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REVIEW

Restoring Homeodynamics: Autophagy, Ageing and the Metabolic Correction of Disease

Andrew Scarborough[1], Yvoni Kyriakidou[1], Derek C. Lee[2], Tomás Duraj[2], Thomas N. Seyfried[2] and Isabella D. Cooper[1,*]

[1]Metabolic Endocrine Cancer Cardiovascular and Ageing Research, Centre for Nutraceuticals, School of Life Sciences, University of Westminster, 115 New Cavendish Street, London, UK
[2]Biology Department, Boston College, Chestnut Hill, MA, USA
*Corresponding Author: Isabella D. Cooper. Email: isabella@bellamitochondria.com or i.cooper@westminster.ac.uk

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ABSTRACT: The global rise in chronic, non-communicable diseases (NCDs) is inextricably linked to metabolic dysfunction, with hyperinsulinaemia acting as a potent upstream driver of ageing and age-related disease. Some of the most burdensome diseases of our time, including type 2 diabetes, cardiovascular disease, cancer, and neurodegenerative conditions, such as Alzheimer's disease (AD), are largely underpinned by insulin resistance as part of a broader system of metabolic and mitochondrial dysfunction. These pathologies are particularly pronounced in the developed world, where obesity and other lifestyle-related conditions are major contributors to disease burden and premature mortality. As an upstream event, persistent insulin signalling biases glucose metabolism, which in turn depletes nicotinamide adenine dinucleotide (NAD^+), suppresses autophagy, mitophagy and mitochondrial biogenesis, indispensable processes that maintain cellular homeodynamics. When compensatory mechanisms ultimately begin to fail, mitochondrial dysfunction and oxidative stress fuel cycles of inflammation, senescence and genomic instability. In this context, therapeutic ketosis offers an attractive strategy for metabolic restoration, with effects across insulin-dependent and downstream signalling pathways. This narrative review considers various approaches for inducing ketosis and autophagy therapeutically, including fasting, varied dietary strategies and exogenous ketogenic agents. Among these agents, ketone monoesters represent an effective and well-characterised option to rapidly elevate circulating levels of bioidentical (R)-β-hydroxybutyrate (BHB). The utilisation of BHB is fundamental to the therapeutic benefits of ketosis, functioning not only as a highly efficient mitochondrial fuel in comparison to glucose, but also a potent signalling molecule that preserves redox balance, inhibits NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome activation, facilitates NAD^+ availability, and epigenetically regulates antioxidant and repair genes. By promoting mitophagy and mitochondrial renewal, BHB may confer protection against the metabolic hallmarks of ageing, with therapeutic potential across a spectrum of diseases linked to hyperinsulinaemia. This model, articulated conceptually through the Concentric Zone Model of Adaptive Balance, proposes that restoring homeodynamics via ketosis represents a powerful strategy for metabolic correction, challenging the traditional paradigm of disease management. Under this conceptual framework, the review aims to examine the potential of therapeutic ketosis to restore metabolic flexibility, facilitate autophagy and regulate key nutrient-sensing pathways associated with ageing and disease.

KEYWORDS: Ageing; autophagy; homeodynamics; hyperinsulinaemia; ketosis; ketogenic diet; ketogenic metabolic therapy (KMT); β-hydroxybutyrate (BHB); metabolic flexibility; mitochondrial dysfunction

1 Introduction

Ageing is increasingly recognised not as passive decline, but as an active, dynamic process underpinned by molecular and cellular dysregulation, reflected in reduced metabolic adaptability, impaired mitochondrial function, and compromised cellular repair systems [1]. Paradoxically, as global life expectancy has risen, this increase has not been matched by an improvement in healthspan, the period of life spent in good health [2,3]. Modern society now faces a sharp rise in chronic non-communicable diseases (NCDs) [4], with an increased prevalence of lifestyle associated conditions, such as type 2 diabetes mellitus (T2DM) [5], cardiovascular disease (CVD) [2,6], many types of cancer [7–9], and neurodegenerative conditions like Alzheimer's disease (AD) [10–12].

The stark rise in T2DM, a clear manifestation of chronic hyperinsulinaemia, is now a growing epidemic in developing and low-income countries and is expected to increase further as metabolic health continues to decline [13]. A similar pattern of worsening health is evident in CVD incidence and mortality [14], which places extra strain on less well-equipped healthcare systems. These conditions share overlapping pathophysiological mechanisms, including hyperinsulinaemia, mitochondrial dysfunction, oxidative stress, and impaired autophagic flux [15]. One particularly notable example of this phenotype is AD, often termed 'type 3 diabetes', indicating a form of insulin resistance in the brain [16]. Such examples establish hyperinsulinaemia as a major upstream driver of a diverse range of lifestyle related conditions. As the situation worsens, it demands a recalibration of the current paradigm of health toward prevention, with hyperinsulinaemia recognised and addressed as a root cause of metabolic dysfunction and biological ageing.

The classical homeostatic model of health, wherein physiological systems strive to maintain a fixed equilibrium, fails to capture the dynamic complexity of ageing. Instead, the concept of homeodynamics takes precedence [17], emphasising the adaptive capacity of biological systems to respond to stress and maintain function across a range of internal and external conditions. This differs from the concept of 'adaptive homeostasis' proposed by Davies [18], which describes the transient expansion or contraction of the homeostatic range in response to mild stress, whereas homeodynamics encompasses the broader, continuous interplay of multiple regulatory systems over the lifespan.

Ageing and chronic disease therefore represent states of diminished homeodynamic capacity, characterised by progressive metabolic inflexibility [19–21], reduced mitochondrial turnover [22], impaired redox signalling [23] and the accumulation of damaged or senescent cells [24,25]. A primary cause of this pathological dysfunction is persistent insulin signalling and the metabolic environment it creates. As a defining feature, chronic hyperinsulinaemia promotes a metabolic shift away from ketone-based metabolism toward glucose dependency. In doing so, it gradually depletes cytosolic nicotinamide adenine dinucleotide (NAD^+) pools and inhibits key pathways including autophagy and mitophagy [26,27]. Over time, this promotes mitochondrial damage [28,29], increased reactive oxygen species (ROS) production [30], and activation of pro-inflammatory cascades, such as the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome [31]. The resulting cellular phenotype is one of high metabolic strain but low repair capacity, a state emblematic of accelerated ageing [32,33], tumourigenesis [34], and neurodegeneration.

An accumulating body of research now suggests that therapeutic ketosis, achieved through ketogenic diets, intermittent fasting, or exogenous ketone supplementation, can counter these processes by elevating levels of the ketone body β-hydroxybutyrate (BHB) [35–37]. Beyond serving as an efficient mitochondrial fuel, increasing evidence illustrates BHB functions as a potent signalling molecule with a broad range of effects, many of which facilitate processes of autophagy and mitophagy [38,39]. Among them, BHB preserves NAD^+ [40,41], activates Sirtuin 1 (SIRT1) and Sirtuin 3 (SIRT3) [42], inhibits histone deacetylases (HDACs) [43]. suppresses the NLRP3 inflammasome [44], and promotes mitochondrial biogenesis and

renewal [45]. In doing so, BHB may restore autophagic capacity, re-establish redox homeostasis, and correct the metabolic imbalances that drive ageing and chronic disease.

This review outlines the diverse proposed effects of therapeutic ketosis in aiding the restoration of homeodynamics, with a particular focus on how BHB supports autophagy, mitophagy, and mitochondrial function. In doing so, it aims to determine whether modulating these crucial cellular processes with ketogenic metabolic therapy (KMT) represents a viable strategy for countering the ageing effects of hyperinsulinaemia and preventing or mitigating a range of chronic diseases.

2 Homeodynamics and the Metabolic Theory of Ageing

The traditional model of homeostasis posits a static equilibrium maintained through tightly regulated feedback loops. Here exists a disconnect that requires addressing in the context of biological ageing. Ageing and disease are not simply the result of a failure to maintain static set points, but rather a progressive erosion of the system's ability to adapt to stress. This decline in adaptive capacity is better described by the concept of homeodynamics, the dynamic interplay of cellular processes that sustain function under ever-changing internal and external conditions. When homeodynamics begin to falter, the organism becomes increasingly susceptible to dysfunction, frailty, and ultimately death.

To outlay these concepts succinctly, we propose a Concentric Zone Model of Adaptive Balance as a visualisation of this dynamism in response to an age and disease related decline. This conceptual framework is shown in Fig. 1. The model illustrates the transition from the more rigid, and perhaps outdated, concept of homeostasis to homeodynamics, which holds similar principles, but is more dynamic and fluid. It argues that with advanced biological age, and through stressors and diseases that carry the hallmarks of ageing, the homeodynamic space is altered, there is less room for metabolic flexibility and whole-body physiological systems become dysfunctional. We suggest that age-related deterioration may be mitigated against or even possibly reversed with the aid of KMT alongside complimentary measures that widen the adaptive range.

At the root of this age-related deterioration, in reference to biological age as opposed to strictly chronological, is progressive metabolic rigidity. In youth, cells are fluid and adaptive, switching seamlessly between glucose, fatty acids, and ketone bodies depending on energetic and hormonal cues [46]. This metabolic flexibility supports resilience under conditions of stress [19], nutrient scarcity [47] or inflammation [48], with chronic overnutrition, particularly in the context of high-glycaemic and insulinogenic diets, this flexibility erodes [21]. Insulin remains persistently elevated, which suppresses ketogenesis [49,50], impairs autophagy [51], and biases metabolism toward anabolic growth and storage signals at the expense of repair [52]. Over time, this imbalance can paradoxically coexist with maladaptive catabolic processes in various tissues, driven by insulin resistance and chronic inflammation.

At the cellular level, this manifests as impaired oxidative phosphorylation (OXPHOS), increased production of ROS, and depletion of NAD^+ [53], a critical cofactor for sirtuins and poly-ADP ribose polymerases (PARPs) involved in DNA repair and mitochondrial maintenance [54]. Cells in this state become less able to clear damaged organelles or proteins and exhibit reduced mitochondrial turnover, leading to the accumulation of dysfunctional mitochondria. Over time, this promotes the emergence of a senescent phenotype: metabolically active but inflammatory, pro-growth, and resistant to apoptosis [55]. While senescence initially acts as a tumour-suppressive barrier, the persistence of senescent cells and their pro-inflammatory secretions creates conditions that can go on to promote malignant transformation [56]. The metabolic theory of ageing ties these concepts together. It proposes that the cumulative burden of metabolic damage, from chronic hyperglycaemia and hyperinsulinaemia, impaired mitochondrial function, oxidative stress, and chronic nutrient signalling, is the principal initiator of ageing and age-related disease.

This framework unites diverse hallmarks of ageing under a metabolic banner, suggesting that the process is neither inevitable nor irreversible. Interventions that evidently restore mitochondrial quality control, suppress pathological nutrient signalling, and recover innate repair processes may not simply delay ageing, but also redefine certain aspects of it. These concepts are not new in the context of human evolution. Evidence suggests that innate stress-response and nutrient-sensing mechanisms were favoured by Darwinian evolution, supporting the survival of Homo sapiens through harsh environments and nutrient scarcity [57–59], with gene-level changes in certain populations exposed to extreme conditions acting as longer-term adaptations [60,61].

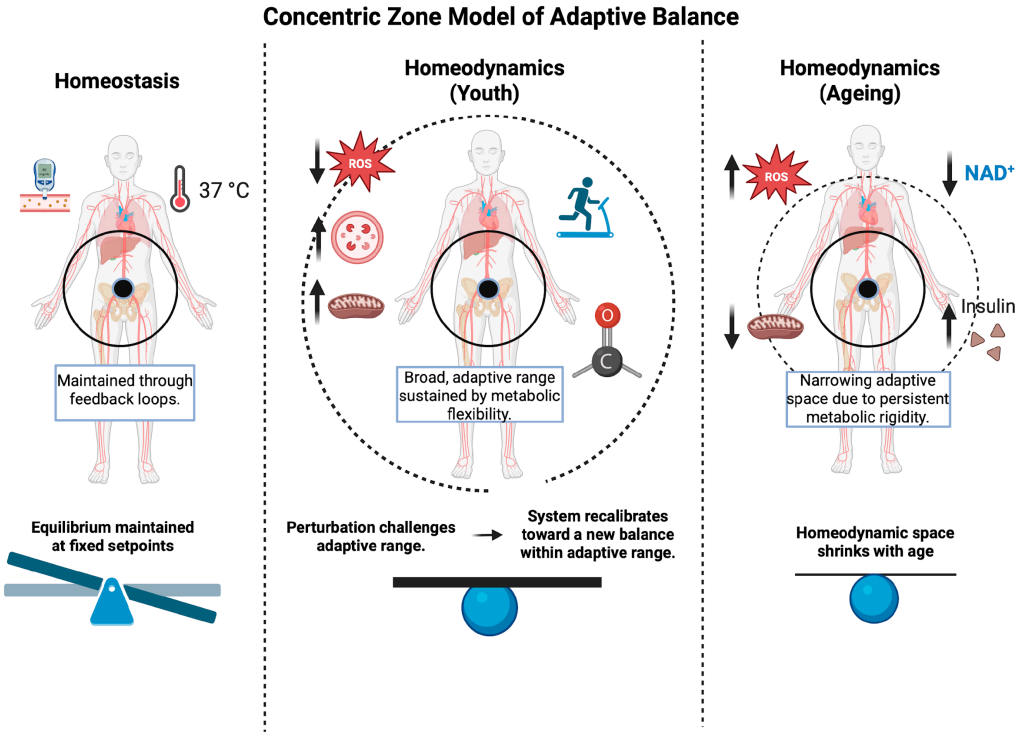

Figure 1: Concentric zone model of adaptive balance. The model depicts the conceptual transition from rigid homeostasis (left) to dynamic homeodynamics (centre) and the narrowing of adaptive capacity with ageing (right). Homeostasis maintains fixed setpoints (e.g., glucose, temperature) through feedback loops but limits flexibility under stress. Youthful homeodynamics reflect a broad adaptive zone sustained by metabolic flexibility, efficient mitochondrial turnover, autophagy, NAD^+ preservation, and low ROS, with exercise, fasting, and ketosis expanding resilience. Ageing narrows this adaptive zone through chronic hyperinsulinaemia, mitochondrial dysfunction, NAD^+ depletion, impaired autophagy, and elevated ROS, promoting senescence and vulnerability to disease. Interventions that have the potential to restore mitochondrial quality control and elevate ketone bodies (principally β-hydroxybutyrate) may assist in re-expanding adaptive capacity. Abbreviations: Nicotinamide adenine dinucleotide (NAD^+); reactive oxygen species (ROS). Firgure created with Biorender.com.

Consistent with theories on evolutionary biology and human brain development, where ketones likely played a pivotal role in meeting the high energetic demands of the growing brain [62,63], it frames cyclical, transient ketosis as a natural, restorative feature of human physiology, which sits at the heart of this model. Arising within a healthy metabolism during fasting, sleep, exercise, or seasonal scarcity of food [64], it represents an innate mechanism that enhances metabolic efficiency, supports cellular maintenance, and contributes to homeodynamic balance [65–67]. Recent human proteomic profiling strengthens this

paradigm further. A 7-day water-only fast has been shown to induce systemic adaptations across >1000 proteins, including extracellular matrix remodelling and brain-specific proteins [68]. In these states, ketones act not as a substitute but as an efficient fuel and signalling molecule, promoting metabolic flexibility and activating protective pathways [67,69]. The concept of therapeutic ketosis builds on this foundation by providing sustained, higher concentrations of circulating BHB. For instance, ketogenic diet therapy (KDT), a distinct approach applied under medical supervision in drug resistant epilepsy, often aims for 2–5 mmol/L in the clinic [70]. As part of a broader approach, treating a range of different conditions, KMT has been proposed as a therapeutic model in cancer [71,72], in the emerging field of metabolic psychiatry [73], and for a range of other chronic and neurodegenerative conditions [66,74–76]. The optimal level of ketosis is unlikely to be universal, varying between individuals and across conditions, with some contexts benefiting from more modest sustained elevations of BHB.

3 Hyperinsulinaemia and Metabolic Dysfunction

Hyperinsulinaemia, defined by chronically elevated circulating insulin, often precedes and drives insulin resistance, T2DM, obesity, and related disorders, yet its pathological influence extends far beyond glycaemic control. Whether insulin resistance occurs in obese or in lean individuals, hyperinsulinaemia would eventually become more established as a primary driver of metabolic dysfunction [77–79]. By keeping cells in a state of nutrient oversupply, hyperinsulinaemia impairs metabolic flexibility, accelerates mitochondrial decline, and progressively undermines homeodynamic resilience.

Although these earlier accounts accurately position hyperinsulinaemia as a causal factor of many NCDs, the associations with biological ageing were less clear. More recent studies have begun to uncover subtle, parallel mechanisms that more broadly characterise the ageing phenotype. For instance, evidence now suggests that sympathetic nervous system (SNS) activation contributes to overnutrition-induced insulin resistance. This is because activation of the SNS increases adrenaline, noradrenaline, glucocorticoids, and subsequent hyperinsulinaemia. It supports the primary hypothesis, that hyperinsulinaemia is the main driver of chronic diseases and ageing. Although its role remains debated, with conflicting reports of both heightened and suppressed activity in states like obesity [80], it provides an applicable, nuanced example of homeodynamics and individual variability. Age-related susceptibility adds an additional layer, with mitochondrial inefficiency, oxidative stress, and sarcopenia contributing to insulin resistance in older individuals [81].

More broadly, this deterioration is so systemic due to insulin being fundamentally a growth and storage hormone, functioning only for brief, infrequent spikes in an evolutionary context of scarce carbohydrates. Modern dietary patterns, with near-continuous carbohydrate exposure, result in relentless insulin synthesis and secretion [50]. Constant insulin secretion above a personal insulin threshold, leads to the inhibition of lipolysis and ketogenesis, lowering circulating BHB, and prevents activation of repair-linked nutrient sensors, such as AMP-activated protein kinase (AMPK) and SIRT1 [82]. Over time, mitochondrial function becomes distorted: ceramides accumulate [83], fission dominates over fusion [84], respiration is compromised, and there is a significant increase in ROS [85]. Damaged mitochondrial DNA, lipids such as cardiolipin, and proteins further erode energy production, creating a vicious cycle of dysfunction and insulin resistance [86]. This progressive decline occurs in a system where insulin sits at the top of key signalling pathways in nearly every cell of the body. It causes selective impairments in phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathways with relative preservation of mitogen-activated protein kinase (MAPK) signalling, linking hyperinsulinaemia not only to metabolic rigidity in multiple organs but also vascular and proliferative complications [87]. Superimposed upon this is the damage from glycation, connecting

chronic nutrient excess to accelerated ageing phenotypes and measurable vascular risk. These overlapping defects redirect the focus from insulin resistance as an isolated metabolic defect to hyperinsulinaemia as a systemic driver of interconnected disturbances across adipose tissue, vasculature, and the nervous system.

The overstimulation of the insulin/insulin-like growth factor (IGF) axis drives inflammatory cascades and endocrine disruption, resulting in elevated leptin and resistin, along with reduced adiponectin. Together, these changes fuel the obesogenic phenotype and heighten the risk for cardiometabolic complications [88,89]. This dysregulated adipokine profile further increases oxidative stress and endothelial dysfunction, compounding cardiovascular risk [90]. What follows is a progressive spiral of mitochondrial insufficiency, as mitochondrial integrity becomes progressively compromised under conditions of nutrient excess. Deficiency in mitochondrial cofactors, such as coenzyme Q10 (CoQ10), selenium, and magnesium, further impairs insulin signalling and reduces efficiency of OXPHOS, exacerbating redox imbalance [91,92]. CoQ10 depletion, observed in metabolic syndrome and T2DM, impairs electron transport chain (ETC) activity and adenosine triphosphate (ATP) generation, while selenium deficiency compromises selenoprotein-dependent antioxidant defences, intensifying inflammatory signalling [93]. Magnesium insufficiency, although common in the general population, takes on greater precedence in insulin-resistant states, as it disrupts insulin receptor autophosphorylation and downstream PI3K/Akt signalling, weakening glucose uptake, and promoting further resistance that compounds hyperinsulinaemia compensation [94]. These observations suggest that micronutrient sufficiency is not peripheral but central to metabolic control.

Ketosis as a Marker of Metabolic Adaptation

In this context, nutritional ketosis, appropriately termed 'euketonaemia' (BHB $\geq$ 0.5 mmol/L) may act synergistically, with β-hydroxybutyrate improving mitochondrial efficiency and lowering oxidative stress, while micronutrients provide the necessary cofactors and trace elements to sustain metabolic flexibility. Furthermore, utilising blood glycaemia levels as a metric to determine metabolic health fails to capture many people with Insulin-Compensated Euglycaemia (ICE). This is determined by an individual's Personalised hyperinsulinaemia threshold (PIT). Hypoketonaemia-ICE determines an individual's PIT detectable via multiple consecutive evening pre-dinner with a minimum three-hour post-prandial test, with BHB levels consistently <0.5 mmol/L. This is where subclinical hyperinsulinaemia persists years before overt pathology presents itself [95,96]. These mindful strategies may offer a more integrated framework for the restoration of homeodynamic capacity, while potentially buffering against the metabolic rigidity that drives cardiometabolic disease.

As part of a broader contextual framework, a state of ketosis in and of itself is not the only defining factor in turning back the clock on the hyperinsulinaemia-associated ageing phenotype. The form of ketogenic diet and the composition of its macronutrients are equally decisive. The quality and ratio of fatty acids, for instance, exert profound effects on mitochondrial dynamics and redox balance. Notably, stearic acid, a long-chain saturated fatty acid abundant in ruminant fat and cocoa butter, has been shown to promote mitochondrial fusion, enhance cristae density, and improve oxidative phosphorylation efficiency, thereby countering lipotoxicity and mitochondrial fragmentation [97,98]. Unlike palmitic acid, which drives ceramide accumulation and insulin resistance, stearic acid has demonstrated neutral or even beneficial effects on lipid metabolism, inflammation, and cardiovascular risk [99,100].

Moreover, the interplay between fatty acid composition and ketone metabolism may dictate the depth and quality of ketosis itself. Medium-chain triglycerides (MCTs), particularly caprylic acid (C8), generate ketones more rapidly and efficiently than long-chain fats, supporting higher circulating BHB and promoting the downstream signalling benefits of ketosis [101,102]. Thus, beyond the absolute presence of ketosis,

it is the integration of micronutrient sufficiency with macronutrient quality that determines the desired effects of ketogenic metabolic therapy. Furthermore, there will be individual variability in how individuals tolerate and metabolise saturated, monounsaturated, and polyunsaturated fats, to qualify the necessity of minimising or preferentially completely eliminating pro-inflammatory lipid species. Keeping in mind that polyunsaturated fat seed oils inhibit intestinal bile reabsorption [103–107], and therefore contribute to the depletion of taurine [108–111], fat soluble vitamins A, D, E, and K, and essential fatty acids omega 3 and 6 [112]. As fat provides the dominant fuel on any ketogenic approach, it is these nuances which will determine whether ketogenic therapy truly facilitates adaptive balance or risks reinforcing metabolic rigidity.

4 Disrupted Nutrient Sensing and Autophagy

The mammalian target of rapamycin (mTOR) signalling pathway is among the most extensively studied in biology, orchestrating nutrient and growth factor signals to regulate cell growth, metabolism, autophagy, and survival. At least five of the twelve defined hallmarks of ageing are modulated by mTOR activity [113], emphasising its importance in ageing biology. Persistent dysregulation of this pathway hastens functional decline and contributes to the pathogenesis of major age-related diseases, including cancer, neurodegeneration, and metabolic disorders. This influence is most clearly revealed under sustained nutrient excess, where hyperinsulinaemia keeps mTOR in a state of continuous activation, tipping the balance away from repair and towards an ageing phenotype.

Chronically elevated insulin signalling creates a perfect storm, whereby mTOR becomes activated, while suppressing AMPK, sirtuins, and other nutrient sensors [114]. In the context of autophagy, this impairs the clearance of damaged proteins and organelles, while compromising mitochondrial turnover [115,116]. In this hostile environment, cells accumulate defective mitochondria and oxidative damage, accelerating biological ageing [117]. The resulting inhibition of mitophagy not only promotes the persistence of dysfunctional organelles but also leads to the visible accrual of lipofuscin, a hallmark pigment of cellular ageing and failed lysosomal clearance [118].

4.1 Therapeutic Targeting of Nutrient-Sensing Pathways

By contrast, nutritional interventions that show potential in reversing these conditions, such as fasting and nutritional ketosis, may re-engage these defective nutrient sensors, restoring autophagic flux, promoting mitochondrial biogenesis, and rebalancing redox homeostasis [40,119]. Consistent with this form of nutrient sensing regulation are profound neuronal changes. Short-term fasting *in vivo* markedly upregulates neuronal autophagy, with increased autophagosomes in cortical neurons [120]. These effects extend to Purkinje cells, with reduced phosphorylated S6, further indicating that these innate repair mechanisms extend to the brain [120]. While these pathways act in concert, with mTOR operating as the master regulator, it is worth expanding on the roles of AMPK, sirtuins, and autophagy–mitophagy in isolation to better appreciate their distinct contributions in the biology of ageing and disease.

4.2 Sirtuins as Hermetic Stressors

A particularly attractive candidate to be exploited by metabolic therapies are sirtuins. Sirtuin proteins, a family of seven NAD^+-dependent deacetylases, act on acetylated lysine residues of diverse substrates. They have gained prominence for their proposed roles in extending lifespan and promoting metabolic resilience when activated. These proteins are distributed widely across the nucleus, cytoplasm, and mitochondria, where they act as metabolic sensors and regulators of genome stability, stress responses, and energy metabolism [121–123]. Their activity as hormetic stressors links nutrient status to cellular adaptation,

giving them great influence on longevity pathways. In metabolic tissues, SIRT1 and SIRT3 in particular coordinate oxidative metabolism, mitochondrial fidelity, and antioxidant defence, while SIRT6 regulates genomic stability and SIRT7 modulates stress resistance in the heart [122].

Despite the compelling evidence linking sirtuins to improved mitochondrial function, stress resistance, and longevity, their roles are not uniformly beneficial. Context is highly relevant, especially in the field of oncology, where sirtuins can act as both tumour suppressors and facilitators of tumour survival, depending on isoform, nutrient status, and metabolic state [123,124]. Tissue-specific effects are also worth consideration therapeutically. SIRT3 has been shown to protect cardiomyocytes from oxidative stress, while SIRT2 downregulation may reduce ischemia–reperfusion damage [121]. Importantly, metabolic environment determines their activation: under fasting and ketosis, SIRT1 and SIRT3 are consistently upregulated, while others, such as SIRT6, remain unchanged [124].

Notably, these effects are not confined to intracellular signalling. Fasting also remodels the gut microbiome, with Christensenella expansion correlating with elevated sirtuin expression and improved metabolic resilience [125], suggesting a microbiome–sirtuin axis with translational potential. By contrast, states of nutrient oversupply and hyperinsulinaemia constrain NAD^+ availability, blunting sirtuin activity and locking cells into metabolic inflexibility. Interventions focused on sirtuin activation, whether through fasting, carbohydrate restriction, ketosis, or by pharmacological means, must account for isoform specificity, tissue context, and the prevailing nutrient state. As seen with rapamycin-induced mTOR inhibition, where longevity benefits have come with trade-offs including infection risk and dyslipidaemia [126], indiscriminate sirtuin activation carries its own liabilities. Therapeutic progress therefore likely relies on precision, targeting the right sirtuins, in the right tissues, under the right metabolic conditions to counteract the maladaptive signalling of hyperinsulinaemia while amplifying protective pathways of repair and resilience.

4.3 The Dual Roles of AMPK in Nutrient Sensing and Autophagy

The roles of AMPK, nutrient sensing, and autophagy are more complex than once appreciated, yet this very complexity illustrates homeodynamics in action. Traditionally described as the master energy sensor, AMPK is now recognised as a dynamic governor that can both restrain and preserve autophagy depending on context. Recent findings show that under nutrient deprivation, AMPK suppresses UNC-51-like kinase 1 (ULK1)-driven autophagy to prevent premature depletion of autophagic systems, while maintaining the integrity of the initiation complex and its associated components for re-engagement once stress subsides [127,128]. In essence, this means that AMPK acts as a safeguard, ensuring that autophagy is not exhausted prematurely, but instead remains available as a controlled, beneficial response to restore cellular homeostasis once nutrient stress is relieved. At a broader level, at least in part, it demonstrates how AMPK functions as a master protector of mitochondrial integrity, simultaneously coordinating fission, mitophagy, and biogenesis to sustain a functional mitochondrial network [129]. This is consistent with its compartmentalised control of metabolism across cellular domains [130], its regulation of ketone homeostasis through stabilisation of succinyl-CoA:3-oxoacid CoA transferase (SCOT) [131], and its integration with nutrient sensors including mTOR, Forkhead box O transcription factors (FOXO proteins), p53, SIRT1, and nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) in ageing pathways [132].

What makes AMPK significant is its dual role in disease. Not only does it offer these protective benefits, but it also acts as part of a more dynamic system, adapting depending on the metabolic context and out of necessity. In cancer, for example, AMPK activation provides the ability to stem tumour growth by rewiring metabolism and supporting anti-tumour immunity [133], yet paradoxically, it can also sustain tumour survival under certain nutrient stress conditions. Clinical findings in humans offer further insight into

these systems as therapeutic targets and explain why this tension exists. For instance, there is evidence that in breast cancer patients undergoing chemotherapy, intermittent fasting combined with a ketogenic diet significantly elevates AMPK levels, while also lowering tumour markers and improving tolerance to treatment [134]. These results provide practical models of how dietary modulation of AMPK can be utilised as a non-pharmacological adjunct to conventional therapy, though its context-dependent effects demand careful protocol design.

5 Mitochondrial Stress and Redox Imbalance

Hyperinsulinaemia drives excess substrate flux into mitochondria, leading to inefficiency, increased ROS generation and reduced ATP output [135,136]. This bioenergetic stress impairs metabolic flexibility, limiting the capacity to switch between fatty acid and glucose oxidation [19]. The result is a vicious cycle of oxidative stress, lipid accumulation and mitochondrial damage [137,138]. At the mechanistic level, nutrient overload saturates the ETC, causing electron leak and superoxide production, particularly at complexes I and III [139]. This overwhelming generation of ROS disrupts mitochondrial membranes, oxidises mitochondrial DNA, and damages proteins critical for oxidative phosphorylation [140]. In almost synchronous fashion, the loss of mitochondrial dynamics, fusion and fission processes which essentially function as quality control in the healthy phenotype, further propagates dysfunction [141]. Impaired mitophagy compounds this problem, allowing defective organelles to accumulate and acting as a chronic source of oxidative stress [140]. Beyond the mitochondria themselves, redox imbalance radically alters cytosolic and nuclear signalling. ROS overproduction activates stress-sensitive kinases, such as c-Jun N-terminal kinase (JNK) and NF-κB, overstimulating insulin and fuelling pro-inflammatory mediators [142,143]. Lipid peroxidation products, such as 4-hydroxynonenal, concurrently impair insulin receptor signalling and damage mitochondrial enzymes [144]. These series of events help to create a state of metabolic rigidity, where flexibility is lost not only at the level of substrate use but also within redox-sensitive gene regulation.

Unique to this process is the emergence of mitochondrial-derived danger signals, including mitochondrial DNA fragments and cardiolipin exposure, which activate innate immune pathways, such as the NLRP3 inflammasome [145,146]. This links bioenergetic stress to systemic inflammation and age-related pathology, positioning mitochondrial redox imbalance as both a local and systemic driver of disease. A particular point of reference in this system lies in the inner mitochondrial membrane and its cristae, the folded structures that house the respiratory machinery. In healthy cells, that do not have defective mitochondria, their integrity has the respiratory capacity to cope with demand and maintain OXPHOS. However, when the metabolic terrain reaches breaking point, the cristae become altered, decreasing in number and depth as function is impaired, oxidative phosphorylation becomes diminished, and cells compensate by forced reliance on aerobic glycolysis. This type of reprogramming is seen not only in immune and stem cells but most notably in cancer, where cristae dysfunction is now recognised as a mediating feature of the Warburg effect [147]. This change in mitochondrial architecture represents much more than local damage, it is a major structural transformation, where structure dictates function, that initiates metabolic reprogramming and strengthens the argument for cancer as a metabolic and endocrine disease.

Ketogenic Metabolic Therapy as a Mitochondrial Intervention

It would be reasonable, therefore, to consider metabolic-endocrine interventions like KMT that lower inflammation, encourage the production of endogenous antioxidants, while lowering insulin and associated growth factors, such as IGF-1, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), monocyte chemoattractant protein 1 (MCP-1), and leptin [50]. Interventions, such as fasting

or ketosis, are aimed at reducing substrate flux and electron leak, thereby restoring redox homeostasis. BHB not only provides a more efficient fuel for the mitochondria to thrive, but also acts as a powerful, almost all-encompassing signalling metabolite, inhibiting NLRP3 inflammasome activation and supporting antioxidant gene expression through histone deacetylase inhibition [44,119]. These multi system effects assist in restoring mitochondrial integrity, and act as both a target and mediator of metabolic therapy, especially as HDAC inhibitors are prized as invaluable therapeutic targets, usually via pharmacological means.

6 Inflammation and Vascular Dysfunction

Insulin acts first and foremost as a growth factor, and when it functions normally, cell growth and development cycles operate in a predictive, supportive fashion, in line with normal immune function, which requires inflammation at the right times to function adequately. When there is chronically excess insulin exposure, then dysfunction develops, through chronic cellular insulin overstimulation, which promotes inflammatory signalling, endothelial dysfunction, and vascular remodelling [148,149]. Hyperinsulinaemia increases sympathetic tone, impairs nitric oxide signalling, and fosters a pro-thrombotic state [150]. The degree to which this happens, and can potentially be rescued, depends largely on biological age. In states of ageing and disease, collectively, these effects will more readily contribute to atherosclerosis, hypertension, and CVD complications, independent of obesity [151]. In these states, systemic circulation becomes flooded by toxic byproducts, such as the increased breakdown of oxidised haem, leading to increased haem oxygenase to help remove oxidised haem, resulting in increased carbon monoxide byproduct, ferritin and bilirubin. The vascular consequences can be severe, which can be worsened further by inactivity and high blood pressure. Here, excess insulin activates the MAPK pathway, stimulating smooth muscle cell proliferation and extracellular matrix deposition, which contribute to arterial stiffening [150]. Meanwhile, reduced PI3K signalling undermines endothelial nitric oxide synthase (eNOS) activity, decreasing nitric oxide bioavailability and promoting vasoconstriction. This is a selective insulin resistance scale weighted too far at one end of the scale; growth-promoting pathways remain overactive while metabolic signalling is blunted. This sets the stage for both vascular remodelling and metabolic inflexibility [152].

Perhaps one of the gravest consequences is the impact of chronic hyperinsulinaemia on endothelial cells, contributing to the overproduction of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), which facilitate monocyte recruitment and plaque initiation [153]. The resulting endothelial activation ramps up NF-κB–mediated inflammatory cascades, bridging metabolic dysfunction with vascular inflammation [154]. Over time, this inflammatory milieu favours the formation of unstable atherosclerotic plaques prone to rupture, implicating insulin excess directly with cardiovascular events [155]. The vascular glycocalyx, which normally acts as a sugar-coated shield on the outer surface of cell membranes, begins to break down and thins under hyperinsulinaemic conditions, further compromising vascular integrity and contributing to microvascular rarefaction [156,157]. As it acts as a protective barrier in normal physiology to protect cells from contaminants with the aid of mucin as a natural coating in the healthy phenotype, when tight junctions allow compounds that promote inflammation and disease through, the result may be catastrophic, potentially resulting in disseminated intravascular coagulopathy (DIC), leading to increased risk of stroke, pulmonary embolisms, and cardiac ischemia [108]. Combined with hypercoagulability driven by insulin induced increased plasminogen activator inhibitor-1 (PAI-1) and fibrinogen levels, this encourages a pro-thrombotic state that magnifies cardiovascular risk [158].

Therapeutic ketosis directly targets these processes, potentially reversing the ageing phenotype, stimulating mucin and clearing toxic material. By lowering insulin demand and restoring endothelial nitric

oxide signalling, ketosis improves vascular compliance and reduces oxidative stress [46]. BHB exerts its anti-inflammatory effects at this level predominantly through inhibiting NLRP3 inflammasome activation in vascular tissues and preserving glycocalyx integrity, with cardiac tissue favouring ketogenic substrates [44,159].

7 Unique Sensitivities of the Brain

The brain, with its limited energy reserves and high metabolic demand, is acutely sensitive to fluctuations in insulin signalling. Chronic hyperinsulinaemia induces central insulin resistance, disrupting glucose uptake, altering neurotransmitter balance, and impairing synaptic plasticity [160,161]. These disturbances contribute to cognitive decline, depressive phenotypes, and increased risk of AD [162,163]. In glial cells, which provide critical metabolic support to neurons, impaired glycolysis and oxidative metabolism worsen excitotoxicity and promote neuroinflammatory cascades [164,165]. Central insulin resistance also disrupts extracellular vesicle communication between astrocytes, oligodendrocytes, and microglia, not least the generation of action potentials across neurons. Astrocytic failure to shuttle lactate disrupts the astrocyte–neuron lactate axis, compromising synaptic activity [166]. Microglial hyperactivation, fuelled by redox stress, amplifies release of pro-inflammatory cytokines, such as interleukin-1 beta (IL-1β) and tumour necrosis factor-alpha (TNF-α), which in turn impair long-term potentiation and accelerate neurodegeneration [167]. Oligodendrocyte vulnerability under hyperinsulinaemic conditions further limits myelin turnover, reducing conduction efficiency [168].

As dynamic cerebral autoregulation becomes impaired, the brain's ability to buffer blood pressure fluctuations declines [169]. This instability increases susceptibility to transient hypoperfusion, white matter lesions, and, over time, stroke and dementia [170]. The spillover of metabolic imbalance into the extracellular milieu fuels gliosis, with astrocytic scarring and microglial activation perpetuating neuroinflammation [171]. Importantly, the failure of neuronal and glial metabolic integration extends beyond energy supply to the redox landscape. Accumulation of mitochondrial ROS and release of oxidised mitochondrial DNA activate innate immune pathways, such as the NLRP3 inflammasome, linking metabolic failure to sterile neuroinflammation [145,172]. These processes converge on impaired neurovascular coupling, where vascular dysfunction and neuronal metabolic stress act synergistically to erode cognitive resilience.

Effects of impaired glucose tolerance on the brain and brain chemistry are extensive and profound. In glucose transporter type 1 (GLUT1) deficiency syndrome, where glucose transporters in the brain become defective, energy supply to the brain can be circumvented by providing ketones as the primary fuel, reducing glucose-related hyperexcitability of neurons to a more depressive phenotype and central nervous system depressant, which can be further supported with magnesium supplementation, acting on the N-methyl-D-aspartate (NMDA) receptor and complementing the effects of ketosis. These types of syndromes and the degree of seizure freedom granted by adopting ketogenic therapies provide powerful arguments about the role of ketones as both central nervous system regulators and metabolic modulators of astrocyte function. There is synergy with migraine disorders, which can be characterised as a brain energy crisis, a protective mechanism that requires circumvention of fuel substrates for relief, where fasting and ketogenic therapies normalise neuronal action potentials.

When following a ketogenic diet, fasting, or consuming MCTs, fats are broken down into free fatty acids that are transported to the liver. Within hepatocytes these are converted into the ketone bodies acetoacetate (AcAc) and BHB. In the context of taking exogenous ketones, such as pure BHB acid, the conversion in the liver is bypassed, rapidly elevating blood ketones within 30–60 min [173,174]. Once released into the circulation, ketones cross the blood–brain barrier via monocarboxylate transporters and are taken up by neurons, where BHB is reconverted to AcAc and metabolised through the tricarboxylic

acid cycle to generate ATP [174]. This is particularly relevant under conditions of neuroinflammation and brain injury, where ketones serve both as efficient fuel and as signalling molecules that mitigate oxidative stress and preserve neuronal function [40,119,175].

Therapeutic ketosis provides a distinct countermeasure by bypassing glucose dependence, BHB as an efficient cerebral fuel, enhancing mitochondrial biogenesis in neurons and glia [75,176]. Beyond fuel substitution, ketone bodies suppress excitotoxicity, dampen NLRP3 activation, and promote gamma-aminobutyric acid (GABA) ergic tone, offering a neuroprotective environment [177]. These mechanisms suggest that restoring metabolic flexibility in the brain may recalibrate glial–neuronal interactions, preserving cognitive function and buffering against the trajectory toward neurodegeneration. Models of traumatic brain injury (TBI) provide valuable insights into mitochondrial quality control that extend far beyond acute injury. These models can act as templates for a host of neuroinflammatory conditions. In TBI, neuronal and glial cells undergo acute metabolic stress, with immediate impacts, including impaired OXPHOS, excessive ROS production, and activation of mitophagy as a compensatory mechanism [178]. These same processes of mitochondrial damage, inflammation, and impaired clearance of dysfunctional organelles are all classic features of chronic neurodegenerative disorders, epilepsy, and brain cancer [179–181]. Therapeutically, research in models of post TBI aggression similar to those presenting in human patients suggest that ketogenic therapies could rescue multiple aspects of post TBI symptoms and the ensuing aggressive behaviours, highlighting a broad spectrum of neurological effects that require further investigation *in vivo* [182]. It would therefore be shortsighted to restrict our focus to individual pathologies when the metabolic derangements are synonymous across all these conditions.

Targeting processes of mitophagy to treat these complex cases, however, requires caveats, as the modulation of mitophagy can act as a double-edged sword in a dose–response manner. While moderate activation promotes the clearance of damaged mitochondria and preserves neuronal function, excessive mitophagy risks depleting mitochondrial pools and worsening neuronal loss [180].

Novel Therapeutic Strategies Targeting Mitophagy

Novel interventions, such as melatonin, fisetin, quercetin, morin, nitroxides, and FUN14 domain-containing protein 1 (FUNDC1) modulation, have shown protective effects in models of TBI, sepsis-associated encephalopathy, Alzheimer's disease, Parkinson's disease, and depression by enhancing mitophagy [183–186], and repressing inflammation [187–189]. Melatonin in particular stands out as an endogenously produced neurohormone with potent antioxidant and mitophagy-inducing capacity, reducing TBI-induced neuronal death and pro-inflammatory cytokine release [190]. Other experimental strategies, including rapamycin, pifithrin analogues, mitochondrial division inhibitors, nitroxides, and nano-pulsed laser therapy, reinforce the breadth of potential avenues targeting mitophagy and mitochondrial repair [178].

Melatonin requires dedicated focus as it is perhaps the most potent endogenous antioxidant and anti-cancer agent available, which readily complements autophagy as a type of self-clearing, a scavenging of free radicals and reactive oxygen species that humans have as innate mechanisms for cellular repair. These mechanisms may be optimised by regulating and habitualising circadian biology and cellular clocks. Its role in re-aligning circadian biology takes on greater significance with the knowledge that endogenous production of melatonin decreases with advancing age. Another endogenous system, the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, is stimulated under ketosis, and sleep represents a prolonged fasted period, so this combination, with autophagy and nutritional ketosis, works in powerful synergy with cellular repair systems, promoting a younger biological phenotype. With a broader view, melatonin is not

exclusive to the brain; it also resides in the gut, where it modulates the gut microbiota, enhances intestinal barrier function and regulates inflammation and motility [191,192].

8 Systemic Effects and Challenges to Adaptive Balance

It is important to highlight sex-based effects of hyperinsulinaemia from an endocrine perspective and how these impact on individual adaptive balance as a concept. In females, chronic insulin excess drives hyperandrogenism by stimulating ovarian theca cells, lowering sex hormone–binding globulin (SHBG), and increasing luteinising hormone action [187]. SHBG therefore functions as a sensitive biomarker of metabolic-endocrine status, with broader implications for cancer risk and reproductive function, while chronic hypoketonaemia has been shown to reduce SHBG production [95]. Together, these changes underpin the pathophysiology of polycystic ovary syndrome (PCOS), a condition increasingly recognised as a systemic metabolic disorder rather than a purely reproductive one [193]. In males, by contrast, hyperinsulinaemia has been linked to reduced testosterone production and altered spermatogenesis, highlighting sex-specific vulnerabilities in the reproductive axis [194].

In oncology, the mitogenic properties of insulin and IGF-1 promote tumour initiation and progression by activating PI3K/Akt and MAPK pathways, stimulating angiogenesis, and inhibiting apoptosis [195]. Hyperinsulinaemia also alters tumour metabolism by increasing glucose and lipid uptake, sustaining the anabolic needs of proliferating cells, and facilitating the Warburg effect [196]. This establishes insulin/IGF signalling as not only a systemic metabolic regulator but also a direct contributor to cancer cell survival. Psychiatric consequences of insulin dysregulation extend beyond neurotransmitter imbalance to structural and functional brain alterations. Chronic hyperinsulinaemia eventually leads to reduced insulin signalling in the central nervous system, a state associated with impaired dopaminergic tone, weakened reward processing, and altered stress responsivity, creating susceptibility to depression and anxiety disorders [197,198]. Evidence also links hyperinsulinaemia with accelerated brain ageing, where metabolic insufficiency predisposes to affective dysregulation and cognitive decline [199].

Viewed through the lens of the Concentric Zone Model of Adaptive Balance, chronic hyperinsulinaemia represents a sustained push beyond the adaptive zone of nutrient sensing. While short bursts of insulin signalling are essential for anabolic repair and growth, persistent elevations tip the system toward maladaptation. The suppression of autophagy, induction of mitochondrial stress, and disruption of circadian–metabolic alignment [200] exemplify how insulin excess narrows adaptive capacity and accelerates the course of ageing. This metabolic rigidity reverberates across multiple organ systems. In the brain, hyperinsulinaemia promotes neuroinflammation [167,201,202], microglial activation [185,189,203], and impaired neurotransmission [76,204,205]. In the heart, as stated previously, excess insulin drives vascular remodelling [83,148,151] and undermines glycocalyx integrity [9,157,159], compounding oxidative stress. In the liver, it accelerates fatty acid malonylation and inflammasome activation [31,44,90,146], while in skeletal muscle it promotes proteolysis and loss of mitochondrial plasticity [29,30]. At the same time, reproductive and endocrine axes are distorted, with hyperandrogenism in women [30,206,207], reduced testosterone in men [194], and an increased risk of hormone-sensitive cancers [195,196].

Overall, these systemic insults demonstrate how chronic insulin excess is more than a biomarker of metabolic dysfunction; it is a mechanistic driver of disease. By narrowing the homeodynamic zone, it reduces resilience and accelerates the transition from health to pathology. Against this backdrop, nutritional ketosis can be understood as a corrective state, restoring adaptive balance by lowering insulin demand, re-engaging autophagic renewal, and supporting mitochondrial efficiency. The therapeutic scope of these

adaptations across neuroinflammation, cardiometabolic disease, liver dysfunction, sarcopenia, obesity, PCOS, and colorectal cancer is illustrated in Fig. 2.

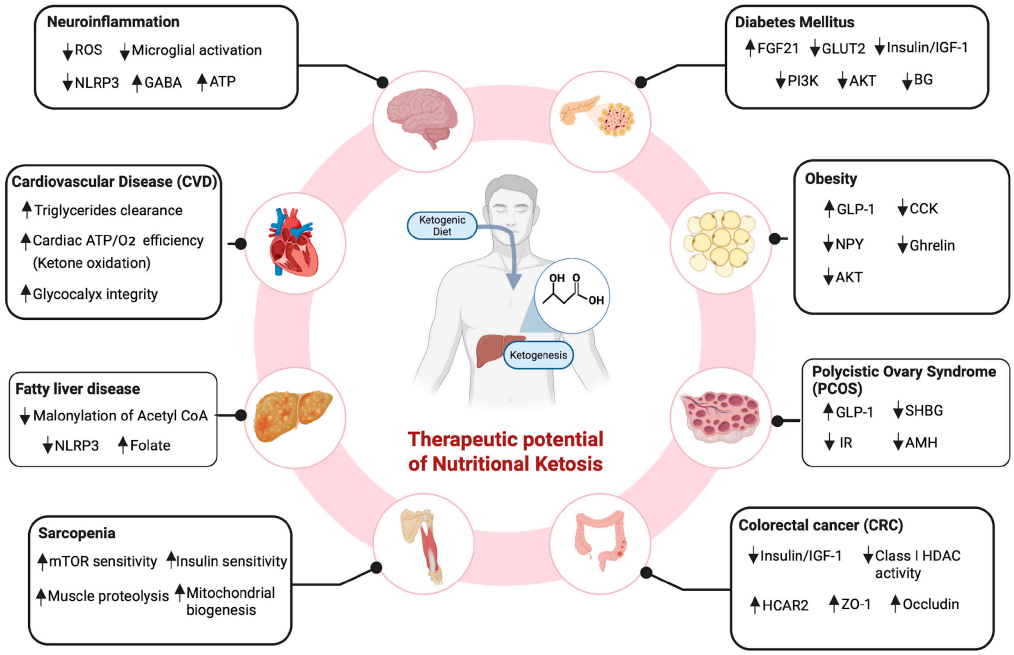

Figure 2: Therapeutic potential of nutritional ketosis in age- and insulin-linked disease. Nutritional ketosis, via β-hydroxybutyrate (BHB), helps counter processes driven by chronic hyperinsulinaemia and ageing across multiple systems. In the brain, BHB supports mitochondrial ATP generation, dampens ROS and NLRP3 activation, and stabilises neurotransmission, protecting against cognitive decline and psychiatric disease. Cardiovascular, hepatic, and skeletal muscle benefits include improved cardiac efficiency, reduced triglyceride burden via VLDLR, preserved glycocalyx function, lower malonyl-CoA, enhanced mitochondrial biogenesis, and reduced proteolysis. In cancer and endocrine disorders, BHB reduces insulin/IGF-1 signalling, inhibits class I HDACs, improves barrier integrity, and modulates GLP-1, SHBG, PI3K/Akt, and FGF21 pathways. Collectively, these actions suggest a state of therapeutic ketosis may act as a systemic metabolic correction with the potential of restoring homeodynamics within adaptive ranges. Abbreviations: Adenosine triphosphate (ATP); blood glucose (BG); fibroblast growth factor 21 (FGF21); glucagon-like peptide 1 (GLP-1); insulin-like growth factor 1 (IGF-1); protein kinase B (Akt); reactive oxygen species (ROS); sex hormone-binding globulin (SHBG); nucleotide-binding domain leucine-rich repeat pyrin domain-containing protein 3 (NLRP3); very low density lipoprotein receptor (VLDLR); coenzyme A (CoA); histone deacetylase (HDAC); phosphoinositide 3-kinase (PI3K). Figure created with Biorender.com.

9 The Role of BHB in Cellular Energetics and Autophagy

BHB is the most abundant circulating ketone body in humans, with biological effects that extend far beyond its traditional framing as an “alternative fuel”. Its levels rise naturally with fasting, ketogenic diets, or through exogenous ketogenic agents, such as ketone esters and MCTs. BHB is a highly conserved metabolite and signalling molecule embedded within the regulation of mitochondrial function, redox balance, gene expression, and cellular stress responses. It does far more than sustain energy; it reprogrammes the way cells adapt, survive, and repair [208,209]. Often framed incorrectly as merely a backup fuel, it is in fact a significant determinant of healthy homeodynamics, especially in the context of metabolic insufficiency in hyperinsulinaemia and biological ageing.

Nutritional ketosis has been utilised clinically for nearly a century in cases of refractory epilepsy [210]. Classical ketogenic protocols, typically high-fat and very-low-carbohydrate, were designed to mimic fasting [211]. Modern adaptations, including MCT-based and modified Atkins diets, as well as low-glycaemic-index approaches, have improved tolerability and broadened therapeutic use [212,213]. Much of the therapeutic promise of ketosis lies in its overlap with calorie restriction, long recognised for promoting longevity and disease prevention. Evidence from human and animal studies [40,119], clinical interventions [213,214], and epidemiology [215] demonstrates that ketosis engages similar nutrient-sensing pathways, including AMPK, SIRT1/3, and mTOR, enhancing stress resistance, mitochondrial quality control, and cellular repair. Exogenous ketone formulations have opened new therapeutic avenues, particularly in conditions where dietary compliance is challenging. Alongside ketone monoesters, nutritional co-therapies, such as 1,3-butanediol, also provide a practical means of elevating circulating BHB [216]. Beyond its role in reversing hyperinsulinaemia, it intersects with adaptive systems that safeguard long-term resilience. Many of these have already been described in this paper, however, master regulators of these processes that can readily be activated purely through diet and lifestyle, such as fibroblast growth factor 21 (FGF21), and circadian rhythmicity, take priority as levers for health restoration. Through their initiation, these axes play a vital role in explaining how nutritional ketosis may restore homeodynamics within the adaptive ranges outlined by the Concentric Zone Model act in practice.

Autophagy, as a conserved lysosomal process that degrades and recycles worn or damaged cellular components, does not maintain energy balance and quality control under fixed parameters. This is because states of stress and nutrient scarcity are variable, and the benefits of hormesis are dependent on healthy, robust physiological systems, or at least their adaptive capabilities and what the system allows. Its predominant form, macro-autophagy, sustains cellular homeodynamics by clearing dysfunctional proteins and organelles, a function that becomes impaired with ageing and metabolic dysfunction. Ketosis intersects with autophagy by mimicking fasting, a potent inducer of autophagy. This overlap is now well documented across tissues including liver, brain, and muscle. In hepatocytes, ketogenic signalling enhances mitochondrial integrity, lipid handling, and redox balance [217], supporting systemic metabolic stability. BHB exerts influence through mitochondrial metabolism and epigenetic regulation, reshaping cellular stress responses [218]. While dose–response thresholds exist, moderate euketonaemia (BHB $\geq$ 0.5 mmol/L) appears to sustain autophagy without adverse consequences [50,95,96,219]. Across neurological conditions, including epilepsy, Alzheimer's, stroke, migraine, and multiple sclerosis, ketosis enhances autophagic flux, reduces neuroinflammation, and supports mitochondrial clearance, offering a unifying mechanism for its neuroprotective effects [220–224].

10 FGF21 as a Mediator of Ketogenic Adaptation

Protein and/or methionine restriction are key mediators of FGF21, a hormone produced in the liver. Acting in response to hormesis, it is produced in response to nutrient stressors including fasting, caloric restriction, ketogenic feeding, protein or methionine restriction, and exercise [225]. Acting via PPARα, it coordinates systemic adaptations by targeting the brain, skeletal muscle, and adipose tissue. A primary role of FGF21 is also to support neuroprotection through autophagy and reduced oxidative stress, linking methionine restriction to systemic adaptations relevant to both ageing and brain health [226,227].

Physical activity provides another layer of hormetic stress with metabolic consequences. Cortisol responses vary with exercise intensity, with vigorous activity transiently lowering cortisol at baseline. It provokes a stronger reactive rise after stress, whereas moderate and distributed exercise offers a more stable profile [228]. When placed in the ideal metabolic conditions of nutritional ketosis, adequate

sleep, the use of electrolytes where appropriate, and exogenous ketones as additional aids, exercise may promote conditioning while buffering maladaptive stress responses. The implications for recovery, cognition, and even athletic performance are now highly compelling, with evidence suggesting ketone supplementation may influence brain-derived neurotropic factor (BDNF) expression, cognitive function, and muscle repair [229]. Importantly, FGF21 signals are adaptive when transient but may reflect unresolved metabolic stress if chronically elevated. Its integration into ketogenic metabolism stresses the fluid interaction between endocrine signals and nutrient sensing in maintaining adaptive balance.

Methionine is a powerful modulator of FGF21. While it is an essential amino acid obtained through diet, in excess it has been implicated in processes linked to ageing, cardiometabolic disease, and cancer. In balance, methionine is a critical precursor for glutathione, a major endogenous antioxidant that protects against oxidative stress, a driver of cellular damage and accelerated ageing. For this reason, long-term dietary restriction may not be advisable, especially for older individuals, where sarcopenia presents a mortality risk and bone remodelling becomes compromised. Nevertheless, experimental evidence indicates that restricting dietary methionine extends lifespan in animal models by reducing oxidative stress, suppressing inflammation, and improving energy homeostasis [230,231]. Some have generalised the findings of methionine restriction to broader protein restriction, largely through the suppression of mTOR, a key regulator of cell growth and metabolism. However, such strategies must be weighed against the recognised role of protein and skeletal muscle in metabolic resilience, glucose regulation, and protection against frailty [232,233]. This is particularly important in ageing and cancer, where muscle mass supports mitochondrial health, hormone regulation, and immune function.

Balanced Strategies Mimicking Methionine Restriction

To overcome this paradox, more balanced approaches that mimic methionine restriction have been proposed. Rather than outright methionine restriction, glycine supplementation appears to provide a less risky approach, avoiding the pitfalls of methionine deficiency [234]. Glycine counters excess methionine by facilitating detoxification of homocysteine and by modulating one-carbon metabolism, effectively mimicking many of the benefits of methionine restriction without reducing dietary protein [235,236]. Mechanistically, glycine increases glutathione biosynthesis, lowers oxidative stress, and enhances mitochondrial activity via haeme biosynthesis. It also supports detoxification through glycine conjugates, curbs gluconeogenesis and appetite via NMDA receptor signalling, regulates cytokines and hormones through glycine receptors, and reduces methyl donor overload by modulating S-adenosylmethionine (SAM) [237,238].

In the context of malignancy, many cancers, including glioblastoma, can become highly dependent on methionine due to impaired homocysteine remethylation, which drives excessive SAM production and dysregulated methylation [239,240]. Methionine Positron Emission Tomography (MET PET) has confirmed these findings and proven useful for identifying tumour activity and aggressiveness [241]. While dietary methionine restriction has been proposed as a tumour-starving strategy, such approaches risk compromising host defences. Balanced approaches that modulate methionine metabolism indirectly, such as via supplementation with glycine or activation of FGF21-mediated pathways by other means referred to here, may hold greater therapeutic promise by supporting systemic homeostasis while exploiting tumour vulnerabilities. These cross-tissue effects are illustrated in Fig. 3.

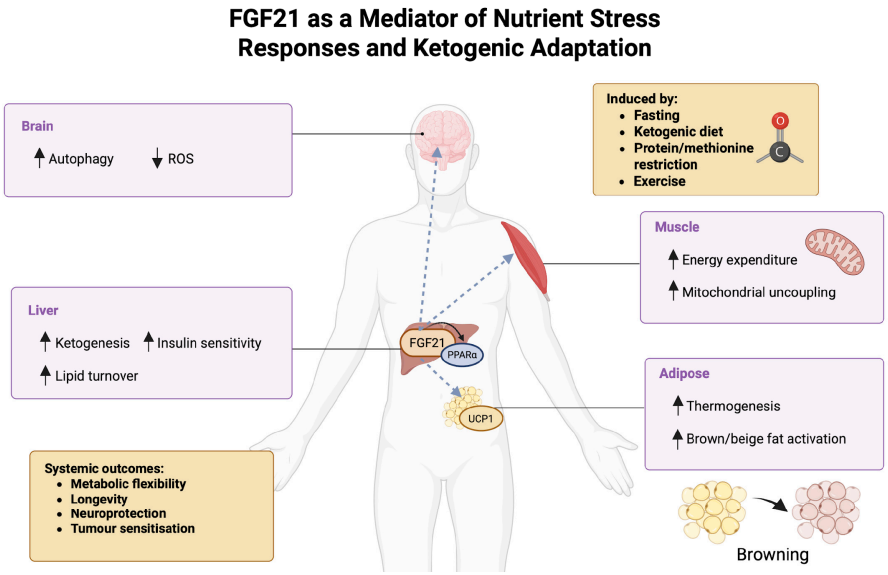

Figure 3: FGF21 as a mediator of nutrient stress responses and ketogenic adaptation. FGF21 is produced primarily in the liver in response to fasting, ketogenic diets, protein/methionine restriction, and exercise. Acting via PPARα, it coordinates systemic adaptations by targeting the brain, muscle, adipose tissue, and liver. In the brain, it enhances autophagy and lowers ROS; in muscle, it increases energy expenditure and mitochondrial uncoupling; in adipose tissue, it drives thermogenesis and browning through UCP1; and in the liver, it promotes ketogenesis, insulin sensitivity, and lipid turnover. Collectively, these effects expand metabolic flexibility, support neuroprotection and longevity, and enhance tumour sensitisation, though chronic FGF21 elevation may indicate unresolved metabolic stress. Abbreviations: Fibroblast growth factor 21 (FGF21; Peroxisome proliferator-activated receptor alpha (PPARa); Uncoupling protein 1 (UCP1); Reactive oxygen species (ROS). Figure created with Biorender.com.

11 Circadian Biology in Ageing, Autophagy and Ketogenic Metabolism

The biology of ageing has long been framed through the "hallmarks of ageing," first nine and now twelve, encompassing genomic instability, telomere attrition, mitochondrial dysfunction, cellular senescence, chronic inflammation, impaired autophagy, and gut dysbiosis [117]. Parallels can be drawn with Hanahan and Weinberg's Hallmarks of Cancer [242]. A classic example of the disease phenotype and perhaps the most appropriate one, exhibiting very similar characteristics and conceptual evolution as new insights emerged. Increasing evidence now provides a highly compelling case for circadian clock dysfunction as an overlooked, yet fundamental driver of ageing and age-related disease. Circadian rhythms are set as endogenous twenty-four-hour cycles that synchronise physiology with environmental cues, governing oscillations in cortisol, melatonin, temperature, feeding, and activity [243]. With age, these rhythms become less robust: cortisol and melatonin peaks are blunted, thermoregulatory variation is reduced, and sleep becomes fragmented. The resulting state of internal misalignment, which is further impacted by modern western diet and lifestyles, undermines anticipatory adaptation, leaving the organism in chronic stress. Consequences include impaired immune function, chronic low-grade inflammation, diminished energetic capacity, and accelerated onset of age-related disease.

11.1 Mechanistic Links between Circadian Disruption and Metabolic Ageing

Mechanistically, circadian disruption interacts with nearly every recognised hallmark of ageing. Misaligned rhythms impair nutrient sensing, weaken autophagy, and disrupt NAD^+ recycling, accelerating mitochondrial dysfunction and redox imbalance [244,245]. These disturbances propagate genomic instability,

senescence, and inflammatory signalling, linking circadian decline directly to neurodegeneration, cancer, and cardiometabolic disease [246,247]. As Wang et al. [248] have clarified, ageing itself reduces circadian resilience, while circadian disruption accelerates ageing through increased oxidative stress, DNA damage, and systemic inflammation. This interdependence suggests that circadian dysfunction is not ancillary but central, with shared pathways connecting it to cancer hallmarks, such as genomic instability and deregulated metabolism. Targeting circadian regulation is now being explored in cancer chronotherapy as a means to exploit tumour vulnerabilities while reducing host toxicity.

Three defining features of circadian integrity deteriorate with age: oscillation, free-running capacity, and entrainment [248,249]. Oscillation refers to the daily hormonal swings that sustain alertness, repair, and restorative sleep. Free-running is where the concept of homeodynamics displays its influence, as it describes the persistence of rhythms under constant conditions, and is dependent upon entrainment. Entrainment, therefore, relates to the synchronisation of internal clocks with light, feeding, psychosocial factors, and activity. As these features degrade, they compound one another. Blunted oscillations impair sleep–wake stability, reduced free-running reflects decline in the suprachiasmatic nucleus, and weakened entrainment promotes chronic misalignment. Importantly, however, circadian clocks remain plastic. Morning light anchors cortisol rhythms while improving general well-being, time-restricted feeding restores oscillatory strength, and exercise timing reinforces entrainment. At the molecular level, circadian biology is finely integrated with NAD^+ metabolism and sirtuin activity, creating a feedback loop in which clock dysfunction lowers NAD^+, while NAD^+ depletion further weakens circadian robustness [250–254]. This cycle may explain why ageing coincides with both circadian flattening and falling NAD^+.

A highly valuable, yet fluid and naturally transient characteristic of circadian and metabolic crosstalk is the bidirectional relationship between circadian disruption and insulin resistance. Misaligned rhythms impair insulin sensitivity through disruption of core clock genes including circadian locomotor output cycles kaput (CLOCK), brain and muscle ARNT-like protein-1 (BMAL1), period (PER), and cryptochrome (CRY), as well as altered melatonin receptor signalling [255–257]. Conversely, insulin resistance destabilises circadian oscillations, feeding back to blunt hormonal cycles and clock-controlled gene expression. Glucokinase, a vitally important glucose sensor responsible for blood glucose regulation, exemplifies this well. Its circadian expression is dependent on CLOCK–BMAL1 binding, and disruption uncouples glucose handling from metabolic demand [258,259]. The result is impaired glucose utilisation, greater glycaemic variability, and progressive metabolic dysfunction. This reciprocal breakdown erodes homeostasis and predisposes to type 2 diabetes and its vascular complications.

11.2 Therapeutic Ketosis as a Circadian Regulator

Therapeutic ketosis provides numerous benefits as a circadian regulator. By lowering insulin, stabilising blood glucose, and reinforcing predictable feeding–fasting cycles, ketosis reduces one of the main disruptors of circadian integrity. BHB not only provides a stable mitochondrial fuel but also directly modulates circadian machinery by supporting NAD^+–sirtuin signalling, histone deacetylase inhibition, and the regulation of clock-controlled genes [40,43]. Keto-adaptation enhances satiety and hunger stability, consolidates sleep cycles, and promotes more efficient slow-wave sleep, synergising with melatonin and the glymphatic system to optimise nightly repair [260–264]. Interventions such as intermittent fasting, time-restricted feeding, and ketogenic nutrition entrain circadian clocks at both central and peripheral levels, strengthening oscillation, preserving NAD^+ pools, and mitigating one of the most pervasive yet underappreciated hallmarks of ageing. Autophagy, FGF21 and circadian rhythmicity represent complementary paths by which ketosis may restore adaptive balance. By sustaining cellular clearance, coordinating endocrine signals and aligning

metabolic rhythms, these processes enlarge the adaptive zone described in the Concentric Model. When they break down progressively with age, the zone contracts, leaving the organism rigid, vulnerable to stress and prone to disease. Their reactivation through nutritional ketosis not only counteracts this decline but re-establishes the dynamic resilience that defines metabolic health, offering a route to preserve both lifespan and healthspan within the framework of the model. These interrelated processes are summarised visually in Fig. 4, which revisits the classical hallmarks of ageing and incorporates circadian clock dysfunction as an emerging hallmark.

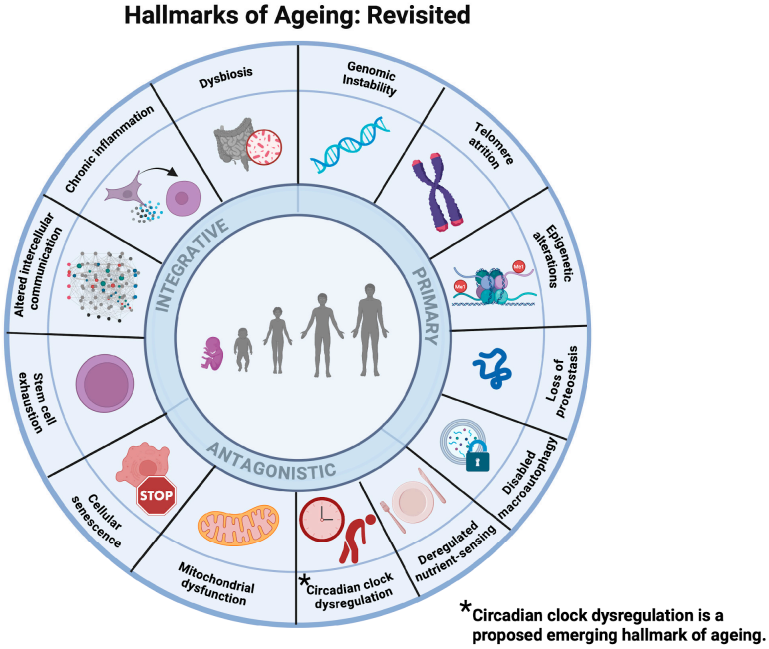

Figure 4: Hallmarks of Ageing: Revisited. The classical hallmarks of ageing framework, adapted from (López-Otín et al., 2013; López-Otín et al., 2023) is shown with the addition of circadian clock dysregulation as a proposed emerging hallmark. Hallmarks are grouped into primary (genomic instability, telomere attrition, epigenetic alterations, proteostasis loss), antagonistic (cellular senescence, mitochondrial dysfunction, deregulated nutrient sensing, circadian dysregulation), and integrative (stem cell exhaustion, altered intercellular communication, chronic inflammation, dysbiosis). Circadian disruption contributes to ageing by impairing NAD^+ recycling, metabolic rhythmicity, and hormonal oscillations, accelerating processes such as inflammation and neurodegeneration. Abbreviations: Nicotinamide adenine dinucleotide (NAD^+). Figure created with Biorender.com.

12 Exogenous Ketones as Adjuncts/Alternatives to Pharmacological Intervention

As has been stated earlier in this paper, NCDs, such as diabetes, Alzheimer's, cancer and CVD, pose immediate threats to morbidity and mortality in the western world. To compound matters further, other prevalent NCDs, while not posing the same level of mortality risk, are increasingly affecting the population by diminishing quality of life and burdening public health systems, with significant societal and economic implications. In the scope of the obesity epidemic and a population who are overfat, undernourished and metabolically broken, quick fix pharmaceutical interventions, in the form of glucagon-like peptide 1 (GLP-1) agonists, present an appealing option, but they are not without consequences. While some situations require urgent attention, there is promise in safer metabolic alternating compounds that can rapidly modulate physiology with supportive mechanisms, although research remains in its infancy compared to achieving a state of ketosis naturally.

Beyond dietary restriction, several exogenous ketogenic agents have been developed to elevate circulating ketones directly. Among these, ketone monoesters stand out as the most promising and clinically validated. Unlike ketone salts or alternative esters, which are limited by gastrointestinal side effects, excess mineral load, and erratic pharmacokinetics, monoesters deliver bioidentical (R)-β-hydroxybutyrate with high bioavailability and minimal electrolyte disturbance. This allows for a rapid, predictable, and sustained rise in blood ketones, often to levels comparable with fasting. Human studies increasingly highlight their therapeutic utility across metabolic, neurological, and performance contexts. Monoesters are considered superior to other exogenous forms because they achieve higher, more durable ketone concentrations without the risk of mineral imbalances. The ketones they deliver are readily metabolised to usable cellular energy, making them an efficient way to induce therapeutic ketosis. While prolonged exercise in the fasted state can augment endogenous ketone production and improve metabolic flexibility, it is not sufficient as a standalone means of achieving sustained therapeutic ketosis. In response to the growing crisis of age-related disease morbidity, with increased prevalence among the young, metabolic interventions are gaining traction as promising therapeutic approaches. One such intervention is the exogenous use of BHB, a ketone body produced endogenously during states of ketosis, which may help mitigate the effects of T2DM. BHB has been shown to improve insulin sensitivity [265,266], reduce inflammation [44,267–270], and protect against oxidative stress [271–273], independent of other nutritional modifications, pharmaceutical interventions or invasive procedures [274]. By acting as an alternative fuel source, exogenous BHB intake, paired with KMT could aid in reducing the reliance on glucose metabolism in these individuals, normalising blood glucose levels, and enhancing metabolic flexibility.

12.1 Neurological Applications of Exogenous Ketones

Perhaps the most notable benefit of the therapeutic potential of BHB extends to the brain, for instance, the societal impact of AD is profound, with millions of individuals worldwide affected and healthcare systems overwhelmed by the rising costs of long-term care. As populations age, the prevalence of Alzheimer's is projected to rise exponentially [275,276], making effective interventions all the more urgent. In this context, metabolic therapies like ingestible exogenous BHB monoesters offer hope of stemming the tide, in principle by providing an alternative energy source for neurons that are unable to utilise glucose efficiently. Emerging evidence suggests that BHB can not only bypass impaired glucose metabolism but also exerts neuroprotective effects and reduces amyloid-beta accumulation [69,203,277–279]. As a caveat, while amyloid beta (AB) is often considered a key hallmark of Alzheimer's pathology, a significant subset of clinically diagnosed AD, at least 10–15%, shows no amyloid accumulation by biomarkers [112,280], suggesting AB is one indicator rather than a sole driving force. Other research has shown that AB can act as a rescuer of damaged OXPHOS, enabling upregulation of glycolysis to support ATP demand [281,282]. Over time, insulin degrading enzyme (IDE) is kept saturated with AB catabolism, reducing its ability to degrade insulin, with downstream effects on insulin handling and uptake [283,284]. Nevertheless, despite these caveats, it is clear that impaired glucose metabolism is a key feature that could potentially be exploited with exogenous BHB supplementation, and therefore, may aid in slowing cognitive decline mitigating the progression of AD.

While pathologically distinct entities with very different aetiology among common neurological conditions, migraine disorders and epilepsy share metabolic phenotypes similar to those observed in AD [285,286]. Both have demonstrated improvements from KMT [287,288], in part due to elevated levels of BHB [43,289,290], which has been shown to reduce oxidative stress and neuroinflammation. Although research on ketogenic diets for epilepsy has been clinically implemented for nearly a century, it is only just emerging for other neurological conditions. The mechanisms appear similar, with some promising results

using strategies that raise BHB, including ketogenic diets [291], fasting [292], the addition of MCTs [293], and/or exogenous ketones [294,295]. Furthermore, these conditions, while not leading causes of mortality, impact quality of life significantly and are examples of how metabolic therapies may offer relief.

12.2 Cardiometabolic and Psychiatric Applications

The diabetes epidemic is not without precedent. Concurrently, CVD presents a major global threat and remains the leading cause of morbidity and mortality globally [296], affecting millions of people and placing a severe financial and healthcare burden on societies. The impact of CVD spans a wide range of conditions, with many of these disorders exacerbated by metabolic dysfunction, such as insulin resistance/hyperinsulinaema [297], and chronic inflammation [298]. Ketone metabolism plays a unique and promising role in cardiovascular health. The heart is highly metabolically flexible, meaning it can use various fuel sources for energy, including fatty acids, glucose, and ketones. Research has shown that ketones, particularly BHB, may offer cardioprotective benefits [299,300], and act as a preferential and highly efficient fuel source for the heart. During periods of metabolic stress, such as heart failure, the heart can become less efficient at using glucose or fatty acids, and ketones can provide an efficient, alternative fuel source [158]. BHB has been found to enhance myocardial efficiency [301], reduce oxidative stress [302], and improve overall cardiac function.

Over the past decade, an ever-pressing issue has been the growing global mental health crisis, with rising rates of depression [303,304], anxiety [305,306], and attention deficit hyperactivity disorder (ADHD) [307,308]. Poor metabolic health is increasingly recognised as a key factor exacerbating these conditions [73]. Depression has become one of the most prevalent mental health disorders [309], contributing to the surge in antidepressant prescriptions [310]. The emerging field of metabolic psychiatry seeks to address these underlying metabolic issues, linking disturbances in energy metabolism, inflammation, and oxidative stress to mental health disorders [311]. Within this framework, BHB shows potential as a therapeutic tool, offering neuroprotective and anti-inflammatory effects [312] while favourably altering brain chemistry [313]. Fundamental mechanisms include enhancing astrocyte glutamate uptake, particularly when paired with KMT, which may help alleviate symptoms by improving brain energy metabolism, increasing levels of neuroinhibitory transmitter GABA in the brain [177,314], and reducing oxidative stress [312]. As metabolic dysfunction becomes more clearly tied to psychiatric conditions, BHB may play a pivotal role in mitigating the burden of these disorders. While evidence of these approaches to better treat mood disorders is encouraging, evidence in humans remains sparse, and further study is necessary to support these findings.

12.3 BHB and Sex-Based Endocrine Dysfunction

Men's health issues, notably high male suicide rates [315], prostate cancer, and the increasing incidence of colorectal cancer in young adults of either gender [316], are deeply concerning, with poor diet and metabolic health playing a critical role [317,318]. In women, conditions like PCOS, breast cancer, and the effects of early menopause and dysregulation of menstrual cycles are often exacerbated by metabolic dysfunction [319], leading to worsening symptoms and increased disease risk. BHB's anti-inflammatory, neuroprotective, and insulin-sensitising properties may help mitigate the progression of these cancers, while improving mental health outcomes and alleviating symptoms in conditions such as PCOS [213] and others associated with endocrine dysregulation. As the burden of these conditions grows across all demographics, BHB represents a promising avenue for addressing these issues.

In respect to cancer, given that insulin and associated growth factors are routinely elevated [206,295, 320,321], progressively influencing their aggressivity, vascularity, and thus their ability to grow and spread, KMT supported with exogenous BHB may be an effective way to increase the efficacy of certain cancer therapies. Additionally, using the glucose-ketone index (GKI) calculator can help measure therapeutic efficacy in the metabolic management of brain cancers and potentially other cancers [322]. Tumour cells are not well adapted to metabolising ketones, but instead, predominantly depend on glucose and glutamine for fuelling [120,323]. Limiting glucose availability for tumours by adapting into ketosis may, therefore, create a metabolically unfavourable environment for tumour growth, whilst also reducing insulin and IGF-1′s growth and division stimulating signals [324].

12.4 Stress, Appetite Regulation and Dietary Sustainability

Overall, despite advances in healthcare, NCDs continue to strain global health systems and the population in a myriad of different ways socioeconomically. BHB, acting as both an energy substrate and signalling molecule, offers a promising solution to the metabolic dysfunctions underlying many NCDs. Additionally, BHB may also regulate appetite via reduced lipolysis and elevation of the appetite-suppressing compound N-L-lactoyl-phenylalanine [325], in turn normalising hunger and satiety hormones, leptin and ghrelin, which often become dysregulated due to stress [326–328], and a lack of sleep [329,330]. Therapeutic use of a BHB monoester could, therefore, reduce overeating and promote better dietary choices, especially in populations reliant on hyperpalatable ultra-processed foods and an increase in popularity of GLP-1 receptor agonists, specifically semaglutide (Ozempic), for the management of diabetes and obesity [331], which have a host of undesirable side effects that can increase the risk of NCDs [332].

In essence, while ketogenic diets and fasting are effective at raising endogenous BHB levels, long-term adherence can be challenging, and there are risks of nutritional imbalances if not implemented adequately. BHB monoester supplementation provides a controlled and accessible way to increase ketone levels without the complications associated with exogenous ketone salts or other additives. Recent advancements in additive-free BHB monoester formulations offer a novel approach to elevating ketone levels rapidly and effectively, with early studies showing promising pharmacokinetic profiles and bioavailability in both healthy volunteers and athletes. Exogenous ketogenic agents, including BHB monoester supplementation, possess a myriad of metabolic and physiological effects, many of which remain unknown. With a focus on its potential applications in managing NCDs, which carry a great burden on society. Future study is necessary to discuss the potential limitations of BHB monoester supplementation as a standalone therapy and outline areas for future research, including its long-term safety, efficacy across diverse populations, and its role as an adjunct to existing treatments.

13 Limitations, Challenges and Future Directions

Euketonaemia, characterised by circulating BHB ($\geq$0.5 mmol/L) as a biomarker to monitor efficacy, (hypoketomaemia is BHB < 0.5 mmol/L) [50,95,96], carry the weight of enormous therapeutic promise, but the path forward is neither linear nor guaranteed. Every promising therapy has its blind spots, and here it is essential to acknowledge them not as reasons for dismissal but as opportunities to refine and evolve the field. What is striking is not the absence of benefit, but the variability in how those benefits are expressed across individuals, contexts, and timescales. The biology itself resists simplification. Responses differ between men and women, across age groups, and even among those who appear outwardly metabolically similar. Behind this heterogeneity lie differences in mitochondrial efficiency, redox balance, hormonal milieu, and the microbial communities that inhabit the gut. Some individuals transition into ketosis seamlessly, others

struggle with fatigue, electrolyte shifts, or protracted adaptation. These disparities point to an urgent need for biomarkers of metabolic responsiveness that can predict who stands to benefit most, and under what conditions, moving the field away from broad generalisation and toward precision application.

Endogenous euketonaemia through fasting or carbohydrate restriction with high fat intake remains the gold standard, however, may be considered challenging to implement long term. Social environments, food culture, and the monotony of a mindset of deprivation all conspire against adherence. For some, the rebound when restriction is broken may undo months of careful progress. Exogenous ketones, particularly BHB monoesters, offer a tempting shortcut, producing rapid and predictable rises in circulating ketones. Yet they cannot reproduce the full systemic adaptations of endogenous euketonaemia, nor have their long-term safety and efficacy been firmly established. The challenge is to position them realistically: not as substitutes but as tools, especially valuable when adherence is compromised, or rapid induction is required in clinical care.

The bigger question is how to more effectively measure individualised, therapeutic euketonaemia. Drugs are judged against single targets and euketonaemia may aid in restoring metabolic function via multiple signalling pathways, with mechanisms extending past that into fuel utilisation, redox homeostasis, inflammation, and gene expression. The question is what to prioritise and in what context. Is it the duration of elevated BHB, reliance on the GKI model, or a focus on the restoration of NAD^+ cycling and mitochondrial efficiency with more targeted, pulsed ketogenic targets? Without clarity on these endpoints, clinical trials will remain fragmented. Progress will require not only larger and longer studies, but smarter design that combines euketonaemia with nutrigenomics, targeted nutrition, exercise, circadian entrainment, and dietary polyphenols, alongside outcome measures that reflect ageing biology itself, not just glycaemic control.

14 Conclusions

Non-communicable diseases and the ageing phenotype are driven by persistent metabolic dysfunction, where impaired autophagy, mitochondrial decline, and circadian disruption accelerate loss of resilience. Euketonaemia, and particularly the ketone body β-hydroxybutyrate (BHB), offers a therapeutic means of addressing these defects. Beyond serving as an efficient fuel, BHB functions as a signalling molecule with growing mechanistic evidence supporting its roles in restoring redox balance, stimulating autophagic repair, and reprogramming nutrient-sensing pathways. Animal models are promising, yet there remains a necessity to confirm these effects *in vivo* in humans. Endocrine mediators, such as FGF21 and circadian alignment, appear to reinforce these effects, providing a multi-faceted conceptual framework in which metabolism, cellular recycling, and rhythmicity converge to sustain health.

Importantly, the benefits of euketonaemia appear scalar, with moderate, sustained levels (*'nutritional ketosis'* as *'euketonaemia'*) conferring protection while extremes may be counterproductive. This principle aligns with the Concentric Zone Model of Adaptive Balance, which emphasises that biological systems function optimally within adaptive zones rather than at extremes.

The challenge for the future is now to better define these adaptive zones for different individuals and disease states across the lifespan, and to translate mechanistic insights into long-term clinical outcomes. This could be aligned with tests of glycation and biological ageing, rather than of chronological age as a fixed metric. Viewed in this light, with these qualifications, euketonaemia as a therapeutic tool is likely not a blunt intervention but a flexible, malleable strategy which shows potential in restoring homeodynamics across ageing and chronic disease. In essence, euketonaemia, via BHB and reduced insulin demand, restores metabolic balance by enhancing autophagy, protecting mitochondria, and aligning circadian rhythms, with its benefits realised within adaptive ranges rather than extremes.

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Abbreviations

AB	Amyloid beta
AcAc	Acetoacetate
AD	Alzheimer's disease
ADHD	Attention deficit hyperactivity disorder
Akt	Protein kinase B
AMPK	AMP-activated protein kinase
ATP	Adenosine triphosphate
BDNF	Brain-derived neurotrophic factor
BG	Blood glucose
BHB	β-hydroxybutyrate
BMAL1	Brain and muscle ARNT-like protein-1
CLOCK	Circadian locomotor output cycles kaput
CoA	Coenzyme A
CoQ10	Coenzyme Q10
CRY	Cryptochrome
CSF	Cerebrospinal fluid
CVD	Cardiovascular disease
DIC	Disseminated intravascular coagulopathy
EGF	Epidermal growth factor
eNOS	Endothelial nitric oxide synthase
ETC	Electron transport chain
FGF21	Fibroblast growth factor 21
FOXO	Forkhead box O transcription factor
FUNDC1	FUN14 domain-containing protein 1
GABA	Gamma-aminobutyric acid
GKI	Glucose-ketone index
GLP-1	Glucagon-like peptide-1
GLUT1	Glucose transporter type 1
HDAC	Histone deacetylase
ICE	Insulin-compensated euglycaemia
IDE	Insulin-degrading enzyme
IGF-1	Insulin-like growth factor-1
IL-1β	Interleukin-1 beta
JNK	c-Jun N-terminal kinase
KDT	Ketogenic Diet Therapy
KMT	Ketogenic Metabolic Therapy

MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
MCT	Medium-chain triglyceride
MET PET	Methionine Positron Emission Tomography
mTOR	Mammalian target of rapamycin
NAD^+	Nicotinamide adenine dinucleotide
NCDs	Non-communicable diseases
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3
NMDA	N-methyl-D-aspartate
Nrf2	Nuclear factor erythroid 2-related factor 2
OXPHOS	Oxidative phosphorylation
PAI-1	Plasminogen activator inhibitor-1
PARPs	Poly-ADP ribose polymerases
PCOS	Polycystic ovary syndrome
PER	Period
PI3K	Phosphoinositide 3-kinase
PIT	Personalised hyperinsulinaemia threshold
PPARα	Peroxisome proliferator-activated receptor alpha
ROS	Reactive oxygen species
SAM	S-adenosylmethionine
SCOT	Succinyl-CoA:3-oxoacid CoA transferase
SHBG	Sex hormone-binding globulin
SIRT	Sirtuin
SNS	Sympathetic nervous system
T2DM	Type 2 diabetes mellitus
TBI	Traumatic brain injury
TNF-α	Tumour necrosis factor-alpha
UCP1	Uncoupling protein 1
ULK1	UNC-51-like kinase 1
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor
VLDLR	Very-low-density lipoprotein receptor

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