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Obesity in the elderly: is faulty metabolism to blame?

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Abstract

The fastest growing segment of the US population, and that of other developed countries, is the oldest-old (aged >85 years). Many children born after the year 2000 in countries with the longest lived residents may live to see their 100th birthday. The combination of reduced mortality along with reduced fertility in developed countries is producing ‘population aging’, and the comorbidities associated with aging are becoming important public health issues. Age-associated obesity is one such important public health issue. Aging is associated with significant changes in body composition, including loss of skeletal muscle mass and increased visceral fat accumulation. The loss of muscle mass is accompanied by a disproportionate decline in muscle strength (up to three-times greater than the loss of mass), indicative of reduced muscle ‘quality’ or muscle dysfunctionality. Aging is characterized by markedly reduced physical activity and a drop in resting metabolic rate that is disproportionate to the loss of muscle mass, with a shift towards preferentially oxidizing carbohydrate at the expense of fat. A combination of these factors may act to increase muscular lipid infiltration and decrease insulin sensitivity; however, the cause and effect relationship remains undetermined. Changes in cellular energy (i.e., ATP) requirement owing to decreased ion channel activity, decreased protein synthesis or increased mitochondrial energy efficiency may underlie the decreased resting metabolic rate. Increasing energy demand through physical activity may alleviate some of the adverse metabolic changes that are associated with aging.

Keywords

aging; body composition; elderly; metabolic rate; mitochondrial function; physical activity

Obesity continues to be a leading public health concern in the USA [1]. The increasing prevalence of obesity in adolescents and adults has captured the attention of the media and scientific world. The prevalence of obesity among the aged and elderly population is less often

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discussed. The fastest growing segment of the US population, and that of other developed countries, is the oldest-old (aged >85 years). Many children born since the year 2000 in countries with the longest lived residents may live to see their 100th birthday, if the present yearly growth in life expectancy continues throughout the 21st century [2]. Although this increase in life expectancy is a remarkable achievement, individuals who attain the oldest-old age category are also the most susceptible to disease and disability [3]. The combination of reduced mortality along with reduced fertility in developed countries is producing 'population aging' [2], and the comorbidities associated with aging are becoming an important research initiative. Age-associated obesity is one such important research initiative [4,5].

Obesity among those aged 65 years and older increased by an average of 3.8% per year during the 1990s in the Netherlands, followed closely by the USA, the UK and Italy [6]. Obesity increases the aged individuals' susceptibility to disability and poor health outcomes, such as arthritis, stroke and diabetes [7]; however, obese elderly individuals do not necessarily die sooner than those who are not obese [8]. Therefore, even if obesity remains stable until the year 2030, the number of diabetes cases is estimated to more than double worldwide [9], with the greatest risk in people aged 65 years and older. Simply stated, obese elderly individuals are more likely to become disabled and will live a larger proportion of their remaining years with a chronic condition, reducing their quality of life and adding to the public healthcare burden.

In this article, we will review the shifts in body composition that occur with age that result in excess fat mass (particularly relative to muscle mass), especially in visceral and ectopic depots. We will discuss changes in caloric intake and energy expenditure with age, including decreases in resting metabolic rate and physical activity, and a shift towards preferential oxidation of carbohydrate, as well as how these factors may be related to the accumulation of excess fat. We will also review the evidence for 'dysfunctional' aged skeletal muscle with particular regard to changes in mitochondrial activity, and how this may impact upon the accumulation of excess body fat. In order to accomplish these goals, we conducted PubMed literature searches using specific keywords that are relevant to our review topic. We included human clinical studies together with appropriate animal studies that investigated outcomes related to our topic of interest, regardless of subject number, study conditions, duration of intervention or testing methods, although we attempted to limit our review to the most recent findings.

Changes in body composition with age

There is a well-known loss of muscle mass with age [10,11], whereas subcutaneous adipose tissue remains relatively stable and ectopic lipid and visceral fat increase [12,13]. Much of these data come from the Health, Aging and Body Composition (Health ABC) study, a longitudinal study of 3075 normal-functioning, community-dwelling men and women aged 70–79 years, designed to determine how changes in body composition influence the risk for functional limitations [14]. Volunteers were assessed at baseline and again after 3 years. Body composition was measured by dual-energy x-ray absorptiometry and computed tomography, and leg strength was measured by isokinetic knee extensor strength. Over the course of 3 years, all groups, regardless of sex or race, lost leg muscle mass and strength, although this loss was almost twofold higher in men compared with women [14]. On average, lean mass declined by 1% per year across genders and races, and accompanying the decline in muscle mass was a three-times greater loss of muscle strength. This decline in muscle 'quantity' and 'quality' with aging suggests a dysfunctional component to aging skeletal muscle. Changes in body weight were also examined in relation to the loss of muscle mass. Those individuals who lost more than 3% body weight over 3 years lost significantly more muscle mass and strength than those who maintained or gained weight; however, a gain in weight did not confer additional benefits in muscle strength, despite slight increases in muscle mass [14].

This inevitable loss of skeletal muscle mass with age has been called ‘sarcopenia’ (i.e., deficiency of relative skeletal muscle mass) [15]. Sarcopenia in old age is associated with impaired functional performance, increased physical disability and increased risk for falls [16]. Sarcopenia is associated with increased fat infiltration of skeletal muscle, but the cross-sectional nature of these observations limits our ability to define the cause and effect. Fat infiltrates skeletal muscle under a variety of conditions, including certain disease states (e.g., muscular dystrophy and McArdle’s disease) [17,18]. Fat may also infiltrate the muscle as a consequence of overweight, obesity or inactivity [19–21], particularly between muscle fibers (i.e., intermuscular lipid). Emerging 5-year longitudinal data from the Health ABC study provide evidence that, regardless of changes in body weight or subcutaneous adipose tissue, fatty infiltration of skeletal muscle increases as a function of age [22]. Moreover, this age-dependent increase in muscle lipid infiltration occurs concomitantly with the disproportionate loss of muscular strength. Again, study volunteers who gained weight over 5 years were not protected from the loss of muscle strength despite small increases in muscle size, and those who lost weight also lost subcutaneous fat and muscle mass; however, intermuscular fat still increased. This study, along with earlier findings [14], clearly indicates that age is independently associated with skeletal muscle lipid infiltration and muscular weakness, indicating a reduced muscle ‘quality’ (i.e., dysfunctionality with age).

Muscular lipid infiltration may play an important role in the adverse metabolic profile associated with muscle loss in aging. Intermuscular fat has been correlated with insulin resistance in numerous studies independently of body weight, fat mass or percentage body fat [23–26]. Muscular lipid accumulation is higher in insulin-resistant and Type 2 diabetic individuals and is related to insulin resistance [27,28]. However, aging is also characterized by the accumulation of visceral fat [29] and hepatic lipid [30], both of which are associated with insulin resistance and metabolic markers of cardiovascular disease and systemic inflammation [31]. Therefore, it is not clear which fat depot is most responsible for the metabolic abnormalities observed with aging, although the mechanism by which intramyocellular lipid accumulation (especially diacylglycerol and ceramide accumulation) contributes to skeletal muscle insulin resistance has been defined and is largely accepted [32]. Furthermore, and most importantly, the mechanism(s) underlying fat accumulation (primarily in ectopic/visceral depots) with age is unknown.

Why does body composition change with age?

Energy intake

Data regarding dietary energy intake are often unreliable and prone to self-reporting error [33]; this also holds true for older adults [34]. Therefore, it is difficult to assess whether changes in dietary intake with age contribute to the observed shifts in body composition. Dietary energy intake does not appear to increase with age and, in fact, most data point to decreased caloric intake with age [35], owing to changes in social environment, family status, taste perception, appetite and chewing abilities [36]. Over the years, inadequate dietary protein has been thought to contribute to the loss of skeletal muscle in aging [37], since suboptimal protein intake (<100% of the recommended daily allowance) has been documented in persons aged 70 years or older [101]. Although cross-sectional data have tended not to support a relationship between protein intake and muscle mass with aging [38,39], recent longitudinal data demonstrated that, over 3 years, elderly volunteers (aged 70–79 years) who were in the highest quintile of dietary protein intake lost approximately 40% less total lean mass and appendicular lean mass compared with those in the lowest quintile [40]. Adjustment for changes in fat mass attenuated the relationship; however, it remained significant, indicating that protein may function independently of changes in body weight in order to maintain lean mass. The effects of dietary intake, particularly protein, on body composition with age warrants further investigation;

however, longer-term intervention studies need to be conducted in order to determine a cause and effect relationship.

Energy expenditure

As stated previously, the available data do not support a role for changes in energy intake in explaining the increase in fat mass and loss of muscle mass observed with aging. Therefore, we are left with the other side of the equation – energy expenditure. Total daily energy expenditure consists of three components: resting metabolic rate (RMR), the thermic effect of food and energy expenditure of physical activity.

Resting metabolic rate—Resting metabolic rate is closely related to body composition. Fat-free mass (FFM), fat mass, gender and age explain approximately 78% of the variability in RMR [41]. Early cross-sectional studies demonstrated significant age-related declines in RMR [42], and we (and others) have recently confirmed these cross-sectional findings [43]. Longitudinal data also support the decline in RMR; Keys *et al.* reported a 1–2% decline in basal metabolic rate per decade from the second to the seventh decade of life [44], and it is likely that metabolic rate continues to decline in later decades. The decrease in RMR can be largely explained by the concomitant decrease in FFM [45] and primarily decreased muscle mass [46]. However, we have recently confirmed earlier reports that RMR decreases with age disproportionately to the decline in FFM [47], indicating that there are additional factors that change with age that act to decrease RMR, besides the loss of metabolically active tissue. It is unknown which variable(s) act independently to reduce RMR; however, reduced activity of the thyroid axis (i.e., decreased T3 serum concentrations) is associated with reduced metabolic rate [47], and reduced activity and sensitivity of the sympathetic nervous system may also be partially responsible [48]. Recently, a decrease in organ volume with age was proposed in order to explain the decrease in metabolic rate; however, data have not supported this hypothesis. Although the volume of most organs is reduced in elderly persons, this decrease does not appear to help to explain the drop in RMR [49].

Respiratory quotient—The respiratory quotient (RQ; production of CO₂ over O₂ consumption in rested and fasting conditions) tends to increase with age [41]. A higher RQ is associated with a higher risk for weight gain [50,51] and implies preferential oxidation of carbohydrate over fat, which could lead to excess fat storage [21]. Indeed, Rising *et al.* found that, over 7 years, RQ increased significantly, while body fat also increased [52]. The preferential use of carbohydrate substrate with age, which coincides with increased body fat, may contribute to increased obesity in older individuals.

Physical activity—The benefits of regular physical activity for maintaining a healthy metabolic profile through increased muscle mass (and/or quality) and decreased fat mass are well known. Physical activity in the elderly, and particularly among the oldest-old, is markedly decreased [43]. Whether the decrease in muscle mass and muscle strength, in combination with reduced exercise endurance, causes reduced physical activity, or *vice versa*, remains under debate. What is certain is that there is a persistent drop in activity levels with age, and this decrease is particularly remarkable among the oldest-old [43]. Exercise training in aged volunteers does not appear to attenuate the loss of muscle mass; however, it does prevent the loss of muscle strength (indicating improved muscle quality) and also inhibits fat infiltration into the muscle [53]. Similarly, large cross-sectional studies demonstrate that aged subjects who have the highest activity energy expenditure have the greatest FFM; however, even a relatively high activity energy expenditure does not appear to protect against the loss of muscle mass over a 5-year follow-up period [54].

In combination, the drop in RMR, the increase in RQ and the reduction of physical activity probably act synergistically to create ideal conditions for the accumulation of body fat and the development of insulin resistance with age (Figure 1 & Table 1). In the next section, we elaborate upon the mechanisms that are potentially responsible for the disproportionate drop in RMR and how increasing physical activity may attenuate the adverse metabolic consequences.

Mitochondrial function with aging: responsible for ‘faulty’ metabolic rate?

Aging is often associated with reduced skeletal muscle mitochondrial function [30,55]. In particular, ATP synthesis in skeletal muscle is reduced in aged persons both *in vivo* at rest [30] and *in vitro* under maximally stimulated conditions [55]. In conjunction with this decline are decreases in mitochondrial enzyme activities [56], protein synthesis rates, gene expression [57] and mitochondrial DNA (mtDNA) abundance [58]. These changes occur concomitantly with an increase in insulin resistance [59] and changes in body composition [60]. However, it is still unknown whether mitochondrial dysfunction is the cause of insulin resistance or whether insulin resistance causes mitochondrial dysfunction, with data supporting both arguments [28,61].

There is a generalized decline in muscle protein synthesis with aging [58,62]. This decrease may occur throughout the whole body; however, evidence supports a decrease in the synthesis of mitochondrial and myosin heavy chain protein and an increase in the synthesis of sarcoplasmic proteins [63]. A decrease in mitochondrial biogenesis is also believed to occur with aging [64]; however, the precise mechanism responsible is unknown. A leading theory is decreased AMP kinase (AMPK) activity in aged cells. Chronic AMPK inactivation is linked to a marked decrease in mitochondrial biogenesis in aged animals [65], and reduced AMPK activity was recently found to be associated with aging-related increases in insulin resistance and decreased intracellular fat oxidation [66]. It is currently unknown whether similar mechanisms are responsible for decreased mitochondrial biogenesis in aged human skeletal muscle, and whether this is a primary defect of aging or a consequence of decreased physical activity. Certainly, experimental data suggest that exercise training (particularly aerobic exercise) increases mitochondrial biogenesis in aged human volunteers.

One recent study found that skeletal muscle ATP synthesis rates were reduced in lean and obese elderly subjects compared with lean and obese young volunteers; however, insulin sensitivity was decreased only in the obese subjects, regardless of age [67]. This suggests a disconnection between mitochondrial function and insulin sensitivity. Furthermore, endurance-trained young and elderly individuals have similar insulin sensitivity, despite persistently lower mitochondrial ATP production in the elderly subjects [68], which indicates that insulin sensitivity can be improved with physical activity without completely restoring mitochondrial function.

Most data suggest a decrease in mitochondrial content as the potential underlying cause of other mitochondrial changes observed with age. However, changes in mitochondrial efficiency may also occur as part of the aging process. This is reflected as a change in the amount of ATP produced per unit of oxygen consumed (termed the P:O ratio), and can be measured *in vivo* and *in vitro*. Animal studies suggest that mitochondrial efficiency may increase with aging [69]. In this animal study, mitochondrial efficiency was tested by measuring the degree of thermodynamic coupling and optimal thermodynamic efficiency, as well as mitochondrial proton leak, determined in both the absence (basal) and presence (fatty acid-induced) of palmitate. In 180 day-old rats, skeletal muscle mitochondria displayed higher respiratory capacity and energy efficiency compared with 60 day-old rats, and fatty acid-induced proton leak was decreased. Moreover, the degree of efficiency was inversely related to insulin

sensitivity (homeostatic model assessment index) [70]. A similar increase in energy efficiency in aged human skeletal muscle may explain the previously mentioned changes in mitochondrial function. In addition, increased mitochondrial efficiency may lead to a reduced utilization of energy substrate (particularly fatty acids), leading to the accumulation of intracellular lipid metabolites, thus contributing to insulin resistance.

Conclusion & future perspective

From our review of the literature, we can summarize the following key points:

- There is an inevitable loss of muscle mass with age and a concomitant increase in fat mass, particularly in the abdominal region;
- Resting metabolic rate, even after adjusting for the loss of lean mass or organ mass, is decreased with age;
- Physical activity also decreases with age, resulting in an overall significant decrease in total daily energy expenditure;
- Although dietary energy intake does not increase significantly, and may actually decrease with age, this does not appear to compensate for the decline in energy expenditure, resulting in body fat accumulation and associated metabolic abnormalities (i.e., insulin resistance).

Still under debate is why metabolic rate declines disproportionately with age (Figure 1). In this article, we offer possible contributing factors: reduced cellular energy (i.e., ATP) requirement owing to decreased ion channel activity, decreased protein synthesis or increased mitochondrial energy efficiency (P:O ratio); changes in the hormonal milieu (e.g., thyroid profile, reduced testosterone and estrogen); and decreased sympathetic nervous system activity/sensitivity. Whether decreased lean mass (especially muscle) is a cause or a consequence of the reduction in physical activity is unknown. However, increasing the amount of daily physical activity does attenuates these negative age-associated changes by increasing the cellular energy requirement. In addition, physical activity enhances insulin sensitivity and may prevent ectopic fat infiltration, even though it might not completely rescue the age-associated changes in skeletal muscle mitochondrial function.

In conclusion, changes in resting metabolic activity occur with age that may contribute to the accumulation of body fat and insulin resistance. The inclusion of daily physical activity and moderate (high protein) caloric intake may help to mediate these age-associated metabolic changes by limiting ectopic fat accumulation (e.g., visceral, skeletal muscle and liver), optimizing mitochondrial activity and largely restoring a healthy metabolic profile. Future studies should focus on physical activity versus dietary (i.e., calorie restriction or specific protein modifications) interventions in aged adults in order to determine the effects on insulin sensitivity, visceral and ectopic fat accumulation and skeletal muscle mitochondrial function. Results may lead to improved recommendations for exercise and diet in the older adult population that aim to maintain optimal body composition and metabolic health.

Executive summary

Introduction

- Obesity is a leading public health concern in the USA and the prevalence of obesity in adults aged 65 years and older is increasing.
- Obese elderly individuals are more likely to become disabled and will live a larger proportion of their remaining years with a chronic condition, reducing their quality of life and adding to the public healthcare burden.

Changes in body composition with age

- Muscle mass decreases with age, whereas subcutaneous adipose tissue remains relatively stable, and ectopic lipid and visceral fat increase.
- On average, muscle mass declines 1% per year; however, muscle strength declines at a rate that is three-times greater. This decline in muscle ‘quality’ with aging suggests a dysfunctional component to aging skeletal muscle.
- Intermuscular fat accumulation is common to aging and has been correlated with insulin resistance in numerous studies independent of body weight, fat mass or percentage body fat.

Why does body composition change with age?

- Dietary energy intake does not appear to increase with age and, in fact, most data point to decreased caloric intake owing to changes in social environment, chewing abilities and taste perception.
- Resting metabolic rate decreases with age, out of proportion to the loss of muscle mass, and may be related to the reduced activity of the thyroid axis, the reduced activity and/or sensitivity of the sympathetic nervous system and decreased organ volume.
- The respiratory quotient tends to increase with age, implying preferential oxidation of carbohydrate over fat.
- Physical activity decreases with age, particularly among the oldest-old. The drop in resting metabolic rate, the increase in respiratory quotient and the reduction in physical activity most likely act synergistically to create ideal conditions for the accumulation of body fat and the development of insulin resistance with age.

Mitochondrial function with aging: responsible for ‘faulty’ metabolic rate?

- Synthesis of ATP in skeletal muscle is reduced in aged persons both *in vivo* at rest and *in vitro* under maximally stimulated conditions.
- There is a generalized decline in muscle protein synthesis with aging along with a decrease in mitochondrial biogenesis, which may be due to decreased AMP kinase activity in aged cells. This suggests a lower energy demand in aged cells.
- Mitochondrial efficiency may increase with aging, producing similar quantities of ATP with less oxygen. The combination of reduced energy demand and greater efficiency may result in a lesser requirement to oxidize energy substrate (particularly fatty acids), leading to accumulation of intracellular lipid metabolites, thus contributing to insulin resistance.
- These mitochondrial changes may underlie the unexplained drop in resting metabolic rate with age.

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Figure 1. Energy expenditure is reduced in elderly individuals

(A) Energy expenditure in kcal/day in young versus elderly individuals. All components of daily energy expenditure are reduced in the elderly population. (B) RMR plotted against FFM in elderly (aged 90–101 years; $n = 103$), old (aged 60–75 years; $n = 58$) and young (aged 20–35 years; $n = 53$) subjects. The data clearly depict a progressive decrease in RMR for a given amount (kg) of FFM from young to old to elderly subjects. Reasons for the decline in RMR per kg of FFM with aging are unclear.

AEE: Activity energy expenditure; FFM: Fat-free mass; RMR: Resting metabolic rate; TEF: Thermic effect of food.

Data from [43].

Table 1

Hypothetical data on energy expenditure and body composition from a sedentary young (~30 years old) male and a sedentary elderly (~75 years old) male.

	Young	Elderly
<i>Energy expenditure (kcal)</i>		
Resting metabolic rate	1600	1350
Thermic effect of food	280	200
Activity energy expenditure	920	450
Physical activity level	1.75	1.48
Total	2800	2000
<i>Body composition</i>		
Weight (kg)	75	75
Body fat (%)	15	25
Fat-free mass (kg)	64	56
Fat mass (kg)	11	19
Visceral adipose tissue	Low	>Three-times higher
Intrahepatic lipid	Low	>Two-times higher
Intramuscular lipid	Low	~30% higher

Data are based loosely on results from the Louisiana Healthy Aging Study, a cross-sectional assessment of predictors for healthy aging in more than 850 men and women aged from 20 to more than 100 years [43].