Effect of Aging on Glucose and Lipid Metabolism During Endurance Exercise

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Endurance exercise increases the use of endogenous fuels to provide energy for working muscles. Elderly subjects oxidize more glucose and less fat during moderate intensity exercise. This shift in substrate use is presumably caused by age-related changes in skeletal muscle, including decreased skeletal muscle respiratory capacity, because adipose tissue lipolysis and plasma fatty acid availability are not rate limiting. Endurance training in elderly subjects increases muscle respiratory capacity, decreases glucose production and oxidation, and increases fat oxidation thereby correcting or compensating for the alterations in substrate oxidation associated with aging.

During resting conditions, skeletal muscle consumes approximately 30% of the body’s total energy requirements. Approximately 80% of the energy consumed results from the oxidation of fat in the form of free fatty acids (FFA) (1, 10). During exercise there is a dramatic increase in energy requirements because of the metabolic needs of working muscles. The rates of fat and glucose oxidation increase up to 10 fold during prolonged mild or moderate intensity exercise (25–65% of maximal oxygen consumption, VO₂max) (24, 31). The relative contribution of carbohydrate and fat as fuel for working muscle is largely dependent on exercise intensity. As exercise intensity increases, there is a progressive increase in the relative oxidation of carbohydrate and a corresponding decrease in the relative oxidation of fat (22, 36). Glucose is made available to skeletal muscle by delivery from plasma (derived from hepatic glycogenolysis and gluconeogenesis) and breakdown of intramuscular glycogen (6). Fatty acids are made available to skeletal muscle by delivery from plasma (derived from adipose tissue triglycerides) and breakdown of intramuscular triglycerides (20). In addition, adipose tissue (4, 5, 18) and skeletal muscle (29) blood flow increase to enhance delivery of substrate to working muscle. It is difficult to evaluate the independent effects of aging on substrate metabolism during exercise because of aging-related changes in body composition and fitness. Aging is associated with a progressive decline in aerobic capacity (13, 34) and muscle mass (12), and a progressive increase in total body fat mass (e.g., 26). However, the hormonal (decreased lipolytic sensitivity to β-adrenergic stimulation [14, 28], lower sympathoadrenal response to exercise [27]), body compositional (increased whole-body [26] and intramuscular [15] fat stores, decreased muscle glycogen stores [32]), vascular (decreased muscle capillarization

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and muscular (increased type-I and decreased type-II fiber size [8], decreased oxidative capacity [32]) alterations that normally occur with aging support the notion that substrate metabolism during exercise may be different in elderly than in young subjects.

In this manuscript, we review the effect of aging on muscle oxidative capacity (enzymes and energetics) and substrate metabolism (glucose and fatty acid kinetics and oxidation) during endurance exercise in human subjects and the effect of training on these processes.

**Muscle Oxidative Capacity**

Data from studies performed in vitro and in vivo have shown that aging is associated with a decline in muscle oxidative capacity (32). Evaluation of skeletal muscle biopsy samples have found that maximal mitochondrial oxidative enzyme activity (citrate synthase, succinate dehydrogenase, b-hydroxyl-CoA-dehydrogenase) is lower in old (age: 57–74 years) than in young (age: 20–38 years) subjects (7, 8, 30) because of both decreased mitochondrial volume density (9) and mitochondrial function (i.e., lower respiratory rate and enzyme activity in muscle mitochondria fractions) (37, 45). Studies performed in vivo found that, compared with young adults, elderly subjects had a lower rate of phosphocreatinine (PCr) resynthesis after exercise, which is directly related to the rate of oxygen consumption during exercise (9, 30). Furthermore, the inorganic phosphate to phosphocreatine (Pi-to-PCr) ratio at any given power output, which reflects the balance between ATP hydrolysis (energy utilization) and ATP resynthesis (energy production), is greater in old than in young men (7). These observations indicate that muscle oxidative capacity and the ability to generate adequate ATP for muscular work are diminished in old compared to young adults and implies that glucose may be preferred over fatty acids as a fuel during exercise in old persons.

**Substrate Metabolism**

Most of the studies investigating the effect of aging on substrate metabolism during exercise focused on measuring the respiratory exchange ratio (RER) to determine whole-body fat and carbohydrate oxidation rates. During brief (3–8 min) stages of incremental exercise, RER at any given absolute exercise intensity was greater in old compared with young subjects (11, 23, 33, 35). This suggests that old subjects rely more on carbohydrate than fat as a fuel during exercise performed at the same absolute intensity, which was supported by higher blood lactate levels during submaximal exercise in older subjects (3, 35, 41, 42). However, given the lower aerobic capacity (VO_{2max}) in old than young persons (e.g., 7, 16, 25, 37–39), a greater dependence on carbohydrate for energy in old persons would be expected during exercise performed at the same absolute, but higher relative, intensity (6, 22, 36). Few studies evaluated the effect of aging on substrate oxidation during more prolonged (≥30 min) exercise, and the results are conflicting. During exercise performed at the same relative intensity, RER has been reported to be lower (16), the same (44), and higher (41) in elderly compared to young subjects. However, these studies did not carefully control for dietary intake, training status (44), and lactate threshold (16), which can affect RER. In a study of sedentary, lean young
(26 ± 2 years) and old (73 ± 2 years) subjects, matched on gender, body mass index, and fat-free mass (FFM), we found that RER was higher (and fat oxidation was lower) in the older subjects during 60 min of cycle ergometer exercise performed at either the same absolute or relative intensity (39). In addition, carbohydrate oxidation, particularly muscle glycogen utilization, was higher in older than younger subjects during exercise performed at the same absolute intensity but lower in older than younger subjects during exercise performed at the same relative intensity (39). Therefore, the available data indicate that aging is associated with significant alterations in substrate oxidation during exercise, manifested by a shift from using fat to carbohydrate as a fuel during prolonged exercise.

A large portion of the increased supply of fatty acids provided to skeletal muscle during exercise is derived from lipolysis of adipose tissue triglycerides. Adipose tissue lipolytic rate increases 2–3 fold during endurance exercise (21, 24, 36) and is mediated by increased β-adrenergic stimulation (2, 17). We have found that total fatty acid rate of appearance (Ra) in plasma during exercise performed at the same relative intensity (50% VO_2max) was ~35% lower in old (73 ± 2 years) than in young (26 ± 2 years) subjects, who were matched on FFM (39). However, fatty acid Ra during exercise performed at the same absolute intensity (~800 ml O_2 consumed/min) was higher (~35%) in the older than in the younger group.

Despite greater FFA release into plasma during exercise performed at the same absolute intensity, whole-body fat oxidation was lower in the old than in the young subjects. Therefore, metabolic alterations within skeletal muscle itself must have been responsible for the lower rate of fat oxidation during exercise in older than younger subjects, because adipose tissue lipolysis and plasma FFA availability were not rate limiting. Therefore, it is likely that the aging-related decrease in muscle respiratory capacity contributes to the shift in substrate oxidation.

**Effect of Endurance Exercise Training**

In young adults, endurance exercise training increases skeletal muscle mitochondrial enzyme activity and respiratory capacity (19). In addition, training increases the oxidation of fatty acids, and spares muscle glycogen and blood glucose utilization during submaximal exercise (19, 20). This response is primarily mediated by an increase in the oxidation of non-plasma fatty acids, presumably derived from intramuscular triglycerides, because training decreases the lipolysis of adipose tissue triglycerides and the oxidation of plasma fatty acids during exercise (20).

Endurance training in elderly people increases skeletal muscle mitochondrial enzymes and respiratory capacity (43). In addition, the Pi-to-PCr ratio in muscle at any given power output in trained older men was lower compared with older sedentary men but similar to the ratio observed in sedentary young men (7).

We evaluated the effect of 16 weeks of supervised endurance training on substrate kinetics and oxidation during cycle ergometer exercise in elderly persons (40). Training did not affect whole-body lipolytic rate but decreased glucose Ra and caused an increase in fat oxidation and a decrease in carbohydrate oxidation during exercise to values observed in untrained young adults. The shift in substrate oxidation was likely due to changes within skeletal muscle itself, possibly an increase in the fractional oxidation of plasma fatty acids taken up by muscle and/or an increase in the use of intramuscular triglycerides, because plasma-free fatty acid availability (FFA Ra) during exercise did not change.
Summary

In summary, aging is associated with a shift in substrate oxidation, from fat to carbohydrate, during moderate intensity endurance exercise. This shift is presumably caused by age-related changes in skeletal muscle itself, including decreased skeletal muscle respiratory capacity, rather than fatty acid availability. Endurance training in elderly subjects increases muscle respiratory capacity, decreases glucose production and oxidation, and increases fat oxidation, thereby correcting or compensating for the alterations in substrate oxidation associated with aging.

References


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