



Time-restricted eating as a gerotherapeutic strategy: Circadian nutrition and healthy longevity

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Abstract

Time-restricted eating (TRE), a form of intermittent fasting that limits food intake within a consistent daily window, has gained attention as a feasible strategy to promote metabolic health and align eating with circadian rhythms. Aging and obesity share overlapping pathophysiological mechanisms, including increased visceral adipose tissue (VAT), chronic inflammation, and circadian disruption, which accelerate cardiometabolic decline and multimorbidity. In this Perspective, we examine TRE within a geroscience framework, integrating evidence from human trials and preclinical models to evaluate its potential relevance for aging-related processes. We discuss how the timing of food intake influences VAT distribution and glucose regulation, with early TRE schedules showing particular promise for enhancing nocturnal glycemic control and reducing abdominal subcutaneous adipose tissue. Drawing on circadian biology and caloric restriction literature, we highlight mechanistic insights linking feeding-fasting cycles to autophagy, nutrient sensing, and longevity. We also consider emerging evidence of sex-specific responses to TRE, which may inform personalized approaches. However, most clinical studies remain short-term and focus on cardiometabolic risk markers rather than validated measures of biological aging or functional outcomes. We therefore emphasize the need to distinguish between demonstrated metabolic benefits and proposed gerotherapeutic effects, and argue that future trials should incorporate biomarkers of biological age, circadian robustness, and physiological resilience. TRE represents a low-cost, scalable, and behaviorally simple intervention that could complement existing strategies in geromedicine to extend healthspan and delay age-related decline.

Keywords: Time-restricted eating, visceral adipose tissue, circadian nutrition

1. Introduction

Aging, marked by progressive physiological decline, is the primary risk factor for the development of most chronic diseases, including obesity, type 2 diabetes, and cardiovascular diseases^[1,2]. A growing body of evidence suggests that excess adiposity contributes to several hallmark features of aging, such as telomere attrition, chronic inflammation, epigenetic alterations, mitochondrial



dysfunction, and loss of proteostasis^[3]. In addition, aging is accompanied by increased visceral adipose tissue (VAT) and circadian disruption, both recognized drivers of cardiometabolic and functional decline^[4,5]. These shared mechanisms indicate that obesity may not only elevate disease risk but also accelerate biological aging, thereby amplifying susceptibility to multimorbidity later in life. In this regard, geromedicine has emerged as a translational field focused on extending healthspan by targeting the biological processes that underlie aging^[6]. Rather than addressing established disease, geromedicine emphasizes early, preventive interventions aimed at preserving physiological resilience and promoting healthy aging across the lifespan^[7].

Several preventive strategies are being investigated to counteract age-related metabolic decline in the context of obesity, including traditional dietary interventions^[8]. Among these, calorie restriction, defined as a reduction in energy intake below energy requirements without malnutrition, remains the most extensively studied nutritional intervention with the potential to attenuate aging in both preclinical models and humans^[8,9]. However, calorie-restricted diets have shown limited long-term adherence and feasibility in free-living populations^[8], reinforcing the need for alternative nutritional approaches that engage metabolic and circadian pathways to promote healthy aging among individuals living with obesity.

Time-restricted eating (TRE) is a form of intermittent fasting in which *ad libitum* food intake is limited to a consistent daily window of 4 to 10 hours, followed by a fasting period of 14 to 20 hours, without calorie counting, relying instead on “watching the clock” to guide the timing of food consumption^[10,11]. TRE has been associated with reductions in body weight and fat mass, improvements in inflammatory markers, and enhanced cardiometabolic parameters, including insulin sensitivity, blood pressure, and oxidative stress, particularly in individuals with overweight or obesity^[12–15]. These effects are thought to be mediated, at least in part, by energy deficit and improved alignment between feeding patterns and endogenous circadian rhythms^[16]. Concentrating food intake earlier in the day (e.g., an eating window from 09:00 to 17:00) may yield greater benefits than late-day eating windows (e.g., 13:00 to 21:00), likely due to stronger circadian alignment and enhanced insulin sensitivity^[17–19]. Furthermore, TRE has been shown to have high adherence and no adverse effects on mood or quality of life in adults with overweight or obesity^[20], supporting its use as a safe and well-tolerated strategy to improve cardiometabolic health^[21].

However, most human evidence to date relies on relatively short-term intervention mainly focused on cardiometabolic outcomes, with limited assessment of biological aging, functional decline, or resilience. This gap highlights the need to critically evaluate whether TRE can move beyond metabolic improvements to meaningfully impact the aging process. In this Perspective, we examine TRE within the framework of geroscience and circadian biology, discussing its potential, limitations, and translational challenges as a strategy to promote healthy longevity.

2. Metabolic Aging and Cardiometabolic Health

A key age-related change in body composition is fat redistribution^[22], characterized by an increase in VAT, a fat depot surrounding internal organs and strongly associated with elevated cardiometabolic risk^[23]. VAT negatively impacts systemic health and the aging process^[4]. However, when the capacity of subcutaneous adipose tissue (SAT) to expand is exceeded, excess energy is redirected toward VAT accumulation or deposited as ectopic fat in organs such as the heart, liver, or pancreas^[23]. Excess VAT releases free fatty acids and proinflammatory cytokines that can impair hepatic function and are thought to play a central role in the development of insulin resistance and type 2 diabetes^[4]. Collectively, adipose tissue-driven metabolic disturbances, both local and systemic, increase susceptibility to a range of metabolic diseases in older adults^[4]. Given the rising prevalence of cardiometabolic diseases with age, reducing both VAT and SAT could represent a promising strategy to improve metabolic health, with potential implications for aging-related processes.

Evidence from human trials suggests that the effects of TRE on VAT are modest and context-dependent^[24–28]. In adults with metabolic dysfunction-associated steatotic liver disease, an 8-week 8-hour TRE intervention found no significant differences between early and late TRE in changes in VAT or SAT assessed with magnetic resonance imaging (MRI), nor in body weight or fat mass^[24]. Similarly, in adults with obesity, studies combining early 8-hour TRE with caloric restriction reported reductions in VAT and SAT, but these were not significantly greater than those achieved with caloric restriction alone after 6 and 12 months^[25,26]. Moreover, a 6-week intervention involving older adults (aged 65–74 years) with obesity observed greater VAT reductions after an 8-hour TRE protocol compared to participants participating in a lifestyle education program, although this effect was observed only in men^[27]. Recently, a 6-month randomized controlled trial in older postmenopausal women with obesity showed that adding TRE to caloric restriction increased VAT loss without differential effects on body weight or nutrient intake, supporting the idea that meal timing may modulate adiposity beyond caloric restriction alone at these ages^[28]. However, whether the timing of the eating window during TRE (e.g., 9:00 to 17:00 versus 13:00 to 21:00) differentially affects VAT reduction remains an open question in aging research.

In this context, we conducted one of the largest multicenter randomized controlled trials to date, assessing the effects of three distinct TRE schedules, an 8-hour eating window in the early part of the day (early TRE), an 8-hour window later in the day (late TRE) and a participant-selected eating window (self-selected TRE), each combined with usual care (UC, a nutritional education program based on the Mediterranean diet) versus UC alone^[29]. Over 12 weeks, we evaluated changes in VAT and abdominal SAT measured by MRI, as well as cardiometabolic health outcomes, in 197 adults (50% women; aged 30–60 years) with overweight or obesity^[30].

Interestingly, VAT significantly decreased across all three TRE groups, unlike in the UC group, yet changes did not significantly differ across TRE schedules. Notably, early TRE resulted in a greater reduction in abdominal SAT than UC^[30]. This finding is clinically relevant, as SAT has been independently associated with insulin sensitivity, regardless of VAT levels^[31–33]. Early TRE also led to meaningful improvements in nocturnal glucose control relative to UC, late TRE, and self-selected TRE^[30]. Nocturnal interstitial glucose decreased approximately by 7–13 mg/dL in the early TRE group versus the other groups, and the nocturnal glucose coefficient of variation (%) was lower than in UC, despite similar 24-hour mean glucose^[30]. However, 24-hour glucose variability was higher in early TRE than in the late and self-selected TRE regimens^[30], so the net impact of early TRE on glycemic variability remains uncertain. All TRE interventions led to a decrease in energy intake of 300–500 kcal/d, which led to an average weight loss of 4–6% and an additional reduction of approximately 3 kg compared with the UC group^[30].

Overall, these findings demonstrate consistent improvements in cardiometabolic health, particularly in adiposity and glycemic regulation, while also highlighting the heterogeneity of responses across populations and intervention designs. Importantly, the magnitude of these effects appears modest and often not independent of concurrent energy restriction, underscoring the need to better define the specific contribution of meal timing. Together, these observations suggest that TRE may represent a feasible alternative to caloric restriction, achieving comparable effects largely through unintentional, non-prescribed energy restriction, although its broader relevance for geroscience remains to be established in humans.

3. Circadian Alignment and Geroprotective Pathways

Aging is increasingly viewed as a circadian disorder^[5]. Central and peripheral clocks coordinate daily oscillations in glucose tolerance, lipid handling, mitochondrial function, and autophagy, which deteriorate with age and are tightly linked to visceral and ectopic fat accumulation. With advancing age, circadian rhythms in clock and metabolic genes lose amplitude and shift, particularly in the liver, favoring inflammatory programs over oxidative and metabolic pathways^[5]. In this context, the timing of food intake acts as a powerful zeitgeber for metabolic tissues and a potential lever for geroprotection. In this context, TRE may constitute a promising strategy to promote circadian regulation and improve metabolic flexibility, potentially eliciting metabolic adaptations beyond those associated with caloric restriction. Mechanistically, aligning the eating–fasting cycle with endogenous circadian rhythms concentrates feeding during the biologically active phase, when mitochondrial oxidative capacity, insulin signaling, and nutrient-sensing pathways, such as mTOR, AMPK, and sirtuins, are optimally synchronized^[34]. The resulting prolonged overnight fasting interval during the biological night may facilitate autophagy, lipid mobilization, and hepatic fat oxidation, while limiting postprandial hyperglycemia and lipotoxicity during a phase of reduced glucose tolerance. Emerging preclinical evidence further supports a direct link between time-restricted feeding and vascular and mitochondrial mechanisms of aging. In aged mice, time-restricted feeding has been shown to restore endothelial function by improving mitochondrial respiration and reducing oxidative stress, indicating that feeding–fasting cycles can modulate key hallmarks of vascular aging^[35]. In addition, recent integrative analyses suggest that circadian-aligned feeding patterns promote metabolic switching, enhance endothelial resilience, and support neurovascular coupling and blood–brain barrier integrity^[36]. Together, these findings provide a mechanistic framework linking nutritional timing to vascular and cerebrovascular aspects of aging, although their translation to humans remains to be established.

Classic 30% caloric-restriction paradigms in male C57BL/6J mice illustrate a stepwise contribution of fasting and circadian alignment^[37]. When the 30% restriction is spread across 24 hours with no prolonged fast (caloric restriction–spread), median lifespan increases by ~10% versus ad libitum^[37]. Concentrating the same caloric restriction into a single daytime meal, thereby imposing a > 12-hour daily fast but misaligning feeding with the nocturnal active phase (caloric restriction day), yields ~20% lifespan extension. When the same restriction and fasting interval are combined with feeding confined to the nocturnal active phase (caloric restriction night), median lifespan is extended by ~35%, indicating that caloric restriction, fasting duration, and circadian alignment act additively to promote longevity independently of energy intake or body weight^[37].

Complementary work demonstrates that imposing a long daily fasting interval by concentrating food into a single meal improves health and extends survival in male mice on both low-sucrose and sucrose-rich diets, despite similar total caloric intake to ad libitum controls and irrespective of macronutrient composition^[38]. These findings underscore that fasting duration and eating pattern, rather than diet composition alone, are key determinants of longevity^[38]. More recently, a study reported that circadian-aligned time-restricted feeding with an 8-hour nocturnal feeding window on a standard, non-obesogenic chow diet improved a composite healthspan index (behavioral rhythms, body composition, frailty, and disease onset) in both sexes. In male C57BL/6J mice, this regimen also extended median lifespan by ~12%, alongside modest voluntary caloric restriction^[39]. These findings suggest that restricting feeding to the active phase may influence healthspan- and lifespan-related outcomes even under non-obesogenic conditions. Importantly, we cannot exclude the possibility of a potential sexual dimorphism in the effects of TRE. A recent study in aged female mice indicates a distinct response to circadian and fasting-based interventions^[40]. Calorie restriction initiated late in life robustly improves healthspan and extends lifespan in female mice even under circadian misalignment, whereas time-restricted feeding alone induces hyperphagia, impaired body-weight maintenance, and weaker systemic benefits. Calorie restriction, but not time-restricted feeding, is associated with reduced neoplastic burden, lower severity of inflammatory lung disease, and a distinct serum metabolomic signature in overnight-fasted female mice. Together, these findings in preclinical models suggest that in females,

prolonged fasting confers maximal benefit only when combined with an imposed reduction in energy intake, highlighting a clear sexual dimorphism in the interaction between circadian alignment, fasting, and aging-related outcomes^[40].

Collectively, findings from preclinical models support the concept that the circadian timing of nutrient intake is a key modulator of aging-related pathways, acting through mechanisms that extend beyond energy balance alone. However, these geroprotective effects have been demonstrated primarily in preclinical models, and their translation to humans remains uncertain. Lifespan studies in mice often involve lifelong or long-term controlled feeding paradigms that are not directly comparable to time-limited or late-life interventions in geriatric clinical settings. In addition, accumulating evidence indicates that the relative contributions of circadian alignment, fasting duration, and caloric intake to healthspan and lifespan may differ by sex. In particular, while circadian-aligned time-restricted feeding is sufficient to promote metabolic health and longevity in males, data from aged female mice suggest that prolonged fasting confers maximal benefit only when paired with an imposed reduction in energy intake, even in the presence of circadian misalignment. These observations underscore the likelihood of sexual dimorphism in the interaction among circadian rhythms, nutritional timing, and aging biology, an issue that warrants systematic investigation. Importantly, these sex-specific differences are also likely to have translational implications in humans, potentially influencing adherence to TRE, compensatory energy intake, body composition responses, hormonal adaptations, and the risk of adverse effects on skeletal muscle and physical function. These dimensions remain insufficiently characterized in clinical settings and represent an important area for future research.

4. Clinical Translation: From Lifestyle to Gerotherapeutics

From a clinical standpoint, TRE is attractive because it compresses caloric restriction, circadian alignment, and behavioral simplicity into a single, low-cost intervention that is accessible to adults with obesity and metabolic dysfunction, including older adults. In our trial, all TRE regimens were delivered on top of Mediterranean diet counseling (UC) yet still produced an additional ~3 kg of weight loss compared with UC alone over 12 weeks, with high adherence (85–88%) and no serious adverse events across TRE schedules^[30]. Similarly, short-term studies in older adults support the feasibility of TRE, reporting high adherence even in populations at risk of mobility impairment. For example, a pilot study in sedentary adults aged ≥ 65 years reported adherence of approximately 84% after a four-week TRE intervention, together with modest weight loss and improvements in walking speed and quality of life^[41]. Conversely, adherence to TRE may be more variable in real-world settings, particularly when strict eating windows are imposed. In a recent 12-week intervention in older adults, combining TRE with a Mediterranean diet improved dietary quality, but only a minority expressed willingness to maintain the fasting regimen long term, primarily due to the challenges associated with modifying habitual meal timing^[42]. Extending beyond traditional clinical populations, a randomized controlled trial in firefighters working 24-hour shifts showed that a 12-week 10-hour TRE intervention was feasible, reduced the daily eating window, and improved quality of life without adverse effects, with additional improvements in glycated hemoglobin and diastolic blood pressure among those with elevated cardiometabolic risk^[43]. Together, these feasibility, safety, and adherence-related findings are critical for real-world implementation among midlife and older adults, in whom complex or highly restrictive diets frequently fail due to poor long-term adherence.

Conceptually, TRE can be viewed as a non-pharmacologic caloric-restriction mimetic that may be layered onto standard geriatric obesity care. However, this characterization is largely based on its cardiometabolic effects, and whether TRE can reproduce the broader geroprotective effects of caloric restriction in humans remains unclear. In our trial^[30], the early TRE regimen combined circadian targeting with constrained self-selection: participants could choose their own 8-hour eating window, provided it started before 10:00, typically resulting in schedules such as 08:00–16:00 or 09:00–17:00. For older adults with obesity, prediabetes, or early cardiometabolic dysfunction, this structured yet flexible early TRE could be used to (i) induce modest weight and SAT loss, (ii) improve nocturnal glycemic control, and (iii) re-entrain behavioral rhythms (meal timing, sleep–wake patterns) that often drift with age. In contrast, purely self-selected TRE windows that extend eating into the biological evening or late night may fail to realign feeding with circadian biology and therefore are likely to yield smaller potential geroprotective benefits.

Importantly, the definition of an “early” window must be adapted to cultural meal times. In Spain, for example, where dinner commonly occurs at 21:00–22:00, a 10:00–18:00 eating window would still represent a substantial phase advance and function as an early TRE pattern in practice^[44]. Our data therefore suggest that “when” patients eat is a modifiable dimension of care that may be at least as important as “how much,” provided that TRE schedules are both circadian-aligned and culturally feasible. This concept aligns with emerging chronotherapeutics data in humans. Notably, a randomized phase 3 trial reported markedly improved survival outcomes when immunochemotherapy was administered earlier versus later in the day, highlighting time-of-day as a clinically meaningful determinant of treatment response^[45].

From a clinical perspective, medication use represents an important consideration when implementing TRE, particularly in older adults, who are more likely to receive glucose-lowering agents, antihypertensives, diuretics, and other chronic therapies. In these individuals, prolonged fasting or altered meal timing may increase the risk of hypoglycemia, hypotension, dizziness, or dehydration. Therefore, TRE should be implemented cautiously in clinical populations and may require medical supervision and individualized adjustment of medication timing or dosage, especially in older adults with multimorbidity or polypharmacy.

In parallel, age-related conditions such as sarcopenia, frailty, and anorexia of aging represent critical considerations for the safe implementation of TRE in older adults^[46]. In this setting, TRE should not be viewed as a stand-alone gerotherapeutic strategy if it unintentionally lowers total energy or protein intake in ways that may compromise skeletal muscle mass, strength, or physical function. Instead, in older adults, TRE may need to be paired with adequate diet quality, sufficient high-quality protein intake, and resistance exercise to preserve lean mass while improving metabolic health. In this context, progressive strength training may represent a pragmatic and effective adjunct to TRE to preserve or improve muscle function while enhancing metabolic outcomes, thereby strengthening the rationale for TRE as a safe and scalable geroscience-informed strategy^[47]. Findings from a recent pilot randomized controlled trial suggest that TRE can be feasible in older populations with obesity and may even improve aspects of physical performance, such as chair stand and walking capacity, following a 9-month intervention, despite modest effects on body weight^[48]. Accordingly, TRE may be most appropriate earlier in the aging trajectory, such as in midlife or in older adults with obesity and preserved function, whereas in advanced age or frailty its use should be individualized and approached with caution, as adherence to TRE may be challenging in older populations despite potential metabolic benefits^[42]. In addition, potential sex-specific responses should be considered, as older women may exhibit distinct adaptations to fasting and energy restriction, which could influence adherence, body composition, and muscle-related outcomes^[27].

5. Integration with Geromedicine: Opportunities and Challenges

From a geromedicine perspective and based on available data, TRE can be considered a pragmatic nutritional intervention within the expanding geroscience toolkit, complementing established strategies such as exercise, caloric restriction, and emerging senotherapeutic approaches. Unlike pharmacologic geroprotectors, TRE simultaneously targets multiple upstream aging mechanisms, including nutrient sensing, circadian regulation, and adipose tissue distribution, while remaining scalable and acceptable in free-living populations. However, a fundamental challenge lies in determining whether TRE can slow the biological clock itself or if its clinical benefits are primarily secondary to the mitigation of metabolic dysfunction. In this context, reductions in adiposity induced by TRE may still be mechanistically relevant, as a lower adipose tissue burden, particularly VAT, could reduce chronic low-grade inflammation, a key effector of aging-related decline. Despite growing evidence for cardiometabolic benefits, critical knowledge gaps remain, highlighting the importance of clearly distinguishing between demonstrated cardiometabolic effects and proposed gerotherapeutic benefits. Most human trials have not incorporated validated biomarkers of biological aging or functional outcomes. Although evidence from caloric restriction and other fasting-based interventions suggests potential effects on epigenetic aging, inflammation, and functional decline, whether TRE itself can meaningfully modulate established hallmarks of aging, such as epigenetic aging rates, chronic low-grade inflammation, proteostasis, or mitochondrial function, remains largely unknown. Equally important, the impact of TRE on age-related functional outcomes, including muscle function, mobility, and fatigue resistance, has been insufficiently explored, particularly in older adults and frail populations. Consequently, while TRE effectively addresses some of the metabolic symptoms of aging, its capacity to slow the biological pace of aging remains a hypothesis requiring validation.

Although preclinical models have shown that circadian timing of nutrient intake and fasting can delay aging and improve cardiometabolic health through mechanisms that extend beyond energy deficit alone, in humans it remains uncertain whether TRE can improve cardiometabolic health independently of caloric restriction. The landmark study by Sutton et al. demonstrated that early TRE improved insulin sensitivity, β -cell function, blood pressure, and oxidative stress in the absence of weight loss, suggesting that meal timing itself may confer metabolic benefits^[12]. However, the broader human evidence remains limited, as the few studies comparing TRE with a prolonged eating window have also involved prescribed or spontaneous energy restriction, making it difficult to disentangle the specific effects of meal timing from those of reduced energy intake.

To advance TRE from a lifestyle recommendation to a bona fide gerotherapeutic strategy, future trials should be explicitly designed within a geroscience framework. This will require integrating validated aging biomarkers (e.g., epigenetic clocks, inflammatory and metabolic aging-related signatures) alongside traditional clinical endpoints. In parallel, resilience-oriented outcomes, such as sleep quality, circadian robustness, and mobility, should be prioritized, because these domains may be more sensitive to circadian-aligned interventions than static disease markers. Such an approach would allow TRE to be evaluated not only for its capacity to reduce disease risk but also for its potential to preserve physiological resilience and extend healthspan across the aging trajectory.

From a geroscience perspective, future TRE trials should systematically incorporate functional and physical performance outcomes, particularly in older adults at risk of sarcopenia and frailty. This includes measures such as skeletal muscle mass (e.g., appendicular lean mass), muscle strength, gait speed, and chair-rise performance, which may provide a more direct link between metabolic improvements and clinically meaningful aging-related outcomes. These approaches will be essential to determine whether TRE can be safely and effectively integrated into aging populations without compromising physical function.

Finally, long-term adherence represents a key challenge for the clinical translation of TRE. Although most human TRE trials have been relatively short, the longest available studies extend to approximately 12 months and indicate that adherence may be feasible over this time frame in selected populations^[49]. However, whether short-term feasibility translates into sustained long-term implementation in broader clinical and real-world settings remains uncertain.

6. Conclusion

There is growing evidence that the timing of food intake is a biologically meaningful determinant of metabolic aging. Beyond caloric quantity or diet composition, the timing of nutrient intake interacts with circadian systems that regulate glucose metabolism, adipose tissue, and cellular maintenance processes that deteriorate with age. In this context, TRE emerges as a feasible strategy to improve cardiometabolic health, with potential implications for metabolic aspects of aging. However, direct evidence linking TRE to modifications in biological aging processes, functional decline, healthspan, or longevity in humans remains limited, and future studies should specifically address these outcomes.

Looking ahead, integrating circadian-aligned nutritional interventions into geromedicine represents a promising translational opportunity. Bridging circadian biology, nutrition, and geromedicine offers a coherent and actionable path to extending healthy longevity by targeting upstream aging mechanisms rather than downstream disease.

Declarations

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Authors contribution

Dote-Montero M, Clavero-Jimeno A: Conceptualization, project administration, writing-original draft, writing-review & editing.
de Cabo R, Labayen I: Writing-review & editing.
Ruiz JR: Conceptualization, writing-original draft, funding acquisition, supervision, writing-review & editing.

Conflicts of interest

Rafael de Cabo serves as an Editorial Board Member of *Geromedicine*. The other authors declare no conflicts of interest.

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