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DISCOVERING PATHWAYS OF SARCOPENIA IN OLDER ADULTS: A ROLE FOR INSULIN RESISTANCE ON MITOCHONDRIA DYSFUNCTION

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Abstract: The precise cause of sarcopenia, skeletal muscle loss and strength, in older persons is unknown. However, there is a strong evidence for muscle loss due to insulin resistance as well as mitochondrial dysfunction over aging. Considering that epidemiological studies have underlined that insulin resistance may have a specific role on skeletal muscle fibre atrophy and mitochondrial dysfunction has also been extensively shown to have a pivotal role on muscle loss in older persons, a combined pathway may not be ruled out. Considering that there is growing evidence for an insulin-related pathway on mitochondrial signaling, we hypothesize that a high degree of insulin resistance will be associated with the development of sarcopenia through specific alterations on mitochondrial functioning. This paper will highlight recent reviews regarding the link between skeletal muscle mitochondrial dysfunction and insulin resistance. We will specifically emphasize possible steps involved in sarcopenia over aging, including potential biomolecular mechanisms of insulin resistance on mitochondrial functioning.

Key words: Insulin resistance, sarcopenia, aging, mitochondria.

Introduction

Sarcopenia, the age-related loss of muscle mass and strength, is a fundamental cause of functional decline, disability and frailty in older persons. In the year 2000, $18.5 billion in health care costs were directly attributable to sarcopenia. This economic burden will increase dramatically over the next decade as persons are living to older ages. The primary causes of sarcopenia include: sedentary lifestyle, malnutrition, oxidative stress, chronic inflammation, and endocrine changes. Moreover, older persons with type 2 diabetes have an increased risk for disability, falls and frailty compared to those without diabetes. Considering that insulin resistance significantly contributes to type 2 diabetes, an insulin resistance-related pathway may have a specific role on skeletal muscle fibre atrophy in older persons with diabetes. Data from the InCHIANTI study showed that insulin resistance substantially increased with aging and was an independent determinant of weaker muscle strength in older persons (1). In addition, data from the HealthABC study (2) showed an excessive loss of skeletal muscle mass in older adults with type 2 diabetes was two times faster than those without diabetes. Such decline in skeletal muscle mass may explain why elders with diabetes are at such a dramatic risk for disability. Unfortunately, up to date the mechanisms leading to skeletal muscle mass loss over aging and in particular in older persons with diabetes are lacking.

Recent studies are investigating the potential changes of mitochondria in skeletal muscle due to the fact that mitochondria have an important role in energy production. Even though the capacity of mitochondria to produce energy, ATP, declines with aging in concert with decreases in maximal energy production during peak walking speeds and inefficient utilization of energy at sustainable walking speeds, this decline seems to be more rapid in type 2 diabetes. Recent studies have shown a decreased activity of mitochondrial oxidative phosphorylation in skeletal muscle of type 2 diabetes (3-4). Considering that there is growing evidence for an insulin-related pathway on mitochondrial signalling, we hypothesize that a high degree of insulin resistance will be associated with the development of sarcopenia through specific alterations in mitochondrial functioning. This paper will highlight potential steps involved in sarcopenia over aging, including potential biomolecular mechanisms of insulin resistance on mitochondrial functioning which may be an important basis for future interventions on sarcopenia driven mitochondrial dysfunction.

Sarcopenia

Age-associated skeletal muscle dysfunction has been well characterized and includes a reduction of muscle mass, strength and, according to several studies, endurance capacity (5-6). These alterations represent a major risk factor for falls, fractures and loss of independence in older persons (7). Sarcopenia, loss of muscle mass, is characterized by a decrease in the total number of skeletal muscle fibers, reduced cross-sectional area of the thigh, and an increase in intramuscular fat content (8). Age-related loss in skeletal muscle mass and the

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factors that may affect such loss are constantly under investigation. Sarcopenia may also be a common pathway by which multiple diseases contribute to the risk of functional limitation and disability in old age, even though many risk factors have still not been fully identified. Considering the growing literature on insulin resistance and mitochondrial dysfunction over aging, one may hypothesize a specific pathway of sarcopenia due to insulin resistance on mitochondrial dysfunction.

Insulin resistance and mitochondrial skeletal muscle changes over aging

As the result of an increase in the ageing of populations in both developing and developed countries, the number of elderly persons continues to rise worldwide with a parallel rise in type 2 (the non-insulin dependent form of diabetes). Furthermore, the incidence of both insulin resistance and type 2 diabetes leads to a significant increase in healthcare challenges and costs (9). Impaired insulin action to stimulate tissue substrate utilization with particular regard to glucose is a common metabolic defect and a defining feature of insulin resistance in both type 2 diabetes and ageing. Skeletal muscle is a key metabolic organ and the major site of insulin-mediated glucose disposal, plays an important role in the metabolic alterations of insulin signaling.

There is growing evidence that age-related changes of hormonal regulation play a role in pathophysiological mechanisms implicated in the pathogenesis of sarcopenia (10). Insulin is known to play a pivotal role in muscle functioning by increasing glucose uptake and promoting intracellular glucose metabolism. The contraction of type I fibers is more dependent on glucose entry and metabolism than is the contraction of type IIa (fast twitch, oxidative, glycolytic) or IIb (fast twitch, glycolytic) fibers (11). Type I fibers are more responsive to insulin and more represented in the muscle of older persons (11). First, age-related insulin resistance is associated with impaired muscle glucose handling that in turn impairs intracellular energy production and results in weaker muscle contraction. Second, a vicious circle connects insulin action and an age-related decline in physical activity that progressively aggravates the degree of insulin resistance. During the aging process, changes both in the contractile efficiency of muscle fibers and in tissue quality, such as pericellular fat infiltration, may also contribute to altered muscle function (12-13). Moreover, insulin resistance could be further worsened by the occurrence of pericellular fat accumulation both directly and through the increased production of pro-inflammatory cytokines such as TNF- and IL-6 that in turn have been associated with lower muscle mass and strength (14). An increased proteolytic state, commonly observed in older persons, reflects a significant depletion in protein activity and has been reported to be associated with risk factors related to muscle strength and function, such as impaired mobility and balance, suggesting a link with sarcopenia (15). It is well known that insulin is capable of preventing protein breakdown by increasing amino acid availability needed for protein synthesis in muscle tissue. Therefore, age-related IR may define protein catabolism and muscle weakness. Furthermore, a decline in aged skeletal muscle strength might also be due to a reduction of L-type calcium channels (16). Insulin has a stimulatory effect on intracellular calcium uptake, thus insulin resistance may negatively affect muscle contraction through this mechanism.

The role of mitochondrial dysfunction in the etiology of sarcopenia has been extensively characterized (17-20). The "mitochondrial dysfunction on muscle over aging" highlights that the aging process is modulated by reactive oxygen species (ROS)-mediated toxicity leading to mitochondrial DNA (mtDNA) deletions and mutations, macromolecular oxidation, electron transport chain (ETC) dysfunction, cellular senescence and cell death. Muscle from older adults have shown: i) an increase in mitochondrial ETC abnormalities marked by the accumulation of cytochrome c oxidase negative and succinate dehydrogenase hyper-positive fibres, ii) accumulation of somatic mtDNA mutations iii) an increase in markers of oxidative stress. Despite a strong relationship between aging and oxidative damage, the literature on the effect of aging on skeletal muscle ETC function remains unclear in humans. Many studies have demonstrated a significant age-related reduction of mitochondrial ETC complex enzymes in human skeletal muscle (21-22). However, it has also been suggested that the age-related reduction in ETC function, reduced mitochondrial complex I, II, III, and IV activity, is not related to the aging process per se, but rather due to other confounding factors, including physical inactivity (23). In fact a previous study reported normal mitochondrial ETC function in the skeletal muscle of physically active older persons (average age of 72±2 years) despite an increase in markers of oxidative damage compared to healthy young individuals (average age of 22±3 years) (24). Hence, the relationship between mitochondrial ETC dysfunction, oxidative stress and sarcopenia remains an important and unresolved issue in aging research that may be influenced by factors other than aging alone.

Age-related decreases in the amount of functionally intact mitochondria with concomitant decline in cellular production of adenosinetriphosphate (ATP), energy-dependent protein synthesis and increased peroxide leakage may contribute to muscle loss (25). Mitochondrial enzymes have been reported to undergo relevant impairment in the muscle of old human beings, as well as laboratory animals. With specific reference to human studies, the number of mitochondria per gram of tissue (and, because of fibre loss, the mitochondrial content per whole muscle) decreases in persons over the age of 50 years. The functional outcome of these changes is a marked reduction in aerobic endurance which appears to be closely related to the density of mitochondria and to their competence in providing adequate amounts of ATP. Furthermore, it is widely known that

the capacity of mitochondria to produce energy as ATP declines with aging in concert with decreases in maximal energy production during peak walking speeds and inefficient utilization of energy at preferred sustainable walking speeds. As documented by images from electron microscopy of different tissues, the ultrastructural features of a given mitochondrial population, in addition to being closely coupled to the organelles' functional performances, undergo significant adaptations according to environmental conditions. Thus, quantitative investigations on mitochondrial morphological parameters, while estimating the cell potential for energy provision, enable to uncover underlying alterations in the cellular hardware related to an impaired metabolism.

Mitochondrial oxidative capacity is decreased in skeletal muscle of obese individuals and is considered a consequence of insulin resistance in humans (26). Age-associated alterations have been reported in skeletal muscle at both transcriptional and functional levels of mitochondrial gene expression (27). Indeed, these data indicate alterations other than those associated with oxidative damage and mtDNA alterations can contribute to muscle mitochondrial alterations with ageing. At the moment, mitochondrial functions are at the center of numerous protocols due to the their significant capacity in oxidizing substrates and generating ATP.

Insulin resistance on mitochondria functioning in sarcopenia

Skeletal muscle has also emerged as a target of acute insulin effects on mitochondria in humans. Hyperinsulinemia in the high–physiological range increased transcript levels of complex I and complex IV subunits of the respiratory chain (28). Interestingly, increments in mitochondrial transcripts were positively related to those of insulin-mediated glucose disposal (29), supporting the hypothesis that muscle mitochondria are mediators of insulin action to increase glucose utilization. A study further characterized the role of insulin in the acute regulation of skeletal muscle mitochondrial function. When insulin was infused into healthy middle-aged subjects, mitochondrial transcript levels, protein synthesis, respiratory chain enzyme activity and the ATP production rate all significantly increased (30). This important study introduced the theory that insulin is a stimulator of muscle mitochondrial function in vivo in humans.

Acute increments in the plasma insulin concentration have been demonstrated to stimulate skeletal muscle mitochondrial gene expression, protein synthesis and function in vivo in healthy individuals. Acute intravenous insulin infusion in an animal model was shown to enhance the mitochondrial protein synthesis rate in a tissue-specific fashion (31). Mitochondrial protein synthesis was increased in skeletal muscle, but not in cardiac muscle and liver. Considering that liver mitochondrial protein synthesis tended to be lower during hyperinsulinemia, the stimulatory effect of insulin seems to be specific to skeletal muscle (31). In addition, these authors showed that such increased mitochondrial protein synthesis was not associated with increments in the synthesis rates of other muscle protein pools, including sarcoplasmic protein and major contractile protein myosin heavy chain (31). Indeed these findings indicate a specific effect of insulin on selectively enhancing muscle mitochondrial protein synthesis in vivo.

It has been observed that basal ATP synthesis rates in skeletal muscle are lower in insulin resistant subjects (32) and studies have provided evidence for dysfunctional mitochondria in insulin resistant states as seen by a down-regulation of genes encoding for mitochondrial enzymes (33, 34) decreased mitochondrial content and lower respiratory chain activity (35).There have also been reports on altered mitochondrial adaptations in skeletal muscle during the development of insulin resistance in adults (36-37), as well as an improvement in mitochondrial capacity to oxidize fat-derived substrates and increase in number (38). Intervention studies on physical activity and mitochondrial function report parallel increases in response to training with a weak relation between mitochondrial activity and insulin sensitivity in older persons (39). However, it is still unknown whether an improvement in insulin resistance through aerobic exercise is able to increase the expression of anti-apoptotic genes (e.g. Bcl-2 or Bak) in older subjects.

There is reasonable debate that mitochondria may also be considered the origin and not the victim in insulin resistance associated skeletal muscle loss (40). This differences lies in the fact that mitochondrial dysfunction causes the production of ROS which in turn begin a vicious cycle with insulin resistance. Anderson et al. (41) demonstrated that dietary fat induced insulin resistance results from increased mitochondrial H2O2 production and this insulin resistance is prevented by use of a mitochondrial targeted antioxidant or overexpression of catalase. However, there is very recent data indicating that a deficiency in the mitochondrial electron transport chain (ETC) in muscle does not cause insulin resistance (42) in contrast to the potential mechanism of "mitochondrial deficiency" in which it is hypothesized that insulin resistance is caused by an accumulation of intramuscular lipids as a result of decreased capacity for fat oxidation (43). Interestingly, a significant role altered fat acid oxidation and lipid storage, impaired insulin signaling and insulin resistance were associated significantly lower mitochondrial phosphorylation capacity in obese type 2 diabetic subjects compared to non-obese diabetics (44), thus strengthening the hypothesis that insulin resistance has a direct role on mitochondrial functional impairment.

Skeletal muscle lipid infiltration, insulin resistance and mitochondria dysfunction

Ageing is associated with changes in muscle size and quality as evidenced by an increase in fat infiltration that has been referred to as myosteatosis. As determined by the computerized

tomography (CT) attenuation coefficient of muscle, lipid infiltration is an important determinant of insulin resistance in healthy (45) and diseased patients (46): it is independent of visceral fat and is associated with decreased muscle strength and physical performance in older persons (47). Muscle attenuation in Hounsfield Units (HU) obtained by CT is a non-invasive measure of muscle density and correlates with intramuscular lipid content obtained by muscle biopsy (47-48). Lower HU reflects higher intramuscular lipid content, and has been used as a reliable parameter in a number of studies on sarcopenia (47-48).

However, whether reduced mitochondrial capacity in skeletal muscle is causative for insulin resistance or, instead, arises as a consequence of insulin resistance impacting muscle loss needs to be clarified. Indeed there are data that support the hypothesis that insulin resistance in humans arises from defects in mitochondrial fatty acid oxidation (32), which leads to an increase in intracellular fatty acid metabolites (acyl CoA and diacylglyerol) capable of interfering with the insulin signaling pathway (49). However, lower oxidative capacity may also result from insulin resistance and high intramyocellular triglycerides by lipotoxic measures. In particular, accumulating fatty acids within myoctyes interact with ROS-forming peroxides which in turn lead to lipotoxic effects on mitochondria (26). Table 1 shows data from recent studies supporting studies supporting mechanisms between insulin resistance and mitochondrial dysfunction.

Even though it was originally believed that thyroid hormones were solely responsible for energy production within mitochondria, we have underlined that recent studies have also show that insulin also plays a role in regulating the efficiency of ATP production especially in muscle cells. However, it is also important to highlight that potential treatment with diverse sex hormones may also improve both insulin resistance and mitochondria dysfunction in muscle cells of older adults. In particular, female sex hormones, estrogen and progesterone, have been recently shown to impact animal and human skeletal muscle with concomitant role on improving insulin resistance (50, 51). In particular, it was shown that in women the ovarian steroid hormones, estradiol and progesterone, influence insulin sensitivity via alterations in the production of mitochondrial H2O2 in skeletal muscle (51) with a direct effect on mitochondrial function in skeletal muscle. The administration of testosterone to hypogonadal elderly men has shown to produce a moderate improvement in body composition (increased lean mass and decreased fat mass), but few studies have reported increases in strength (52). The risks associated with testosterone replacement are still not clear. Few studies have reported adverse effects, but few have administered to elderly subjects doses high enough to produce substantial anabolic effects and impact insulin resistance substantially. However, whether the use of sex hormones can significantly impact sarcopenia by improving insulin resistance and/or mitochondria dysfunction in older persons with type 2 diabetes remains to discovered.

Conclusions

The mechanisms explaining the development of sarcopenia in older diabetics remain controversial, however mitochondrial

Table 1
Some studies supporting the relationship between insulin resistance and mitochondrial dysfunction

Author (year)	Type of study (n)	Mean age (years)	Insulin sensitivity technique	Mitochondrial function assessment	Findings
Brehm A (2006) (56)	Human (n=8)	21 ± 1	Euglycemic-hyperinsulinemic clamp	Skeletal muscle ATP synthase flux	During the high-insulin period, flux through ATP synthase increased; Under insulin-stimulated conditions, increased lipid levels reduced the increase in insulin-stimulated ATP synthase flux & impair glucose transport
Fleischman A (2007)(57)	Human (n=16)	31 ± 2	Euglycemic-hyperinsulinemic clamp	Mito DNA/nuclear DNA in muscle	Altered mitochondrial function in muscle may be an important factor in the development of insulin resistance.
Petersen KF (2003)(32)	Human (n=15 elders) (n=13 young)	70 ± 2 27 ±2	Euglycemic-hyperinsulinemic clamp	Mitochondrial oxidative activity in skeletal muscle by 13C NMR and phosphorylation activity by 31P NMR	Rates of mitochondrial oxidative and phosphorylation activity were reduced by ~40% in the elderly vs. young controls; Insulin resistance in the elderly is related to increases in intramyocellular fatty acid metabolites that may be a result of an age-associated reduction in mitochondrial oxidative and phosphorylation activity
Bonnard C (37) (2008)	Animal (mice) (HFHSD) (SD)		Glucose and insulin tolerance tests	Mitochondrial density (mtDNA/ nuclear DNA in the skeletal muscle)	HFHSD-induced mitochondrial alterations in skeletal muscle are a consequence of hyperglycemia- and hyperlipidemia-induced ROS production in mice, which result from mitochondrial overfunctioning and an increase in NAD(P)H oxidase in response to insulin resistance
Han DH (2011)(42)	Animal (rats)		Insulin levels, Expression GLUT-4 in skeletal muscle	Mito proteins, ETC markers	Deficiency of the electron transport chain (ETC), and imbalance between the ETC and -oxidation pathways, does not cause muscle insulin resistance.
Hoeks J (2010)(26)	Human (n=12)	24 ± 1	Euglycemic-hyperinsulinemic clamp	Mito DNA copy no., citrate synthase activity	Insulin resistance has secondary negative effects on mitochondrial function

HFHSD= high-fat, high-sucrose diet, SD= standard diet

dysfunction, due to altered insulin signaling, may have a crucial role in aging and in particular in patients with type 2 diabetes. Even though a recent study speculated that the defects in mitochondrial content/morphology in aging occurred independently of insulin resistance, the authors did not determine the type of muscle fiber in relation to mitochondria and insulin resistance (53). Considering that type I fibers are more responsive to insulin and have a greater mitochondrial content, a specific role played by insulin resistance in sarcopenia cannot be overruled. Structural changes in intracellular lipid content and mitochondria have been related to aberrant lipid metabolism, mitochondrial dysfunction and oxidative stress, however the impact of an altered insulin pathway on mitochondrial activity in specific muscle fibers remains unknown. Furthermore, changes in mitochondrial function, oxidative stress, and chronic inflammation observed in skeletal muscle of older persons with type 2 diabetes during regular aerobic physical training need to be investigated according to fiber type. Some studies have reported no difference between muscle fiber type and mitochondrial function, however data on older sarcopenic individuals with type 2 diabetes are lacking.

Insulin resistance, that also leads to type 2 diabetes, has been considered to be responsible of the development of skeletal muscle lipid deposition that also characterizes sarcopenia as a consequence of severe fat infiltration. Insulin resistance in skeletal muscle in obesity or type 2 diabetes is associated with reduced muscle oxidative capacity (54).

As insulin resistance characterizes type 2 diabetes, it is conceivable that mitochondrial defects occur in this disease, in particular in skeletal muscle. The study by Stump et al (30) provided further important evidence in this regard by demonstrating that the acute stimulation of mitochondrial ATP production observed in healthy individuals was not achieved by insulin in age-matched individuals with type 2 diabetes. A defective response of skeletal muscle mitochondria to acute insulin-induced stimulation occurs in humans with type 2 diabetes. An altered mitochondrial response to insulin could therefore contribute to impaired substrate utilization, as an integral component of insulin resistance in this disease. These results are particularly relevant to the post-prandial period, when plasma insulin concentrations increase in an acute fashion to levels comparable to those achieved in the study.

Physical activity plays an important role in delaying or preventing the development of type 2 diabetes in individuals at risk, both directly by improving insulin sensitivity and indirectly by producing beneficial changes in the body mass and body composition. Regular physical activity leads to a number of beneficial physiological changes that favorably modulate muscle and liver insulin sensitivity, muscle glucose uptake and utilization, and overall glycemic control. Moreover, a lifestyle that includes an adequate physical activity is reported to improve lipid profile, decrease body weight and the percentage of body fat, lower blood pressure, reduce the risk of cardiovascular disease. Regular physical activity may contribute to prevent or delay neuropathy, retinopathy, may reduce stress, feelings of anxiety, and may positively counteract the physiological functional decline that occurs with aging.

A sedentary lifestyle has a negative impact on mitochondrial function, and the stimulatory effects of aerobic exercise on muscle mitochondrial oxidative capacity have long been recognized and confirmed in ageing individuals. Interestingly, however, parallel declines in mitochondrial succinate dehydrogenase and oxygen consumption were reported in a longitudinal study of elite distance runners who maintained intense training programs through middle age (55), indicating that physical activity per se is not sufficient for the complete prevention of age-related deleterious skeletal muscle changes. Reduced blood flow is also a potentially important factor in impaired ageing mitochondrial function, through a reduction in oxygen supply that can limit oxidative metabolism and protein turnover, as well as, in the development of lower muscle mass over time in older persons (48).

In conclusion, mitochondrial dysfunction is associated with insulin resistance and type 2 diabetes. Even though the past literature has largely suggested that primary and/or genetic abnormalities in mitochondrial function may lead to accumulation of toxic lipid species in muscle, impairing insulin action on glucose metabolism, new data promote a direct role of insulin resistance pathways on mitochondrial dysfunction.

Conflict of Interest: No author has any conflict of interest.

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