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Lipid metabolism in the elderly

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Adiposity increases with age. The size of the adipose tissue mass is determined by the balance between the recruitment of lipid substrates (ie free fatty acids) from adipose tissue and their subsequent oxidation by respiring tissues. Thus, change in the liberation of free fatty acids from adipocytes, the capacity of respiring tissue to oxidize free fatty acids or a combination of both may contribute to the age-related increase in body fat. This review focuses on studies that have examined the effect of age on free fatty acid release and the capacity of respiring tissues to oxidize fat. *In vitro* studies have shown that hormonal and pharmacological stimulation of lipolysis diminished with age. Despite this cellular defect, however, *in vivo* studies suggest that fatty acids are recruited from adipose tissue in excess of the energy demands of the body in older individuals. The capacity of respiring tissues, in particular skeletal muscle, to oxidize fat declines with age. The age-related decrease in fat oxidation is related to a reduction in both the quantity and oxidative capacity of respiring tissue. Taken together, these results suggest that an age-related decrease in the capacity of respiring tissues to oxidize fat, rather than decreased free fatty acid release, is a more likely determinant of lipid imbalance and the age-related increase in adiposity. Interventions designed to increase the mass or oxidative capacity of respiring tissue, therefore, may be effective in counteracting the age-related reduction in fat oxidation.
Descriptors: aging; lipid metabolism; free fatty acids; adipose tissue; fat-free mass
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Introduction

Aging is associated with undesirable changes in body composition. Body fat increases with age (Brozek, 1952; Poehlman *et al*, 1995) and is preferentially stored in the abdominal compartment (Shimokata *et al*, 1989). Body fat accumulation, especially in the abdominal region, increases the risk for cardiovascular disease and diabetes in the elderly (Bjorntorp, 1992; Després *et al*, 1994; Hubert *et al*, 1983). Recent estimates suggest that the elderly population (>65 y) will double by the year 2040 (Brock *et al*, 1990). Thus, understanding the mechanisms regulating changes in adiposity with age has important public health implications.

Several studies suggest that a reduced capacity to oxidize fat may contribute to fat accumulation (Raben *et al*, 1994; Zurlo *et al*, 1990). Aging is associated with reduced fat oxidation at rest (Nagy *et al*, 1996), following a meal (Roberts *et al*, 1996) and during exercise (Sial *et al*, 1996). The age-related reduction in fat oxidation, therefore, may promote the accumulation of total and central body fat. At present, however, the mechanisms underlying changes in fat oxidation with age are not clear.

Fat oxidation is primarily a function of two processes, the release of fatty acids from adipose tissue and the capacity of respiring tissues to oxidize fatty acids. Changes in fat oxidation with age, therefore, may be due to a reduction in the recruitment of free fatty acids from adipose tissue, a reduced capacity of respiring tissues to oxidize free fatty acids or a combination of both. In this review, we consider studies that have examined the effect of age on adipose tissue free fatty acid release and the capacity of respiring tissues to oxidize fat.

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Effects of age on the recruitment of fat substrates: *in vitro* studies

Lipolysis is regulated by numerous hormones, including catecholamines, glucagon, adrenocorticotropic hormone, growth hormone, prostaglandins, thyroid hormones, glucocorticoids and sex steroid hormones (Bjorntorp, 1991; Remade & Hauses, 1989). Hormonal regulation of lipolysis may be affected by the aging process. Thus, the following section will consider studies that have used *in vitro* approaches to examine age-related changes in the regulation of lipolysis in isolated adipocytes.

Early studies showed that the ability of catecholamines to stimulate lipolysis was reduced in elderly subjects (James *et al*, 1971; Östman *et al* 1969) as a result of decreased adipose tissue adrenergic responsiveness (Dillon *et al*, 1984; Vestal *et al*, 1979). Studies in rodents provide insight into the mechanisms underlying age-related changes in lipolysis. A diminished response of the receptor/G protein/adenylyl cyclase membrane complex or alterations in the cyclic AMP signaling pathway have been shown to occur with age in rats (Gregerman, 1994). Other studies have shown increased sensitivity to antilipolytic agents, such as adenosine, in older rats (Green & Johnson, 1989; Hoffman *et al*, 1984). A recent study comparing young lean versus old obese Sprague Dawley rats was performed to examine age effects on stimulatory (G_S) and inhibitory (G_i GTP-binding proteins. G_{i1} and G_{i2} concentrations were markedly higher in adipocyte membranes of older rats compared to younger rats. The authors did not, however, find age-related differences in adenosine receptors or adenylyl cyclase activity. This led them to propose that higher concentrations of G_{i1} and G_{i2} in older rats were likely to explain observed age effects on stimulated lipolysis (Green *et al*, 1995). Although it is difficult to extrapolate results obtained in rodents to humans, these studies provide insight into the sub-cellular basis for changes in lipolysis with age.

A recent study by Lönnqvist *et al* (1990) examined this issue in humans. Subcutaneous adipocytes isolated from young and elderly individuals were treated with various hormones and pharmacological agents to identify the step in the lipolytic signal transduction pathway that was affected by age. Similar to prior studies, basal lipolysis did not differ between age groups. However, when stimulated through α-adrenoreceptors by either isoprenaline or norepinephrine, lipolysis was markedly reduced in older individuals. Inhibition of lipolysis through α_2-adrencceptors was not affected by age. Using agents acting selectively at different levels of the lipolytic cascade and radioligand experiments, the investigators found that the reduction in agonist-induced lipolysis in the elderly was most likely attributable to decreased activation of protein kinase A, the hormone-sensitive lipase complex or a combination of both (Lönnqvist *et al*, 1990).

In summary, according to previous studies in both rats and humans, aging diminishes catecholamine stimulation of lipolysis. Although mechanisms involved in this reduction are unclear at present, they may involve protein kinase A, the hormone-sensitive lipase complex, the G-protein adenylyl cyclase complex or other steps in the cyclic AMP signaling cascade. Further studies are needed to elucidate the sub-cellular mechanisms underlying age-related changes in lipid mobilization. It should be kept in mind, however, that *in vitro* measurements of lipolysis in isolated adipocytes do not always correlate with *in vivo* measures (Lillioja *et al*, 1986).

Effects of age on the recruitment of fat substrates: *in vivo* studies

The effect of age on the *in vivo* rate of appearance of free fatty acids in the circulation has been studied under a variety of experimental conditions using isotope dilution methodology. In response to brief starvation (60–82 h), Klein *et al* (1986) found a similar rate of appearance of palmitate, a proxy measure of adipose tissue free fatty acid release, between younger and older individuals. However, when palmitate appearance was expressed per unit of fat mass, a 60% lower rate of appearance of palmitate was noted in older individuals suggesting that the lipolytic response to fasting is diminished with age. Similarly, Arciero and co-workers showed that the lipolytic response to caffeine was reduced in older compared to younger men (Arciero *et al*, 1995). After caffeine ingestion (5 mg/kg fat-free mass), the rate of appearance of free fatty acids increased 125% in younger subjects, but did not change in older men. However, because (1) the dose of caffeine was given relative to fat-free mass and (2) fat mass was greater in older compared to younger men, the exposure of adipose tissue to caffeine was twice as great in younger (40 mg/kg fat mass) compared to older men (17 mg/kg fat mass). Thus, whether the decreased lipolytic response to caffeine in the elderly men was due to age, *per se*, or the dose of caffeine cannot be determined.

Studies by Sial *et al* (1996) showed that the lipolytic response to exercise was reduced with age. During 60 minutes of submaximal exercise (50% of VO_2 max), the rate of appearance of free fatty acids was lower in older compared to younger individuals. Collectively, these results suggest, in agreement with *in vitro* experiments, that the lipolytic response to a variety of experimental conditions is reduced with age.

One possible conclusion from the aforementioned *in vitro* and *in vivo* results is that age is associated with a reduced capacity to mobilize free fatty acids from adipose tissue stores. Reduced free fatty acid mobilization may, in turn, decrease fat oxidation by limiting substrate supply (Groop *et al*, 1991). However, when the age-related impairment in free fatty acid mobilization is examined in the context of the energy demands of the body, a different conclusion is reached. That is, when examined relative to the energy needs of the body, free fatty acid release is not impaired in the elderly. In fact, free fatty acids are released in excess of energy needs in older individuals when compared to younger controls. For example, under resting conditions, free fatty acid rate of appearance is greater in older men and women despite reduced resting energy expenditure (Bonadonna *et al*, 1994; Toth *et al*, 1996). Moreover, during exercise of the same caloric expenditure, the rate of appearance of free fatty acid was greater in older compared to younger individuals (Sial *et al*, 1996). Finally, following a brief fast, the rate of appearance of palmitate was 26% higher in older compared to younger individuals when expressed relative to lean body mass, the metabolically-active component of body mass. Thus, when considered relative to the energy demands of the body or the metabolically-active tissue mass, aging is not associated with impaired free fatty acid release.

The mechanisms underlying the age-related increase in free fatty acid release relative to the energy demands of the body are not known. In humans, the release of free fatty acids is primarily regulated by inhibitory modulators, such as insulin (Kather *et al*, 1985). Aging is associated with reduced sensitivity to the anti-lipolytic effect of insulin in isolated adipocytes (Bolinder *et al*, 1983). Moreover, *in vivo* studies show that both the time course for the suppression of plasma free fatty acids (Coon *et al*, 1992) and the dose–response suppression of free fatty acid appearance by insulin (Bonadonna *et al*, 1994) are diminished with age. Thus, resistance to the anti-lipolytic effect of insulin may account for the excess release of free fatty acids in older individuals. It should be pointed out, however, that increased free fatty acid release in older individuals may simply result from increased adipose tissue mass. Indeed, the rate of appearance of free fatty acids are either similar between older and younger individuals or greater in younger individuals when expressed per unit adipose tissue mass (Bonadonna *et al* 1994; Klein *et al*, 1986). Whatever the mechanism, reduced free fatty acid availability secondary to diminished release of free fatty acids from adipose tissue *does not* appear to be a factor contributing to reduced fat oxidation with age.

Effect of age on fat oxidation

On an absolute basis (mg/min or μmol/min), resting, postabsorptive fat oxidation declines with age (Calles-Escandon *et al*, 1995; Nagy *et al*, 1996). However, because aging is also associated with a reduction in resting energy expenditure (Poehlman & Horton, 1990), the decline in the absolute rate of fat oxidation may simply result from a decrease in energy expenditure. In support of this contention, we and others have found no difference in postabsorptive respiratory quotient between younger and older men (Roberts *et al*, 1996; Toth *et al*, 1996). Because respiratory quotient is an indicator of the relative proportion of fat being oxidized and is not dependent on resting

energy expenditure, these results suggest no effect of age on postabsorptive fat oxidation. Moreover, Nagy *et al* (1996) found that statistical control for resting energy expenditure abolished the age-related decline in fat oxidation. Taken together, these results suggest that the age-related decline in the absolute rate of resting fat oxidation is the result of reductions in resting energy expenditure. Thus, aging does not appear to be characterized by a reduction in resting, postabsorptive fat oxidation.

In contrast, age is associated with a reduction in fat oxidation during exercise (Sial *et al*, 1996) and in the postprandial state (Roberts *et al*, 1996). Sial *et al* (1996) found that during exercise of the same caloric expenditure, older individuals oxidized less fat than younger individuals. The difference in fat oxidation between the age groups was not due to differences in energy needs since, by design, the energy expended during exercise was similar in both groups. Moreover, because the rate of appearance of free fatty acids during exercise was higher in older compared to younger subjects, the reduced fat oxidation in older individuals is not likely explained by a reduced availability of free fatty acids. In the postprandial state, Roberts and coworkers found a greater increase in the respiratory quotient in older compared to younger subjects indicating reduced fat oxidation (Roberts *et al*, 1996). Because respiratory quotient was examined, age-related differences in postprandial fat oxidation were likely independent of postprandial caloric expenditure. Taken together, these findings suggest that the ability to increase fat oxidation in response to increased free fatty acid availability (during exercise or postprandial) is impaired with age and that this defect is not explained by an age-related decrease in energy expenditure.

Why is fat oxidation reduced in older individuals during exercise and following a meal? Substrate availability is not a likely explanation since free fatty acid release is similar or higher during exercise and following a meal in older compared to younger individuals (Jackson *et al*, 1982; Sial *et al*, 1996). Thus, in older individuals, it would appear as if the respiring tissue mass did not respond to increased free fatty acid availability by increasing fat oxidation. The capacity of metabolically active tissue to oxidize fat is a function of both the mass and oxidative capacity of these tissues. Changes in the size and/or oxidative capacity of metabolically active tissue, therefore, may contribute to age-related differences in fat oxidation. The following section will review studies that have examined age-related changes in the size and oxidative capacity of metabolically active tissue to explore the possible mechanisms underlying the age-related reduction in the capacity to oxidize fat.

Mass of metabolically active tissue

In humans, fat-free mass is the best proxy measure of the metabolically active tissue mass. Fat-free mass declines with age in both men and women (Brozek, 1952; Flynn *et al*, 1977; Poehlman *et al*, 1992; 1993). Thus, it is plausible to hypothesize that the reduction in fat-free mass with age partially explains the decline in fat oxidation. Under resting conditions, this hypothesis is probably true. Fat-free mass is the primary determinant of resting energy expenditure and, as detailed above, the age-related reduction in resting energy expenditure largely accounts for the decrease in the absolute rate of fat oxidation. Changes in fat-free mass, however, are not a likely cause of decreased fat oxidation during exercise and in the postprandial state. In both cases, the lower fat oxidation in older individuals was found to be independent of energy expenditure. Therefore, changes in the oxidative capacity of fat-free tissue, rather than changes in tissue mass, are a more likely explanation for the age-related reduction in exercising and postprandial fat oxidation.

Oxidative capacity of fat-free mass

Fat-free mass is a heterogenous compartment composed of several different tissue and organ systems. To examine systematically the effect of age on this compartment of body mass, the oxidative capacity of each organ and tissue system should be measured in both younger and older individuals. This is not feasible, however, because of methodological and anatomical constraints. Presently, skeletal muscle is the only tissue that has been studied in detail. Because skeletal muscle is the primary tissue responsible for changes in substrate oxidation during exercise, the data reviewed below will be helpful in exploring the basis for age-related differences in exercising fat oxidation. Following a meal, however, skeletal muscle accounts for a smaller portion of changes in postprandial metabolism (ie 30–35%), with splanchnic tissues accounting for the majority ($\sim$50%; Jensen *et al*, 1995). Thus, changes in the oxidative capacity of skeletal muscle are not likely to be the sole contributor to age-related changes in postprandial fat oxidation. This caveat notwithstanding, the following section will review studies that have examined changes in skeletal muscle oxidative capacity with age.

The majority of studies examining the effect of age on the oxidative capacity of skeletal muscle have measured the activity of various skeletal muscle enzymes. In general, the glycolytic capacity of skeletal muscle is maintained with age (Rogers & Evans, 1993). In contrast, the activity of enzymes involved in oxidative metabolism (eg succinate dehydrogenase; citrate synthase; cytochrome c oxidase) and β-oxidation of fatty acids (eg H 3-hydroxyacyl-CoA dehydrogenase) are reduced with age (Coggan *et al*, 1992a, b; Rooyackers *et al*, 1996). These enzymatic changes would have the net effect of decreasing fat oxidation relative to glucose oxidation and may partially explain the reduction in exercising fat oxidation observed in older individuals (Sial *et al*, 1996). Evidence to support this notion is provided by studies which show an increase in both the activity of enzymes involved in fat oxidation (Coggan *et al*, 1992a, b) and exercising fat oxidation (Sial *et al* 1998) following training. Furthermore, because endurance training is not associated with increased free fatty acid release in the elderly (Poehlman *et al*, 1994; Sial *et al*, 1998), changes in fat oxidation are likely due to intrinsic changes in the ability of skeletal muscle to oxidize fat during exercise and not to differences in free fatty acid availability. Collectively, these results suggest that age-related reductions in the capacity of skeletal muscle to oxidize fat may partially explain the lower exercising and postprandial fat oxidation in older individuals. Moreover, these studies suggest that aerobic exercise may be effective in counteracting the age-related reduction in the oxidative capacity of skeletal muscle.

Consequences of age-related changes in lipid metabolism

The picture that emerges from the above discussion of changes in lipid metabolism with age is one of increased

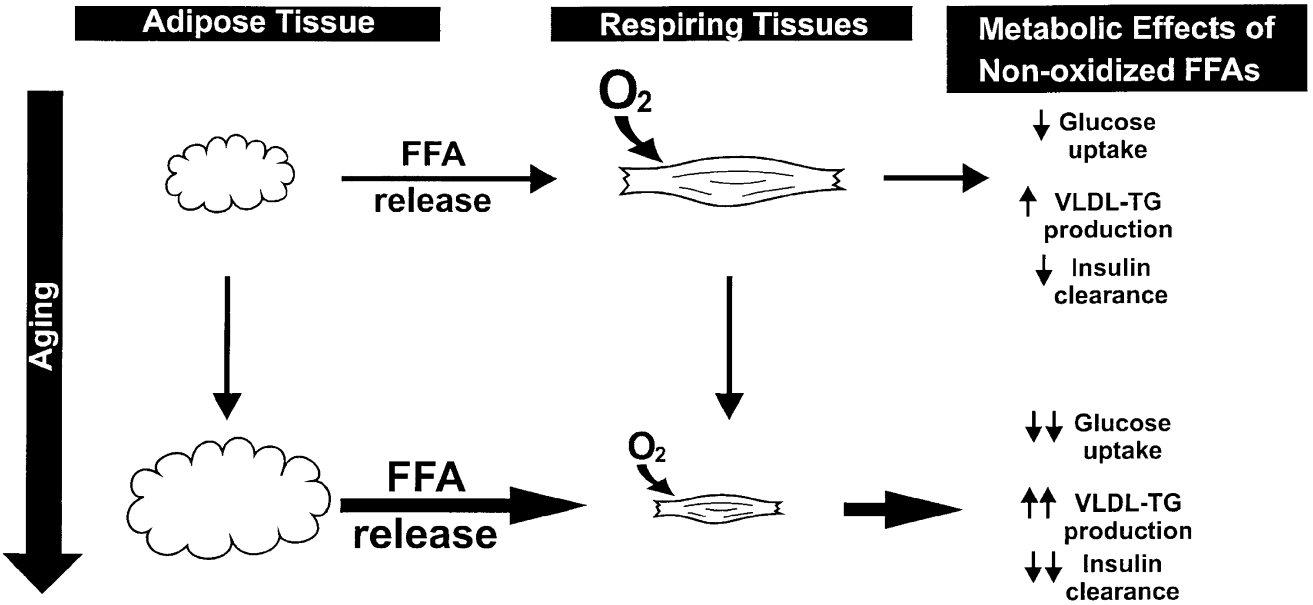

Figure 1 Age-related changes in adipose tissue free fatty acid release, capacity of tissues to oxidize free fatty acids and the metabolic effects of non-oxidized free fatty acids. Aging is associated with an increase in adipose tissue mass and a reduction in the mass of oxidative tissue and its capacity to oxidize fat (O_2). The increased release of free fatty acids in older individuals in excess of the energy needs and/or oxidative capacity of respiring tissues increases the amount of non-oxidized free fatty acids. Excess non-oxidized free fatty acids with age may have several adverse metabolic effects.

availability of free fatty acids in excess of the energy needs or the oxidative capacity of fat-free tissue (Figure 1). Aside from the effects that these changes in lipid metabolism may have on body fat accumulation, their immediate consequence is to increase plasma free fatty acid concentration and/or the non-oxidative disposal of free fatty acids. Increased plasma free fatty acid concentration and increased non-oxidative disposal have several adverse consequences. An increase in plasma free fatty acid concentration could lead to increased glucose production (Fanelli *et al*, 1993), impaired insulin-stimulated glucose uptake (Boden *et al*, 1994) and decreased hepatic insulin extraction (Peiris *et al*, 1986). Together, these changes would have the net effect of promoting the development of hyperinsulinemia and insulin resistance.

The primary route for the non-oxidative disposal of free fatty acids is incorporation into triglyceride-rich VLDL particles in the liver (Havel *et al*, 1970; Wolfe *et al*, 1990). Thus, increased non-oxidative disposal of free fatty acids with age would contribute to the development of an atherogenic lipid profile. Collectively, changes in lipid metabolism with age that contribute to increased plasma free fatty acid concentrations or increased non-oxidative disposal may contribute to increased risk for the development of diabetes and cardiovascular disease. Interventions that increase the capacity of respiring tissues to utilize free fatty acids, therefore, may be beneficial in preventing the development of chronic disease in the elderly.

Summary

Although free fatty acid release is impaired with age under a number of experimental conditions, when examined relative to the energy needs of the metabolically-active tissue, the release of free fatty acids is actually greater in older compared to younger individuals. Thus, free fatty acid availability does not appear to be rate limiting for fat oxidation. Instead, a reduction in the size and/or oxidative capacity of the metabolically-active tissue mass is probably a more likely determinant of reduced fat oxidation. The reduction in oxidative capacity of skeletal muscle with age, however, does not appear to be an immutable consequence of the aging process. Aerobic exercise training increases fat oxidation both at rest and during exercise, possibly by increasing the enzymatic capacity for fat oxidation. Thus, if reduced fat oxidation contributes to age-related changes in adiposity and risk for chronic disease, interventions designed to increase the quantity or oxidative capacity of metabolically active tissue may be effective in improving the health status of elderly individuals.

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