Human evidence	Monitoring	Key caution
Obesity/insulin resistance	Sustainable energy deficit	Caloric Restriction (CR)/time-restricted eating (TRE) improve weight and metabolic risk (1–5)	Weight, waist, blood pressure (BP), glucose, lipids	TRE is not consistently superior to CR
Type 2 diabetes	Improve metabolic control safely	Benefit possible with medication adjustment (4,71)	Hemoglobin A1c (HbA1c), continuous glucose monitor (CGM), hypoglycemia, medications	Insulin/secretagogues require supervision
MASLD	Weight loss and metabolic improvement	Human benefit linked mainly to weight loss (15,16)	Alanine aminotransferase (ALT)/aspartate aminotransferase (AST), fibrosis risk, imaging	Hepatic flux is not clinically measurable
Cardiovascular risk	Improve established risk factors	Primarily indirect metabolic benefit (1,2,72)	BP, lipids, glycemia, symptoms	Not an autophagy-specific indication
Neurodegeneration	Research hypothesis only	Strong mechanism; insufficient intervention evidence (10,11)	Cognition, function, nutrition	Not disease-modifying therapy
Cancer	Oncology-specific decision	Autophagy may support or oppose therapy (12–14)	Weight, toxicity, response	Avoid generalized fasting advice
Healthy aging	Support function and metabolic health	CR improves health-span markers (1,2,9)	Function, body composition, metabolic risk	Human lifespan extension unproven
Frailty/sarcopenia	Preserve muscle and nutrition	Nutrition guidance favors adequate intake (19,20)	Weight, grip strength, gait	Avoid aggressive fasting
Long COVID	Research only	Hypothesis-generating evidence (17,18)	Symptoms, function, nutrition	No current therapeutic indication

Table 2. Candidate Approaches for Monitoring Autophagy or an Autophagy-Compatible State

Approach	Examples	What it indicates	Advantages	Limitations
Static proteins	Microtubule-associated protein 1 light chain 3-II (LC3-II), sequestosome 1 (p62), Beclin-1	Pathway components/ accumulation	Widely used	Cannot distinguish formation from blockade
Flux assays	Lysosomal inhibitor comparison	Dynamic degradation	Closest to true flux	Complex; not routine
Microscopy	Electron microscopy (EM), fluorescence puncta	Structure and localization	Spatial detail	Morphology is not flux
Peripheral blood mononuclear cell (PBMC) assays	Blood-cell flux	Accessible systemic response	Repeatable sampling	May not reflect target organs
Nutrient signaling	AMP-activated protein kinase (AMPK), mechanistic target of rapamycin complex 1 (mTORC1), Unc-51-like autophagy-activating kinase 1 (ULK1), transcription factor EB (TFEB)	Upstream compatibility	Mechanistic relevance	Not completed degradation
Metabolic proxies	Beta-hydroxybutyrate (BHB), glucose, insulin, continuous glucose monitoring (CGM)	Fasting/CR metabolic state	Scalable	Not autophagy-specific
Clinical outcomes	Weight, liver fat, function, cognition	Patient benefit	Actionable	Cannot attribute mechanism
Future panels	Extracellular vesicles, multi-omics	Potential systemic activity	Non-invasive potential	Validation and thresholds needed

Figure 1. Mechanistic relationship between fasting, caloric restriction, and autophagy



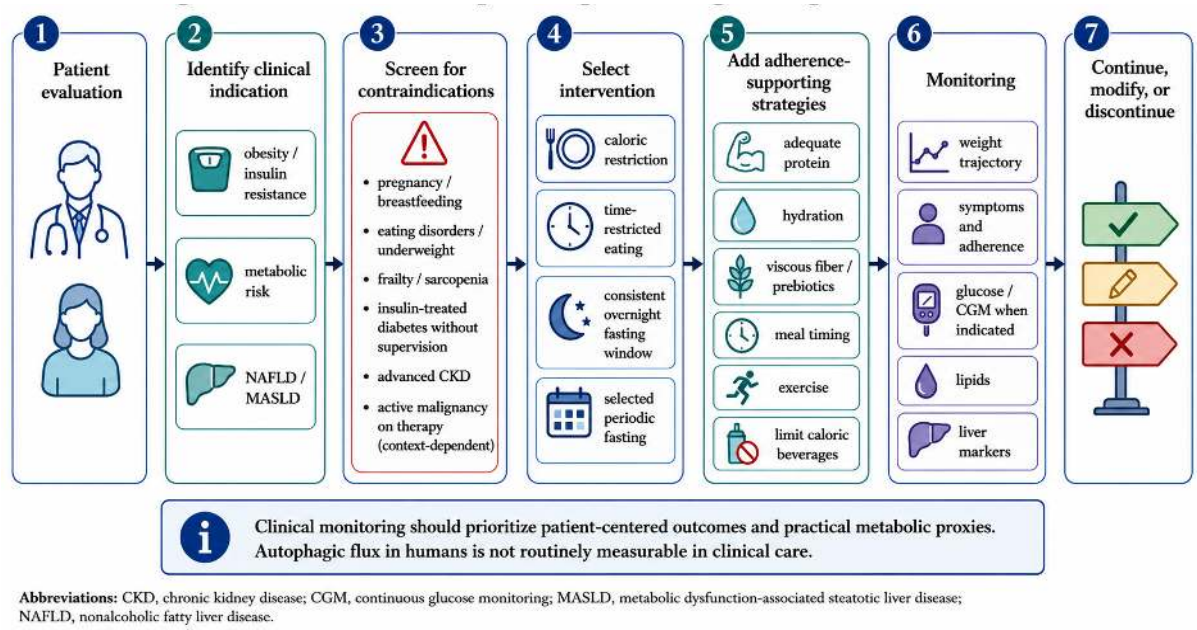
Legend: Mechanistic relationship between fasting, caloric restriction, and autophagy. Fasting and CR reduce nutrient-related signaling and increase cellular energy stress, favoring AMPK activation, mTORC1 inhibition, ULK1-mediated autophagy initiation, and TFEB-associated lysosomal biogenesis. The potential physiologic effects are context-dependent and should not be interpreted as universal clinical benefit.

Figure 2. Conceptual relationship between static biomarkers, autophagic flux, and clinical outcomes

Static biomarkers LC3-II, p62, Beclin-1	→	**Dynamic flux formation → fusion → degradation**	→	**Clinical outcomes metabolic, functional, disease-specific**

Legend: Static biomarkers, autophagic flux, and clinical outcomes. Static marker changes do not by themselves establish increased flux, and increased flux does not guarantee clinical benefit. Clinical interpretation requires dynamic assessment when feasible and correlation with patient-centered outcomes.

Figure 3. Clinical roadmap for implementing fasting or caloric restriction



Legend: Clinical roadmap for implementing fasting or caloric restriction. Implementation begins with a clear indication and contraindication screening, followed by selection of a feasible intervention, adherence-supporting strategies, outcome monitoring, and a decision to continue, modify, or discontinue treatment.

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