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The translation of age-related body composition findings from rodents to humans

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Abstract

The objective of this review is to highlight changes in body composition in rodent models as a result of healthy aging in order to enhance translational research. Aging is associated with alterations in body composition, particularly fat mass and fat-free mass, which may be accompanied by adverse health effects, especially nearing middle- to old-age. In humans, it is generally understood that fat mass tends to increase while fat-free mass concurrently declines with aging. However, the effect of aging on body composition in rodent models is less-well studied, and how these changes compare and contrast with observations in humans has not yet been fully elucidated. Though, it appears as though the constituent-level alterations occur in humans and rodents at different life phases thereby having a potential effect on the outcomes of basic biomedical research. Though highly strain-dependent, this review suggests that FM changes begin at a much earlier life phase in rodents than in humans. Conversely, FFM appears to increase throughout middle-age and into old age in rodents whereas middle-age is associated with the initiation the subsequent decline of FFM in humans. Given the essentiality of rodent models in basic biomedical research, careful consideration of these differences in age-related BC findings is imperative when the research is aimed for human translation.

Introduction

Body composition, particularly the amount and topography of body fat mass (FM) and the amount and constituents of fat-free mass (FFM), is an essential biomarker for health and longevity. In children and adults, the ongoing epidemic of obesity, characterized by an excess accumulation of body fat, has uncovered the importance of FM in both short- and long-term health. Thus, the measurement of body composition has become an increasingly valuable diagnostic and management tool and has implications in various disorders and

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

pathological states including, but not limited to, metabolic syndrome, type 2 diabetes, cardiovascular disease, cancer, chronic obstructive pulmonary disease, and eating disorders, as well as in healthy growth and development and physical training.^{1–5}

The use of animal models continues to be the cornerstone of basic biomedical research due to interspecies similarities in anatomy, physiology, and genetics. Experimentation with rats and mice has provided valuable insight into the etiologies and mechanisms of human disease and has allowed for the assessment of novel treatments before their application in humans. By association, the evaluation of body composition in animal models is an important outcome measure in research ultimately aimed for human translation.

Several methods are available for assessing body composition in both humans and animal models. In clinical practice, assessments of BC include simple measurements or indices including body weight (BW), skinfold thickness, body mass index (BMI, calculated as weight/height²), waist-hip ratio, and waist circumference. However, methods that assess both FM and FFM provide a more comprehensive depiction of nutritional status. Among such methods, dual-energy X-ray absorptiometry (DXA) is the most suitable as it measures appendicular and whole-body lean mass and FM regardless of FFM hydration.⁶ The “gold standard” for assessing the BC of animal models is chemical carcass analysis; however, this method is a lengthy and terminal procedure. Non-invasive, *in vivo* techniques include DXA, computed tomography (CT), magnetic resonance imaging (MRI), total body electrical conductivity (TOBEC), isotope dilution, and quantitative magnetic resonance (QMR).^{7–11}

In most mammals, including humans, healthy aging is associated with alterations in body weight (BW) and BC, specifically in FM and FFM, and BMD, with marked interspecific and intraspecific differences in the degree and rate of change. With regards to humans, there is a general agreement that BW and body fat percentage (BF%) generally increase with age due to the accumulation of FM and subsequent decline in FFM.¹² The rate of BW and FM increase varies by sex and ethnicity and may be attenuated by external factors, like a decline in physical activity, poor nutrition, and the onset of diseases, as well as age-related endocrine and metabolic alterations.^{13–17} Nevertheless, detrimental physiological effects often accompany age-related changes in BC. An increase in FM, particularly visceral abdominal tissue, is associated with cardiovascular disease, stroke, and type 2 diabetes mellitus.^{18–20} The age-related involuntary decline in physical strength related to the degenerative loss in skeletal muscle (SKM) is a condition medically defined as sarcopenia. More recently, a syndrome known as sarcopenic obesity (SO) has emerged.²¹ Characterized by the co-presence of high FM and sarcopenia, SO is associated with an increased risk of frailty, disability, morbidity and mortality than sarcopenia or obesity alone.²²

The growth pattern of rodents is similar to that of humans. Though, differing strains of rats and mice exhibit wide-ranging adiposity levels at any given time point throughout their lifespan suggesting that genetics strongly influence BC and BW in aging.^{23–25} In the laboratory setting, extrinsic factors may also intentionally or unintentionally influence BC, including nutritional manipulations, the opportunity for exercise, and other environmental conditions related to animal husbandry and housing (e.g. noise, temperature, cage density).^{26–28}

This review aims to discuss fundamental changes in BW and BC, specifically, fat and fat-free mass, in both humans and mice and rat models occurring throughout the lifespan but particularly during middle-age through senescence.

Body weight and aging

Concerning BW, both rodents and humans exhibit a linear increase with age. In humans, several cross-sectional and longitudinal studies suggest that BW increases during early to middle adulthood^{12,29}, peaking or slightly increasing into old age^{30–32}, and then either remains stable or gradually declines.^{33,34} Using longitudinal data from the HUNT Study in Norway, a prospective-population based study with an 11-year follow-up conducted on over 45,000 men and women, Drøyvold *et al.* found that BW steadily increased up until the seventh decade.³⁵ Though the rate of increase in BW appears to subsequently decline with age as the men and women in the age groups 20–29 and 60–69 years had the highest and lowest mean increase in BW, respectively. After 70 years of age, BW, on average, began to decline steadily.³⁵ Similarly, Jackson *et al.* found that the increase in BW leveled off around age 69 in men.³⁴ After that, it decreased at a non-linear rate with an average loss of 0.8 and 1.97 kg in the seventh and eighth decades, respectively.

In the laboratory setting, *ad libitum* fed mice typically experience a peak in BW around 20 to 24 months of age.^{23,36–38} As a result of a longer lifespan, rats experience this peak later, at around 24 to 32 months of age.^{23,39,40} When considering the current human life expectancy (80 years) and the average life expectancy for rodents (24 months and 3 years for mice and rats, respectively), BW peaks at a similar life phase across species during old age.^{41,42} Specifically, the BW peak observed in mice and rats is equivalent to 67 – 80 and 53 – 71 human years, respectively, as a correlation of average lifespans.^{41,42}

Furthermore, methods to correlate murine developmental stage to human age are proposed by Dutta *et al.*⁴¹ and Sengupta.⁴² Rodent and human reproductive senescence cycle with acyclicity occurring at around 15 months in mice and between 15 and 20 months in rats. When the average onset of menopause (51 years) is considered, 8.82 mice days and 11.8 rat days are equivalent to one human year. Thus, the peak in BW begins to occur at the equivalent of around 68 – 80 years in mice and 59 – 73 years in rats.^{41,42}

Unintentional weight loss by both humans and rodents is a physiological marker for imminent death.^{43,44} In humans, it has been reported that BW may begin to decline in the 7th decade³⁵ due to the onset of psychiatric conditions, malignancy, and nonmalignant gastrointestinal diseases.⁴⁵ Thus, in relatively healthy elderly populations, BW may remain relatively stable throughout the 7th decade of life and beyond.^{32,46} Similarly, rodents may experience a decline in BW in old age or BW may remain relatively stable up until the end of life. The decline in BW reportedly begins around 22 to 26 months in mice^{23,36–38} and 28 to 32 months in rats^{23,39,40}, which correlates to about 73 – 87 and 62 – 71 human years for mice and rats, respectively.^{41,42} Furthermore, BW maintenance up until the post-senescence phase is observed within rodent strains. In male and female Hsd:ICR (CD1) mice, the age-related decline in BW began just two months before death.⁴³ Similarly, in healthy BN rats, BW plateaus at around 25 months of age up and a gradual decline begins at around 32

months of age, the strain's 50% survival rate.³⁹ However, because the average post-senescence period is markedly shorter in mice (60 days) than in rats (485 days), the BW stability observed by mice up until the end of life is substantially greater than the average human life expectancy. When the average human female senescence phase (10,585 days) is considered, weight stability observed in 26-month-old mice is correlated with 109 human years.^{41,42} Nevertheless, age-related BW changes occur in similar life phases in both humans and rodents (Table 1).

Fat mass and aging

In humans, FM follows a similar trajectory as BW during aging. Using longitudinal data from the Fels Study, Guo *et al.* observed a peak FM and FM% between 40 and 60 years of age for both sexes with an approximate annual gain of 0.37 kg in men and 0.41 kg in women.¹² In a cross-sectional study of 1,866 Italian men and women, Coin *et al.* observed a progressive accumulation of FM beyond the fifth decade with a peak in median body fat mass index occurring around 70–80 years of age.⁴⁷ Furthermore, sex may also be an influencer of age-related FM alterations. After a 6-year follow-up of 557 pre- and postmenopausal French women, aged 31–89 years taking part in the Os de Femmes de Lyon (OFELY) Study, Sornay-Rendu *et al.* reported significant increases in FM until the seventh decade.⁴⁸ In contrast, Visser *et al.* measured body composition changes during a 1- and 2-year follow-up of 2,040 men and women aged 70–79, using serial DXA data from the Health, Aging, and Body Composition (Health ABC) Study.³⁰ An increase in total body fat was observed only in men. Nevertheless, maximum adiposity appears to be obtained between 70 and 80 years of age irrespective of sex.^{12,34,49}

The occurrence of further changes in FM in subsequent years post-peak in BW remains unclear as it is highly variable among studies; however, FM appears to stabilize or gradually decline in old age, which may be attenuated by the presence or acquisition of disease. Jackson *et al.* measured body composition changes by DXA in 7,265 men aged 20 – 96 years taking part in the Aerobics Center Longitudinal Study.³⁴ The investigators observed that FM increased with aging, stabilized and then decreased slightly (0.25 kg) in the eighth decade.

Concerning rodents, mice reach maximum adiposity between 1 and 2 years of life^{36–38,50,51}, which correlates to approximately 40 – 80 human years.⁴¹ Furthermore, FM tends to decline at a slow rate with observations reportedly between 17 and 24 months of age in mice or soon thereafter^{36,38,50,51}, which is the equivalent to an estimated 57 – 80 human years.⁴¹ In rats, FM peaks between 20 and 31 months of age^{39,52–54}, which is the equivalent to anywhere between 44 and 71 human years of life when lifespans and life phases are considered. Thus, rodent strains that achieve maximum adiposity later in life are more closely correlated with the FM peak observed by humans. For example, FM peaks in BN rats at around 29 to 30 months followed by a gradual decline beginning at around 32 months of age³⁹ or the equivalent to a peak and decline in FM at around 65 and 75 human years, respectively.⁴²

Fat-free mass and aging

Fat-free mass (FFM) is composed of all non-fat tissues within the body including bone, total body water, muscle, organ tissues, and connective tissue, whereas lean body mass (LBM) includes the small percentage of essential fat found internally in organs and bone marrow. However, the usage of the terms FFM and LBM are often interchangeable.⁵⁵

Bone mass and LBM increases throughout childhood and adolescence to a point at which it peaks or plateaus. In females, the LBM peaks between 18 and 20 years of age and in males between 18 and 23 years of age, according to a longitudinal and cross-sectional study which assessed the bone mineral density, bone mineral content and LBM of 511 participants aged 13 to 29 years via DXA.⁵⁶

As a result of healthy aging, both the composition and contents of FFM change and the progressive decline is attributable primarily to a decrease in skeletal muscle and bone mass. Longitudinal and cross-sectional observations suggest that the decrease in FFM begins at an earlier age than FM loss, around 40 – 50 years.¹² Similarly, Jackson *et al.* reported that FFM was found to increase slightly from age 20 to 47 years and then decreased by 0.42 kg and progressively to 1.96 kg in the fifth and eighth decade, respectively.³⁴ However, the longitudinal study by Hughes *et al.*³² reported a 2.0% decline in FFM after 60 years of age in men, but not in women. Though for both sexes, greater baseline LBM or lesser baseline FFM results in a more significant degenerative loss of LBM.⁵⁷ Nonetheless, age-related FFM loss appears to be ameliorated through physical activity as losses are reportedly smaller in active than in sedentary individuals.^{12,58}

At the component level, SKM declines from approximately 40–50% of total body weight during young adulthood to 25% between 75 and 80 years of age.^{59,60} Furthermore, several prospective studies have suggested that muscle mass decreases by approximately 6% per decade after mid-life.⁶¹ Goodpaster *et al.*⁶² analyzed 3-year data from the Health, Aging, and Body Composition Study (HealthABC) to measure changes in skeletal muscle strength, mass, and quality in older, well-functioning Caucasian and African American adults. Irrespective of race and gender groups, they found a significant decrease in the amount of leg lean mass and strength over a 3-year period. Moreover, this decrease in strength and muscle quality was predominantly due to an accelerated loss of muscle mass and associated with increased fatness. Similarly, in a longitudinal study in older adults, aged 68 to 78 years, Fantin *et al.*⁶³ found that total FM did not change significantly at 5.5-year follow-up; however total, appendicular, and leg FFM significantly decreased independent of weight change, and the decline in FFM significantly increases the risk of developing a worsening disability.

In rodents, several longitudinal and cross-sectional studies suggest that FFM peaks during old age, nearing the second year of life with observations beginning at 18 months through 26 and 32 months for mice and rats, respectively.^{36,51,64} Unlike humans, FFM appears to remain relatively stable until the end of life.^{39,65–68} In C57BL/6J mice, LBM was reported to peak around 21 weeks of age and to also remain relatively stable up until the end of life,

around 24 months³⁸, which means that the alterations well into the 7th decade of human life when both lifespans and life phases are considered.⁴¹

Similarly, subsequent decline in FFM observed by the BN rat occurs at the beginning of the 7th human decade⁴² as a result of senescence observed at around 32 months of age.³⁹ Additionally, rats experience declines in SKM with age as seen in humans. In male Harlan SD rats, the SKM of the hind limb declines rapidly after 18 months of age, such that by 27 months, some are 60% smaller than at 6 months.^{69,70} However, bone mass, which accounts for 2.5% of BW, does not decline with age in rats.³⁹

As seen in humans, the opportunity for exercise in rodents has shown to mitigate the loss of FFM while concurrently preventing gains in BW and FM.²⁸ Compared to controls, physically active male and female C57BL/6J mice showed approximately 16% lower BW, 50% lower FM, and 15% greater LBM despite a window of opportunity for the voluntary exercise of only one year.⁷¹ Though, irrespective of exercise, FFM alterations as a result of the normal aging process appears to occur at a considerably later age in rodents than in humans.

Conclusion

Aging is associated with physiological and pathophysiological alterations in both humans and rodents with fundamental differences observed particularly in middle-age through senescence. Though highly strain-dependent, this review suggests that FM changes begin at a much earlier life phase in rodents than in humans. Conversely, FFM appears to increase throughout middle-age and into old age in rodents whereas middle-age is associated with the initiation the subsequent decline of FFM in humans. Given the essentiality of rodent models in basic biomedical research, careful consideration of these differences in age-related BC findings is imperative when the research is aimed for human translation.

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Table 1.

Age at peak body weight, fat mass, and fat-free mass in humans and rodents.

BODY WEIGHT			
Peak			
	Age	Life Span Correlation	Life Phase Correlation
Humans	70 – 80 yrs. ⁽¹²⁾		
Mice	20 – 24 mos. ^(23,36–38)	67 – 80 yrs.	68 – 80 yrs.
Rats	24 – 32 mos. ^(23,39,40)	53 – 71 yrs.	59 – 73 yrs.
Decline			
	Age	Life Span Correlation	Life Phase Correlation
Humans	7 th decade or stable ^(32,35)		
Mice	22 – 26 mos. ^(23,36–38)	73 – 87 yrs.	75 – 109 yrs.
Rats	28 – 32 mos. ⁽²³⁾ or stable until approaching end-of-life. ^(39,40)	62 – 71 yrs.	65 – 73 yrs.
ABSOLUTE FAT MASS			
Peak			
	Age	Life Span Correlation	Life Phase Correlation
Humans	70 – 80 yrs. ^(12,32,34,48,49,72)		
Mice	12 – 24 mos. ^(36–38,50,51)	40 – 80 yrs.	41 – 80 yrs.
Rats	20 – 31 mos. ^(26,39,53,73)	44 – 68 yrs.	52– 71 yrs.
Decline			
	Age	Life Span Correlation	Life Phase Correlation
Humans	>80 yrs. ⁽⁷⁴⁾		
Mice	17 – 24 mos. ^(36–38,50,51)	57 – 80 yrs.	58 – 80 yrs.
Rats	28 – 32 mos. ^(39,73)	62 – 71 yrs.	66 – 73 yrs.
FAT-FREE MASS			
Peak			
	Age	Life Span Correlation	Life Phase Correlation
Humans	18 – 23 yrs. ⁽⁵⁶⁾		
Mice	18 – 26 mos. ^(36,37,50)	60 – 87 yrs.	61 – 109 yrs.
Rats	28 – 32 mos. ^(39,73)	62 – 71 yrs.	66 – 73 yrs.
Decline			
	Age	Life Span Correlation	Life Phase Correlation
Humans	50 – 60 yrs. ^(12,32,72,75)		
Mice	22 – 27 mos. ⁽³⁶⁾ or stable until approaching end-of-life. ^(38,51)	73 – 90 yrs.	75 – 123 yrs.
Rats	28 – 32 mos. or stable until approaching end-of-life. ^(39,67,68,73)	62 – 71 yrs.	66 – 73 yrs.

Adapted from Sengupta (42) and Dutta *et al.* (41)**Life Span Correlation:** Assumes the average life expectancy of humans (80 years), mice (24 months), and rats (3 years).

Life Phase Correlation: Assumes the average reproductive senescence in mice (between 15 and 20 months) and rats (15 months) equivalent to the average age at onset of menopause (51 years) and the average days at which the female human survives the post-senescent phase (10,585) as equivalent to the post-senescence period in mice (2 months) and rats (485 days).

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