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Opinion

Reprogramming the mitochondrial–circadian energy code with incretins

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Mitochondrial dysfunction, circadian disruption, and the accumulation of senescent cells converge to impair metabolic flexibility, a unifying phenotype of obesity and aging. We frame obesity as a nutrient-driven and aging as a time-driven expression of a disrupted mitochondrial–circadian energy code, with shared outputs: impaired substrate switching and flattened energy rhythms. This opinion argues that restoring code integrity, indexed clinically by gains in metabolic flexibility, should guide therapy. Beyond appetite and glycemia, GLP-1 (glucagon-like peptide-1) and dual GLP-1/GIP (glucose-dependent insulinotropic polypeptide) agonists may enhance mitochondrial efficiency, support circadian alignment, and temper prosenescent signaling across target tissues (muscle, liver, adipose, islets, and brain). We outline how node-specific and combination strategies (senolytics/senomorphics, mitophagy/NAD$^+$ support, and chrono-entrainment) could reprogram systemic energy coordination, improve durability of response, and delay age-related metabolic decline.

Highlights

Mitochondrial dysfunction, circadian misalignment, and senescent cell buildup converge to drive metabolic inflexibility in obesity and aging, motivating an integrated 'mitochondrial–circadian energy code'.

Strain in one node can amplify dysregulation across the network; conversely, improving a single node may help recoordinate system-level metabolism.

GLP-1 and dual GLP-1/GIP agonists may act beyond appetite and glycemia, with emerging evidence for effects on fat oxidation/mitochondrial readouts and circadian organization.

Metabolic flexibility (fasting fat oxidation, change in respiratory quotient to insulin, acylcarnitine signatures) provides a practical surrogate for code integrity and reversibility.

Combining incretin therapy with senescence-, mitochondria-, and clock-targeted levers could improve the durability of metabolic benefits and help mitigate age-related metabolic decline.

Obesity and aging: increasing 'epidemics' with shared hallmarks

Obesity and aging are intertwined drivers of cardiometabolic morbidity (https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight; https://www.who.int/news-room/fact-sheets/detail/ageing-and-health). Evidence increasingly indicates that mitochondrial dysfunction, **circadian desynchronization** (see Glossary), and **senescent cell** accumulation converge on a shared physiological endpoint—impaired metabolic flexibility—yet how these processes couple into a self-reinforcing network in humans remains incompletely defined [1–5]. Defining this integration could reveal upstream drivers of chronic metabolic dysfunction and identify new therapeutic targets.

In this opinion article, we define the 'mitochondrial–circadian energy code' as a set of coupled rules that translate nutrient availability and time cues into coordinated substrate choice and energy expenditure across tissues. The code is implemented through shared biochemical currencies [e.g., redox/NAD$^+$–NADH balance, acetyl-CoA–linked protein acetylation, **reactive oxygen species (ROS)** as signaling versus damage, and ATP/adenosine monophosphate (AMP)-sensitive pathways, such as adenosine monophosphate-activated protein kinase (AMPK)–sirtuin 1 (SIRT1)–peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α)] that jointly tune mitochondrial flux, clock amplitude/phase, and stress responses that shape senescent burden. When these currencies drift out of range, local defects [e.g., reduced lipid oxidation, damped clock amplitude, and **senescence-associated secretory phenotype (SASP)** costs] can scale into impaired metabolic flexibility and blunted diurnal energy rhythms (Figure 1, Key figure). Here, 'circadian' denotes temporal gating of bioenergetic fluxes (i.e., how feeding–fasting timing and clock amplitude/phase organize mitochondrial substrate selection, redox balance, and quality control). Clinically, the code is read out not by clock genes *per se*, but by concordant changes in metabolic flexibility [e.g., fat oxidation/**Delta respiratory quotient (ΔRQ)**] and

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Key figure

The mitochondrial–circadian energy code

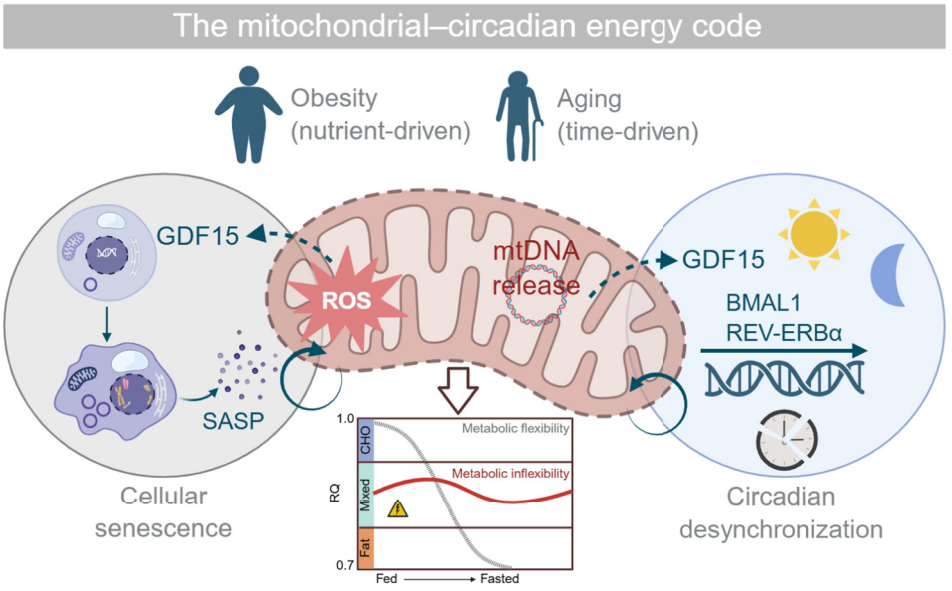

Figure 1. Obesity (nutrient-driven) and aging (time-driven) converge on a shared bioenergetic vulnerability arising from coupled dysfunction of mitochondria, circadian clocks, and cellular senescence. Mitochondrial stress outputs (e.g., excess ROS and mtDNA release) can impair OXPHOS and substrate selection. Senescent cells, via a proinflammatory SASP, further increase bioenergetic and redox load, while circadian desynchronization (reduced amplitude/phase coherence) destabilizes the daily organization of mitochondrial metabolism. GDF15 is depicted as a stress-induced signal linking peripheral distress to brain-mediated energy conservation responses. Mechanistically, GDF15 signals via the GFRAL–RET receptor complex in the area postrema and nucleus tractus solitarius; peripheral metabolic effects are therefore expected to be largely indirect, via brainstem-driven autonomic/endocrine outputs, and should be interpreted as testable links rather than established tissue-autonomous signaling (dashed arrows). Together, these nodes are proposed to interact as a self-reinforcing network that promotes metabolic inflexibility. Inset: metabolic flexibility (gray) is reflected by appropriate fed-to-fasted shifts in respiratory quotient (RQ), whereas metabolic inflexibility (red) shows a flattened RQ trajectory and reduced ΔRQ during insulin-stimulated conditions, indicating impaired substrate switching. BMAL1: brain and muscle Arnt-like protein-1; CHO: carbohydrate; GDF15: growth differentiation factor 15; GDNF: glial cell line-derived neurotrophic factor; GFRAL: GDNF family receptor alpha-like; OXPHOS: oxidative phosphorylation; mtDNA: mitochondrial DNA; RET: REarranged during Transfection; REV-ERBα: nuclear receptor subfamily 1 group D member 1 (NR1D1); ROS: reactive oxygen species; RQ: respiratory quotient; ΔRQ: change in RQ; SASP: senescence-associated secretory phenotype. Figure created with BioRender.com.

rhythm integrity from time-resolved physiological readouts (e.g., wearable-derived phase/amplitude proxies; discussed below).

Operationally, we treat the code as a hierarchy in which nutrient/time cues set core biochemical currencies; these currencies constrain mitochondrial flux and clock amplitude, and downstream stress programs shape senescent burden—together determining metabolic flexibility as the measurable clinical output. A minimal 'syntax' of the code is that (i) mitochondrial redox state (NAD^+/NADH) and acetyl-CoA availability tune acetylation/deacetylation programs, including SIRT1-dependent regulation of core clock components [e.g., brain and muscle Arnt-like protein-1 (**BMAL1**) and period circadian clock 2 (PER2)], thereby shaping clock amplitude and phase; (ii) ROS act as signaling intermediates that engage redox-sensitive stress pathways [e.g., **nuclear factor erythroid 2-related factor 2**

Glossary

AP/NTS: area postrema and nucleus tractus solitarius—brainstem hubs integrating visceral input to regulate appetite, autonomic output, and energy balance.
BMAL1: core circadian transcription factor (with CLOCK) driving rhythmic gene expression and coordinating metabolic programs.
Circadian clock: an endogenous molecular timekeeping system that generates ~24-hour rhythms in gene expression, physiology, metabolism, and behaviour, synchronizing biological functions with the daily light–dark cycle.
Circadian desynchronization: misalignment between central (SCN) and peripheral clocks or between behavior (sleep/feeding) and internal circadian phase.
Delta respiratory quotient (ΔRQ): change in respiratory quotient (RQ = $V^{\cdot}CO_2/V^{\cdot}O_2$) during insulin/glucose stimulation; proxy of substrate switching and metabolic flexibility.
Dual GLP-1/GIP receptor agonists: agents activating GLP-1 and GIP receptors to improve glycemia and induce weight loss, with potential pleiotropic metabolic effects.
FGFR1c/β-Klotho: endocrine FGF21 receptor complex comprising FGFR1c and the co-receptor β-Klotho (KLB).
GFRAL–RET: brainstem receptor complex for GDF15, formed by GFRAL and the coreceptor RET.
Growth differentiation factor 15 (GDF15): stress-induced mitokine; signals centrally via GFRAL to modulate energy balance responses.
Incretins: meal-stimulated gut hormones that potentiate glucose-dependent insulin secretion; mainly GLP-1 and GIP.
Integrated Stress Response (ISR): cellular stress program that transiently suppresses global translation while inducing adaptive genes; chronic activation can promote metabolic dysfunction.
Magnetic resonance imaging proton density fat fraction (MRI-PDFF): quantitative MRI endpoint for hepatic fat fraction (fat ÷ [fat + water]), used to assess steatosis and treatment response.
Mitochondrial unfolded protein response (UPR^{mt}): mitochondrial proteostasis stress program inducing chaperones/proteases and quality

(NRF2)/integrated stress response (ISR)], intersecting with clock-controlled transcription; and (iii) clock-driven feeding–fasting rhythms gate mitochondrial substrate flux, **mitophagy**, and redox balance, coupling back to mitochondrial function. Together, these links explain how outputs of one node can serve as inputs to another.

We argue that obesity is the nutrient-driven phenotype of a disrupted mitochondrial–circadian energy code, shaped by caloric excess, lipotoxic stress, and feeding-time misalignment, whereas aging is its time-driven counterpart, shaped by cumulative mitochondrial damage, senescent cell accrual, and hormonal decline. We view this as a 'continuum': in healthy aging, the code may drift gradually without overt metabolic disease, whereas dysfunctional adiposity can accelerate disruption and increase the likelihood of clinically meaningful metabolic inflexibility. Both trajectories converge on impaired substrate switching, blunted energy rhythms, and often compensatory neuroendocrine 'energy conservation' responses.

In the nutrient-driven trajectory, persistent overnutrition and inactivity overload mitochondrial fatty acid handling, sustain ISR/**mitochondrial unfolded protein response (UPR^{mt})** signaling, and weaken clock amplitude through irregular feeding windows, promoting early metabolic inflexibility, ectopic lipid storage, and postprandial hyperinsulinemia—features that are comparatively rapidly improved by energy deficit, **time-restricted feeding (TRF)**, and **incretin**-based therapies [6]. In the time-driven trajectory, mitochondrial DNA (mtDNA) oxidative damage, impaired mitophagy, and rising senescent cell burden disrupt peripheral clocks and lock tissues into a high-SASP, bioenergetically costly state [7–9], yielding a more entrenched metabolic inflexibility that is only partly reversible unless senescence and mitochondrial quality control are directly targeted [6]. A key implication is context-dependent node dominance. In nutrient-driven obesity, mitochondrial substrate overload and feeding-time misalignment are proposed early entry pressures that can be sufficient to impair metabolic flexibility, whereas senescent burden may emerge variably as a contingent amplifier with chronicity and tissue stress. By contrast, in time-driven aging, declining mitochondrial quality control (including cumulative mtDNA damage and impaired mitophagy) together with rising senescent cell burden are proposed to be more consistently present and to constrain reversibility. These distinctions generate testable predictions for stratified therapy and trial design: biomarker-led profiling (Figure 2) may help distinguish predominant mitochondrial/circadian disruption from dominant senescence/quality control constraints, informing escalation toward combination approaches when reversibility is limited.

Despite different drivers, both routes collapse the same code—mitochondrial substrate utilization, circadian rhythmicity, and senescent burden—explaining why obesity and aging share phenotypes yet differ in reversibility, tempo, and therapeutic leverage [6,7]. We use this framework to highlight combined therapeutic strategies (pharmacological, lifestyle, and chronomodulatory) to treat obesity and age-related metabolic decline, and to inform prevention and trial design aimed at improving health span.

Metabolic flexibility: the clinical phenotype we must restore

Metabolic flexibility, the capacity to switch between lipid and glucose oxidation according to cellular demand, is a measurable phenotype that predicts future metabolic health [6]. In obesity and insulin resistance, skeletal muscle displays reduced fasting fat oxidation and a blunted rise in respiratory quotient (ΔRQ) during insulin stimulation, consistent with impaired substrate switching [10].

Aging adds an independent, time-driven constraint. Older adults exhibit reduced skeletal muscle mitochondrial respiration, lower oxidative enzyme activity, and slower ATP production kinetics, correlating with lower fat oxidation and insulin resistance [11,12]. A shift toward glycolysis and disruption of energy-sensing pathways (e.g., AMPK–SIRT–PGC-1α) further promote metabolic

control genes; chronic activation may be maladaptive.
Mitohormesis: adaptive response in which mild mitochondrial stress triggers protective pathways that may support stress resistance.
Mitokine: stress-inducible secreted factor released with mitochondrial dysfunction to signal mitochondrial strain systemically (e.g., GDF15 and FGF21).
Mitophagy: selective autophagic removal of damaged mitochondria to preserve mitochondrial quality control.
NAD$^+$ precursors: compounds that raise cellular NAD$^+$ availability and support redox and mitochondrial metabolism.
Nobiletin: polymethoxyflavone and ROR agonist that can enhance circadian clock amplitude in preclinical models.
NRF2: redox-sensitive transcription factor (NFE2L2) that activates antioxidant and cytoprotective genes; links oxidative stress to metabolic and inflammatory programs.
Oxidative phosphorylation (OXPHOS): mitochondrial process coupling electron transport to ATP synthesis.
PPAR pathways: nuclear receptor networks (PPARα/γ/δ) regulating lipid oxidation, adipogenesis/insulin sensitivity, and inflammation.
Reactive oxygen species (ROS): reactive oxygen-containing molecules acting as signals at physiological levels but causing oxidative damage in excess.
REV-ERBα: nuclear receptor that represses BMAL1 and shapes circadian phase and metabolic gene timing.
Senescence-associated secretory phenotype (SASP): proinflammatory secretome of senescent cells that remodels tissue microenvironments and propagates dysfunction.
Senescent cells: cells in stable growth arrest that remain metabolically active and often secrete SASP, contributing to tissue dysfunction in aging and chronic disease.
Senolytics: interventions that selectively eliminate senescent cells.
Senomorphic strategies: interventions that suppress SASP and senescence-associated signaling without eliminating senescent cells.
Time-restricted feeding (TRF): eating pattern that confines daily intake to a time window (e.g., 6–10 h) to align feeding–fasting cycles with circadian rhythms, without changing calories.

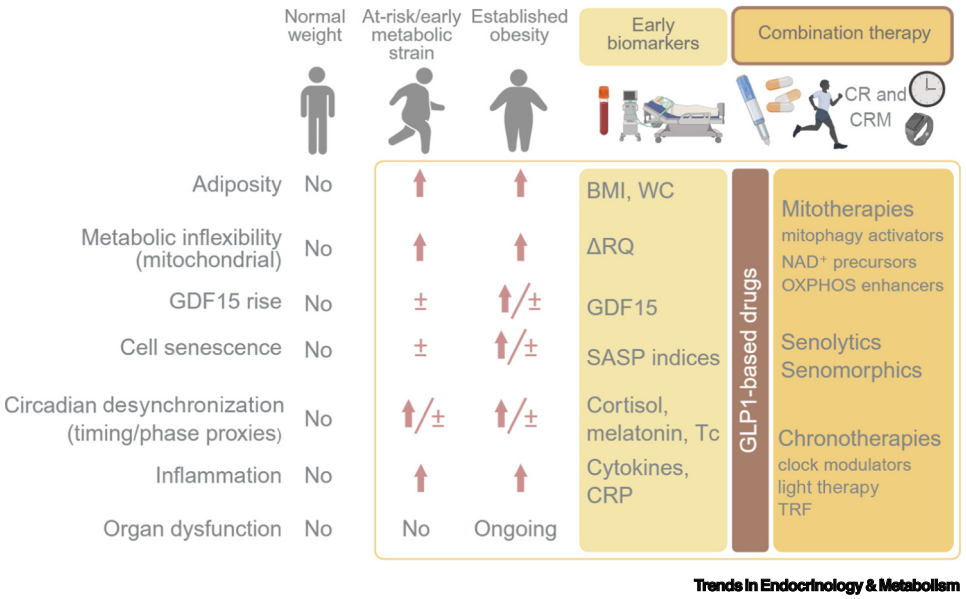

Figure 2. Biomarker-guided escalation toward combination therapy in obesity. This schematic links biomarker profiling to mechanism-guided treatment escalation along a continuum from normal weight to an at-risk/early metabolic state and established obesity, mapping progressive strain across the mitochondrial–circadian energy code. In the at-risk/early metabolic strain state, actionable signals may include reduced metabolic flexibility (lower fasting fat oxidation and blunted ΔRQ during clamp or mixed-meal testing), early circadian disruption reflected by wearable-derived timing/phase–amplitude proxies (irregular sleep–activity–light patterns, damped skin temperature rhythms, or flattened diurnal cortisol slope), and low-grade inflammation. In this stage, rises in circulating GDF15 and senescence/SASP burden may be variable and context dependent. With established obesity, these alterations often intensify and may be accompanied by higher senescence/SASP burden and organ dysfunction. The 'Early biomarkers' panel highlights feasible measures for triage and longitudinal monitoring (BMI, WC, ΔRQ, GDF15, inflammatory markers, and selected endocrine/chronobiological indices). Wearables (actigraphy, skin temperature, heart rate/HRV, and light exposure) and optional CGM provide person-specific, time-resolved rhythm readouts to inform behavioral scheduling and treatment timing. GLP-1-based therapies are shown as a foundational platform, with potential to improve weight and glycemic control and to influence multiple nodes. The 'Combination therapy' panel illustrates how add-ons—mitochondrial-targeted approaches, senolytics/senomorphics, and chrono-entrainment (TRF and light timing)—may be layered based on the dominant biomarker profile. BMI: body mass index [body weight (kilograms) divided by height squared (meters)]; CGM: continuous glucose monitoring; CR: caloric restriction; CRM: caloric restriction mimetics; CRP: C-reactive protein; GDF15: growth differentiation factor 15; GLP-1: glucagon-like peptide-1; HRV: heart rate variability; OXPHOS: oxidative phosphorylation; ΔRQ: change in respiratory quotient; SASP: senescence-associated secretory phenotype; Tc: skin temperature; TRF: time-restricted feeding; WC: waist circumference. Figure created with BioRender.com.

inflexibility and unhealthy aging [13]. Endurance-type training can partially reverse age-related declines in mitochondrial function and improve substrate switching, supporting a causal contribution of the mitochondrial node [14]. Together, this phenotype-first perspective motivates the mitochondrial–circadian energy code framework developed below (Figure 1) [3,4,12].

Mitochondrial dysfunction and bioenergetic collapse

Causes and mechanisms

Across metabolically active tissues (skeletal muscle, liver, and adipose), mitochondrial defects reduce **oxidative phosphorylation (OXPHOS)**, constrain fatty acid β-oxidation, and increase ROS, thereby impairing insulin signaling and substrate switching. Clinical studies link reduced mitochondrial activity to intramyocellular lipid accumulation and insulin resistance in obesity and type 2 diabetes (T2D) and report reduced OXPHOS capacity, impaired lipid oxidation, and mitochondrial morphological alterations [12,15–17]. Mitochondria also trigger integrated stress programs, including the UPR^{mt} and ISR, that initially support proteostasis but can entrench

maladaptive signaling when chronically activated during overnutrition and aging [18]. Similar processes operate in aging, where mtDNA mutations and oxidative damage, coupled with diminished mitophagy, contribute to progressive bioenergetic decline [2].

Obesogens and epigenetic modifications

Environmental endocrine-disrupting obesogens can bias energy balance by promoting adipogenesis, altering nuclear receptor signaling (e.g., **PPAR pathways**), and disrupting mitochondrial function [19,20]. Mechanistically, obesogens and nutrient overload converge on epigenetic programs that regulate mitochondrial biogenesis and oxidative capacity. For example, non-CpG hypermethylation of the PPARGC1A gene (encoding PGC-1α protein) promoter is associated with reduced mitochondrial content in human T2D and is inducible by fatty acids, implicating DNA methyltransferases in the repression of mitochondrial genes [21]. Epigenetic changes at other metabolic loci (e.g., the insulin promoter) further illustrate how chromatin marks can embed obesogenic signaling into durable transcriptional states that blunt metabolic flexibility [22].

Metabolic memory in obesity and aging

Metabolic memory, first described in diabetes, posits that early metabolic insults leave persistent oxidative and epigenetic imprints that continue to drive pathology even after partial risk factor normalization [23]. Mitochondrial ROS can act as an upstream signal, stabilizing pro-inflammatory and stress response transcriptional programs via histone/DNA modifications and altered mitochondrial–nuclear crosstalk [24]. We propose that this paradigm extends to obesity and aging: repeated cycles of nutrient overload and circadian misalignment may imprint mitochondrial-epigenetic states that sustain metabolic inflexibility and senescent burden. In parallel, age-associated epigenetic changes accumulate across the lifespan [25], helping explain the persistence of obese/insulin-resistant phenotypes and the trajectory of age-related decline despite short-term improvements.

Cellular senescence: an energetic burden

Cellular senescence is a state of essentially irreversible cell cycle arrest, typically accompanied by DNA damage and the development of an SASP [2,5]. The SASP comprises proinflammatory cytokines, proteases, miRNAs, and other bioactive factors. Although senescence can be beneficial in development, wound repair, and tumor suppression, its chronic accumulation, driven by aging, obesity, and other stressors, has detrimental metabolic consequences. Robust experimental evidence implicates senescent cells in age-related disease phenotypes, including obesity, diabetes, and cardiovascular disorders [2,26]. White adipose tissue (WAT) appears particularly susceptible, both as part of aging and in obesity or T2D, irrespective of chronological age [27]. While the contribution of adipocyte senescence to human metabolic disease is still being defined, senescent features in subcutaneous adipose tissue from individuals with severe obesity correlate with adverse fat distribution and impaired glucose regulation [5,28].

Senescent cells also remain metabolically active: maintaining the SASP imposes a sustained bioenergetic demand without productive tissue function [7]. In adipose tissue, obesity accelerates senescence in adipocytes and the stromal vascular fraction, whereas aging promotes a broader, multiorgan senescent burden [27].

Mitochondrial dysfunction, senescence, and GDF15 signal

Mitochondria are a major source of ROS, which, at physiological levels, act as signaling molecules but, in excess, promote oxidative damage to DNA, lipids, and proteins [29]. This oxidative burden can trigger cellular senescence: ROS contribute to sustaining senescent hallmarks, including genomic injury [30] and telomere attrition [31], while nonmitochondrial ROS, broader redox

imbalance, and impaired antioxidant defenses also contribute [32,33]. In this sense, mitochondria integrate cellular stress signals that can contribute to tissue dysfunction.

Importantly, 'mitochondrial dysfunction' in metabolic disease and aging often reflects impaired mitochondrial quality control, not merely reduced OXPHOS. Quality control integrates mitochondrial dynamics (fusion–fission), mitophagy, and coordinated biogenesis/proteostasis to remove damaged organelles and restore capacity after stress. When these processes are constrained, damaged mitochondria accumulate, redox stress rises, and substrate flux becomes less adaptable—consistent with impaired fat oxidation, reduced switching capacity, and blunted diurnal bioenergetic rhythms. More broadly, nutrient-driven overload can outpace quality control and sustain maladaptive stress signaling, whereas aging progressively constrains quality control, increasing the likelihood that senescent burden and inflammatory tone further entrench dysfunction (Box 1).

Growth differentiation factor 15 (GDF15; originally macrophage inhibitory cytokine-1) is a stress-responsive cytokine induced by mitochondrial dysfunction, diverse cellular stressors, and UPR^{mt} activation [34], fitting the definition of a '**mitokine**' [39] (Box 1). A conceptual model proposes that GDF15 signals to the brain the energetic burden imposed by senescent cell accumulation in metabolically active tissues during aging, engaging central energy conservation programs [7]. In humans, GDF15 is low in healthy young individuals [34] but rises in multiple acute and chronic pathological states (including obesity, insulin resistance, T2D, cardiovascular disease, neurodegeneration, chronic kidney disease, and cancer) and increases with age irrespective of health status, supporting its use as a biomarker of biological aging [34–37].

Box 1. GDF15–GFRAL: stress signal and uncertainty

GDF15 is increasingly viewed as a systemic stress signal that links mitochondrial/proteostatic strain to brain-mediated adaptations in energy balance, yet its role in human aging remains incompletely defined. It is induced by mitochondrial dysfunction and diverse cellular stressors, including UPR^{mt}-related programs, and has been proposed to participate in **mitohormesis** under mild stress [34]. Consistent with a multiorgan 'stress secretome', GDF15 is produced by several metabolically active tissues, including skeletal muscle, liver, heart, and brain [34].

In humans, circulating GDF15 is low in healthy young individuals [34] but rises across multiple pathological contexts (including obesity, insulin resistance/T2D, cardiovascular disease, neurodegeneration, chronic kidney disease, and cancer) and increases progressively with age, supporting its use as a biomarker of biological aging [34–37]. However, interpretation requires caution: associations with frailty and mortality coexist with increases during exercise or acute stress that may be adaptive. In this framework, we therefore treat GDF15 primarily as a context-dependent sentinel of integrated stress load rather than a directional therapeutic target (Figure I).

Mechanistically, current evidence supports signaling mainly through the GFRAL–RET receptor complex in the area postrema (**AP**) and nucleus tractus solitarius (**NTS**), brainstem hubs implicated in energy balance control [34]. This axis appears predominantly stress responsive, with GDF15 increasing during exercise, fasting, and high-fat feeding [34,38]. Because GFRAL expression is restricted to the caudal brainstem, putative peripheral mechanisms remain unclear; systemic effects are expected to be largely indirect, mediated by autonomic and endocrine outputs rather than direct receptor engagement in peripheral organs (Figure I) [34]. Accordingly, whether chronic age-related elevations are predominantly maladaptive (contributing to decline) or compensatory (buffering stress) remains unresolved.

Mitochondrial stress also induces other circulating signals. FGF21, a stress-inducible mitokine/hepatokine, rises with mitochondrial and metabolic strain and can coordinate adaptive changes in substrate handling and energy expenditure via peripheral receptor complexes. In this framework, FGF21 is treated as a complementary, context-dependent component of the stress secretome that may report (and potentially mediate) 'code strain' alongside GDF15. Exercise-responsive myokines such as interleukin-6 can acutely support lipid mobilization and glucose homeostasis, whereas irisin has been linked to adipose remodeling/thermogenic programming in some contexts, although its causal relevance in humans remains debated. Collectively, these signals support the view that GDF15 is best interpreted within a broader stress secretome, alongside concordant readouts of metabolic flexibility and rhythm integrity.

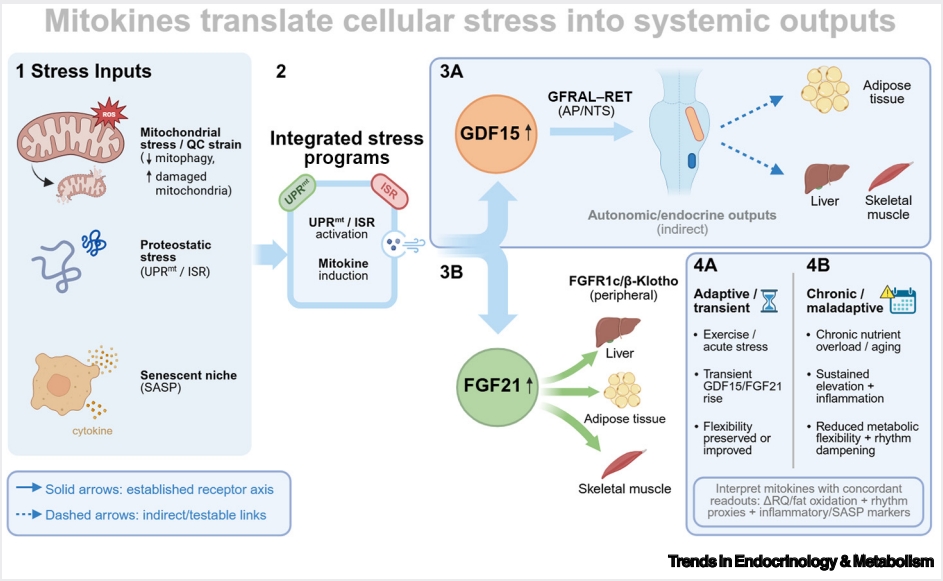

Figure I. Mitokines as a stress-to-system layer. Mitochondrial/proteostatic stress engages UPR^{mt}/ISR programs that induce mitokines, including GDF15 and FGF21. GDF15 signals via the brainstem-restricted GFRAL–RET axis with largely indirect peripheral effects, whereas FGF21 acts via peripheral receptor complexes; mitokine changes should be interpreted alongside concordant readouts of metabolic flexibility, rhythm integrity, and inflammatory/SASP tone. AP: area postrema; FGF21: fibroblast growth factor 21; FGFR1c/β-Klotho: fibroblast growth factor receptor 1c and β-Klotho; GDF15: growth differentiation factor 15; GFRAL: GDNF family receptor alpha-like; ISR: integrated stress response; NTS: nucleus tractus solitarius; QC: quality control; RET: REarranged during Transfection; ΔRQ:, change in respiratory quotient; SASP: senescence-associated secretory phenotype; UPR$^{mt:}$ mitochondrial unfolded protein response. Figure created with BioRender.com.

We do not view GDF15 as the sole or hierarchically dominant messenger. Rather, we use it as a clinically tractable sentinel of integrated mitochondrial/proteostatic and inflammatory stress with a defined brainstem receptor axis [GDNF family receptor alpha-like/REarranged during Transfection (**GFRAL/RET**)], while recognizing that mitochondrial strain elicits a broader secretome [e.g., fibroblast growth factor 21 (FGF21) — acting on **FGFR1c/β-Klotho** receptor complex in key metabolic tissues and some brain regions — and exercise-responsive myokines] that can also influence substrate use and energy balance (Box 1). Clinically, GDF15 should be interpreted as a context-dependent stress-load marker: reductions that track with improved metabolic flexibility (ΔRQ/fat oxidation), stronger rhythm indices, and lower inflammatory/SASP signatures are consistent with reduced 'code strain', whereas isolated changes (including exercise- or acute stress-related increases) may be adaptive and should be interpreted alongside concordant readouts before guiding escalation (Figure 2).

Circadian desynchronization: a temporal dimension of energy collapse

Whole-body energy homeostasis depends on coordinated nutrient intake and utilization, bioenergetic capacity, and energy expenditure organized across feeding–fasting cycles and circadian rhythms. An intrinsic ~24-h timing system (the **circadian clock**) aligns sleep–wake behavior, thermoregulation, hormone secretion, locomotor activity, and appetite with predictable daily environmental changes [40,41]. In mammals, the master clock in the suprachiasmatic nucleus (SCN) is primarily entrained by retinal light input and synchronizes peripheral clocks across mitochondrial-rich tissues through neural, hormonal, and behavioral cues, including feeding timing [41,42].

Because peripheral clocks operate within metabolically active tissues, their disruption can exacerbate metabolic inflexibility. Mitochondrial processes themselves show daily oscillations,

including OXPHOS, mitophagy, and redox balance [43,44]. Disruption of these rhythms has been linked to insulin resistance and obesity [3,45], whereas high-fat feeding blunts mitochondrial oscillations [4,46], and aging fragments circadian timing at both peripheral and central levels [47].

Senescence and circadian timing also interact bidirectionally. Senescent cells show altered clock gene expression and weakened rhythmicity; for example, oxidative stress-induced premature senescence lengthens the circadian period and delays the phase [9]. Conversely, circadian disruption promotes senescent cell accumulation in metabolically active tissues, accompanied by mitochondrial dysfunction and impaired energy metabolism [48]. Together, these observations suggest that disrupted clocks in mitochondria-rich tissues can amplify metabolic inflexibility, with effects likely depending on tissue context, stage, and senescent burden. Even a minority of senescent cells can exert outsized effects via SASP-mediated paracrine/endocrine signaling and clock-regulated neuroendocrine outputs.

GDF15 is also under circadian control: core clock components (including BMAL1 and **REV-ERBα**) regulate its expression, and circulating GDF15 shows diurnal variation [49,50]. Whether this rhythmicity is distorted in obesity and aging, and how it relates to metabolic flexibility in humans, remains insufficiently defined.

Collectively, these findings support a testable model in which mitochondrial redox/ROS stress and senescent burden can weaken peripheral clock amplitude and alignment (e.g., via NAD^+/SIRT1- and redox-sensitive signaling), thereby disrupting the temporal organization of substrate flux and worsening metabolic inflexibility; stress outputs (including GDF15) may further engage compensatory, energy-conserving brain circuits.

The mitochondrial–circadian energy code

We propose that mitochondrial dysfunction, cellular senescence, and circadian desynchronization are not independent hallmarks of metabolic decline but interacting processes within a coupled network—a mitochondrial–circadian energy code—that can amplify metabolic inflexibility. An overview of the proposed network is shown in Figure 1.

In this framework, impaired mitochondrial function lowers oxidative capacity and increases ROS, disrupting mitochondrial flexibility and the timing of substrate utilization. These changes can favor senescence in metabolically active tissues (notably adipose, muscle, and liver), where sustaining the SASP imposes a continuous bioenergetic burden. Senescent cells may, in turn, blunt circadian rhythms by altering core clock gene expression and dampening mitochondrial oscillations. Circadian misalignment can further reinforce the cycle by uncoupling feeding–fasting patterns from mitochondrial substrate use and by perturbing hormonal and neural signals that coordinate peripheral clocks. Among these signals, the GDF15–GFRAL brainstem axis may contribute to adaptive energy conservation responses under stress; if persistently engaged, it could help maintain lower energy expenditure and physical activity, thereby reinforcing metabolic inflexibility.

Therapeutic implications

Restoring metabolic flexibility is a clinically meaningful surrogate of code integrity, linking mitochondrial adaptability, circadian alignment, and senescent burden. In practice, improvements in fasting fat oxidation, ΔRQ during insulin stimulation, and selected acylcarnitine/postprandial metabolite profiles can index network recoordination. Nutrient-driven phenotypes should prioritize incretin-centered strategies combined with chrono-entrainment, whereas time-driven phenotypes will often require combination approaches, for example, GLP-1 or GLP-1/GIP agonists plus senescence-targeting and mitochondria-targeted interventions, to achieve comparable

improvements in metabolic flexibility and energy rhythmicity [51,52] (Table 1). Early evidence that GLP-1 analogs may enhance mitochondrial efficiency and support circadian alignment further supports driver-informed treatment selection (Figure 2) [52,65].

GLP-1 and GLP-1/GIP receptor agonists

GLP-1 receptor agonists (e.g., liraglutide, dulaglutide, and semaglutide) and **dual GLP-1/GIP receptor agonists** (e.g., tirzepatide) are now widely prescribed for diabetes and obesity [66]. Although their principal clinical effects reflect reduced energy intake via central satiety pathways, emerging evidence suggests additional actions relevant to the mitochondrial–circadian energy code, including improved fat oxidation/mitochondrial function and potential effects on circadian organization and stress signaling [52,56]. To distinguish evidence strength by model system, we summarize representative studies in Table 1 (human *in vivo*, animal *in vivo*, and *in vitro*/*ex vivo*), mapped to code-relevant readouts (metabolic flexibility/mitochondria, circadian indices, and senescence/SASP).

Endogenous incretin biology is time-structured: GLP-1 (and GIP) secretion varies across the day and is influenced by intestinal clock programs in preclinical models [58,59,67,68]. High-fat feeding/obesity blunts these rhythms in animals and is associated with lower basal and postprandial GLP-1 responses in humans [58,60,69–71].

Selected preclinical studies suggest GLP-1 signaling can modulate senescence-related phenotypes, including reduced senescence markers and improved microglial mitochondrial metabolism in an Alzheimer's disease mouse model, as well as the protection of endothelial cells from oxidative stress-induced senescence *in vitro* [64]. However, mechanistic confirmation in humans is needed (Table 1).

Targeting senescent cell burden

Lowering senescent cell burden and SASP secretion may help restore metabolic flexibility by reducing mitochondrial stress and supporting circadian amplitude, consistent with code integrity as a therapeutic target. In obese mice, pharmacological clearance or genetic ablation of $p16^{Ink4a+}$ cells restores mitochondrial function, improves substrate switching, and reduces inflammation [51,72]. Although **senolytics** are not approved for metabolic disease, combining them with metabolic agents (e.g., metformin and GLP-1 receptor agonists) could, in principle, interrupt reciprocal reinforcement between mitochondrial dysfunction and senescence. Consistently, genetic or pharmacological senolysis (e.g., dasatinib plus quercetin) improves substrate flexibility, attenuates inflammation, and enhances adipose mitochondrial function in preclinical models [51]. Early human studies further show that intermittent dasatinib–quercetin reduces senescence markers in diabetic kidney disease, supporting feasibility and target engagement [72]. Whether these approaches improve broader metabolic endpoints in humans remains to be established. Mechanistically, lowering SASP could reduce chronic ISR/UPR^{mt} activation, improve redox balance, and facilitate circadian re-entrainment of peripheral tissues. **Senomorphic strategies** (e.g., mTOR inhibition/rapamycin and metformin) that dampen SASP without eliminating senescent cells may complement senolytics where tissue turnover is limited [73].

Enhancing mitochondrial adaptability

Improving mitochondrial quality control and oxidative capacity may reverse bioenergetic rigidity and indirectly attenuate both senescence and circadian fragmentation, consistent with the mitochondrial–circadian energy code as an integrated hub of tissue and systemic metabolic balance. Candidate levers include mitophagy activators, **NAD^+ precursors**, caloric restriction (CR), and CR mimetics [74]. The mitophagy activator urolithin A is safe and induces a mitochondrial

Table 1. Incretin-based therapies and code-relevant readouts (evidence stratified by model system). Representative (nonexhaustive) studies curated to separate evidence strength by setting; code readouts include metabolic flexibility/mitochondria, circadian indices, and senescence/SASP[a] markers. Human RCTs establish efficacy, whereas mechanistic node claims rely mainly on preclinical/*in vitro* evidence and require dedicated human phenotyping trials

A. Human *in vivo* (highest translational weight)					
Therapy	Population/design	Code-relevant readouts reported	Key finding relevant to 'code'	Key limitations/caveats	Refs
Semaglutide 2.4 mg weekly	Adults with overweight/obesity; RCT (STEP 1)	Primarily clinical endpoints (weight and metabolic risk)	Large sustained weight loss; establishes 'platform' efficacy for obesity treatment	No direct mitochondrial/ circadian/senescence mechanistic readouts; weight-loss confounding	[53]
Tirzepatide weekly (5–15 mg)	Adults with obesity; RCT (SURMOUNT-1)	Primarily clinical endpoints (weight and cardiometabolic risk)	Very large weight loss; supports incretins as foundational platform	Mechanistic node readouts largely indirect; need phenotyping trials	[54]
Liraglutide (1.8–3.0 mg daily)	Adults with obesity; metabolic chamber/indirect calorimetry study	RQ↓ and fat oxidation↑ (metabolic flexibility proxy)	Lower 24-h RQ with higher fat oxidation versus placebo, consistent with improved substrate use	Older study; does not map clocks/senescence; appetite/weight effects may contribute	[55]
Tirzepatide during weight loss	Human calorimetry-focused mechanistic study (conference report)	Sleeping metabolic rate/indirect calorimetry endpoints	Designed to quantify EE/substrate oxidation adaptation under tirzepatide	Limited tissue/node biology	[56]
Systematic review	GLP-1-based therapies and skeletal muscle mitochondria (obesity/T2D)	Muscle mitochondrial function outcomes across studies	Synthesizes emerging evidence for muscle mitochondrial effects of GLP-1-based therapies	Heterogeneity; causality versus weight loss often unresolved	[57]
B. Animal *in vivo* (mechanistic mapping; causality testable)					
Therapy/axis	Model/design	Code-relevant readouts reported	Key finding relevant to 'code'	Key limitations/caveats	Refs
Clock → GLP-1 rhythm (ARNTL/BMAL1 in L cells)	Mouse genetic/physiology; GLP-1 secretion rhythmicity	Circadian GLP-1 secretion; clock control	Demonstrates intestinal clock control of time-dependent GLP-1 release (context for 'alignment' claims)	Not a therapy study; translational relevance indirect	[58]
Clock → GLP-1 rhythm (BMAL1 targets)	Mouse; L-cell clock-dependent GLP-1 secretion	Circadian secretion machinery	Supports mechanistic coupling between clock programs and GLP-1 release	Not therapy; details may exceed needs—keep as context anchor	[59]
Tirzepatide (preclinical energetics)	Obese mice; energy expenditure/metabolic adaptation	Energy expenditure adaptation; indirect calorimetry-style outcomes	Suggests tirzepatide can modify energy expenditure adaptation in mice	Mouse context; diet/caloric restriction confounding; translation uncertain	[56]
GLP-1 analogues and circadian/islet rhythm	Summarized preclinical evidence	Islet rhythmic function/GLP-1 rhythmicity	Preclinical literature supports influence on rhythmic islet outputs	Secondary source; keep claims cautious ('reported/suggested')	[60]
C. *In vitro/ex vivo* (mechanistic plausibility; lowest translational weight)					
Therapy	System	Code-relevant readouts reported	Key finding relevant to 'code'	Key limitations/caveats	Refs
GLP-1/ exendin-4	Human endothelial cells; oxidative stress-induced senescence	Senescence markers/ DNA damage; ROS stress protection	GLP-1 and exendin-4 attenuate oxidative stress-induced endothelial senescence (cellular stress node)	*In vitro*; does not establish organism-level metabolic flexibility	[61]
Exendin-4	Vascular cells; ANG II-induced senescence	Senescence pathways in vascular cells	Exendin-4 reported to prevent ANG II-induced premature senescence (stress/senescence node)	Cell type-specific; mechanism may not generalize	[62]
Exendin-4	Inflammation-induced senescence in stromal cells	Senescence markers; SIRT1 pathway involvement	Exendin-4 reported to mitigate inflammation-induced senescence via SIRT1-linked signaling	*In vitro*; disease relevance indirect	[63]

Table 1. (continued)

C. *In vitro/ex vivo* (mechanistic plausibility; lowest translational weight)					
Therapy	System	Code-relevant readouts reported	Key finding relevant to 'code'	Key limitations/caveats	Refs
GLP-1RA and microglial senescence/ metabolism	Brain immune cells/AD model	Senescence markers; OXPHOS-related metabolism; phagocytosis	Suggests GLP-1RA may reduce microglial senescence markers and improve mitochondrial metabolism (hypothesis-generating)	Preprint; interpret cautiously	[64]

[a]AD: Alzheimer's dementia; ANG II: angiotensin II; ARNTL: aryl hydrocarbon receptor nuclear translocator-like (also BMAL1); EE: energy expenditure.

health signature in humans [75], with emerging trials reporting improved muscle performance in older adults [54,76]. NAD^+ precursors (e.g., nicotinamide riboside) raise NAD^+ levels in humans and show vascular/metabolic signals consistent with enhanced mitochondrial function [77], although results are heterogeneous and likely dose dependent and population dependent. Exercise and CR remain potent physiological 'mitotherapies', increasing mitochondrial biogenesis (PGC-1α) [78] and mitophagy flux, thereby improving substrate switching and lowering upstream redox stress linked to prosenescent signaling. Taken together, strengthening the mitochondrial node could reduce chronic ISR and UPR^{mt} pressure, temper SASP induction, and support circadian amplitude, with metabolic flexibility serving as a practical integrative endpoint.

Circadian entrainment strategies

Re-establishing circadian alignment can coordinate peripheral clocks with mitochondrial function and may attenuate prosenescent signaling, with metabolic flexibility as a systems-level readout [79]. Light therapy, TRF, and behavioral alignment to light–dark cycles improve metabolic outcomes (e.g., insulin sensitivity and blood pressure) even without weight loss in humans [80,81] and prevent diet-induced metabolic disease in animal models [82]. Mechanistically, greater clock amplitude synchronizes mitochondrial OXPHOS, redox defenses, and mitophagy cycles [43], potentially limiting oxidative stress that promotes SASP. Pharmacological clock modulators are emerging: **nobiletin**, an retinoid acid receptor-related orphan receptor (ROR) agonist and clock amplitude enhancer, improves metabolic homeostasis and circadian robustness in preclinical models [83,84], suggesting a path toward adjunct chronopharmacology. This systems view supports combination strategies (e.g., GLP-1 or GLP-1/GIP agonists paired with senescence- or mitochondria-targeted interventions alongside chrono-entrainment) to achieve larger and more durable gains in metabolic flexibility and trajectories of healthy aging.

Target tissues and expected readouts

Below, we summarize key tissues and readouts to test code integrity and reversibility across nutrient-driven and time-driven states. In skeletal muscle, higher fasting fat oxidation, improved mitochondrial respiratory capacity, and a stronger ΔRQ response to insulin indicate improved substrate switching; practical levers include exercise, mitophagy activators (e.g., urolithin A), and NAD^+ precursors [75,77]. In the liver, reductions in hepatic fat [e.g., **magnetic resonance imaging proton density fat fraction (MRI-PDFF)**], improved β-oxidation and rhythmic transcriptional outputs, and lower fasting glucose can be tracked during GLP-1 or GLP-1/GIP therapy, TRF/chrono-entrainment, and mitochondrial support (mitophagy/NAD^+-linked approaches) [66,77,80].

Within WAT (visceral and subcutaneous), therapeutic success via CR and/or exercise (including resistance training) can be indexed by lower $p16^{INK4a}$/SASP burden, a healthier adipokine profile, and improved mitochondrial efficiency [27,85]. Senolytics (dasatinib plus quercetin) or senomorphics (e.g., rapamycin and metformin), potentially combined with GLP-1-based therapy,

may reduce chronic ISR/UPR^{mt} pressure and support systemic metabolic flexibility [51,72]. In brown/beige adipose tissue, thermogenic programming (e.g., UCP1 expression) and diurnal thermogenesis may be enhanced by clock amplitude modulators (such as nobiletin) and by TRF/light-based entrainment, with the potential to increase 24-h energy expenditure and smooth substrate cycling [80,83].

At the level of pancreatic islets, re-establishing circadian, GLP-1-dependent insulinotropic dynamics (including first-phase insulin secretion) through GLP-1 agonists and feeding-time regularization may improve substrate partitioning in the liver and muscle [58,67]. In the brain, aligning SCN-driven sleep–wake and feeding schedules and modulating GDF15–GFRAL tone through chronobehavioral scheduling and GLP-1-based therapy may help coordinate peripheral clocks and energy conservation responses (Box 1 and Table 1) [80,86]. No single biomarker is treated as dispositive; instead, decisions are guided by concordant changes in metabolic flexibility, rhythm integrity, and inflammatory/senescence load.

Concluding remarks and future perspectives

Obesity and aging, though distinct in origin, converge on a shared bioenergetic vulnerability: the collapse of a mitochondrial–circadian energy code that normally integrates mitochondrial adaptability, circadian rhythmicity, and regulation of senescent cell burden. Clinically, this collapse is reflected by impaired metabolic flexibility—blunted substrate switching and flattened diurnal energy rhythms—and motivates therapies aimed at restoring code integrity rather than targeting single symptoms alone.

Several issues must be addressed to translate this framework into clinical strategies (see Outstanding questions). First, causal ordering among mitochondrial dysfunction, senescent cell accumulation, and circadian desynchronization must be established in humans. Because much of the current evidence is cross-sectional or derived from animal models, priority designs include interventions that selectively perturb one node (e.g., senolysis, mitophagy activation, or chrono-entrainment) while quantifying network-level responses across tissues.

Second, validated, scalable biomarkers of code integrity and reversibility are needed. Candidate readouts include metabolic flexibility metrics (fasting fat oxidation and ΔRQ during insulin stimulation), diurnal metabolite/acylcarnitine signatures, selected mitochondrial functional assays (muscle/adipose), and integrated measures of senescence/SASP and circadian phase/amplitude (blood and wearables). Emerging reagentless, reset-capable affinity sensors could extend continuous monitoring beyond glucose to short protein panels reporting inflammatory tone and cardiometabolic load, paralleling high-frequency biomarker strategies used in cardiology (e.g., high-sensitivity troponin and natriuretic peptides) [87].

Third, the pleiotropy of incretin-based therapies (GLP-1 and GLP-1/GIP) warrants mechanistic trials integrating mitochondrial phenotyping, clock profiling, and senescence markers, ideally stratifying participants by predominant nutrient-driven versus time-driven phenotype. Nutrient-driven phenotypes may show greater short-term reversibility, whereas time-driven phenotypes may require combination strategies (e.g., incretin therapy plus senolytics/senomorphics, mitophagy inducers, NAD^+ repletion, and chrono-entrainment).

Fourth, the feasibility and durability of combination strategies should be tested in factorial randomized controlled trials (RCTs) using metabolic flexibility as the primary integrative endpoint, complemented by tissue-relevant secondary outcomes (e.g., MRI-PDFF for the liver, UCP1/thermogenesis for brown fat, islet insulinotropic dynamics, and diurnal GDF15 profiles). Trials should

Outstanding questions

In humans, do senolysis, mitophagy activation, or chrono-entrainment (single-node perturbations) induce measurable improvements in the other nodes, and on what timescale?

Which minimal biomarker panel best captures code integrity and reversibility (e.g., change in respiratory quotient, fasting/postprandial acylcarnitines, tissue oxidative phosphorylation assays, senescence-associated secretory phenotype indices, clock phase/amplitude from blood transcriptomics and wearables, or diurnal growth differentiation factor 15)?

Do GLP-1 or GLP-1/GIP agonists directly modulate mitochondrial function, circadian alignment, and senescent burden, or are these effects largely secondary to weight loss?

Which clinical and/or multiomics features best define **nutrient-driven** versus **time-driven** phenotypes (e.g., age, sex, adipose distribution, fitness, mitochondrial DNA damage, senescence load, or circadian disruption)?

Which combination regimens (e.g., incretins with or without senolytics, urolithin A/NAD^+ precursors, or nobiletin/time-restricted feeding/light therapy) show additivity or synergy in metabolic flexibility and organ-level endpoints (e.g., magnetic resonance imaging proton density fat fraction, uncoupling protein 1 (UCP1)/thermogenesis, or islet insulinotropic dynamics)?

Can aligning feeding, light, and medication timing with an individual's circadian phase improve efficacy and durability while reducing relapse in real-world practice?

What are the long-term metabolic, cardiovascular, and neurocognitive consequences of sustained 'code re-entrainment' in older adults and in youth with obesity?

Box 2. Implementing mitochondrial–circadian energy code in clinics

In obesity and aging, impaired **metabolic flexibility** (poor fed–fasted substrate switching) is a practical integrative phenotype that complements weight, HbA1c, and standard risk markers when considering reversibility and relapse risk. When feasible, **indirect calorimetry/RQ** (fasted ± postmeal; ΔRQ on clamp in research settings) should be added to quantify substrate switching; if not, **fasting triglycerides and liver enzymes** should be followed as imperfect proxies of ectopic lipid handling and metabolic strain. **Circadian factors matter clinically as well**. Sleep–wake regularity, light exposure, and meal timing (e.g., time-restricted eating) can shape metabolic control; capture a brief sleep/meal-timing history and, when available, use wearable proxies (sleep regularity; resting heart rate/heart rate variability trends) to flag misalignment that may blunt response.

In older adults, interpreting risk through **inflammation and function** (high sensitivity C-reactive protein assay (hs-CRP)/C-reactive protein, unintentional weight loss, sarcopenia screening such as grip strength/chair stand, and polypharmacy) may help distinguish more reversible nutrient-driven phenotypes from more time-driven, less reversible patterns. Additionally, clinicians should **escalate treatment based on concordant change:** GLP-1 or GLP-1/GIP agonists provide a foundational platform but decisions should rely on convergent shifts across metabolic flexibility proxies, rhythm integrity, and inflammatory/senescence-related burden rather than any single biomarker.

also prespecify network-propagation hypotheses and quantify whether improving one node is accompanied by gains in others.

Finally, personalization and timing are likely to shape durability. Aligning dosing and behavior with individual circadian phase (e.g., early TRF, light timing, sleep–wake regularity, and chronopharmacology) may amplify efficacy and reduce relapse, especially when combined with interventions that reduce SASP tone and restore mitochondrial quality control (Figure 2).

Overall, we present the mitochondrial–circadian energy code as a testable framework to interpret shared metabolic phenotypes across obesity and aging, and to prioritize mechanism-rich interventions. Next steps include prospective human validation using scalable, dynamic biomarkers and trial designs that explicitly test network coupling across tissues (Box 2).

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Declaration of interests

The authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT (OpenAI, San Francisco, CA) in order to refine grammar and phrasing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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