

# Muscle mitochondrial changes with aging and exercise<sup>1-4</sup>

Ian R Lanza and K Sreekumaran Nair

## ABSTRACT

Aging has been reported to be accompanied by reduced mitochondrial function and insulin sensitivity. Whether these deleterious effects result from chronological age or lifestyle-related factors such as adiposity and physical inactivity remains debatable. The beneficial effects of exercise on mitochondrial function and insulin sensitivity are well documented; however, it is unclear whether exercise can effectively prevent, reverse, or delay the onset of these age-related dysfunctions. Other investigators and we have found that endurance exercise enhances mitochondrial function across the life span, highlighting the beneficial role of exercise in combating age-related mitochondrial dysfunction. The literature is mixed concerning the ability of endurance exercise to normalize age-related insulin resistance; however, emerging evidence points to adiposity rather than age per se as a primary determinant of age-related declines in insulin sensitivity. Recent data from our laboratory also shed some light on the controversial relation between mitochondrial function and insulin sensitivity. Although some investigators purport a causal role of mitochondrial dysfunction in the etiology of insulin resistance, we provide evidence that the reverse may be true based on the fact that insulin stimulates mitochondrial function in healthy control subjects but not in patients with type 2 diabetes. Furthermore, we find that these 2 variables are completely dissociated in some populations, such as Asian Indians, who exhibit elevated mitochondrial capacity despite marked insulin resistance compared with European Americans. Our data not only point to regular endurance exercise as a viable strategy to delay the onset of age-related dysfunctions but they suggest that mitochondrial function and insulin resistance may be linked by additional factors such as physical activity. *Am J Clin Nutr* 2009(suppl);89:467S–71S.

## INTRODUCTION

The rapidly growing proportion of humans >60 y has spawned much interest in understanding the effects of old age on skeletal muscle, given its vital role in maintaining physical function, health, and quality of life across the life span. Although declines in muscle mass, strength, and maximal endurance with old age are well documented, the impact of aging per se on mitochondrial function is debatable and has received much attention at multiple levels. Substantial data support the view that mitochondrial function declines with old age. Indeed, oxidative capacity has been shown to be impaired with old age as evidenced by decreased mitochondrial enzyme activities (1, 2) and maximal ATP synthesis in permeabilized muscle fibers and isolated mitochondria (2, 3). Furthermore, underlying molecular and cellular disturbances, such as reduced mitochondrial protein synthesis rates (1), lower mitochondrial protein content (2), fewer gene transcripts

for mitochondrial proteins (2, 4), decreased mitochondrial DNA (mtDNA) abundance (2, 5, 6), and increased DNA oxidative damage (2, 7), in older compared with young humans have been observed. This notion has been confirmed in vivo by phosphorous magnetic resonance spectroscopy (<sup>31</sup>P-MRS)-based measures of basal (8) and maximal (9) oxidative ATP production in skeletal muscle. However, both in vitro studies (10) and in vivo studies using <sup>31</sup>P-MRS (11) have contradicted the notion of an age-related decline in muscle mitochondrial oxidative capacity. A unifying theme discussed in many of these works (10–13) is whether age-related changes in mitochondrial function are inevitable consequences of chronological age or are secondary to age-associated declines in physical activity, as observed in organisms such as nematodes (14), rodents (15), and humans (16). Spontaneous physical activity (defined as hypothalamic-regulated physical activity distinct from purposeful, voluntary activity) has been implicated in human obesity (17) and hypothesized to be reduced with senescence as a consequence of mitochondrial dysfunction (18). A vicious cycle has been proposed whereby a sedentary lifestyle leads to decreased mitochondrial function, decreased spontaneous physical activity, and, in turn, further decreases in mitochondrial function to the point where physical function is impaired.

## EFFECTS OF ENDURANCE EXERCISE ON MITOCHONDRIAL FUNCTION

Since the publication of Holloszy's (19) pioneering work, an extensive body of literature has accumulated demonstrating that endurance exercise effectively stimulates mitochondrial biogenesis and increases muscle oxidative capacity. We recently investigated distinct mechanisms underlying exercise-induced improvements in mitochondrial function in a murine model of endurance training (20). Eight weeks of treadmill training (80% peak O<sub>2</sub> uptake, 5 d/wk) augmented mitochondrial function, as reflected by increased mitochondrial enzyme activities (Figure 1A), maximal rate of ATP synthesis in isolated mitochondria (Figure 1B), and whole-body maximal O<sub>2</sub> uptake (Figure 1C).

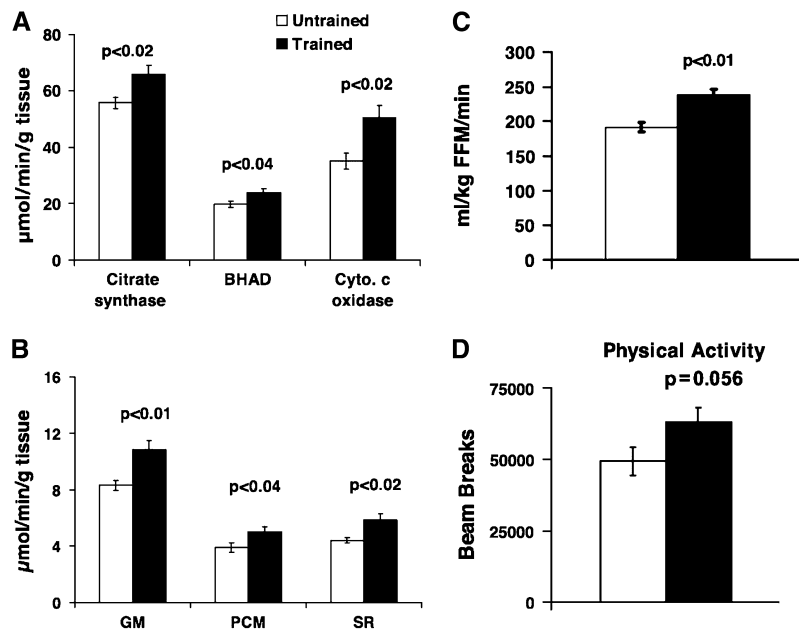
<sup>1</sup> From the Division of Endocrinology, Endocrinology Research Unit, Mayo Clinic College of Medicine, Rochester, MN.

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<sup>4</sup> Reprints not available. Address correspondence to KS Nair, Mayo Clinic, 200 First Street SW, Joseph 5-194, Rochester, MN 55905. E-mail: nair.sree@mayo.edu.

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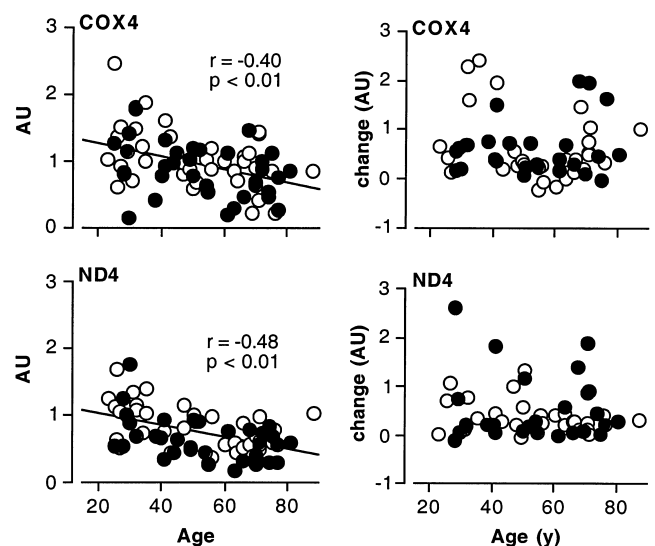


**FIGURE 1.** A: Training effects on mitochondrial function,  $\dot{V}O_2$  peak, and spontaneous activity. Citrate synthase, L-3-hydroxyacyl coenzyme A dehydrogenase (BHAD), and cytochrome *c* oxidase activities increased with 8 wk of endurance exercise in Friend virus B-type (FVB) mice ( $n = 8$  per group). B: Exercise also increased mitochondrial ATP production rates with the use of substrate combinations glutamate + malate (GM), palmitoyl-L-carnitine + malate (PCM), and succinate + rotenone (SR) ( $n = 8$  per group). Maximal oxygen uptake expressed per unit of fat-free mass (FFM) ( $n = 8$  per group) (C) and spontaneous physical activity (D) increased with exercise training ( $n = 12$  untrained, 8 trained). Data are presented as means  $\pm$  SEMs. Reprinted with permission from reference 20.

Exercise-induced increases in mitochondrial function were accompanied by increased transcript levels of nuclear and mitochondrial genes encoding mitochondrial proteins, mitochondrial DNA abundance, and expression of peroxisome proliferator activated receptor  $\gamma$  coactivator 1 $\alpha$  (PGC1 $\alpha$ ; protein) and mitochondrial transcription factor A (TFAM; mRNA). A key finding of this study was that exercise training also increased spontaneous physical activity (Figure 1D) as measured with infrared photocell sensors and was significantly correlated with mitochondrial ATP production capacity. This study has important implications for aging because it supports the notion of a relation between mitochondrial function and spontaneous physical activity; that is, endurance training increases mitochondrial function, stimulates spontaneous physical activity, and is a viable approach to interrupt the vicious cycle of aging.

Indeed, there has been enormous interest in the potential utility of exercise as an intervention to prevent, reverse, or delay age-related mitochondrial and other metabolic dysfunctions in humans. An inclusive review of the numerous investigations into the adaptations of young and older individuals to exercise is beyond the scope of this short review. Briefly, older adults enrolled in exercise training programs respond with increased  $\dot{V}O_2$  peak (21–23), mitochondrial content (5, 24), oxidative enzyme activities (5, 21, 23), muscle protein synthesis rates (25, 26), mitochondrial protein gene transcripts (23), and mitochondrial DNA copy number (5). For example, we investigated the effects of a 16-wk aerobic exercise program on several markers of mitochondrial function in previously sedentary individuals aged 21–87 y (23). Regression analyses revealed an age-related decline in citrate synthase (CS) and cytochrome *c* oxidase (COX) activities, 2 common markers of mitochondrial function. Furthermore, mRNA expression of COX4 and NADH dehydrogenase subunit 4 (ND4) also declined with age, as shown in **Figure 2**. In this study, we found that a 4-mo

endurance-training program increased CS and COX activity as well as the mRNA expression of mitochondrial genes (COX4 and ND4) and transcription factors (PGC1 $\alpha$ , NRF1, and TFAM). An important finding in this investigation was that the response to aerobic exercise training did not differ by age, as shown for COX and ND4 mRNA abundance in Figure 2. These data underscore the



**FIGURE 2.** mRNA expression of mitochondrial proteins with age and exercise. mRNA transcripts of cytochrome *c* oxidase 4 (COX4) and NADH dehydrogenase 4 (ND4) declined significantly with age in men (open circles) and women (solid circles) combined (left panels). Exercise increased mRNA expression of COX4 and ND4, with no age differences in the absolute differences between pre- and posttraining measurements (right panels). Data are normalized to 28S rRNA;  $n = 78$ . AU, arbitrary units. Reprinted with permission from reference 23.

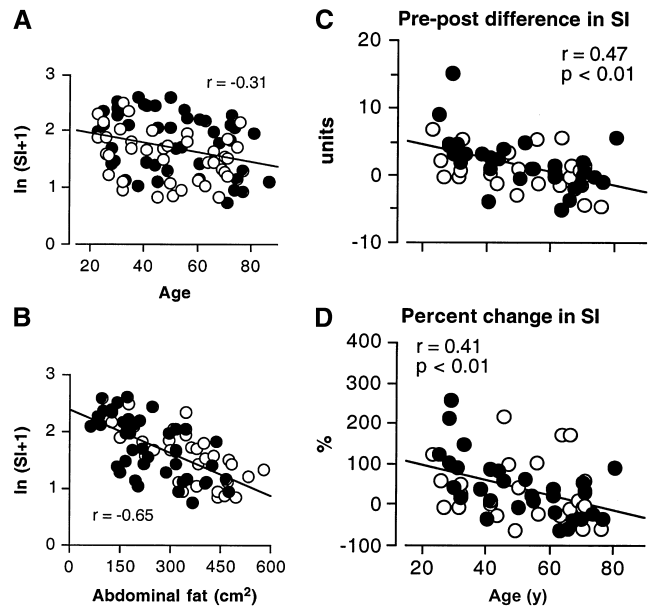
notion that endurance exercise confers significant improvements in mitochondrial function regardless of age.

Although numerous studies demonstrated a robust adaptability of older skeletal muscle to training, the function of older muscle after training often remained at or below the level of young untrained subjects and well below the level of young subjects who engaged in similar training (5, 21, 23, 25). A lingering question is whether older muscle is less adaptable to exercise training than young muscle or whether the volume and duration of most training regimes are insufficient to reveal the full potential for adaptation in both age groups. Indeed, practical considerations limit most prospective training studies to weeks or months in duration, whereas the chronic effects of aging manifest over the bulk of the entire life span. Long-term training studies in previously sedentary individuals or longitudinal studies of habitual exercisers are needed to determine the extent to which regular endurance exercise is able to prevent or delay the onset of age-related mitochondrial dysfunction.

#### DETERMINANTS OF AGE-RELATED DECLINES IN INSULIN SENSITIVITY AND THE EFFECTS OF EXERCISE

In addition to age-related mitochondrial defects, numerous investigators have shown impaired glucose tolerance and insulin sensitivity in older adults (8, 23, 27, 28). Once again, however, the literature is divided concerning whether age per se is an independent predictor of insulin resistance. Numerous groups have found that body composition and physical fitness are primary determinants of age-related insulin resistance (23, 29–31). For example, Basu et al (29) measured insulin action in 67 elderly and 21 young individuals by means of mixed meal and intravenous glucose-tolerance test models. Both models indicated decreased insulin action in the elderly but not after adjustments for percentage body fat and visceral fat were made. Similarly, we previously reported an age-related decline in insulin sensitivity that was more strongly correlated to abdominal adiposity than to the chronological age of the participants (Figure 3, A and B) (23). This appears to be a recurrent finding in the literature. Although some investigators report age-related declines in insulin sensitivity despite matching age groups for body mass index (BMI) (8, 32), there are many reports demonstrating that body composition and central adiposity, but not age, are powerful predictors of whole-body insulin action (23, 28–31).

Regardless of the exact determinants, insulin resistance is prevalent in the elderly and is implicated in the development of type 2 diabetes and metabolic syndrome with age. The onus is on clinicians and researchers to investigate and use effective strategies to prevent or delay the onset of age-related insulin resistance. One such strategy is exercise, which has well-documented effects on increasing insulin action (33). These beneficial effects of exercise on insulin action have been observed in the elderly as well (34–36). Similar to the effects of exercise on mitochondrial function, there remains some question as to whether the insulin-sensitizing effects of exercise are lessened with old age. Data from our laboratory showed that 16 wk of moderately intense cycling increased GLUT4 mRNA and protein expression to similar levels in young and older adults, although the increment in whole-body insulin sensitivity with training was blunted in the older group (Figure 3, C and D). This study suggests that the beneficial effects

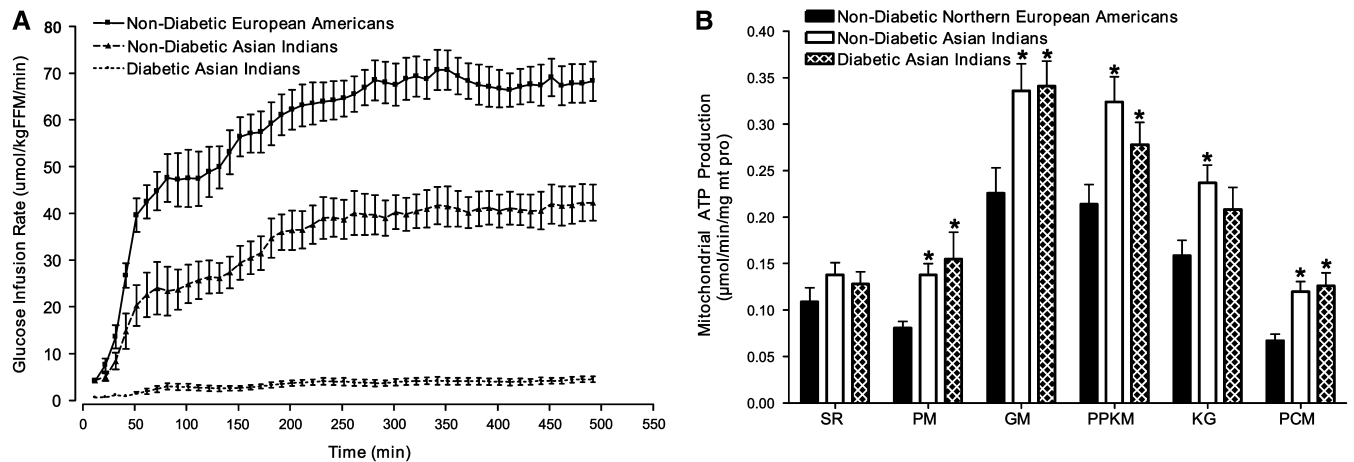


**FIGURE 3.** Relation between insulin sensitivity and age, abdominal fat content, and postexercise change in insulin sensitivity. The insulin sensitivity index (SI) was more closely related to abdominal adiposity (B) than age (A) in men (open circles) and women (solid circles) combined. The difference between pre- and posttraining SI (C) and the percentage change in SI (D) were inversely related to age, indicating blunted increases in insulin sensitivity with training in older individuals;  $n = 78$ . Reprinted with permission from reference 23.

of exercise on insulin sensitivity may be blunted, slower to occur, or more rapidly lost after exercise; however, additional longer-term prospective training studies or cross-sectional comparisons of chronically endurance-trained young and older individuals are required to more completely address this issue. Nevertheless, endurance exercise training is a promising tool for combating the insulin resistance that would likely otherwise occur in sedentary, overweight individuals as they age.

#### CONTROVERSIAL RELATION BETWEEN MITOCHONDRIAL FUNCTION AND INSULIN SENSITIVITY

Concurrent impairments in mitochondrial function and insulin sensitivity are often observed not only with old age (2, 8, 23) but also in people with type 2 diabetes (37) and obese individuals (38). The associations between insulin resistance and mitochondrial dysfunction have prompted 3 distinct hypotheses concerning this relation: 1) insulin resistance may be a consequence of mitochondrial dysfunction, 2) mitochondrial dysfunction may result from insulin resistance, and 3) mitochondrial dysfunction and insulin resistance may be coincidental. Some recent data from our laboratory point to impaired insulin sensitivity as a determinant of mitochondrial dysfunction rather than the reverse. A report by Stump et al (39) demonstrates that an 8-h insulin infusion (1.5 mU/kg fat-free mass/min) in humans increased the capacity for skeletal muscle mitochondrial ATP production in parallel with increased mitochondrial enzyme activities, mRNA expression of mitochondrial proteins, and fractional synthesis rates of mitochondrial proteins. The effect of insulin on stimulating mitochondrial ATP production was absent in people with type 2 diabetes, which was later confirmed in a larger cohort of type 2



**FIGURE 4.** Insulin sensitivity and mitochondrial ATP production in nondiabetic European Americans and diabetic and nondiabetic Asian Indians. Glucose infusion rates per unit of fat-free mass (FFM) during an 8-h euglycemic hyperinsulinemic clamp were significantly lower in Asian Indians compared with European Americans (A). ATP production rates with substrates succinate + rotenone (SR), pyruvate + malate (PM), glutamate + malate (GM), palmitoyl-L-carnitine +  $\alpha$ -ketoglutarate + malate (PPKM),  $\alpha$ -ketoglutarate (KG), and palmitoyl-L-carnitine + malate (PCM) were significantly higher in Asian Indians than in European Americans despite lower insulin sensitivity. Data presented as means  $\pm$  SEMs;  $n = 13$  per group. \*Significantly ( $P < 0.05$ ) different from European Americans. Reprinted with permission from reference 41.

diabetic and nondiabetic subjects (40). Moreover, in contrast to aging populations in which mtDNA copy number and maximal ATP production are reduced (2, 5, 6), individuals with type 2 diabetes have no reduction in baseline mtDNA copy number or ATP production despite blunted increments in ATP production with increasing insulin levels (40). These studies have not only established a role for insulin as a key regulator of mitochondrial function, they also support the hypothesis that mitochondrial dysfunction in insulin-resistant individuals may be a consequence of impaired insulin signaling and possibly reduced fuel metabolism.

We and other investigators recently reported a dissociation between mitochondrial function and insulin sensitivity. As discussed above, we showed that 16 wk of aerobic exercise training increases mitochondrial oxidative capacity but not insulin sensitivity in older adults (23). More recently, we further demonstrated this apparent dissociation in Asian Indian adults who, despite stark insulin resistance, exhibited higher oxidative capacity and mtDNA abundance compared with people of northern European descent (41) (**Figure 4**). Other examples of this dissociation can be seen in recently published work from other groups. For example, Toledo et al (42) showed that weight loss by diet without exercise significantly improves insulin sensitivity but not mitochondrial oxidative capacity. Others have found that mitochondrial function is normal in skeletal muscle of patients with type 2 diabetes (43). Pospisilik et al (44) demonstrated that apoptosis-inducing factor (AIF) knockout mice exhibit reduced mitochondrial capacity but are more insulin-sensitive than control animals. These data underscore the fact that, although mitochondrial dysfunction and insulin resistance often occur commensurately in some populations, an accumulating body of evidence suggests that this relation may be coincidental or linked by some common factor such as physical inactivity.

## CONCLUSIONS

In conclusion, there is emerging evidence that although mitochondrial dysfunction and insulin resistance are often considered hallmarks of the aging process, many of these detrimental effects

appear to be secondary to physical inactivity and adiposity rather than chronological age. Numerous investigations by our group and others have demonstrated clear beneficial effects of endurance-exercise training on mitochondrial function and insulin sensitivity in young and older adults. The extent to which regular endurance exercise is able to prevent, delay, or reverse such detrimental effects of aging will be revealed by longitudinal studies of habitual exercisers, longer-term training studies, or cross-sectional comparisons of sedentary and chronically endurance-trained young and older adults. It remains to be shown whether decreased activity levels are an obligatory or preventable consequence of aging in humans and other species. Evidence suggests that deliberate maintenance of motor activities may slow the decline in spontaneous activity, mitochondrial function, and insulin action that occurs with old age. (Other articles in this supplement to the Journal include references 45 and 46.)

The authors' responsibilities were as follows—IRL: contributed to writing of the manuscript; KSN: conceived and designed the studies, interpreted the findings, and contributed to writing of the manuscript. Both authors read and edited the draft of the manuscript. Neither author had any financial or personal conflicts of interest.

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