GeroScience
https://doi.org/10.1007/s11357-024-01101-7

ORIGINAL ARTICLE

Metabolic dysfunction and the development of physical frailty: an aging war of attrition

William A. Fountain · Taylor S. Bopp · Michael Bene · Jeremy D. Walston

Received: 1 February 2024 / Accepted: 13 February 2024

Abstract The World Health Organization recently declared 2021–2030 the decade of healthy aging. Such emphasis on healthy aging requires an understanding of the biologic challenges aging populations face. Physical frailty is a syndrome of vulnerability that puts a subset of older adults at high risk for adverse health outcomes including functional and cognitive decline, falls, hospitalization, and mortality. The physiology driving physical frailty is complex with age-related biological changes, dysregulated stress response systems, chronic inflammatory pathway activation, and altered energy metabolism all likely contributing. Indeed, a series of recent studies suggests circulating metabolomic distinctions can be made between frail and non-frail older adults. For example, marked restrictions on glycolytic and mitochondrial energy production have been independently observed in frail older adults and collectively appear to yield a reliance on the highly fatigable ATP-phosphocreatine (PCr) energy system. Further, there is evidence that age-associated impairments in the primary ATP generating systems (glycolysis, TCA cycle, electron transport) yield cumulative deficits and fail to adequately support the ATP-PCr system. This in turn may acutely contribute to several major components of the physical frailty phenotype including muscular fatigue, weakness, slow walking speed and, over time, result in low physical activity and accelerate reductions in lean body mass. This review describes specific age-associated metabolic declines and how they can collectively lead to metabolic inflexibility, ATP-PCr reliance, and the development of physical frailty. Further investigation remains necessary to understand the etiology of age-associated metabolic deficits and develop targeted preventive strategies that maintain robust metabolic health in older adults.

Keywords Aging · Frailty · Metabolism · Skeletal muscle · Energy

W. A. Fountain · T. S. Bopp · M. Bene · J. D. Walston (✉)
Division of Geriatric Medicine and Gerontology, Johns Hopkins University School of Medicine, Baltimore, MD 21224, USA
e-mail: jwalston@jhmi.edu

Introduction

Physical frailty is a common syndrome in older adults that is highly associated with adverse health outcomes including falls, hospitalization, worsening chronic disease states, the development of disability, and early mortality. It is detected by a screening exam in community dwelling older adults that includes measures of grip strength, walking speed, physical activity, unintentional weight loss, and fatigue [1]. These variables are in part driven by age-related declines in muscle mass and power. The underlying etiology that drives physical frailty is complex. Age-related biological changes, chronic disease states, and environmental influences have all been hypothesized to drive a

Published online: 24 February 2024

series of physiological changes that are characteristic of physical frailty (Fig. 1). These include dysregulated stress response systems, chronic inflammatory pathway activation, and altered energy metabolism [2].

In humans, energy metabolism consists of several pathways responsible for the transport and breakdown of dietary substrates including glucose and fatty acids to generate ATP via mitochondrial electron transport chains (ETC) and the tricarboxylic acid (TCA) cycle (Fig. 2). Investigations focusing on these pathways provide foundational evidence in characterizing the progression from physical robustness to clinical frailty. It is now apparent that the integrity of bioenergetic systems plays a role in the transition from robust to frail. To understand the role of bioenergetics in the development of physical frailty, we discuss the major cellular energy-producing pathways as they relate to recently identified differences between frail and non-frail older adults. Much of the insight gained into physical frailty has been through the study of skeletal muscle tissue, which will be the primary focus of this review as it is an integral component of clinical frailty assessments.

Glucose and fatty acids: the major bioenergetic substrates

The impact of aging on cellular function is reasonably predictable, often characterized by the chronic expression of inflammatory and senescence-associated profiles [3–5]. However, the impact of aging on physical function is highly heterogeneous. For example, older masters-level athletes regularly outperform their untrained peers while physically frail adults of the same age have difficulties performing simple daily tasks due to extreme muscle weakness and fatigue [1, 6]. One potential explanation for this disparity could be the significant differences in metabolic health and function. Muscle weakness and fatigue are clinical indicators of frailty and inherently rely on bioenergetic systems. Specific age and frailty associated impairments in the transport and metabolism of glucose and fatty acids have recently been observed and provide insight into the mechanisms linking metabolic dysfunction and frailty pathogenesis.

Glucose and aging

In most human tissues, glucose serves as the preferred substrate for ATP production during periods of elevated metabolic demand [7]. Blood glucose levels can be impacted by local and systemic factors such as dietary intake, physical activity, and circulating insulin levels. Advanced age also appears to negatively impact the ability to efficiently clear glucose from the bloodstream [8]. Two decades ago, the Baltimore Longitudinal Study of Aging reported that after an average 11-year follow-up, 57% of adults progressed

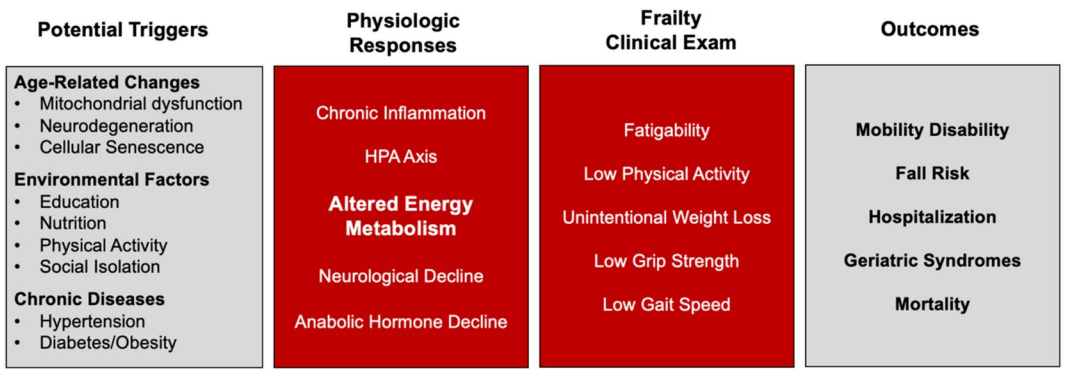

Fig. 1 Conceptual framework of triggers and physiological changes that influence physical frailty and adverse health outcomes. The etiology of physical frailty is thought to be multifactorial with dynamic, systemic physiological responses to various triggers resulting in the clinical presentation of physical frailty. Altered energy metabolism likely plays a central role in the development of physical frailty due to its robust influence on the physical function of skeletal muscle tissue. Specific age- and frailty-associated metabolic impairments have been independently observed and likely accumulate in a subset of individuals. Therefore, the cumulative attrition of multiple metabolic systems may yield a functional threshold indicating the development of physical frailty

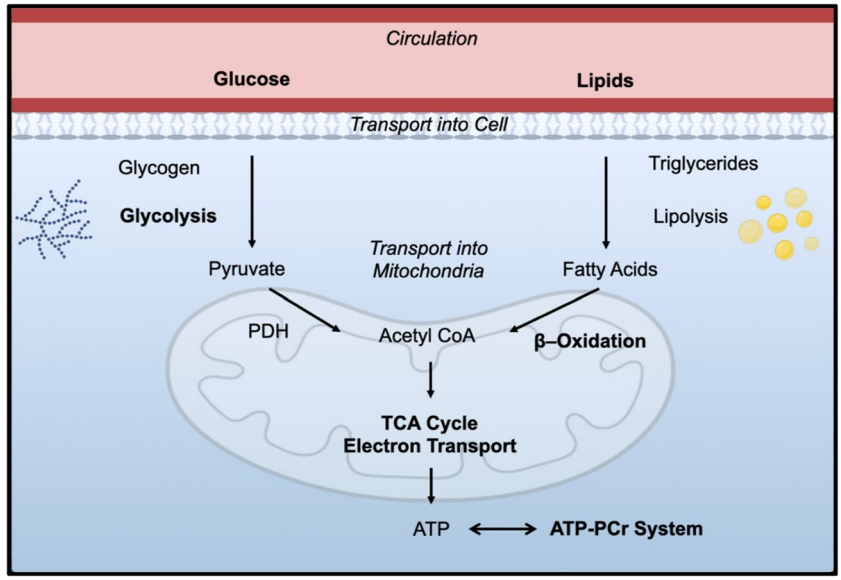

Fig. 2 Introduction to major bioenergetic systems in human skeletal muscle. To be utilized for energy production, circulating glucose and lipids must first be transported into the active cell where they can either be stored or enter their respective oxidative pathways. Glycolysis is responsible for the conversion of glucose to pyruvate, an important metabolic intermediate. Pyruvate dehydrogenase (PDH) then catalyzes the transformation of pyruvate into acetyl-CoA in the mitochondria. Similarly, intracellular fatty acids are shuttled into the mitochondria to generate acetyl-CoA through β-oxidation. Acetyl-CoA is one of the most essential metabolic intermediates as it is the primary substrate of the tricarboxylic acid cycle (TCA). In conjunction with the electron transport chain, most cellular energy is produced by the mitochondria in the form of adenosine triphosphate (ATP). Therefore, mitochondrial ATP generation is essential for the optimal function of the ATP-phosphocreatine (PCr) system. Importantly, ATP-PCr acts as an emergency energy reserve with the rapid interconversion of PCr + ADP to creatine (Cr) + ATP fueling brief periods of elevated metabolic demands

from normal to impaired glucose tolerance as measured by elevated fasting levels of glucose and insulin [8]. Adults over the age of 65 exhibited an even faster annual rate of progression from normal to impaired glucose tolerance than those under 65, indicating the likelihood of accelerated impairments in glucose transport with advancing age [8]. Although the etiology of this glucose intolerance is likely heterogeneous, expression of the main protein responsible for facilitating the diffusion of glucose across the cell membrane into skeletal muscle and other tissues, GLUT4, declines with age [9–12].

The relationship between GLUT4 and glycemic control has been illustrated in a cohort of adults with impaired glucose tolerance [10]. In this investigation of young (29 years) and older (64 years) adults, Gaster et al. implemented oral glucose tolerance tests (OGTT) to examine the dynamic metabolic response to glucose ingestion. The authors found that the older adults were unable to effectively clear glucose from the bloodstream 2 h following ingestion (pre: 5.5 ± 0.3, post: 8.0 ± 0.5 mmol/L, $P < 0.05$). The expression of GLUT4 in the glycolytic type II muscle fibers was 25% lower in the older compared to young adults which likely contributed to the observed glucose intolerance [10]. Although type I fibers can indeed perform glycolysis, they store less glycogen and exhibit lower glycolytic enzyme activity than type II fibers. Thus, the overall glycolytic capacity of aging skeletal muscle is likely impacted by the declines seen in type II fibers [10, 13, 14]. In addition, there was no effect of age on GLUT4 expression in type I fibers [10]. It is important to note that regardless of age, whole body insulin sensitivity and skeletal muscle GLUT4 expression can increase with as little as 1 week of exercise training [15].

Glucose and frailty

Impairments in glucose transport are particularly evident in frail older adults [2, 16]. Distinct OGTT

responses associated with physical frailty were first noted in the Cardiovascular Health Study, where frail older adults were found to have higher circulating glucose (+12%) and insulin (+9%) levels 2 h after the glucose challenge when compared to the non-frail [17]. Importantly, this difference persisted after those with diabetes were excluded. The Women's Health and Aging Study subsequently identified similar patterns with non-diabetic frail older women exhibiting higher circulating glucose (+30%) and insulin (+42%) levels over a 2-h period than robust non-diabetic controls [16]. Such marked reductions in the capacity to clear glucose from the bloodstream indicate that dysregulated skeletal muscle glucose transport is associated with physical frailty status. Similar impairments in glucose transport at rest, in response to feeding, and exercise have also been reported in sarcopenic individuals [18]. GLUT4 levels have not yet been evaluated in frail human skeletal muscle tissue which represents a major opportunity to improve the etiological understanding of physical frailty.

Fatty acids and aging

Aging is typically associated with an increase in the proportion of total body fat and decreases in lean body mass. Although these changes in body composition have been observed for decades, the underlying biological mechanisms that drive this change have yet to be fully elucidated due to the strong influence of physical activity status and nutritional habits. Increases in circulating triglycerides, cholesterol, and low-density lipoproteins have long been associated with the risk of cardiovascular disease and recently reviewed as biomarkers of premature aging [19, 20]. Indeed, lifestyle factors have a robust influence on heterogeneity in body composition and circulating lipid profiles. However, there are common biological mechanisms underlying age-associated changes in lipid metabolism [21, 22]. In the context of the current review, we will discuss the influence of age on triglyceride and fatty acid metabolism as other lipid subclasses (e.g., sphingolipids, glycerophospholipids, ceramides) are not directly involved in cellular energy production.

Fatty acids are stored as triglycerides in multiple tissues including adipose, liver, and skeletal muscle. In addition to key lifestyle factors such as diet and physical activity, the fatty acid content of a given tissue is regulated by the balance of fatty acid synthesis and oxidation. Under resting conditions, fatty acids serve as the primary substrate for β-oxidation and synthesis of acetyl-CoA. The rate at which fatty acids are oxidized (i.e., broken down for cellular energy) is largely regulated by mitochondrial activity. Transport of fatty acids into the mitochondria is facilitated by carnitine, through carnitine palmitoyl transferase (CPT) proteins [7]. Intracellular fatty acid levels can be at least partially maintained through the conversion of acetyl-CoA into malonyl-CoA, a substrate of the fatty acid synthase enzyme. In other words, acetyl-CoA is readily available to be recycled toward the synthesis of fatty acids when there is low activity in mitochondrial ATP-generating systems, providing one potential mechanism of the age-associated increase in intracellular fat content [22]. This is particularly relevant in sedentary populations of older adults who may not sufficiently stimulate mitochondrial pathways preventing the accumulation of acetyl-CoA and exhibit increased fatty infiltration of muscle tissue.

Fatty acids and frailty

Information regarding changes to fatty acid transport and metabolism in frail older adults is scarce but provides valuable insight into the physiologic distinctions between frail and non-frail. Transcriptomic analysis has found that genes related to fatty acid transport such as *CPT1b* are downregulated in adults particularly at risk for developing frailty, or considered "pre-frail" [23]. Altered carnitine levels in the serum and skeletal muscle tissue have been associated with frailty status, yet these findings have been restricted to specific carnitine isoforms [24–26]. Interestingly, it has been shown that frailty progression can be slowed or even prevented by supplementing the endogenous carnitine pool and supporting fatty acid transport into the mitochondria [27–29]. Quantification of CPT in frail human skeletal muscle tissue has yet to be performed and represents another significant limitation to our understanding of physical frailty pathogenesis. This area of research is beginning to highlight that the combination of (1) impaired fatty acid transport into the mitochondria and (2) impaired glucose transport into the cell may be a key difference between frail and non-frail older adults (Fig. 3).

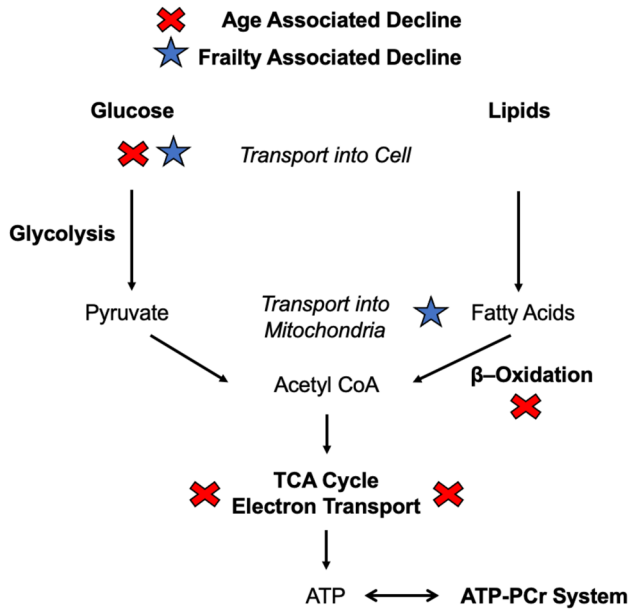

Fig. 3 Hypothesized limitations of bioenergetic systems in physical frailty. Frail older adults are often characterized by marked muscle weakness and chronic fatigue. These symptoms could potentially be explained by a combination of known age-associated metabolic alterations. First, non-diabetic frail individuals have been reported to have transient glucose intolerance, suggestive of impaired skeletal muscle glucose uptake [16]. Second, frail individuals appear to have impaired CPT1-mediated fatty acid transport into the mitochondria [27–29]. In addition, protein expression of mitochondrial energy systems including β-oxidation, TCA cycle, and the electron transport chain have all been shown to be downregulated with age [13, 35, 54–56]. It is plausible that these impairments could reach a cumulative metabolic deficit reaching a threshold in certain individuals where the highly fatigable substrate-level phosphorylation systems (anaerobic glycolysis, ATP-PCr) become exhausted, resulting in the hallmark muscle weakness and fatigue identified in physically frail populations

Integrating metabolic pathways with mitochondrial deficits

Altered cellular bioenergetics have remained central to the hallmarks of aging since they were originally outlined 10 years ago [2, 30, 31]. As a result, aspects of aging-related changes in mitochondrial function have been thoroughly investigated [32–35]. Mitochondria have the distinct responsibility to shift from fatty acid oxidation to the much faster oxidation of carbohydrates in response to increased metabolic demands. The mitochondrial regulation of glucose and fatty acid metabolism originally outlined by Randle is fundamental to the discussion of metabolic alterations due to aging and frailty [36]. Acetyl-CoA is a central regulatory metabolite which serves as the terminal product of both glycolysis and β-oxidation and is also the primary substrate for the TCA cycle. The concentration of acetyl-CoA within the mitochondria is therefore regulated by the rate of its production (i.e., glycolysis, β-oxidation) and consumption (i.e., TCA cycle).

Under conditions of metabolic stress, substrate selection becomes increasingly relevant to the generation of acetyl-CoA as a natural competition ensues between glucose and fatty acid oxidation to prevent metabolite accumulation. The innate ability to shift between metabolic substrates in response to fluctuating energy supply and demand (e.g., feeding, fasting, physical activity) has been conceptualized as metabolic flexibility [37]. When mitochondria fail to efficiently shift in response to energetic stress, "metabolic inflexibility" ensues causing multi-system metabolic dysfunction [38]. This phenomenon has also been classically referred to as "mitochondrial inertia" and "acetyl group deficits" [39]. Chronic energy imbalances such as overnutrition and low physical activity, features often related to aging and physical frailty, are common causes of metabolic inflexibility [38]. When bioenergetic substrates such

as glucose and fatty acids accumulate in excess, a natural competition between the two exists within the mitochondria and results in elevated production of harmful free radicals [38]. Metabolic inflexibility has also been described in several chronic disease states including obesity, diabetes, heart disease, and liver disease [40–43]. Established anti-aging and healthspan-extending interventions such as calorie restriction, intermittent fasting, and regular physical activity have been shown to reduce the biological stress associated with metabolic inflexibility [38, 39, 44, 45]. Supplementing the endogenous NAD^+ pool has also received recent attention due to similar substrate-clearance mechanisms [46, 47]. Animal models of calorie restriction and intermittent fasting are also promising in the field of frailty [48–51]. Maintaining a physically active lifestyle through advanced age has long been viewed as an effective approach to prevent age-associated declines in physical function related to the frailty phenotype [52, 53]. Collectively, the theme of enhancing the effectiveness of mitochondrial shifts between metabolic substrates is evident in anti-aging and anti-frailty interventions.

Precise measurement of metabolic activity through two key enzymes regulating the concentration of acetyl-CoA (pyruvate dehydrogenase, PDH; citrate synthase, CS) indicates that under insulin stimulation, older adults ($n = 15$, 69 ± 1 years) are unable to efficiently switch from fatty acid to carbohydrate oxidation [54]. Importantly, there was no difference in the relative contribution of fatty acids to total energy expenditure between young and older participants. Young participants were able to increase the ratio of glycolytic to oxidative (PDH/CS) activity threefold, while the older participants exhibited no change in the balance of glycolytic to oxidative activity in conjunction with a ~ 40% lower rate of muscle glucose uptake [54]. These data indicate that with age, metabolic flexibility becomes impaired. This phenomenon likely further restricts oxidative phosphorylation as protein expression in the electron transport chain is also downregulated in aging populations [13]. In summary, advanced age has been independently associated with impaired glucose transport and a reduced capacity for anaerobic glycolysis despite an increased reliance on glycolytic energy production [55, 56]. Although much is known about the impact of aging on specific components of these metabolic pathways (Table 1), there is no information available regarding the relationship between substrate transport mechanisms and physical frailty.

Technological advancements allowing for precise kinetic measurements of another bioenergetic pathway, the ATP-phosphocreatine (PCr) system, have provided additional insight on the impact of aging on energy production [35, 57, 58]. The ATP-PCr system is designed to provide an immediate, but limited, supply of ATP upon the initiation of muscle contraction [59, 60]. Within milliseconds of increased ATP consumption and ADP availability, creatine kinase catalyzes the phosphorylation of ADP from PCr to generate ATP and creatine for approximately 10–15 s. Regulatory metabolites that activate anaerobic glycolysis which normally fuels the first 30–90 s of muscle contraction preventing a complete reliance on PCr stores. Finally, under aerobic conditions, pyruvate is transferred into the mitochondria to produce supplemental acetyl-CoA for the TCA cycle and ETC [59, 60]. The transition between substrate level phosphorylation (PCr, anaerobic glycolysis) and mitochondrial oxidative phosphorylation (TCA, ETC) is also based on the premise of metabolic flexibility, which is believed to be a casualty of advanced age [54]. While TCA and ETC produce substantial amounts of energy in the form of ATP, some of that ATP is utilized to regenerate PCr stores. However, as previously discussed, older adults tend to exhibit reduced efficiency in the mitochondrial components (i.e., TCA and ETC) which are responsible for supporting the ATP-PCr system.

Metabolic attrition and physical frailty: preliminary insights

Since its inception, the physical frailty phenotype has been identified by clinically administered physical measurements and questionnaires [1]. A clear consensus on the underlying molecular mechanisms driving the phenotypic progression from robust to frail has yet to be fully established. We have discussed the relationships between sedentary aging, impaired glucose transport, and mitochondrial substrate selection, which independently play a role in the development of weakness and fatigability later in life [13, 35, 54–56]. Should these factors develop in conjunction with one another, there could be an increase in the relative contribution of fatigable

Table 1 Components of major bioenergetic systems in aging human skeletal muscle

	Brief description	Aging	Ref
ATP-PCr system			
Creatine kinase	ATP synthesis	↓↔	[71]
Glucose transport			
GLUT4	Cellular glucose uptake	↓	[11]
Glycolysis			
Hexokinase	Initiation of glycolysis	↓	[72]
Phosphofructokinase	Rate limiting		
GAPDH	Regulates NAD/NADH	↓	[73]
Pyruvate kinase	Pyruvate synthesis	↓	[74]
Pyruvate dehydrogenase	Acetyl-CoA synthesis		
Lactate dehydrogenase	Pyruvate ↔ lactate	↓	[72]
Pyruvate transport			
MPC	Mito. pyruvate uptake		
Fatty acid transport			
FAT/CD36	Cellular FA uptake		
CPT	Mito. FA uptake		
Fatty acid (β) oxidation			
β-HAD	Rate limiting	↓	[75]
Thiolases	Acetyl-CoA synthesis		
TCA cycle			
Citrate synthase	Acetyl-CoA enters TCA	↓	[75]
Succinate dehydrogenase	Connect TCA to ETC	↓	[75]
Electron transport (complex)			
NADH dehydrogenase (I)	Generate H + gradient	↓	[13]
Succinate dehydrogenase (II)	Connect TCA to ETC	↓	[13]
Cytochrome c reductase (III)	Generate H + gradient	↓	[13]
Cytochrome c oxidase (IV)	Generate H + gradient	↓	[13]
ATP synthase (V)	ATP synthesis	↓	[13]

PCr, phosphocreatine; *GLUT4*, glucose transporter 4; *GAPDH*, glyceraldehyde 3-phosphate dehydrogenase; *MPC*, mitochondrial pyruvate carrier; *FAT*, fatty acid translocase; *CPT*, carnitine palmitoyl transferase; *β-HAD*, beta hydroxyacyl-CoA dehydrogenase; *Mito.*, mitochondrial; *FA*, fatty acid

energy systems to support activities of daily living. It is plausible that in a subset of older individuals, these metabolic deficits accumulate simultaneously, catalyzing the development and presentation of physical frailty diagnostic criteria: muscular weakness, fatigability, slow walking speed, low physical activity, and unintentional weight loss. The existence of this hypothetical mechanism has yet to be evaluated, yet its components have been independently discussed and warrant future investigation (Fig. 3).

The first assessment of the ATP-PCr system in frailty using the gold-standard in vivo magnetic resonance approach was published in 2014 utilizing the IL-10$^{tm/tm}$ mouse model [61]. The IL-10$^{tm/tm}$ mouse was generated to serve as a model of frailty by creating a net pro-inflammatory environment with global suppression of the IL-10 gene [62]. The authors characterized the IL-10$^{tm/tm}$ mouse as having lower skeletal muscle [PCr] and creatine kinase activity with twofold higher [P_i] than wild type mice. Differences in basal concentrations of these metabolites have not been observed in similar measures of human skeletal muscle [63]. Notably, in vitro biochemical analyses of creatine kinase protein levels and total activity were not different between IL-10$^{tm/tm}$ and wild type mice [61]. In fact, the in vitro metabolic activities of adenylate kinase, hexokinase, and citrate synthase could not explain the reductions in PCr observed in vivo, suggesting that more complex regulatory mechanisms were involved in this mouse model of frailty [61].

Lewsey and colleagues provide a valuable, comprehensive analysis of the ATP-PCr system in a cross-sectional comparison of frail ($n = 11$,

80.5 ± 2.7 years), non-frail ($n = 12$, 78.8 ± 2.0 years), and healthy middle aged ($n = 11$, 50.5 ± 2.1 years) men and women [63]. While these authors did not directly control for physical activity status, it should be noted that the criteria used to meet frail status (self-reported low physical activity, fatigue, weakness, slowness, and unintentional weight loss) sufficiently addresses the confounding influence. Notably, there were no differences in the concentration of ATP, PCr, or P_i at rest or at the end of a fatiguing exercise protocol between the groups ($P > 0.05$). These data indicate that the PCr system itself does not seem to be impaired in the physically frail. However, the mean rate of PCr depletion during exercise was tenfold higher in frail old compared to healthy middle-aged and fourfold higher in frail compared to non-frail older adults ($P < 0.05$). These findings are strongly associated with increased fatigability, lower peak oxygen consumption (VO_2), and lower mitochondrial oxidative capacity. Importantly, these differences were not influenced by skeletal muscle mass and normalized to the amount of work performed. The recovery of PCr following exercise has been shown to be delayed in both frail and pre-frail individuals, likely related to reductions in oxidative activity seen with advanced age [23, 63, 64]. These impairments in oxidative metabolic systems may in turn cause frail individuals to rely on the contribution of PCr system to a greater extent than their robust counterparts.

Metabolomic analysis of plasma and skeletal muscle samples from young ($n = 30$, 21.7 ± 2.5 years), healthy older ($n = 66$, 71.7 ± 5.2 years), and frail older ($n = 43$, 77.5 ± 8.0 years) participants before and after a resistance exercise training intervention provides further evidence for a metabolic basis of frailty [65]. Prior to beginning the training program, distinct metabolomic profiles were apparent. Differences observed between young and healthy old plasma samples were driven by acylcarnitines and amino acids, which could potentially be explained by the skeletal muscle metabolome [65]. A derivative of L-carnitine and precursor to acetyl-CoA, acetylcarnitine, was 51% lower in the muscle of healthy old participants compared to young ($P < 0.01$). Several TCA cycle intermediates were also reduced (range: 18–24%, $P < 0.05$) in healthy old compared to young muscle. These data suggest age-associated alterations in circulating compounds facilitating fatty acid transport and oxidation. Reductions in five amino acids including the three branched-chain amino acids were also observed, while the arginine/proline associated metabolites showed bidirectional changes [65].

Several important metabolites were found to be differentially expressed in the skeletal muscle of frail subjects [65]. Carnitine and several of its derivatives were lower in frail compared to healthy old muscle (range: 23–58%, $P < 0.05$). Citric acid, the product of the first and rate limiting step of the TCA cycle, was 46% lower in frail compared to healthy individuals ($P < 0.01$) and a surprising fourteen amino acids were also less abundant in frail muscle (range: 10–23%, $P < 0.05$). These data further implicate the reduced capacity to shuttle fatty acids into the mitochondria as a potential limiting factor for energy production and proteostasis in frail older adults, who likely also exhibit impaired glucose tolerance [16, 65]. Importantly, exercise training increased skeletal muscle glucose levels and several carnitine derivatives in this cohort of frail older adults suggesting the potential for restoration of metabolic flexibility [65].

In summary, frail phenotypes appear to be associated with impairments in glucose transport across cellular membranes and fatty acid transport across mitochondrial membranes. Reductions in the efficiency to fuel mitochondrial oxidative phosphorylation appears to shift the burden of ATP production toward substrate level phosphorylation, specifically the highly fatigable ATP-PCr system [63]. Importantly, metabolites associated with ATP-PCr system activity have been shown to reduce contractile force (i.e., fatigue) in isolated skeletal muscle fibers [66–68]. This can directly contribute toward the hallmark reports of chronic exhaustion, muscle weakness, slow walking speed, and difficulty performing simple daily tasks by frail older adults. Metabolic inflexibility, specifically within skeletal muscle tissue, should be considered a contributing factor toward the development of physical frailty.

Future directions

The proposed metabolic origin of physical frailty is not without limitations and further investigation remains necessary. The effect of aging on glucose and fatty acid transport proteins have been well characterized, but similar investigations in frail older adults are not yet published. Transcriptomic comparisons made between healthy ($n = 11$, 70.0 ± 6.7 years) and

pre-frail adults ($n = 10$, 70.2 ± 5.8 years) indicate that the most differentially expressed gene sets in skeletal muscle tissue are related to the mitochondria [23]. Interestingly, pre-frail adults exhibited impaired PCr kinetics along with reduced expression and activity of mitochondrial respiratory proteins. In support of the current discussion, genes encoding the proteins responsible for fatty acid transport (*CPT1b*, *FABP3*, *ACSL1*, *SLC25A20*), lactate metabolism (*LDHB*), and the ATP-PCr system (*CKMT2*) were all significantly downregulated in muscle obtained from pre-frail older adults [23]. Protein-level confirmation of these findings, and dynamic metabolic flexibility tests, would provide compelling evidence toward the proposed metabolic origins of physical frailty. Indeed, plasma proteomic analysis reinforces the strong relationship between metabolic regulatory factors (e.g., GDF15, FABP3, FABP4) and the development of physical frailty [69]. While similar hypotheses are being made in brain tissue [70], future investigations incorporating skeletal muscle-specific analyses will lead to better understanding of the biological roots of clinically identifiable physical frailty.

Declarations

Competing interests The authors declare no competing interests.

References

1. Fried L, et al. Frailty in older adults: evidence for a phenotype. J Gerontol. 2001;56:M146–57.
2. Fried L, et al. The physical frailty syndrome as a transition from homeostatic symphony to cacophony. Nat Aging. 2021;1:36–46.
3. Alvarez-Rodriguez L, et al. Aging is associated with circulating cytokine dysregulation. Cell Immunol. 2012;273(2):124–32.
4. Ferrucci L, et al. The origins of age-related proinflammatory state. Blood. 2005;105(6):2294–9.
5. Furman D, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019;25:1822–32.
6. Gries K, Trappe S. The aging athlete: paradigm of healthy aging. Int J Sports Med. 2022;8:661–78.
7. Judge A, Dodd M. Metabolism. Essays Biochem. 2020;64:607–47.
8. Meigs J, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. Diabetes. 2003;52:1475–84.
9. DeFronzo R, et al. The effect of insulin on the disposal of intravenous glucose: results from indirect calorimetry and hepatic and femoral venous catheterization. Diabetes. 1981;30:1000–7.
10. Gaster M, et al. Direct evidence of fiber type-dependent GLUT-4 expression in human skeletal muscle. Am J Physiol Endocrinol Metab. 2000;278:E910–6.
11. Houmard JA, et al. Skeletal muscle GLUT4 protein concentration and aging in humans. Diabetes. 1995;44(5):555–60.
12. Santos J, et al. The effect of age on glucose uptake and GLUT1 and GLUT4 expression in rat skeletal muscle. Cell Biochem Funct. 2012;30:191–7.
13. Murgia M, et al. Single muscle fiber proteomics reveals fiber-type-specific features of human muscle aging. Cell Rep. 2017;19(11):1–15.
14 Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell Metab. 2013;17(2):162–84.
15. Cox J, et al. Effect of aging on response to exercise training in humans: skeletal muscle GLUT-4 and insulin sensitivity. J Appl Physiol. 1999;86:2019–25.
16. Kalyani R, et al. Frailty status and altered glucose-insulin dynamics. J Gerontol. 2012;67:1300–6.
17. Walston J, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch Intern Med. 2002;162:2333–41.
18. Shoemaker M, et al. Differences in muscle energy metabolism and metabolic flexibility between sarcopenic and nonsarcopenic older adults. J Cachexia Sarcopenia Muscle. 2022;13:1224–37.
19. Mutlu A, Duffy J, Wang M. Lipid metabolism and lipid signals in aging and longevity. Dev Cell. 2021;56:1394–407.
20. Baba M, et al. The impact of the blood lipids levels on arterial stiffness. J Cardiovasc Dev Dis. 2023;10:1–20.
21. Li X, et al. Lipid metabolism dysfunction induced by age-dependent DNA methylation accelerates aging. Signal Transduct Target Ther. 2022;7:1–12.
22. Johnson A, Stolzing A. The role of lipid metabolism in aging, lifespan regulation, and age-related disease. Aging Cell. 2019;18:e13048.
23. Andreux P, et al. Mitochondrial function is impaired in the skeletal muscle of pre-frail elderly. Sci Rep. 2018;8:8548.
24. Rattray N, et al. Metabolic dysregulation in vitamin E and carnitine shuttle energy mechanisms associate with human frailty. Nat Commun. 2019;10:5027.
25. Malaguarnera G, et al. Carnitine serum levels in frail older adults. Nutrients. 2020;12:3887.
26. Hoek M, et al. Intramuscular short-chain acylcarnitines in elderly people are decreased in (pre-)frail females, but not in males. FASEB J. 2020;34:11658–71.
27. Malaguarnera G, et al. Acetyl-L-carnitine slows the progression from prefrailty to frailty in older subjects: a randomized interventional clinical trial. Curr Pharm Design. 2022;28:3158–66.
28. Badrasawi M et al. Efficacy of L-carnitine supplementation on frailty status and its biomarkers, nutritional status, and physical and cognitive function among prefrail older

adults: a double-blind, randomized, placebo-controlled clinical trial. Clin Interv Aging. 2016;1675–1686.
29. Crentsil V. Mechanistic contribution of carnitine deficiency to geriatric frailty. Ageing Res Rev. 2010;9:265–8.
30. López-Otín C, et al. The hallmarks of aging. Cell. 2013;153:1194–217.
31. López-Otín C, et al. Hallmarks of aging: an expanding universe. Cell. 2023;186:243–78.
32. Ubaida-Mohein C, et al. Discovery proteomics in aging human skeletal muscle finds change in spliceosome, immunity, proteostasis and mitochondria. Elife. 2019;8:e49874.
33. Ubaida-Mohein C, et al. Unbiased proteomics, histochemistry, and mitochondrial DNA copy number reveal better mitochondrial health in muscle of high-functioning octogenarians. Elife. 2022;11:e74335.
34. Zampino M, et al. Poor mitochondrial health and systemic inflammation? Test of a classic hypothesis in the Baltimore Longitudinal Study of Aging. Geroscience. 2020;42:1175–82.
35. Liu F, et al. Association of mitochondrial function, substrate utilization, and anaerobic metabolism with age-related perceived fatigability. J Gerontol A Biol Sci Med Sci. 2020;76:426–33.
36. Randle P. Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years. Diabetes Metab Rev. 1998;14:263–83.
37. Goodpaster B, Sparks L. Metabolic flexibility in health and disease. Cell Metab. 2017;25(25):1027–36.
38. Muoio D. Metabolic inflexibility: when mitochondrial indecision leads to metabolic gridlock. Cell. 2014;159:1253–62.
39. Greenhaff P, et al. An acetyl group deficit limits mitochondrial ATP production at the onset of exercise. Biochem Soc Trans. 2002;30:275–80.
40. Prior S, et al. Metabolic inflexibility during submaximal aerobic exercise is associated with glucose intolerance in obese older adults. Obesity. 2014;22:451–7.
41. Ukropcova B, et al. Family history of diabetes links impaired substrate switching and reduced mitochondrial content in skeletal muscle. Diabetes. 2007;56:720–7.
42. Turer A, et al. Energetics and metabolism in the failing heart: important but poorly understood. Curr Opin Clin Nutr Metab Care. 2010;13:458–65.
43. Lee S, et al. Metabolic inflexibility and insulin resistance in obese adolescents with non-alcoholic fatty liver disease. Pediatr Diabetes. 2015;16:211–8.
44. Mancilla R et al. Skeletal muscle mitochondrial inertia is associated with carnitine acetyltransferase activity and physical function in humans. JCI insight. 2022;8.
45. Bergouignan A, et al. Effect of contrasted levels of habitual physical activity on metabolic flexibility. J Appl Physiol. 2013;114:371–9.
46. Covarrubias A, et al. NAD+ metabolism and its roles in cellular processes during ageing. Nat Rev Mol Cell Bio. 2021;22:119–41.
47. Fang E, et al. NAD+ in aging: molecular mechanisms and translational implications. Trends Mol Med. 2017;23:899–916.
48. Arum O, et al. Prevention of neuromusculoskeletal frailty in slow-aging Ames dwarf mice: longitudinal investigation of interaction of longevity genes and caloric restriction. PLoS One. 2013;8:e72255.
49. Kane A, et al. Impact of longevity interventions on a validated mouse clinical frailty index. J Gerontol A Biol Sci Med Sci. 2016;71:333–9.
50. Todorovic S, et al. Effects of different dietary protocols on general activity and frailty of male Wistar rats during aging. J Gerontol A Biol Sci Med Sci. 2018;73:1036–44.
51. Yamada Y, et al. Caloric restriction and healthy life span: frail phenotype of nonhuman primates in the Wisconsin National Primate Research Center caloric restriction study. J Gerontol A Biol Sci Med Sci. 2017;73:273–8.
52. Fried L. Interventions for human frailty: physical activity as a model. Cold Spring Harb Perspect Med. 2016;6:a025916.
53. Travers J, et al. Building resilience and reversing frailty: a randomised controlled trial of a primary care intervention for older adults. Age Ageing. 2023;52:1–9.
54. Petersen KF, et al. Effect of aging on muscle mitochondrial substrate utilization in humans. Proc Natl Acad Sci U S A. 2015;112(36):11330–4.
55. Sial S, et al. Fat and carbohydrate metabolism during exercise in elderly and young subjects. Am J Physiol Endocrinol Metab. 1996;271:E983–9.
56. Mittendorfer B, Klein S. Effect of aging on glucose and lipid metabolism during endurance exercise. Int J Sport Nutr Exerc Metab. 2001;11:S86–91.
57. Kent J, Fitzgerald L. In vivo mitochondrial function in aging skeletal muscle: capacity, flux, and patterns of use. J Appl Physiol. 2016;121:996–1003.
58. Adelnia F, et al. Moderate-to-vigorous physical activity is associated with higher muscle oxidative capacity in older adults. J Am Geriatr Soc. 2019;67:1695–9.
59. Hargreaves M, Spriet LL. Exercise metabolism: fuels for the fire. Cold Spring Harb Perspect Med. 2018;8(8).
60. Hargreaves M, Spriet L. Skeletal muscle energy metabolism during exercise. Nat Metabolism. 2020;2:817–28.
61. Akki A, et al. Skeletal muscle ATP kinetics are impaired in frail mice. Age. 2014;36:21–30.
62. Walston J, et al. The physical and biological characterization of a frail mouse model. J Gerontol. 2008;63:391–8.
63. Lewsey S, et al. Exercise intolerance and rapid skeletal muscle energetic decline in human age-associated frailty. JCI insight. 2020;5:e141246.
64. Varadhan R, et al. Relationship of physical frailty to phosphocreatine recovery in muscle after mild stress in the oldest-old women. J Frailty Aging. 2019;8:162–8.
65. Fazelzadeh P, et al. The muscle metabolome differs between healthy and frail older adults. J Proteome Res. 2016;15:499–509.
66. Debold EP, et al. Muscle fatigue from the perspective of a single crossbridge. Med Sci Sports Exerc. 2016;48(11):2270–80.
67. Sundberg C, et al. Effects of elevated H+ and Pi on the contractile mechanics of skeletal muscle fibres from

young and old men: implications for muscle fatigue in humans. J Physiol. 2018;596:3993–4015.
68. Sundberg C, et al. Bioenergetic basis for the increased fatigability with ageing. J Physiol. 2019;597:4943–57.
69. Liu F, et al. Late-life plasma proteins associated with prevalent and incident frailty: a proteomic analysis. Aging Cell. 2023;00:1–14.
70. Mattson M, Arumugam T. Hallmarks of brain aging: adaptive and pathological modification by metabolic states. Cell Metab. 2018;27:1176–99.
71. Kaczor J, et al. The effect of aging on anaerobic and aerobic enzyme activities in human skeletal muscle. J Gerontol. 2006;61:339–44.
72. Pastoris O, et al. The effects of aging on enzyme activities and metabolite concentrations in skeletal muscle from sedentary male and female subjects. Exp Gerontol. 2000;35:95–104.
73. Vigelsø A, et al. GAPDH and β-actin protein decreases with aging, making stain-free technology a superior loading control in western blotting of human skeletal muscle. J Appl Physiol. 2015;118:386–94.
74. Gelfi C, et al. The human muscle proteome in aging. J Proteome Res. 2006;5:1344–53.
75. Coggan A, et al. Histochemical and enzymatic comparison of the gastrocnemius muscle of young and elderly men and women. J Gerontol. 1992;47:B71–6.