

2024-02-02

# Mitochondrial involvement in sarcopenia

Affourtit, C

<https://pearl.plymouth.ac.uk/handle/10026.1/22018>

---

10.1111/apha.14107

Acta Physiologica

Wiley

---

*All content in PEARL is protected by copyright law. Author manuscripts are made available in accordance with publisher policies. Please cite only the published version using the details provided on the item record or document. In the absence of an open licence (e.g. Creative Commons), permissions for further reuse of content should be sought from the publisher or author.*

## REVIEW ARTICLE

# Mitochondrial involvement in sarcopenia

Charles Affourtit  | Jane E. Carré School of Biomedical Sciences,  
University of Plymouth, Plymouth, UK**Correspondence**Charles Affourtit and Jane E. Carré,  
School of Biomedical Sciences,  
University of Plymouth, John Bull  
Building, Plymouth Science Park, 16  
Research Way, PL6 8BU, Plymouth, UK.  
Email: [charles.affourtit@plymouth.ac.uk](mailto:charles.affourtit@plymouth.ac.uk)  
and [jane.carre@plymouth.ac.uk](mailto:jane.carre@plymouth.ac.uk)**Funding information**Innovate UK, Grant/Award Number:  
10073099; University of Plymouth's  
Proof-of-Concept Fund**Abstract**

Sarcopenia lowers the quality-of-life for millions of people across the world, as accelerated loss of skeletal muscle mass and function contributes to both age- and disease-related frailty. Physical activity remains the only proven therapy for sarcopenia to date, but alternatives are much sought after to manage this progressive muscle disorder in individuals who are unable to exercise. Mitochondria have been widely implicated in the etiology of sarcopenia and are increasingly suggested as attractive therapeutic targets to help restore the perturbed balance between protein synthesis and breakdown that underpins skeletal muscle atrophy. Reviewing current literature, we note that mitochondrial bioenergetic changes in sarcopenia are generally interpreted as intrinsic dysfunction that renders muscle cells incapable of making sufficient ATP to fuel protein synthesis. Based on the reported mitochondrial effects of therapeutic interventions, however, we argue that the observed bioenergetic changes may instead reflect an adaptation to pathologically decreased energy expenditure in sarcopenic muscle. Discrimination between these mechanistic possibilities will be crucial for improving the management of sarcopenia.

**KEYWORDS**

cellular bioenergetics, sarcopenia, skeletal muscle mitochondria

## 1 | INTRODUCTION

Populations are aging rapidly in all parts of the world, but extended lifetime is generally not spent in best health, because of age-related disorders that are linked to the functional decline of various organs.<sup>1</sup> Sarcopenia, for instance, may be defined as a progressive and generalized skeletal muscle disorder that involves accelerated loss of muscle mass and function,<sup>2</sup> and contributes significantly to the frailty that compromises the quality-of-life for millions of elderly individuals worldwide.<sup>3,4</sup> The underlying causes of sarcopenia include malnutrition, inactivity, and disease, as well as drugs and hospital admission.<sup>2</sup> Skeletal muscle

quality is thus not only lost with old age (primary sarcopenia) but also in association with diseases such as cancer,<sup>5</sup> type 2 diabetes,<sup>6</sup> cardiovascular disease,<sup>7</sup> chronic obstructive pulmonary disease,<sup>8</sup> chronic kidney disease,<sup>9</sup> advanced liver disease,<sup>10</sup> as well as with acute and chronic critical illness.<sup>11</sup> Obesity is an important risk factor for these chronic disorders, and disease-related secondary sarcopenia also occurs in individuals with excess body fat.<sup>12</sup> The estimated global prevalence of sarcopenia is imprecise, between 10% and 27%, as epidemiology statistics are confounded by variable classification and cut-off points for skeletal muscle mass and function,<sup>13,14</sup> but loss of muscle quality with age clearly adds to overall healthcare costs.<sup>15</sup>

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2024 The Authors. *Acta Physiologica* published by John Wiley & Sons Ltd on behalf of Scandinavian Physiological Society.

While functional and structural muscle phenotypes share some similarities between primary and secondary sarcopenias, differences in the underlying pathology are likely to complicate the clinical management of elderly people, who often suffer from sarcopenia with multiple causes.<sup>2</sup> Exercise is recommended as the primary treatment of sarcopenia,<sup>16</sup> possibly with dietary supplements to improve benefits,<sup>14</sup> while no single anti-sarcopenic drug has been approved to date.<sup>2,14</sup> Novel therapeutic solutions are much needed to treat sarcopenia in frail elderly and diseased individuals, who are unable to restore skeletal muscle quality through increased physical activity.

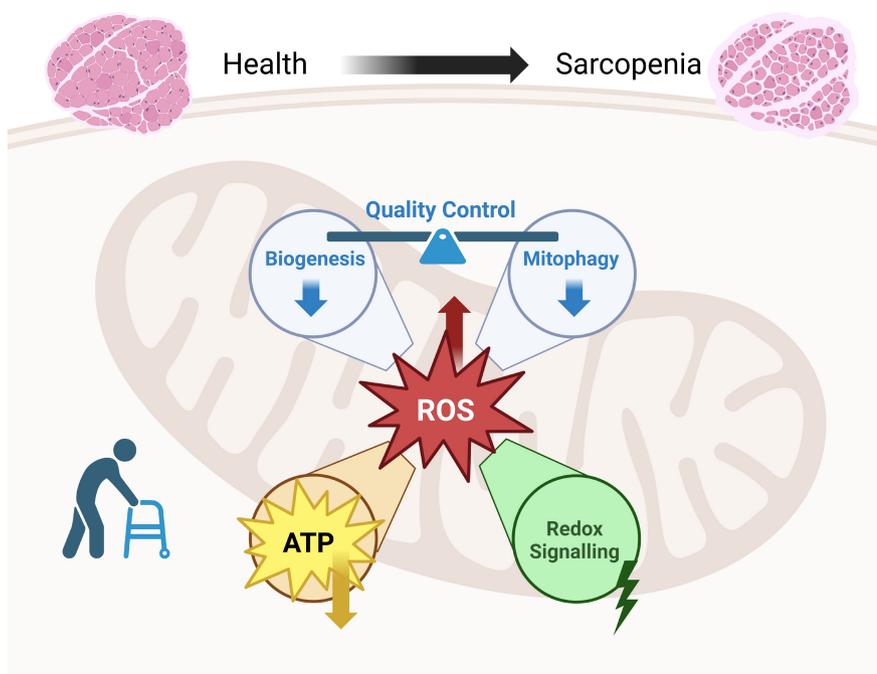
The notion that exercise and nutrition are major pillars in sarcopenia management<sup>17</sup> strongly suggests the involvement of bioenergetic failure in disease development. Indeed, compromised ATP synthesis capacity has been recognized as an important feature of primary and secondary sarcopenia for some time.<sup>18,19</sup> Many aspects of mitochondrial function and dysfunction have been implicated in different types of sarcopenia,<sup>20–23</sup> but causal interrelations with other cellular defects that are associated with this multifactorial muscle disorder have not been established conclusively. Such defects include loss of skeletal muscle insulin sensitivity<sup>24</sup> and a perturbed balance between myocellular protein synthesis and protein breakdown that favors muscle protein loss.<sup>25</sup> Since insulin resistance and perturbed proteostasis are both associated with inflammation<sup>26</sup> and oxidative stress,<sup>27</sup> these cellular defects are also likely functionally related to the observed changes in mitochondrial

activity. Primary sarcopenia is further characterized by hormonal changes,<sup>28</sup> a decline in the number of skeletal muscle satellite cells,<sup>29–32</sup> muscle fiber type transitions,<sup>33</sup> the loss of neuromuscular junctions,<sup>34</sup> and by fat infiltration within and between muscle fibers.<sup>2</sup> Secondary sarcopenia is complicated by the pathological milieu, as muscle dysfunction may be triggered or exacerbated by therapeutics such as corticosteroids<sup>35</sup> and by disease-specific manifestations such as the toxic retention of solutes in chronic kidney disease.<sup>36</sup>

In this review, we give our perspective on mitochondrial involvement in sarcopenia, stressing the incompletely understood interrelation between myocellular proteostasis and bioenergetics. Citing human studies where possible, we explore how exercise and nutrition affect sarcopenic muscle mitochondria, and we briefly reflect on the promise and risk of emerging mitochondria-focused management strategies.

## 2 | MITOCHONDRIAL CHANGES IN SARCOPENIC MUSCLE

Age-dependent decline in aerobic capacity coincides with changes in skeletal muscle energy metabolism,<sup>37,38</sup> and mitochondrial dysfunction has been identified as hallmark of aging.<sup>39</sup> Sarcopenia appears invariably linked with oxidative stress (Figure 1), a unifying pathological condition that is at least partly responsible for compromised mitochondrial quality control,<sup>40,41</sup> mitochondrial bioenergetics,<sup>14,42</sup> and mitochondrial redox biology<sup>43</sup> in sarcopenic muscle.



**FIGURE 1** Mitochondrial changes in sarcopenic muscle. Loss of skeletal muscle mass and function with age is characterized by increased production of reactive oxygen species (ROS), decreased oxidative phosphorylation, mitochondrial biogenesis, and mitophagy, and perturbed redox signaling. Created with [BioRender.com](#).

## 2.1 | Mitochondrial redox biology

Oxidative stress results from a decreased expression of antioxidant defense systems and from the increased formation of reactive oxygen species (ROS) that, to a large extent, is accounted for by mitochondria.<sup>43–48</sup> High ROS levels interfere with the mitochondrial redox biology that contributes to the physiological regulation of insulin<sup>49</sup> and other anabolic signaling pathways,<sup>50</sup> and thus inhibit protein synthesis.<sup>51</sup> Consequent perturbation of proteostasis<sup>25</sup> is made worse by stimulatory effects of high ROS levels on proteolysis: oxidation of proteins by ROS renders them generally more susceptible to proteasome-mediated breakdown, at least partly because oxidation causes unfolding.<sup>52</sup> Indeed, prevention by ROS of the activation of the mammalian target of rapamycin complex 1 (mTORC1) increases expression of muscle-specific E3 ligases that effect proteasome-mediated protein breakdown.<sup>43</sup> Increased autophagy through ROS-prevented activation of mTORC1<sup>53</sup> as well as ROS-induced expression of calcium-activated proteases<sup>54</sup> further tip the proteostasis balance toward loss of protein. ROS thus provokes skeletal muscle dysfunction and atrophy, and clinical studies have indeed demonstrated that oxidative damage increases with age<sup>55</sup> and is associated with impaired muscle strength.<sup>56</sup>

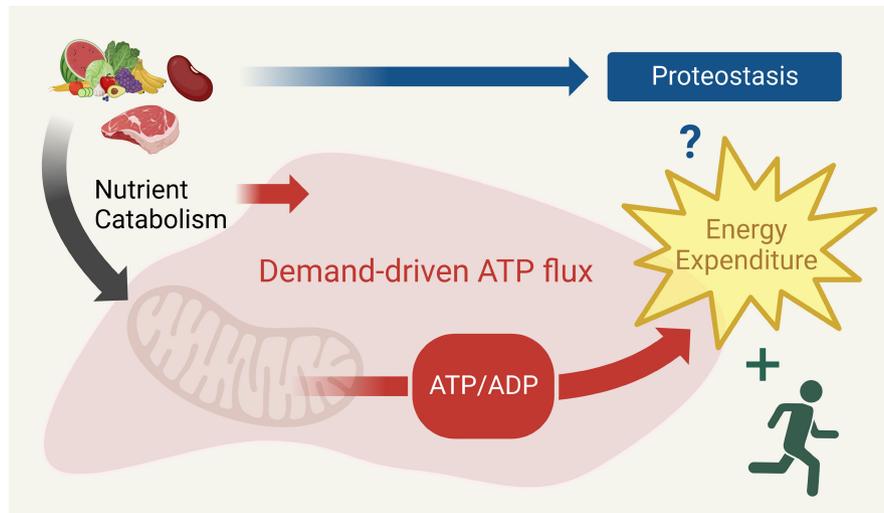
Oxidative stress that leads to sarcopenia during aging,<sup>57</sup> inactivity,<sup>58</sup> and chronic disease<sup>59</sup> is likely related to a persistent state of low-grade systemic inflammation<sup>26</sup> in which production of ROS is stimulated by proinflammatory cytokines.<sup>60</sup> Conditions in which sarcopenia develops are furthermore characterized by a perturbed bioenergetic balance where nutrient availability in muscle cells outweighs energy expenditure,<sup>12</sup> and nutrient catabolism creates a reduced cellular environment that permits ROS generation.<sup>20</sup> ROS likely exacerbate inflammation<sup>61</sup> and may thus reinforce their own formation. Preventing ROS levels in muscle tissue from becoming too high seems an attractive therapeutic option to combat sarcopenia, and certain nutritional and mitochondria-targeted pharmacological interventions (see below for detail) indeed have an antioxidant rationale. However, antioxidant-based therapies might be counterproductive, as insulin and anabolic signaling paths crucial for proteostasis are regulated physiologically by ROS.<sup>49,50</sup> Because of this ROS duality, the anti-sarcopenic promise of antioxidant therapies has been questioned.<sup>62</sup> Future antioxidant-based interventions will likely benefit from a more complete understanding of mitochondrial redox biology, and from more detailed insight in the molecular nature and origin of the ROS responsible for the progressive shift toward oxidative stress that is evident as primary and secondary sarcopenia develop.

## 2.2 | Mitochondrial quality control

Mitochondrial biogenesis, mitophagy and structural dynamics are important for mitochondrial quality control, as these processes maintain functional capacity,<sup>63,64</sup> remove redundant or dysfunctional organelles,<sup>65</sup> and remodel organelle morphology,<sup>66</sup> respectively. Regulation of these processes is reviewed in detail by others,<sup>40,64</sup> and it suffices to mention here that such regulation is disrupted in both primary and secondary sarcopenic skeletal muscle, at least partly owing to oxidative stress, such that the myocellular ability to replace dysfunctional with functional mitochondria is lowered.<sup>67</sup> Functional capacity furthermore depends on regulation of the highly variable turnover of individual mitochondrial proteins,<sup>68</sup> which may change in aging skeletal muscle. Compromised quality control of mitochondria likely contributes to the decreased oxidative capacity of sarcopenic muscle,<sup>14,42</sup> although it remains also possible that molecular signs of attenuated mitochondrial biogenesis reflect a lowered demand for oxidative capacity. It is, for example, possible that anabolic resistance of protein synthesis<sup>69</sup> lowers total energy expenditure, which is expected to decrease oxidative ATP synthesis given that control of skeletal muscle energy metabolism is demand-driven<sup>70</sup> (Figure 2) and given that a significant proportion of overall muscle ATP supply (approximately 20%) is generally allocated to protein synthesis.<sup>71,72</sup> In this respect, it is worth stressing that therapeutic interventions aimed at boosting oxidative capacity through improved mitochondrial biogenesis would be of limited success if demand for such increased capacity remained low.

## 2.3 | Mitochondrial bioenergetics

Skeletal muscle bioenergetics have been investigated extensively in human with phosphorus-31 magnetic resonance spectroscopy (<sup>31</sup>P MRS).<sup>73</sup> For instance, in vivo measurements of the rate by which phosphocreatine (PCr) is recovered after exercise have provided much insight in the capacity of oxidative phosphorylation in healthy individuals as well as people living with chronic disease. Indeed, <sup>31</sup>P MRS established relatively early on that the PCr recovery rate of skeletal muscle decreases with age<sup>19,74,75</sup> as sarcopenia develops. Secondary sarcopenia is also associated with decreased PCr recovery rates, as, for example, revealed in patients with dialysis-dependent chronic kidney disease,<sup>76</sup> chronic lung disease,<sup>77</sup> thyroid disorders,<sup>78</sup> and heart failure.<sup>77</sup> These (patho)physiological observations are corroborated by studies on human skeletal muscle biopsies that



**FIGURE 2** Demand-driven energy metabolism in skeletal muscle. Cellular energy metabolism may be viewed from a top-down perspective as the interaction between processes that supply ATP by substrate-level and oxidative phosphorylation, and processes that demand ATP. In healthy skeletal muscle, total ATP flux is largely controlled by energy expenditure, which is increased by physical activity. Nutrients are catabolic fuels for ATP synthesis and stimuli for anabolic ATP-consuming processes, such as protein synthesis. Created with [BioRender.com](https://www.biorender.com).

also demonstrate an age-dependent decline in the rate of PCr recovery after exercise.<sup>74,79</sup> In vivo and ex vivo data thus both strongly suggest that the oxidative ATP synthesis capacity of sarcopenic skeletal muscle is lower than that of healthy muscle. Perturbed calcium handling in sarcopenic muscle<sup>80</sup> may further dysregulate oxidative metabolism. Notably, age effects on oxidative capacity remain generally heterogeneous.<sup>81</sup> Variable habitual physical activity as well as the sex of the studied individuals contribute to this heterogeneity, as does the variety of skeletal muscle groups probed<sup>81</sup>—these variables need to be taken into account when age effects on mitochondrial ATP synthesis are interpreted. Notably, age does not only decrease the capacity of skeletal muscle oxidative phosphorylation but also the efficiency by which mitochondrial respiration and ATP synthesis are coupled.<sup>42,82</sup>

PCr-recovery-after-exercise measurements remain arguably the most reliable, albeit indirect, way to quantify oxidative mitochondrial ATP supply in human,<sup>83–85</sup> but obtained information is restricted to bioenergetic capacity and offers limited insight in ATP synthesis activity under conditions of varying energy demand. In this respect, it is noteworthy that the causal relation between decreased oxidative capacity and perturbed proteostasis in aged skeletal muscle remains uncertain. Explicitly or implicitly, it is often argued that the rate of protein synthesis is lowered in sarcopenia because dysfunctional mitochondria are unable to sufficiently sustain this and other anabolic processes energetically,<sup>20–23,86</sup> but it is equally conceivable that the decreased oxidative phosphorylation capacity is an adaptation to lowered ATP demand from the depressed

anabolism that follows from insulin and anabolic resistance<sup>69,87</sup> (Figure 2).

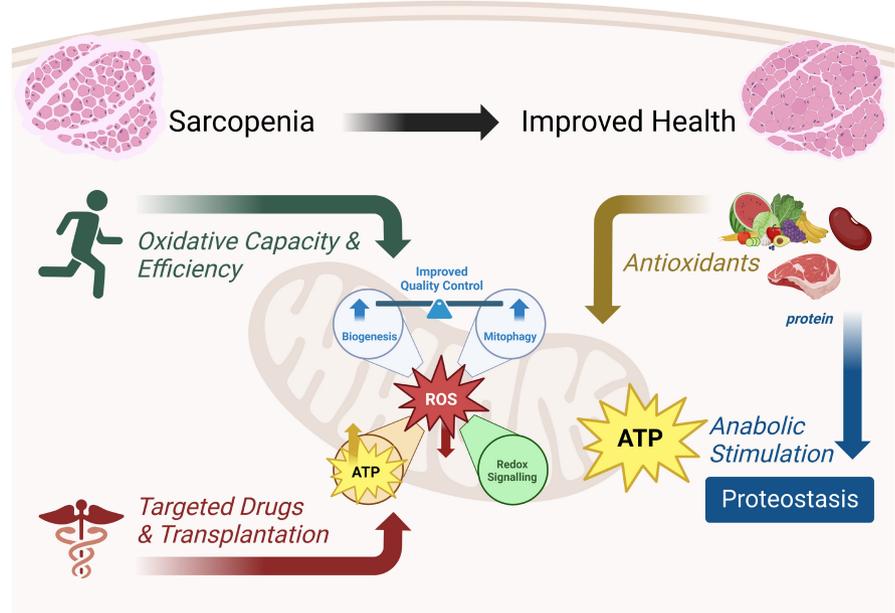
### 3 | RESPONSE OF SKELETAL MUSCLE MITOCHONDRIA TO THERAPEUTIC INTERVENTIONS

Current management of sarcopenia aims to build muscle mass by increasing physical activity, improving nutrition, and by optimizing hormonal homeostasis.<sup>17</sup> To date, exercise remains the sole proven therapy of these three management pillars.<sup>88,89</sup> Dietary supplementation seems only beneficial when combined with exercise,<sup>2,14,90</sup> and although the pharmacological use of vitamin D and testosterone is supported by evidence from human trials,<sup>91</sup> no anti-sarcopenic drugs have yet been approved. Next, we will explore how different sarcopenia management approaches affect skeletal muscle mitochondria (Figure 3).

#### 3.1 | Exercise

Physical activity increases ATP consumption by skeletal muscle cells to fuel contraction. The consequent drop of the myocellular energy charge triggers AMP-activated kinase (AMPK),<sup>92</sup> a master regulator of cellular energy metabolism that helps adjust ATP supply to meet ATP demand.<sup>93</sup> Moreover, physical activity acutely stimulates the production of ROS by skeletal muscle mitochondria<sup>94</sup> and thus causes mild endogenous oxidative stress that activates AMPK further.<sup>95,96</sup> Exercise protects against

**FIGURE 3** Effects of anti-sarcopenic interventions on skeletal muscle mitochondria. Exercise improves mitochondrial quality control and increases both the capacity and efficiency of oxidative phosphorylation, at least partly, through attenuation of oxidative stress. Some nutrient supplements contain antioxidants, while branched-chain amino acids, leucine, in particular, may improve proteostasis through energy-demanding anabolic stimulation. Mitochondria have been suggested as therapeutic targets. Created with [BioRender.com](https://www.biorender.com).



oxidative stress in the longer term, however, because skeletal muscle cells upregulate expression of antioxidant defense systems in response to the acute increase in ROS.<sup>97</sup> This mitohormetic response<sup>98</sup> likely contributes to the benefits of physical activity for mitochondrial activity in aged skeletal muscle. Long-term positive effects of exercise include a boosted oxidative capacity,<sup>99</sup> with evidence for increased ATP synthesis capacity *in vivo*<sup>100–102</sup> and for an increased activity of mitochondrial respiratory complexes *ex vivo*.<sup>103–107</sup> Related to this oxidative benefit, exercise increases mitochondrial biogenesis<sup>108</sup> and mitochondrial mass,<sup>106</sup> and improves mitochondrial quality control<sup>40</sup> through effects on structural dynamics and autophagy.<sup>104,109–111</sup>

With ROS as important culprit of the mitochondrial defects in sarcopenic muscle (Figure 1), it is perhaps not surprising that exercise should rescue such defects, since it strengthens the cells' antioxidant defense. Interestingly, however, exercise-induced increases in muscle mass and function do not always involve increased oxidative capacity, as the nature of mitochondrial effects appears to depend on the type of exercise.<sup>42</sup> Both endurance and resistance training increase skeletal muscle quality in sarcopenia, but while the benefit of endurance exercise is consistently linked with clear stimulation of mitochondrial biogenesis and increased oxidative capacity,<sup>112–116</sup> mitochondrial effects of resistance exercise are less clear.<sup>113,117–120</sup> Resistance training does not affect mitochondrial biogenesis or mitochondrial content but does indeed alter intrinsic mitochondrial function.<sup>121,122</sup> For instance, resistance exercise changes the mitochondrial transcriptome<sup>123</sup> and increases specific abundance of mitochondrial respiratory complexes,<sup>124</sup> which is consistent with the observation that resistance exercise increases

ATP synthesis capacity without changing mitochondrial content,<sup>112,125</sup> and may indicate increased coupling efficiency of oxidative phosphorylation.<sup>42</sup>

AMPK is activated during exercise by a decreased ATP/AMP ratio<sup>92</sup> and by increased ROS levels.<sup>95,96</sup> Skeletal muscle fibers demand much ATP during both endurance and resistance exercise<sup>126</sup> and increase their production of ROS in acute response to both types of physical activity.<sup>127</sup> The different mitochondrial effects of endurance and resistance training are thus unlikely related to these cellular signals *per se* but are more likely owing to differential fiber type recruitment during different types of exercise.<sup>42</sup> Resistance exercise draws predominantly on fast-twitch type 2 fibers, which obtain more of their ATP from glycolysis than their slow-twitch type 1 counterparts.<sup>128</sup> The type of exercise thus seems to dictate which skeletal muscle fiber type accounts most for the increased muscle mass and function provoked by physical activity. Endurance training induces the formation of type 1 fibers, which is reflected by increased mitochondrial mass, while resistance training does not increase mitochondrial mass in newly formed type 2 fibers but improves mitochondrial ATP synthesis efficiency. Notably, resistance exercise amplifies the rise in mitochondrial oxidative capacity of sarcopenic skeletal muscle established by endurance exercise.<sup>129,130</sup> The ability of aged muscle to increase mitochondrial mass in response to endurance exercise<sup>131</sup> indicates that the mechanisms that regulate mitochondrial functional capacity remain intact in elderly individuals. Whether or not this is also the case for the secondary sarcopenia that develops in disease is less clear. For example, while the transcript level of peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  is increased in non-dialysed

individuals with chronic kidney disease following 12 weeks of aerobic physical activity, mitochondrial mass appears unaffected.<sup>132</sup>

### 3.2 | Nutrition

Appropriate nutrition is an essential aspect of current sarcopenia management.<sup>17</sup> Many dietary supplements have been explored, including both macro- and micronutrients such as protein,<sup>133</sup> unsaturated lipids<sup>134</sup> and vitamins,<sup>135</sup> as well as a range of polyphenols from natural sources,<sup>136</sup> but it should be emphasized that nutritional support is generally only effective in combination with exercise.<sup>2,14,90</sup> Benefit from polyphenols, vitamin D and polyunsaturated fatty acids may be related to the antioxidant properties of these nutrients,<sup>137–139</sup> but it is unclear to what extent their use as dietary supplements actually affects mitochondrial ROS production in sarcopenic muscle (Figure 3). The bioenergetic relation between dietary protein and mitochondrial activity is dual, since amino acids, specifically, leucine, are oxidative metabolic fuels,<sup>140</sup> allowing ATP synthesis when broken down through oxidative catabolism, as well as anabolic stimulants of protein synthesis,<sup>69,141</sup> provoking ATP consumption<sup>142</sup> (Figure 2).

Protein supplementation remains at the forefront of the nutritional management of primary and secondary sarcopenia, which is unsurprising as perturbed proteostasis is a key feature of this muscle disorder.<sup>25,143</sup> With age, muscle protein synthesis loses its sensitivity to anabolic stimuli such as essential dietary amino acids,<sup>69</sup> and, together with lost insulin inhibition of protein breakdown,<sup>144</sup> this anabolic resistance perturbs proteostasis.<sup>69,141,145–147</sup> Dietary protein supplements seek to overcome anabolic resistance but have limited benefit per se, as they appear most beneficial when administered together with exercise.<sup>148</sup> This observation suggests that both catabolic and anabolic stimuli are required to restore skeletal muscle mass and function in sarcopenia. Branched-chain amino acids—leucine in particular—have been recognized to add ‘biological value’ to essential amino acid and protein supplements,<sup>149</sup> as they appear able to stimulate both anabolic and catabolic processes.<sup>150–153</sup>

In healthy skeletal muscle, leucine acutely increases protein synthesis in the postprandial state through mTOR activation by various signals, including acetyl CoA, leucyl-tRNA and sestrin.<sup>154</sup> Perhaps to meet energy demand from this anabolic stimulation,<sup>155</sup> it is suggested by rodent pre-clinical studies that leucine also triggers an adaptive catabolic response that involves AMPK and that increases skeletal muscle mitochondrial biogenesis, mtDNA content, fatty acid oxidation and glucose uptake.<sup>156</sup> The apparently parallel occurrence of catabolic and anabolic

stimulation is complex,<sup>124,156</sup> and indeed paradoxical, as AMPK is a well-established mTORC1 de-activator.<sup>150,151</sup> Leucine-induced catabolic and anabolic responses are thus likely separated temporally and spatially, through involvement of different fiber types.<sup>157</sup>

Protein contributes 10%–15% to total fuel oxidation in the postabsorptive state in resting skeletal muscle,<sup>158</sup> and catabolism of branched-chain amino acids accounts for about two-thirds of this contribution.<sup>158</sup> Insulin inhibition of protein breakdown is lost in sarcopenic muscle, which likely increases branched-chain-amino-acid-driven oxidative catabolism in older individuals.<sup>159</sup> The systemic oxidation of branched-chain amino acids occurs predominantly in skeletal muscle mitochondria<sup>158,160</sup> and oxidation rate is sensitive to nutrition-related changes in intramuscular branched-chain amino acid concentration.<sup>160</sup> The oxidation rate of branched-chain amino acids in elderly individuals is also increased by endurance<sup>161–163</sup> and resistance exercise,<sup>164,165</sup> as is the anabolic response to leucine, again suggesting that both anabolic and catabolic stimuli are necessary to obtain maximum benefit from nutrition in sarcopenia.

The notion that protein supplementation is most effective for management of sarcopenia when combined with physical activity,<sup>148</sup> suggests that bioenergetic processes triggered by energy demand may need to be active to obtain full benefit from anabolic stimuli. Supplemented amino acids may indeed only be usable as catabolic carbon fuel for ATP synthesis if demand for ATP is stimulated, for example, by exercise. It is worth emphasizing that increased intake of macronutrients without increasing energy expenditure may do more harm than good, as such intake is expected to create an overly reduced cellular environment that promotes ROS generation. Notably in this respect, obesity-related skeletal muscle insulin resistance arises at least in part because of imbalanced bioenergetics that increase ROS to pathological levels.<sup>49</sup> Moreover, loss of skeletal muscle insulin sensitivity is an early feature of uremic sarcopenia.<sup>166</sup> Nutrients with strong antioxidant properties may protect against excessively high ROS levels but may inadvertently attenuate any adaptive hormetic benefit from exercise that depends on an acute increase in ROS production.<sup>167</sup>

### 3.3 | Pharmacological intervention

Anti-sarcopenic drugs have not been approved to date,<sup>2,14,168</sup> as there is insufficient support from human trials to justify pharmacological interventions in clinical practice other than vitamin D in elderly women and testosterone in elderly men.<sup>91</sup> Vitamin D is thus an example of ‘Foods for Special Medical Purposes’ and, like

other nutrients discussed above, is sometimes referred to as a nutraceutical.<sup>169</sup> Despite lack of clinical trial evidence, numerous pharmacological approaches have been suggested. Drugs that have been investigated include testosterone, testosterone derivatives (melatonin), and selective androgen receptor modulators or SARMS,<sup>170</sup> which not only increase the number of skeletal muscle satellite cells,<sup>171</sup> but all also have beneficial effects on muscle fibers per se.<sup>172,173</sup> Inhibitory antibodies against proinflammatory cytokines<sup>174</sup> and myostatin inhibitors<sup>175</sup> are other examples of drugs that have been explored. Therapeutics that have been linked explicitly to mitochondrial function include growth hormone replacement,<sup>176</sup> which increases mitochondrial oxidative capacity, improves proteostasis, and has anti-sarcopenic benefit for elderly people,<sup>177</sup> ghrelin and ghrelin receptor agonists, which increase oxidative capacity in sarcopenia linked to chronic disease,<sup>178–180</sup> and 5-aminolevulinic acid, which improves muscle quality in mice while increasing mitochondrial content.<sup>181</sup>

The noticeable lack of drug approval is likely related to a limited number of randomized clinical trials, which are generally hampered by the range of sarcopenia definitions and by the difficulty of identifying primary endpoints.<sup>168</sup> Other therapeutic approaches are much sought after, and mitochondria have attracted much attention in this respect.<sup>182–184</sup>

Mitochondrial medicine is a rapidly developing field,<sup>182–184</sup> and approaches for delivering mitochondria-targeted drugs have been reviewed recently by others.<sup>185,186</sup> Exercise has been recognized as a ‘natural medicine’ for skeletal muscle mitochondria,<sup>187</sup> but it may well become possible in the foreseeable future to improve the activity of these organelles in sarcopenic muscle with targeted drugs. Drugs that are passively or actively delivered to skeletal muscle mitochondria hold promise to preserve mitochondrial quality and functionality by lowering oxidative stress.<sup>188</sup> Although in its infancy, several preclinical studies have offered proof-of-principle for this potential therapeutic approach. For instance, MitoQ and MitoTEMPOL, which are a mitochondria-targeted antioxidant and superoxide dismutase mimetic, respectively, have been shown to improve muscle strength and mass by altering bioenergetics in several disease mouse models,<sup>189–191</sup> while the mitochondria-targeted Szeto-Schiller peptide SS31 has been reported to increase exercise tolerance in aged mice.<sup>192</sup>

Mitochondrial transplantation is a therapeutic approach with much potential, but also very much in its infancy. The introduction of healthy mitochondria to dysfunctional cells or tissues has been trialed to increase oxidative capacity in various disease contexts,<sup>193</sup> while work with cell and animal models suggests the approach may help combat muscle atrophy.<sup>194–197</sup>

## 4 | CONCLUDING REMARKS

Imbalanced protein synthesis and breakdown in skeletal muscle accounts for muscle atrophy associated with old age and disease.<sup>25,143</sup> Decreased oxidative capacity is a central feature of both primary and secondary sarcopenia,<sup>19,74–78</sup> but the causal interrelation between altered bioenergetics and perturbed proteostasis remains unclear (Figure 2). It appears that mitochondrial bioenergetic changes in sarcopenia are broadly interpreted as an intrinsic dysfunction that renders skeletal muscle cells incapable of producing sufficient ATP to sustain protein synthesis. The general benefit of exercise for skeletal muscle mass and function in elderly and diseased individuals, however, demonstrates that this apparent insufficiency is readily overcome when energy expenditure is increased. This observation indicates that sarcopenic muscle has retained mechanisms to produce ATP when needed, and it suggests that the decreased oxidative capacity may be an adaptation to pathologically dampened energy demand. It is thus conceivable that impaired protein synthesis is one of the causes of lowered mitochondrial ATP synthesis in sarcopenic muscle, because this defect contributes to decreased total ATP consumption. Anabolic and insulin resistance that is responsible for the compromised balance between protein synthesis and breakdown is likely related to the inflammation and oxidative stress that typify sarcopenic conditions. The bioenergetic imbalance between nutrient supply and energy expenditure promotes oxidative stress, which may exacerbate mitochondrial and cellular defects. The observation that nutrition is only effective as an anti-sarcopenic intervention when applied with exercise, is consistent with this order of events. We emphasize that dietary supplements without increased physical activity may do more harm than good if compromised energy expenditure were at the root of muscle dysfunction, as they would distort the bioenergetic balance further and increase the risk of high ROS production. Notably, therapies based on mitochondrial transplantation would also be inconsequential if the bioenergetic changes seen in sarcopenia were secondary to pathologically diminished energy expenditure, i.e., if the oxidative capacity was increased without the need for such capacity. In conclusion, to achieve positive clinical outcomes it will be very important to obtain a more precise understanding of the causal interrelations between proteostasis, cellular bioenergetics and redox biology in both healthy and sarcopenic skeletal muscle.

## AUTHOR CONTRIBUTIONS

**Charles Affourtit:** Conceptualization; Visualization; Writing – review & editing; Writing – original draft.  
**Jane E. Carré:** Conceptualization; Writing – original draft; Writing – review & editing.

## ACKNOWLEDGMENTS

Work in the authors' laboratories is currently supported by Innovate UK ('Better Food for All' grant 10073099) and the University of Plymouth's Proof-of-Concept Fund.

## CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest regarding the publication of this review.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

## ORCID

Charles Affourtit  <https://orcid.org/0000-0003-1776-9943>

Jane E. Carré  <https://orcid.org/0000-0002-0699-104X>

## REFERENCES

1. Beard JR, Officer A, de Carvalho IA, et al. The world report on ageing and health: a policy framework for healthy ageing. *Lancet*. 2016;387(10033):2145-2154.
2. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. *Lancet*. 2019;393(10191):2636-2646.
3. Landi F, Calvani R, Cesari M, et al. Sarcopenia as the biological substrate of physical frailty. *Clin Geriatr Med*. 2015;31(3):367-374.
4. Davies B, García F, Ara I, Artalejo FR, Rodríguez-Mañas L, Walter S. Relationship between sarcopenia and frailty in the Toledo study of healthy aging: a population based cross-sectional study. *J Am Méd Dir Assoc*. 2018;19(4):282-286.
5. Carson JA, Hardee JP, VanderVeen BN. The emerging role of skeletal muscle oxidative metabolism as a biological target and cellular regulator of cancer-induced muscle wasting. *Semin Cell Dev Biol*. 2016;54:53-67.
6. Chen H, Huang X, Dong M, Wen S, Zhou L, Yuan X. The association between sarcopenia and diabetes: from pathophysiology mechanism to therapeutic strategy. *Diabetes, Metab Syndr Obes*. 2023;16:1541-1554.
7. He N, Zhang Y, Zhang L, Zhang S, Ye H. Relationship between sarcopenia and cardiovascular diseases in the elderly: an overview. *Frontiers in Cardiovascular Medicine*. 2021;8:743710.
8. He J, Li H, Yao J, Wang Y. Prevalence of sarcopenia in patients with COPD through different musculature measurements: an updated meta-analysis and meta-regression. *Front Nutr*. 2023;10:1137371.
9. Sabatino A, Cuppari L, Stenvinkel P, Lindholm B, Avesani CM. Sarcopenia in chronic kidney disease: what have we learned so far? *J Nephrol*. 2021;34(4):1347-1372.
10. Mikolasevic I, Pavic T, Kanizaj TF, Bender DV, Domislovic V, Krznaric Z. Nonalcoholic fatty liver disease and sarcopenia: where do we stand? *Can J Gastroenterol Hepatol*. 2020;2020:8859719.
11. Fazzini B, Märkl T, Costas C, et al. The rate and assessment of muscle wasting during critical illness: a systematic review and meta-analysis. *Crit Care*. 2023;27(1):2.
12. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. *Nat Rev Endocrinol*. 2018;14(9):513-537.
13. Petermann-Rocha F, Balntzi V, Gray SR, et al. Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle*. 2022;13(1):86-99.
14. Hahm J-H, Nirmala FS, Ha TY, Ahn J. Nutritional approaches targeting mitochondria for the prevention of sarcopenia. *Nutrition Reviews*. 2023; nuad084. <https://doi.org/10.1093/nutrit/nuad084>
15. Norman K, Otten L. Financial impact of sarcopenia or low muscle mass—a short review. *Clin Nutr*. 2019;38(4):1489-1495.
16. Dent E, Morley JE, Cruz-Jentoft AJ, et al. International clinical practice guidelines for sarcopenia (ICFSR): screening, diagnosis and management. *J Nutr, Heal Aging*. 2018;22(10):1148-1161.
17. Sgrò P, Sansone M, Sansone A, et al. Physical exercise, nutrition and hormones: three pillars to fight sarcopenia. *Aging Male*. 2019;22(2):75-88.
18. Nishida A, Kubo K, Nihei H. Impaired muscle energy metabolism in uremia as monitored by 31P-NMR. *Nihon Jinzo Gakkai Shi*. 1991;33(1):65-73.
19. Taylor D, Kemp G, Thompson C, Radda G. Ageing: effects on oxidative function of skeletal muscle in vivo. *Mol Cell Biochem*. 1997;174(1-2):321-324.
20. Hyatt HW, Powers SK. Mitochondrial dysfunction is a common denominator linking skeletal muscle wasting due to disease, aging, and prolonged inactivity. *Antioxidants*. 2021;10(4):588.
21. Bellanti F, Buglio AL, Vendemiale G. Mitochondrial impairment in sarcopenia. *Biology*. 2021;10(1):31.
22. Chen X, Ji Y, Liu R, et al. Mitochondrial dysfunction: roles in skeletal muscle atrophy. *J Transl Med*. 2023;21(1):503.
23. Coen PM, Musci RV, Hinkley JM, Miller BF. Mitochondria as a target for mitigating sarcopenia. *Front Physiol*. 2019;9:1883.
24. Liu Z, Zhu C. Causal relationship between insulin resistance and sarcopenia. *Diabetol Metab Syndr*. 2023;15(1):46.
25. Paez HG, Pitzer CR, Alway SE. Age-related dysfunction in proteostasis and cellular quality control in the development of sarcopenia. *Cell*. 2023;12(2):249.
26. Antuña E, Cachán-Vega C, Bermejo-Millo JC, et al. Inflammaging: implications in sarcopenia. *Int J Mol Sci*. 2022;23(23):15039.
27. Zhang H, Qi G, Wang K, et al. Oxidative stress: roles in skeletal muscle atrophy. *Biochem Pharmacol*. 2023;214:115664.
28. Gungor O, Ulu S, Hasbal NB, Anker SD, Kalantar-Zadeh K. Effects of hormonal changes on sarcopenia in chronic kidney disease: where are we now and what can we do? *J Cachexia Sarcopenia Muscle*. 2021;12(6):1380-1392.
29. Day K, Shefer G, Shearer A, Yablonka-Reuveni Z. The depletion of skeletal muscle satellite cells with age is concomitant with reduced capacity of single progenitors to produce reserve progeny. *Dev Biol*. 2010;340(2):330-343.
30. Verdijk LB, Dirks ML, Snijders T, et al. Reduced satellite cell numbers with spinal cord injury and aging in humans. *Med Sci Sports Exerc*. 2012;44(12):2322-2330.
31. Verdijk LB, Snijders T, Drost M, Delhaas T, Kadi F, van Loon LJC. Satellite cells in human skeletal muscle; from birth to old age. *Age*. 2014;36(2):545-557.

32. Huo F, Liu Q, Liu H. Contribution of muscle satellite cells to sarcopenia. *Front Physiol.* 2022;13:892749.
33. Ciciliot S, Rossi AC, Dyar KA, Blaauw B, Schiaffino S. Muscle type and fiber type specificity in muscle wasting. *Int J Biochem Cell Biol.* 2013;45(10):2191-2199.
34. Arnold WD, Clark BC. Neuromuscular junction transmission failure in aging and sarcopenia: the nexus of the neurological and muscular systems. *Ageing Res Rev.* 2023;89:101966.
35. Lee M-K, Jeong HH, Kim M-J, Ryu H, Baek J, Lee B. Nutrients against glucocorticoid-induced muscle atrophy. *Food.* 2022;11(5):687.
36. Sato E, Mori T, Mishima E, et al. Metabolic alterations by indoxyl sulfate in skeletal muscle induce uremic sarcopenia in chronic kidney disease. *Sci Rep.* 2016;6(1):36618.
37. Russ DW, Kent-Braun JA. Is skeletal muscle oxidative capacity decreased in old age? *Sports Med.* 2004;34(4):221-229.
38. McGregor RA, Cameron-Smith D, Poppitt SD. It is not just muscle mass: a review of muscle quality, composition and metabolism during ageing as determinants of muscle function and mobility in later life. *Longev Heal.* 2014;3(1):9.
39. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell.* 2013;153(6):1194-1217.
40. Kim Y, Triolo M, Hood DA. Impact of aging and exercise on mitochondrial quality control in skeletal muscle. *Oxid Med Cell Longev.* 2017;2017:3165396.
41. Hood DA, Memme JM, Oliveira AN, Triolo M. Maintenance of skeletal muscle mitochondria in health, exercise, and aging. *Annu Rev Physiol.* 2019;81(1):19-41.
42. Harper C, Gopalan V, Goh J. Exercise rescues mitochondrial coupling in aged skeletal muscle: a comparison of different modalities in preventing sarcopenia. *J Transl Med.* 2021;19(1):71.
43. Powers SK, Morton AB, Ahn B, Smuder AJ. Redox control of skeletal muscle atrophy. *Free Radic Biol Med.* 2016;98:208-217.
44. Carmeli E, Coleman R, Reznick AZ. The biochemistry of aging muscle. *Exp Gerontol.* 2002;37(4):477-489.
45. Fulle S, Protasi F, Tano GD, et al. The contribution of reactive oxygen species to sarcopenia and muscle ageing. *Exp Gerontol.* 2004;39(1):17-24.
46. Doria E, Buonocore D, Focarelli A, Marzatico F. Relationship between human aging muscle and oxidative system pathway. *Oxid Med Cell Longev.* 2012;2012:830257.
47. Marzetti E, Calvani R, Cesari M, et al. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. *Int J Biochem Cell Biol.* 2013;45(10):2288-2301.
48. Baumann CW, Kwak D, Liu HM, Thompson LV. Age-induced oxidative stress: how does it influence skeletal muscle quantity and quality? *J Appl Physiol.* 2016;121(5):1047-1052.
49. Tiganis T. Reactive oxygen species and insulin resistance: the good, the bad and the ugly. *Trends Pharmacol Sci.* 2011;32(2):82-89.
50. Tan PL, Shavlakadze T, Grounds MD, Arthur PG. Differential thiol oxidation of the signaling proteins Akt, PTEN or PP2A determines whether Akt phosphorylation is enhanced or inhibited by oxidative stress in C2C12 myotubes derived from skeletal muscle. *Int J Biochem Cell Biol.* 2015;62:72-79.
51. Forrester SJ, Kikuchi DS, Hernandez MS, Xu Q, Griendling KK. Reactive oxygen species in metabolic and inflammatory signaling. *Circ Res.* 2018;122(6):877-902.
52. Davies KJ, Delsignore ME, Lin SW. Protein damage and degradation by oxygen radicals. II. Modification of amino acids. *J Biol Chem.* 1987;262(20):9902-9907.
53. Navarro-Yepes J, Burns M, Anandhan A, et al. Oxidative stress, redox signaling, and autophagy: cell death versus survival. *Antioxid Redox Signal.* 2014;21(1):66-85.
54. Dargelos E, Brulé C, Stuelsatz P, et al. Up-regulation of calcium-dependent proteolysis in human myoblasts under acute oxidative stress. *Exp Cell Res.* 2010;316(1):115-125.
55. Mecocci P, Fanó G, Fulle S, et al. Age-dependent increases in oxidative damage to DNA, lipids, and proteins in human skeletal muscle. *Free Radic Biol Med.* 1999;26(3-4):303-308.
56. Howard C, Ferrucci L, Sun K, et al. Oxidative protein damage is associated with poor grip strength among older women living in the community. *J Appl Physiol.* 2007;103(1):17-20.
57. Meng S-J, Yu L-J. Oxidative stress, molecular inflammation and sarcopenia. *Int J Mol Sci.* 2010;11(4):1509-1526.
58. Powers SK, Smuder AJ, Judge AR. Oxidative stress and disuse muscle atrophy. *Curr Opin Clin Nutr Metab Care.* 2012;15(3):240-245.
59. Dozio E, Vettoretti S, Lungarella G, Messa P, Romanelli MMC. Sarcopenia in chronic kidney disease: focus on advanced glycation end products as mediators and markers of oxidative stress. *Biomedicine.* 2021;9(4):405.
60. Langen RCJ, Schols AMWJ, Kelders MCJM, van der Velden JLJ, Wouters EFM, Janssen-Heininger YMW. Tumor necrosis factor- $\alpha$  inhibits myogenesis through redox-dependent and -independent pathways. *Am J Physiol Cell Physiol.* 2002;283(3):C714-C721.
61. Chen M, Wang Y, Deng S, Lian Z, Yu K. Skeletal muscle oxidative stress and inflammation in aging: focus on antioxidant and anti-inflammatory therapy. *Front Cell Dev Biol.* 2022;10:964130.
62. Damiano S, Muscariello E, Rosa GL, Maro MD, Mondola P, Santillo M. Dual role of reactive oxygen species in muscle function: can antioxidant dietary supplements counteract age-related sarcopenia? *Int J Mol Sci.* 2019;20(15):3815.
63. Konopka AR, Suer MK, Wolff CA, Harber MP. Markers of human skeletal muscle mitochondrial biogenesis and quality control: effects of age and aerobic exercise training. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences.* 2014;69(4):371-378.
64. Romanello V, Sandri M. Mitochondrial quality control and muscle mass maintenance. *Front Physiol.* 2016;6:422.
65. Chatzinikita E, Maridaki M, Palikaras K, Koutsilieris M, Philippou A. The role of mitophagy in skeletal muscle damage and regeneration. *Cell.* 2023;12(5):716.
66. Liesa M, Shirihai OS. Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. *Cell Metab.* 2013;17(4):491-506.
67. Sligar J, DeBruin DA, Saner NJ, Philp AM, Philp A. The importance of mitochondrial quality control for maintaining skeletal muscle function across health span. *Am J Physiol Cell Physiol.* 2022;322(3):C461-C467.
68. Karunadharma PP, Basisty N, Chiao YA, et al. Respiratory chain protein turnover rates in mice are highly heterogeneous but strikingly conserved across tissues, ages, and treatments. *FASEB J.* 2015;29(8):3582-3592.
69. Cuthbertson D, Smith K, Babraj J, et al. Anabolic signaling deficits underlie amino acid resistance of wasting, aging muscle. *FASEB J.* 2005;19(3):1-22.

70. Affourtit C. Mitochondrial involvement in skeletal muscle insulin resistance: a case of imbalanced bioenergetics. *Biochim Biophys Acta (BBA)-Bioenerg.* 2016;1857(10):1678-1693.
71. Buttgerief F, Brand MD. A hierarchy of ATP-consuming processes in mammalian cells. *Biochem J.* 1995;312(1):163-167.
72. Nisir RB, Affourtit C. Palmitate-induced changes in energy demand cause reallocation of ATP supply in rat and human skeletal muscle cells. *Biochim Biophys Acta (BBA)-Bioenerg.* 2016;1857(9):1403-1411.
73. Meyerspeer M, Boesch C, Cameron D, et al. 31P magnetic resonance spectroscopy in skeletal muscle: Experts' consensus recommendations. *NMR Biomed.* 2021;34(5):e4246.
74. Conley KE, Jubrias SA, Esselman PC. Oxidative capacity and ageing in human muscle. *J Physiol.* 2000;526(1):203-210.
75. Layec G, Haseler LJ, Richardson RS. Reduced muscle oxidative capacity is independent of O<sub>2</sub> availability in elderly people. *Age.* 2013;35(4):1183-1192.
76. Thompson CH, Kemp GJ, Taylor DJ, Ledingham JGG, Radda GK, Rajagopalan B. Effect of chronic uraemia on skeletal muscle metabolism in man. *Nephrol Dial Transplant.* 1993;8(3):218-222.
77. Tada H, Kato H, Misawa T, et al. 31P-nuclear magnetic resonance evidence of abnormal skeletal muscle metabolism in patients with chronic lung disease and congestive heart failure. *Eur Respir J.* 1992;5(2):163-169.
78. Khushu S, Rana P, Sekhri T, Sripathy G, Tripathi RP. Bioenergetic impairment in human calf muscle in thyroid disorders: a 31P MRS study. *Magn Reson Imaging.* 2010;28(5):683-689.
79. Tian Q, Mitchell BA, Zampino M, Fishbein KW, Spencer RG, Ferrucci L. Muscle mitochondrial energetics predicts mobility decline in well-functioning older adults: the baltimore longitudinal study of aging. *Aging Cell.* 2022;21(2):e13552.
80. Qaisar R, Pharaoh G, Bhaskaran S, et al. Restoration of sarcoplasmic reticulum Ca<sup>2+</sup> ATPase (SERCA) activity prevents age-related muscle atrophy and weakness in mice. *Int J Mol Sci.* 2020;22(1):37.
81. Fitzgerald LF, Christie AD, Kent JA. Heterogeneous effects of old age on human muscle oxidative capacity in vivo: a systematic review and meta-analysis. *Appl Physiol Nutr Metab.* 2016;41(11):1137-1145.
82. Conley KE, Jubrias SA, Cress ME, Esselman P. Exercise efficiency is reduced by mitochondrial uncoupling in the elderly. *Exp Physiol.* 2013;98(3):768-777.
83. Kemp GJ, Brindle KM. What do magnetic resonance-based measurements of pi→ATP flux tell us about skeletal muscle metabolism? *Diabetes.* 2012;61(8):1927-1934.
84. Kemp GJ, Ahmad RE, Nicolay K, Prompers JJ. Quantification of skeletal muscle mitochondrial function by 31P magnetic resonance spectroscopy techniques: a quantitative review. *Acta Physiologica.* 2015;213(1):107-144.
85. Liu Y, Gu Y, Yu X. Assessing tissue metabolism by phosphorous-31 magnetic resonance spectroscopy and imaging: a methodology review. *Quant Imaging Med Surg.* 2017;7(6):707-726.
86. Moinard C, Fontaine E. Direct or indirect regulation of muscle protein synthesis by energy status? *Clin Nutr.* 2021;40(4):1893-1896.
87. Cleasby ME, Jamieson PM, Atherton PJ. Insulin resistance and sarcopenia: mechanistic links between common co-morbidities. *J Endocrinol.* 2016;229(2):R67-R81.
88. Wang H, Huang WY, Zhao Y. Efficacy of exercise on muscle function and physical performance in older adults with sarcopenia: an updated systematic review and meta-analysis. *Int J Environ Res Public Heal.* 2022;19(13):8212.
89. Smith C, Woessner MN, Sim M, Levinger I. Sarcopenia definition: does it really matter? Implications for resistance training. *Ageing Res Rev.* 2022;78:101617.
90. Yoshimura Y, Wakabayashi H, Yamada M, Kim H, Harada A, Arai H. Interventions for treating sarcopenia: a systematic review and meta-analysis of randomized controlled studies. *J Am Méd Dir Assoc.* 2017;18(6):553.e1-553.e16.
91. Spiegeleer AD, Beckwée D, Bautmans I, Petrovic M, (BSGG) SGD group of the BS of G and G. Pharmacological interventions to improve muscle mass, muscle strength and physical performance in older people: an umbrella review of systematic reviews and meta-analyses. *Drugs Aging.* 2018;35(8):719-734.
92. Richter EA, Ruderman NB. AMPK and the biochemistry of exercise: implications for human health and disease. *Biochem J.* 2009;418(2):261-275.
93. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. *Nat Rev Mol Cell Biol.* 2012;13(4):251-262.
94. Mason S, Wadley GD. Skeletal muscle reactive oxygen species: a target of good cop/bad cop for exercise and disease. *Redox Rep.* 2014;19(3):97-106.
95. Shao D, Oka S, Liu T, et al. A redox-dependent mechanism for regulation of AMPK activation by Thioredoxin1 during energy starvation. *Cell Metab.* 2014;19(2):232-245.
96. Hinchey EC, Gruszczuk AV, Willows R, et al. Mitochondria-derived ROS activate AMP-activated protein kinase (AMPK) indirectly. *J Biol Chem.* 2018;293(44):17208-17217.
97. Lesmana R, Parameswari C, Mandagi GF, et al. The role of exercise-induced reactive oxygen species (ROS) hormesis in aging: friend or foe. *Cell Physiol Biochem.* 2022;56(6):692-706.
98. Merry TL, Ristow M. Mitohormesis in exercise training. *Free Radic Biol Med.* 2016;98:123-130.
99. Turner DL, Hoppeler H, Claassen H, et al. Effects of endurance training on oxidative capacity and structural composition of human arm and leg muscles. *Acta Physiol Scand.* 1997;161(4):459-464.
100. Cannon DT, Bimson WE, Hampson SA, et al. Skeletal muscle ATP turnover by 31P magnetic resonance spectroscopy during moderate and heavy bilateral knee extension. *J Physiol.* 2014;592(23):5287-5300.
101. Rzanny R, Stutzig N, Hiepe P, Gussew A, Thorhauer H-A, Reichenbach JR. The reproducibility of different metabolic markers for muscle fiber type distributions investigated by functional 31P-MRS during dynamic exercise. *Zeitschrift für Medizinische Physik.* 2016;26(4):323-338.
102. Sleight A, Savage DB, Williams GB, et al. 31P magnetization transfer measurements of Pi→ATP flux in exercising human muscle. *J Appl Physiol.* 2016;120(6):649-656.
103. Proctor DN, Sinning WE, Walro JM, Sieck GC, Lemon PW. Oxidative capacity of human muscle fiber types: effects of age and training status. *J Appl Physiol.* 1995;78(6):2033-2038.
104. Balan E, Schwalm C, Naslain D, Nielens H, Francaux M, Deldicque L. Regular endurance exercise promotes fission, mitophagy, and oxidative phosphorylation in human skeletal muscle independently of age. *Front Physiol.* 2019;10:1088.

105. Short KR, Vittone JL, Bigelow ML, et al. Impact of aerobic exercise training on age-related changes in insulin sensitivity and muscle oxidative capacity. *Diabetes*. 2003;52(8):1888-1896.
106. Menshikova EV, Ritov VB, Fairfull L, Ferrell RE, Kelley DE, Goodpaster BH. Effects of exercise on mitochondrial content and function in aging human skeletal muscle. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. 2006;61(6):534-540.
107. Broskey NT, Greggio C, Boss A, et al. Skeletal muscle mitochondria in the elderly: effects of physical fitness and exercise training. *J Clin Endocrinol Metab*. 2014;99(5):1852-1861.
108. Freyssenet D, Berthon P, Denis C. Mitochondrial biogenesis in skeletal muscle in response to endurance exercises. *Arch Physiol Biochem*. 1996;104(2):129-141.
109. Tezze C, Romanello V, Desbats MA, et al. Age-associated loss of OPA1 in muscle impacts muscle mass, metabolic homeostasis, systemic inflammation, and epithelial senescence. *Cell Metab*. 2017;25(6):1374-1389.e6.
110. Axelrod CL, Fealy CE, Mulya A, Kirwan JP. Exercise training remodels human skeletal muscle mitochondrial fission and fusion machinery towards a pro-elongation phenotype. *Acta Physiologica*. 2019;225(4):e13216.
111. Guan Y, Drake JC, Yan Z. Exercise-induced mitophagy in skeletal muscle and heart. *Exerc Sport Sci Rev*. 2019;47(3):151-156.
112. Conley KE, Jubrias SA, Cress ME, Esselman PC. Elevated energy coupling and aerobic capacity improves exercise performance in endurance-trained elderly subjects. *Exp Physiol*. 2013;98(4):899-907.
113. Chen H, Chung Y, Chen Y, Ho S, Wu H. Effects of different types of exercise on body composition, muscle strength, and IGF-1 in the elderly with sarcopenic obesity. *J Am Geriatr Soc*. 2017;65(4):827-832.
114. Fritzen AM, Andersen SP, Qadri KAN, et al. Effect of aerobic exercise training and deconditioning on oxidative capacity and muscle mitochondrial enzyme machinery in young and elderly individuals. *J Clin Med*. 2020;9(10):3113.
115. Chrøis KM, Dohlmann TL, Søgaard D, et al. Mitochondrial adaptations to high intensity interval training in older females and males. *Eur J Sport Sci*. 2020;20(1):135-145.
116. Zhu Y, Zhou X, Zhu A, Xiong S, Xie J, Bai Z. Advances in exercise to alleviate sarcopenia in older adults by improving mitochondrial dysfunction. *Front Physiol*. 2023;14:1196426.
117. Marcos-Pardo PJ, Orquín-Castrillón FJ, Gea-García GM, et al. Effects of a moderate-to-high intensity resistance circuit training on fat mass, functional capacity, muscular strength, and quality of life in elderly: a randomized controlled trial. *Sci Rep*. 2019;9(1):7830.
118. Bårdstu HB, Andersen V, Fimland MS, et al. Effectiveness of a resistance training program on physical function, muscle strength, and body composition in community-dwelling older adults receiving home care: a cluster-randomized controlled trial. *European Review of Aging and Physical Activity*. 2020;17(1):11.
119. Cervantes JM d C, Cervantes MHM, Torres RM. Effect of a resistance training program on sarcopenia and functionality of the older adults living in a nursing home. *J Nutr, Heal Aging*. 2019;23(9):829-836.
120. Vikberg S, Sörlén N, Brandén L, et al. Effects of resistance training on functional strength and muscle mass in 70-year-old individuals with pre-sarcopenia: a randomized controlled trial. *J Am Méd Dir Assoc*. 2019;20(1):28-34.
121. Parise G, Brose AN, Tarnopolsky MA. Resistance exercise training decreases oxidative damage to DNA and increases cytochrome oxidase activity in older adults. *Exp Gerontol*. 2005;40(3):173-180.
122. Porter C, Reidy PT, Bhattarai N, Sidossis LS, Rasmussen BB. Resistance exercise training alters mitochondrial function in human skeletal muscle. *Med Sci Sports Exerc*. 2015;47(9):1922-1931.
123. Melov S, Tarnopolsky MA, Beckman K, Felkey K, Hubbard A. Resistance exercise reverses aging in human skeletal muscle. *PLoS One*. 2007;2(5):e465.
124. Mesquita PHC, Lamb DA, Parry HA, et al. Acute and chronic effects of resistance training on skeletal muscle markers of mitochondrial remodeling in older adults. *Physiol Rep*. 2020;8(15):e14526.
125. Jubrias SA, Esselman PC, Price LB, Cress ME, Conley KE. Large energetic adaptations of elderly muscle to resistance and endurance training. *J Appl Physiol*. 2001;90(5):1663-1670.
126. Hargreaves M, Spriet LL. Skeletal muscle energy metabolism during exercise. *Nat Metab*. 2020;2(9):817-828.
127. He F, Li J, Liu Z, Chuang C-C, Yang W, Zuo L. Redox mechanism of reactive oxygen species in exercise. *Front Physiol*. 2016;7:486.
128. Plotkin DL, Roberts MD, Haun CT, Schoenfeld BJ. Muscle fiber type transitions with exercise training: shifting perspectives. *Sports*. 2021;9(9):127.
129. Wang L, Mascher H, Psilander N, Blomstrand E, Sahlin K. Resistance exercise enhances the molecular signaling of mitochondrial biogenesis induced by endurance exercise in human skeletal muscle. *J Appl Physiol*. 2011;111(5):1335-1344.
130. Irving BA, Lanza IR, Henderson GC, Rao RR, Spiegelman BM, Nair KS. Combined training enhances skeletal muscle mitochondrial oxidative capacity independent of age. *J Clin Endocrinol Metab*. 2015;100(4):1654-1663.
131. Cogley JN, Bartlett JD, Kayani A, et al. PGC-1 $\alpha$  transcriptional response and mitochondrial adaptation to acute exercise is maintained in skeletal muscle of sedentary elderly males. *Biogerontology*. 2012;13(6):621-631.
132. Watson EL, Baker LA, Wilkinson TJ, et al. Reductions in skeletal muscle mitochondrial mass are not restored following exercise training in patients with chronic kidney disease. *FASEB J*. 2020;34(1):1755-1767.
133. Hou V, Madden K. Assessing the effects of dietary protein supplementation on sarcopenia in community-dwelling older adults. *Can Geriatr J*. 2022;25(4):390-403.
134. Bird JK, Troesch B, Warnke I, Calder PC. The effect of long chain omega-3 polyunsaturated fatty acids on muscle mass and function in sarcopenia: a scoping systematic review and meta-analysis. *Clin Nutr ESPEN*. 2021;46:73-86.
135. Gkekakos NK, Anagnostis P, Siolos P, et al. The effect of vitamin D supplementation on sarcopenia indices: a systematic review and meta-analysis of randomized controlled trials. *Endocrine Abstracts*. 2019;63:98. doi:10.1530/endoabs.63.p98
136. Salucci S, Falcieri E. Polyphenols and their potential role in preventing skeletal muscle atrophy. *Nutr Res*. 2020;74:10-22.
137. Alamir T, Shafie Z, Adwani S. Antioxidant role of vitamin D and its correlation with vitamin D deficiency in adults: a systematic review. *Int J Med Dev Ctries*. 2021;5:948-953.

138. Tsao R. Chemistry and biochemistry of dietary polyphenols. *Nutrients*. 2010;2(12):1231-1246.
139. Oppedisano F, Macri R, Gliozzi M, et al. The anti-inflammatory and antioxidant properties of n-3 PUFAs: their role in cardiovascular protection. *Biomedicine*. 2020;8(9):306.
140. Wagenmakers AJM. Skeletal muscle metabolism in exercise and diabetes. *Adv Exp Med Biol*. 1998;441:307-319.
141. Volpi E, Ferrando AA, Yeckel CW, Tipton KD, Wolfe RR. Exogenous amino acids stimulate net muscle protein synthesis in the elderly. *J Clin Invest*. 1998;101(9):2000-2007.
142. Princiotta MF, Finzi D, Qian S-B, et al. Quantitating protein synthesis, degradation, and endogenous antigen processing. *Immunity*. 2003;18(3):343-354.
143. Gielen E, Beckwée D, Delaere A, et al. Nutritional interventions to improve muscle mass, muscle strength, and physical performance in older people: an umbrella review of systematic reviews and meta-analyses. *Nutr Rev*. 2021;79(2):121-147.
144. Wilkes EA, Selby AL, Atherton PJ, et al. Blunting of insulin inhibition of proteolysis in legs of older subjects may contribute to age-related sarcopenia. *Am J Clin Nutr*. 2009;90(5):1343-1350.
145. Rennie MJ. Anabolic resistance: the effects of aging, sexual dimorphism, and immobilization on human muscle protein turnover. This paper is one of a selection of papers published in this special issue, entitled 14th International Biochemistry of Exercise Conference Muscles as Molecular and Metabolic Machines, and has undergone the Journals usual peer review process. *Appl Physiol Nutr Metab*. 2009;34(3):377-381.
146. Burd NA, Gorissen SH, van Loon LJC. Anabolic resistance of muscle protein synthesis with aging. *Exerc Sport Sci Rev*. 2013;41(3):169-173.
147. Moore DR, Churchward-Venne TA, Witard O, et al. Protein ingestion to stimulate myofibrillar protein synthesis requires greater relative protein intakes in healthy older versus younger men. *J Gerontol A: Biol Sci Med Sci*. 2015;70(1):57-62.
148. Deutz NEP, Bauer JM, Barazzoni R, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN expert group. *Clin Nutr*. 2014;33(6):929-936.
149. Hoffman JR, Falvo MJ. Protein—which is best? *J Sports Sci Med*. 2004;3(3):118-130.
150. Du M, Shen QW, Zhu MJ, Ford SP. Leucine stimulates mammalian target of rapamycin signaling in C2C12 myoblasts in part through inhibition of adenosine monophosphate-activated protein kinase1. *J Anim Sci*. 2007;85(4):919-927.
151. Wilson GJ, Layman DK, Moulton CJ, et al. Leucine or carbohydrate supplementation reduces AMPK and eEF2 phosphorylation and extends postprandial muscle protein synthesis in rats. *American Journal of Physiology. Endocrinology and Metabolism*. 2011;301(6):E1236-E1242.
152. Wall BT, Hamer HM, de Lange A, et al. Leucine co-ingestion improves post-prandial muscle protein accretion in elderly men. *Clin Nutr*. 2013;32(3):412-419.
153. Gannon NP, Vaughan RA. Leucine-induced anabolic-catabolism: two sides of the same coin. *Amino Acids*. 2016;48(2):321-336.
154. Son SM, Park SJ, Lee H, et al. Leucine signals to mTORC1 via its metabolite acetyl-coenzyme A. *Cell Metab*. 2019;29(1):192-201.e7.
155. Rennie MJ, Bohé J, Smith K, Wackerhage H, Greenhaff P. Branched-chain amino acids as fuels and anabolic signals in human muscle. *J Nutr*. 2006;136(1):264S-268S.
156. Hinkle JS, Rivera CN, Vaughan RA. Branched-chain amino acids and mitochondrial biogenesis: an overview and mechanistic summary. *Mol Nutr Food Res*. 2022;66(20):2200109.
157. Wilkinson SB, Phillips SM, Atherton PJ, et al. Differential effects of resistance and endurance exercise in the fed state on signalling molecule phosphorylation and protein synthesis in human muscle. *J Physiol*. 2008;586(15):3701-3717.
158. Neinst M, Murashige D, Arany Z. Branched chain amino acids. *Annu Rev Physiol*. 2018;81(1):1-26.
159. Brook MS, Wilkinson DJ, Phillips BE, et al. Skeletal muscle homeostasis and plasticity in youth and ageing: impact of nutrition and exercise. *Acta Physiologica*. 2016;216(1):15-41.
160. Brosnan JT, Brosnan ME. Branched-chain amino acids: enzyme and substrate regulation 1–3. *J Nutr*. 2006;136(1):207S-211S.
161. Knapik J, Meredith C, Jones B, Fielding R, Young V, Evans W. Leucine metabolism during fasting and exercise. *J Appl Physiol*. 1991;70(1):43-47.
162. el-Khoury AE, Forslund A, Olsson R, et al. Moderate exercise at energy balance does not affect 24-h leucine oxidation or nitrogen retention in healthy men. *American Journal of Physiology. Endocrinology and Metabolism*. 1997;273(2):E394-E407.
163. Bowtell JL, Leese GP, Smith K, et al. Modulation of whole body protein metabolism, during and after exercise, by variation of dietary protein. *J Appl Physiol*. 1998;85(5):1744-1752.
164. Biolo G, Maggi SP, Williams BD, Tipton KD, Wolfe RR. Increased rates of muscle protein turnover and amino acid transport after resistance exercise in humans. *American Journal of Physiology. Endocrinology and Metabolism*. 1995;268(3):E514-E520.
165. Phillips SM, Tipton KD, Aarsland A, Wolf SE, Wolfe RR. Mixed muscle protein synthesis and breakdown after resistance exercise in humans. *Am J Physiol Endocrinol Metab*. 1997;273(1):E99-E107.
166. Spoto B, Pisano A, Zoccali C. Insulin resistance in chronic kidney disease: a systematic review. *American Journal of Physiology - Renal Physiology*. 2016;311(6):F1087-F1108.
167. Ristow M, Zarse K, Oberbach A, et al. Antioxidants prevent health-promoting effects of physical exercise in humans. *Proc Natl Acad Sci*. 2009;106(21):8665-8670.
168. Iolascon G, Moretti A, de Sire A, Toro G, Gimigliano F. Pharmacological therapy of sarcopenia: past, present and future. *Clin Cases Miner Bone Metab*. 2018;15:407-415.
169. Kim Y-C, Ki S-W, Kim H, Kang S, Kim H, Go G. Recent advances in nutraceuticals for the treatment of sarcopenic obesity. *Nutrients*. 2023;15(17):3854.
170. Kwak JY, Kwon K-S. Pharmacological interventions for treatment of sarcopenia: current status of drug development for sarcopenia. *Ann Geriatr Med Res*. 2019;23(3):98-104.
171. Sinha-Hikim I, Roth SM, Lee MI, Bhasin S. Testosterone-induced muscle hypertrophy is associated with an increase in satellite cell number in healthy, young men. *American Journal of Physiology. Endocrinology and Metabolism*. 2003;285(1):E197-E205.
172. Sinha-Hikim I, Artaza J, Woodhouse L, et al. Testosterone-induced increase in muscle size in healthy young men is associated with muscle fiber hypertrophy. *American Journal of Physiology. Endocrinology and Metabolism*. 2002;283(1):E154-E164.

173. Singh R, Artaza JN, Taylor WE, Gonzalez-Cadavid NF, Bhasin S. Androgens stimulate myogenic differentiation and inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway. *Endocrinology*. 2003;144(11):5081-5088.
174. Subramaniam K, Fallon K, Ruut T, et al. Infliximab reverses inflammatory muscle wasting (sarcopenia) in Crohn's disease. *Aliment Pharmacol Ther*. 2015;41(5):419-428.
175. Suh J, Lee Y-S. Myostatin inhibitors: panacea or predicament for musculoskeletal disorders? *J Bone Metab*. 2020;27(3):151-165.
176. Briocche T, Kireev RA, Cuesta S, et al. Growth hormone replacement therapy prevents sarcopenia by a dual mechanism: improvement of protein balance and of antioxidant defenses. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. 2014;69(10):1186-1198.
177. Kim MJ, Morley JE. The hormonal fountains of youth: myth or reality? *J Endocrinol Invest*. 2005;28(11 Suppl Proceedings):5-14.
178. Molfino A, Amabile MI, Fanelli FR, Muscaritoli M. Novel therapeutic options for cachexia and sarcopenia. *Expert Opin Biol Ther*. 2016;16(10):1239-1244.
179. Molfino A, Gioia G, Muscaritoli M. The hunger hormone ghrelin in cachexia. *Expert Opin Biol Ther*. 2013;13(4):465-468.
180. Pietra C, Takeda Y, Tazawa-Ogata N, et al. Anamorelin HCl (ONO-7643), a novel ghrelin receptor agonist, for the treatment of cancer anorexia-cachexia syndrome: preclinical profile. *J Cachexia Sarcopenia Muscle*. 2014;5(4):329-337.
181. Fujii C, Miyashita K, Mitsuishi M, et al. Treatment of sarcopenia and glucose intolerance through mitochondrial activation by 5-aminolevulinic acid. *Sci Rep*. 2017;7(1):4013.
182. Murphy MP, Smith RAJ. Drug delivery to mitochondria: the key to mitochondrial medicine. *Adv Drug Deliv Rev*. 2000;41(2):235-250.
183. Armstrong JS. Mitochondrial medicine: pharmacological targeting of mitochondria in disease. *Br J Pharmacol*. 2007;151(8):1154-1165.
184. Almikhlafl MA, Karami MM, Jana A, et al. Mitochondrial medicine: a promising therapeutic option against various neurodegenerative disorders. *Curr Neuropharmacol*. 2023;21(5):1165-1183.
185. Bottani E, Brunetti D. Advances in mitochondria-targeted drug delivery. *Pharmaceutics*. 2023;15(8):2089.
186. Khan T, Waseem R, Zehra Z, et al. Mitochondrial dysfunction: pathophysiology and mitochondria-targeted drug delivery approaches. *Pharmaceutics*. 2022;14(12):2657.
187. Oliveira AN, Richards BJ, Slavin M, Hood DA. Exercise is muscle mitochondrial medicine. *Exerc Sport Sci Rev*. 2021;49(2):67-76.
188. Bellanti F, Buglio AL, Vendemiale G. Muscle delivery of mitochondria-targeted drugs for the treatment of sarcopenia: rationale and perspectives. *Pharmaceutics*. 2022;14(12):2588.
189. Pin F, Huot JR, Bonetto A. The mitochondria-targeting agent MitoQ improves muscle atrophy, weakness and oxidative metabolism in C26 tumor-bearing mice. *Front Cell Dev Biol*. 2022;10:861622.
190. Liu Y, Perumal E, Bi X, Wang Y, Ding W. Potential mechanisms of uremic muscle wasting and the protective role of the mitochondria-targeted antioxidant Mito-TEMPO. *Int Urol Nephrol*. 2020;52(8):1551-1561.
191. Supinski GS, Wang L, Schroder EA, Callahan LAP. MitoTEMPOL, a mitochondrial targeted antioxidant, prevents sepsis-induced diaphragm dysfunction. *Am J Physiol Lung Cell Mol Physiol*. 2020;319(2):L228-L238.
192. Campbell MD, Duan J, Samuelson AT, et al. Improving mitochondrial function with SS-31 reverses age-related redox stress and improves exercise tolerance in aged mice. *Free Radic Biol Med*. 2019;134:268-281.
193. Turkel I, Ozerklig B, Yilmaz M, Ulger O, Kubat GB, Tuncer M. Mitochondrial transplantation as a possible therapeutic option for sarcopenia. *J Mol Med*. 2023;101(6):645-669.
194. Orfany A, Arriola CG, Doulamis IP, et al. Mitochondrial transplantation ameliorates acute limb ischemia. *J Vasc Surg*. 2020;71(3):1014-1026.
195. Kim MJ, Hwang JW, Yun C-K, Lee Y, Choi Y-S. Delivery of exogenous mitochondria via centrifugation enhances cellular metabolic function. *Sci Rep*. 2018;8(1):3330.
196. Kim MJ, Lee JM, Min K, et al. Xenogeneic transplantation of mitochondria induces muscle regeneration in an in vivo rat model of dexamethasone-induced atrophy. *J Muscle Res Cell Motil*. 2023. <https://doi.org/10.1007/s10974-023-09643-7>
197. Alway SE, Paez HG, Pitzer CR, et al. Mitochondria transplant therapy improves regeneration and restoration of injured skeletal muscle. *J Cachexia Sarcopenia Muscle*. 2023;14(1):493-507.

**How to cite this article:** Affourtit C, Carré JE. Mitochondrial involvement in sarcopenia. *Acta Physiol*. 2024;00:e14107. doi:[10.1111/apha.14107](https://doi.org/10.1111/apha.14107)