Underpin Sarcopenia, Cardiovascular and Metabolic Diseases

Subjects: Physiology

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Worldwide, the main reason for all-cause mortality is attributed to non-communicable diseases, namely, cardiovascular disease (CVD) and metabolic diseases (MDs). CVD refers to conditions affecting the heart and blood vessels, such as coronary artery disease, heart failure and hypertension. MDs refer to disorders of processing nutrients and the use of energy. These conditions can include diabetes, obesity and metabolic syndrome, among others. Both CVD and MDs can have serious consequences, including heart attacks, stroke and organ damage. CVD remains the leading cause of death worldwide.

Keywords: aerobic training ; behaviour change ; cardiovascular disease ; metabolic diseases

1. The Role of Mitochondria in Cellular Processes and Substrate Utilisation and Its Implications for Sarcopenia, Insulin Resistance and Age-Related Muscle Dysfunction

Metabolic diseases are often underpinned by the interrelated pattern of metabolic abnormalities such as atherogenic dyslipidaemia, insulin resistance (hyperglycaemia and hyperinsulinaemia), abdominal obesity and inflammation [1][2]. In this following section, the potential mechanisms that intrinsically link skeletal muscle dysfunction, MDs and ageing are explored.

Mitochondria are crucial for diverse cellular processes, including substrate utilisation, calcium homeostasis, cell proliferation, quality control (e.g., fussion, fission and mitophagy) and apoptosis [3][4]. Mitochondrial dysfunction compromises cell homeostasis and exercise capacity and is a central mediator in the pathogenesis of sarcopenia [3]. However, the molecular basis of the relationship between mitochondrial dysfunction and sarcopenia is multifactorial and poorly understood. Human muscle biopsies have established that the mitochondrial content, measured directly using transmission electron microscopy, is lower in the skeletal muscle of older individuals than in young individuals [5][6], possibly due to differences in the size [7] or number of (subsarcolemmal) mitochondria [6]. As peak oxygen uptake is strongly related to skeletal muscle mitochondrial content in older individuals [8], a reduced content may restrict the performance of daily living tasks. Mitochondrial enzyme activities in β-oxidation (e.g., β-hydroxyacyl-CoA dehydrogenase), tricarboxylic acid (e.g., citrate synthase) and respiratory chain pathways (e.g., succinate dehydrogenase and cytochrome C oxidase) are also lower in the skeletal muscle of older individuals than in young individuals [6][9][10][11]. These findings are accompanied by a lower in vivo oxidative capacity [5][12] and the uncoupling of adenosine triphosphate resynthesis to oxygen consumption [13]. The dual inferiorities of lower mitochondrial content and oxidative capacity are supported by a reduced expression of genes in the tricarboxylic acid and respiratory chain pathways [14][15], mitochondrial ribosomes [14] and in vivo mitochondrial protein synthesis rates with age [16].

Middle-aged patients with obesity and type II diabetes (TIID) also have lower mitochondrial content and size in their skeletal muscle compared to lean age-matched controls, measured using transmission electron microscopy [17][18][19]. This is accompanied by lower in vitro oxidative capacity and respiratory enzyme activity [17][18][19]. Furthermore, in vivo oxidative capacity is impaired in older patients with TIID [20][21], which is linked to lower basal and maximal mitochondrial respiration compared to age-matched controls [21]. Thus, lower mitochondrial function is not only important in the development of sarcopenia but is also suggested to be a contributing factor to the development of insulin resistance [22]. However, some studies that used transmission electron microscopy [23] or citrate synthase activity as a strong biomarker of mitochondrial content [24] reported no difference in the mitochondrial content between middle-aged and older patients with TIID and controls [25][26]. As a result, it is unclear whether a lower mitochondrial content occurs in human skeletal muscle with insulin resistance. Nevertheless, evidence suggests that the skeletal muscle mitochondrial content is

correlated with markers of insulin resistance in ageing [27] and TIID [17][18][19], but causation cannot be assumed. Lower mitochondrial respiratory function in the skeletal muscle of patients with TIID compared with controls has also been reported in some, but not all studies, as previously reviewed [28]. The reason for this discrepancy remains unclear, but it may be related to differences in measurement techniques, the normalisation of the respiratory function to the mitochondrial content and/or the physical activity status of the participants [28].

Mitochondria have numerous functions, including the generation of adenosine triphosphate from the oxidation of carbohydrate and fat. Lipid droplets, which store fatty acids such as triacylglycerol, can be in physical contact with the mitochondrial membrane in the subsarcolemmal and intermyofibrillar regions of human skeletal muscle [29]. The attachment of lipid droplets to mitochondria facilitates the channelling of lipid droplet-derived fatty acids to the mitochondria for oxidation based on the energy needs of the cell [30]. Compared to younger individuals, the intramyocellular lipid droplet size and content are elevated in older adults [6] and in individuals with TIID compared to controls [23][29]. Region-specific lipid droplet morphology may be important in ageing and MDs, as the subsarcolemmal lipid droplet size is larger in older individuals [6] and in patients with TIID compared to controls [23][31]. It is worth noting the excessive accumulation of very large subsarcolemmal lipid droplets in muscle fibres with a low subsarcolemmal mitochondrial content in patients with TIID. This may be important, as larger subsarcolemmal lipid droplets have been linked to reduced insulin sensitivity [23][32].

Increased plasma fatty acid uptake and decreased fatty acid oxidation may contribute to the accumulation of intramuscular lipid droplets [28]. A lower mitochondrial content correlates with lower fasting fat oxidation [19], and a negative association between age and fatty acid oxidation in human skeletal muscle primary myotubes has been reported [33]. This finding is in line with lower rates of whole-body fat oxidation rates observed at rest [34][35] and during endurance exercise at the same absolute and relative exercise intensity in older individuals compared to young individuals [36]. Alterations in substrate utilisation with ageing are distinct from those in obesity and TIID. In individuals with obesity, fat oxidation is lower under fasting conditions compared to lean controls [37]. However, the insulin-mediated inhibition of fat oxidation and a consequent switch towards carbohydrate oxidation are impaired in obesity and TIID [37][38]. Individuals with obesity and impaired glucose tolerance exhibit higher rates of fat oxidation and blunted increases in carbohydrate oxidation when transitioning from rest to exercise compared to controls [39][40]. Mitochondria are thought to be functional components in adapting substrate utilisation to substrate availability and energetic demand, termed metabolic flexibility [41]. However, metabolic inflexibility may occur when there is a mismatch between fatty acid supply, uptake and oxidation in skeletal muscle [42][43], leading to the accumulation of fatty acid metabolites that can cause insulin resistance and potentially mitochondrial dysfunction [44].

2. The Role of Lipid Metabolism and Adipose Tissue Dysfunction in Metabolic Disorders and Cardiovascular Disease

In healthy adipose tissue, excess energy is primarily stored in subcutaneous adipose tissue. However, lipid storage can also occur in other tissues, including visceral adipose tissue visceral adipose tissue, which can lead to inflammation over time. With dysfunctional adipose tissue as observed with MDs and ageing [45], there may be a lipid spillover, which is deposited as visceral adipose tissue and a variety of organs, including muscle tissue [46]. Mendelian randomisation has demonstrated a causal effect of visceral adipose tissue on MDs (hypertension, heart attack/angina, T2D and hyperlipidaemia) by identifying 102 novel loci (i.e., genes) associated with visceral adipose tissue [47]. Visceral adipose tissue has a higher lipolytic rate compared to subcutaneous adipose tissue, which is attributed to the heightened effect of pro-lipolytic catecholamines and reduced effect of anti-lipolytic insulin [46][48]. Consequently, increased lipolysis in visceral adipose tissue leads to a higher flux of free fatty acids to the liver, ultimately resulting in the elevated synthesis of very-low-density lipoprotein and hepatic insulin resistance [48]. Increased levels of very-low-density lipoprotein and chylomicrons create greater competition for lipoprotein lipase, allowing for greater cholesterol ester transfer protein activity with low-density lipoprotein (LDL). Hepatic lipase has a higher affinity for the now triglyceride-enriched LDL, triggering small-dense LDL (sdLDL) production [49]. The prevalence of sdLDL particles underpins atherogenic dyslipidaemia along with high triglyceride levels, and low levels of high-density lipoprotein cholesterol (HDL-C) and are highly associated with increased CVD risk [1][2].

Lipoproteins come in different sizes, densities and lipid content [50]. Two phenotypes, A and B, have been identified to indicate CVD risk [51]; phenotype A has more large and buoyant LDL (lbLDL), while phenotype B has more sdLDL [50][51], which is associated with low HDL-C, high triglycerides levels and metabolic diseases [52][53]. Numerous epidemiological studies have confirmed the reliability of LDL-C as an indicator of CVD risk and that LDL is a causative factor of CVD [54][55][56]. In cases where there is discordance between the two measures, the LDL particle (LDL-P) number may better estimate the CVD risk than LDL-C [57]. When LDL-P is greater than LDL-C, it shows a greater association with CVD

events and markers of metabolic health [57][58]. Circulating sdLDL particles have a higher risk of CVD events compared to larger and buoyant lbLDL particles [50][52] because an sdLDL particle has less cholesterol than an lbLDL particle, which leads to a greater number of sdLDL particles when cholesterol is equal [58].

Elevated triglyceride concentrations are associated with at least a 2-fold increase in CVD and mortality risk [59][60]; however, adjusting for HDL-C levels reduces this risk [54]. Although higher HDL-C levels are associated with reduced CVD risk [54][55], therapies that increase HDL-C do not reduce CVD risk [61][62]. HDL, through reverse cholesterol transport, carries cholesterol to the liver for removal and exerts anti-inflammatory effects on peripheral tissues, including arterial lesions [63][64]. Cholesterol efflux from macrophages may offer atheroprotection and is inversely associated with CVD independent of HDL-C concentrations [65][66]. Therefore, the functionality of HDL rather than HDL-C may have a more causal relationship with CVD [67]. Exercise increases HDL-C concentrations in a dose-response manner and has the potential to improve the anti-inflammatory effects and cholesterol efflux capacity of HDL [68]. Triglycerides alone are unlikely to cause atherosclerosis; however, they may act as a marker for triglyceride-rich lipoproteins (TRLs) rich in cholesterol, which are more efficient contributors to atherosclerosis [69][70]. For example, TRLs can enter the arterial intima and undergo direct phagocytosis by macrophages, contributing to foam cell formation, inflammation and atherosclerotic plaques [69][70]. In addition to being involved in lipid storage, mobilisation and lipoprotein metabolism, adipocytes are also endocrine tissues that release cytokines and adipokines [71]. An increase in visceral adipose tissue and atherogenic dyslipidaemia leads to a pro-inflammatory state characterised by elevated C-reactive protein and tumour necrosis factor-α concentrations that are associated with sarcopenia and MDs [72][73]. Given these mechanisms, practitioners should prioritise interventions that can improve HDL functionality, reduce visceral adipose tissue, and improve atherogenic dyslipidaemia, such as exercise and dietary modifications.

3. Dysfunctional Cellular Metabolism and Insulin Resistance: Implications for Cardiovascular and Metabolic Diseases

This pro-inflammatory state and elevated supply of free fatty acids to the vascular tissues lead to degenerative changes in the extracellular matrix, leading to endothelial insulin resistanceand dysfunction and ultimately hypertension [74]. Insulin resistance of the endothelial cells increases vascular tone due to the disruption of the balance of vasodilators (nitric oxide, prostacyclin) and vasoconstrictors (endothelin, angiotensin), contributing to vascular stiffness [75] and potentially reducing insulin and nutrient delivery to the muscle fibres [76]. Diminished insulin PI3K/Akt signalling in vascular tissue leads to a reduction in nitric oxide production via blunted endothelial nitric oxide synthase action [77]. Consequently, intracellular Ca2+ concentrations remain elevated in vascular smooth muscle cells, allowing vascular contractions to continue, thus limiting the dilation of vascular tissues and increasing vascular tone [77]. Conversely, endothelin-1 production continues via insulin-dependent mitogen-activated protein kinase signalling, leading to vasoconstriction [78]. A reduction in tissue perfusion, such as in skeletal muscle, can lead to a reduction in insulin and nutrient availability and therefore could have consequences for the maintenance of muscle mass and blood glucose clearance with age [76]. Furthermore, along with mitochondrial dysfunction, insulin resistance and prohypertensive factors also stimulate reactive oxygen species, triggering downstream signalling that leads to vascular dysfunction and endothelium permeability, thus contributing to the development of atherosclerosis [79][80].

Dysfunctional cellular metabolism, characterised by lipotoxicity, inflammation, oxidative stress and mitochondrial dysfunction, is implicated in the development of insulin-resistant tissue [81][82], which is a key feature of CVD and MDs [83][84][85]. In healthy insulin-sensitive tissue, insulin binds to the insulin receptor, thus activating the key multifunctional protein kinase Akt, elevating anabolic signalling and reducing catabolic signalling [86]. The activation of Akt initiates downstream signalling, resulting in GLUT4 trafficking and fusion with the cell membrane, allowing cellular glucose uptake [87]. However, within insulin-resistant tissues, this signalling cascade is diminished due to metabolic disturbances primarily upstream of Akt, resulting in reduced glucose uptake [81][82]. Skeletal muscle is the largest tissue for insulin-induced glucose uptake, accounting for ~75% of insulin-stimulated glucose uptake [88] (although adipose tissue and the liver are also involved) [89]. Insulin resistance in adipose tissue triggers an increase in the production of free fatty acids, which can then be deposited in other tissues such as muscle and the liver [90]. Excessive intramyocellular lipid accumulation leads to the build-up of diacylglycerol and ceramide [44], impairing insulin signalling and reducing glucose uptake, glucose oxidation and glycogen synthesis while diminishing its anti-catabolic effects [82]. In summary, excessive fat storage in muscle cells disrupts normal signalling pathways, leading to reduced insulin sensitivity and impaired glucose utilisation. An increase in the supply of free fatty acids can also stimulate liver steatosis, resulting in atherogenic lipoprotein metabolism and diminished insulin stimulation causing hepatic glucose production, further increasing hyperglycaemia [91]. This in turn exacerbates hyperglycaemia, resulting in advanced glycated end products, further stimulating inflammation and the development of MDs [92]. Ultimately, peripheral insulin resistance causes a myriad of metabolic disturbances, triggering a vicious cycle of

lipotoxicity, inflammation, oxidative stress and further insulin resistance. These processes are associated with ageing and negatively impact skeletal muscle mass and quality, exacerbating MDs and reducing quality of life.

4. The Role of Mitochondrial Dysfunction and Reactive Oxygen Species in Obesity-Induced Insulin Resistance and Ageing

Obesity is associated with increased mitochondrial reactive oxygen species (ROS) emission, whereas even a single high-fat meal increases ROS emission in lean healthy controls, suggesting the involvement of an elevated supply of free fatty acids in ROS production [93]. The chronically elevated production of ROS by mitochondria and other sources in skeletal muscle is associated with mitochondrial dysfunction in ageing [94] and obesity-induced insulin resistance [95], while ROS production and oxidative damage remain low in healthy individuals. However, ROS levels can be elevated when substrate delivery to the mitochondria is high, while mitochondrial adenosine triphosphate resynthesis rates are low, such as when a high-fat diet and a physically inactive lifestyle are combined [93]. Elevated ROS levels, beyond the capacity of endogenous antioxidants to scavenge the ROS, cause oxidative damage to mitochondria DNA (mtDNA) and mutations in mtDNA coding regions for respiratory chain proteins, leading to defects in respiratory chain function, the uncoupling of oxidative phosphorylation and further increases in ROS levels in a feedforward mechanism [95][96]. High ROS levels lead to the destruction of mitochondria and, if spread across the mitochondrial reticulum, cell death [97].

5. The Importance of Physical Activity and Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1α in Maintaining Mitochondrial Quality Control and Skeletal Muscle Health

Mitochondrial quality control in skeletal muscle involves biogenesis, fusion (exchanging components within healthy mitochondria to form an extended mitochondrial network) and fission (removing components), ultimately impacting skeletal muscle mass [98]. Peroxisome proliferator-activated receptor-gamma coactivator 1α (PGC-1α) is a key regulator of mitochondrial biogenesis and function and plays a role in fission/fusion [99]. PGC-1α transcription networks are also positively associated with appendicular lean mass index and hand grip strength [14]. Consequently, a sufficient intramyocellular PGC-1α content is important for skeletal muscle health and protection against sarcopenia [94][99]. In physically active individuals, ageing alone does not decrease the gene expression or protein content of PGC-1α, mitochondrial fission, or fusion proteins [100][101]. Sarcopenia of human skeletal muscle is associated with the downregulation of PGC-1α messenger ribonucleic acid and transcription signatures for PGC-1α networks in fission and fusion compared with controls [14][102]. Similarly, the downregulation of PGC-1α messenger ribonucleic acid [103] and lower fission and fusion protein contents have been observed in the skeletal muscle of patients with TIID compared with controls [104]. These findings highlight the crucial role of PGC-1α in maintaining skeletal muscle health and function and suggest its potential as a therapeutic target for age-related and metabolic disorders. Therefore, a reduction in PGC-1α and an impairment of mitochondrial fission and fusion processes are potential contributors to both sarcopenia and MDs.

A common factor in many studies of ageing, mitochondrial dysfunction and MDs in humans is the participant's habitual physical activity status; for example, masters athletes have a greater mitochondrial content, oxidative and respiratory enzyme gene expression and activity and in vivo respiratory capacity relative to controls [8][101]. Consequently, master athletes have a well-maintained mitochondrial content and function despite their older age. Moreover, physically inactive elderly individuals retain the ability to adapt to exercise training. It is well known that muscle mass and strength can increase in the elderly following resistance-type exercise training [105]. Mitochondrial content and function also increase in older individuals following endurance-type exercise training [8][106]. This can increase the capacity to oxidise fat during exercise [107], contributing to a reduction in visceral fat mass [108] and chronic low-grade inflammation following exercise training [109]. PGC-1α [8] and mitochondrial fission and fusion proteins are also elevated in masters athletes, suggesting improvements in mitochondrial quality control processes following exercise training [101]. Together, the chronic responses of skeletal muscle to exercise training contribute to improved insulin sensitivity in older individuals [110]. Consequently, physical inactivity, rather than ageing, is a major contributor to the age-related decline in muscle quality [8]. Exercise is strongly indicated to improve skeletal muscle quality in older individuals to protect against the development of mitochondrial dysfunction, sarcopenia, CVD and MDs.

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