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Obesity and related consequences to ageing

Magdalena Jura · Leslie.P. Kozak

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Abstract Obesity has become a major public health problem. Given the current increase in life expectancy, the prevalence of obesity also raises steadily among older age groups. The increase in life expectancy is often accompanied with additional years of susceptibility to chronic ill health associated with obesity in the elderly. Both obesity and ageing are conditions leading to serious health problems and increased risk for disease and death. Ageing is associated with an increase in abdominal obesity, a major contributor to insulin resistance and the metabolic syndrome. Obesity in the elderly is thus a serious concern and comprehension of the key mechanisms of ageing and age-related diseases has become a necessary matter. Here, we aimed to identify similarities underlying mechanisms related to both obesity and ageing. We bring together evidence that age-related changes in body fat distribution and metabolism might be key factors of a vicious cycle that can accelerate the ageing process and onset of age-related diseases.

Keywords Metabolic syndrome · Lean mass · Brown adipose tissue · Expandability

M. Jura · L. Kozak (✉)
Institute of Animal Reproduction and Food Research, Polish Academy of Science, ul. Tuwima 10, 10-748 Olsztyn, Poland
e-mail: l.kozak@pan.olsztyn.pl

M. Jura
e-mail: m.jura@pan.olsztyn.pl

Introduction

Recent improvements in public health care and impressive advances in medical science have significantly extended life expectancy, and the proportion of people over 65 continues to rise. Accompanying advancing age chronic diseases, such as stroke, heart attacks, and diabetes, are more frequent (Kirkland 2013). Comprehension of the key mechanisms of ageing and age-related diseases has become an essential matter. Currently, a major global health problem has emerged because of the growing frequency of obesity, a condition that increases the prevalence of associated diseases, morbidity, and premature mortality (Willett et al. 1999). Obesity is a very complex and multifactorial problem. Body weight can be affected by environmental conditions, genetic factors, and by energy imbalance when energy intake exceeds energy expenditure (Haslam and James 2005). Also, socio-economic conditions play a crucial role in the obesity development (Sacks et al. 2009). Both genders and all racial groups at all ages are dealing with obesity (Yosipovitch et al. 2007; Obesity and overweight by WHO). Additionally, ageing is associated with an increase in abdominal white adipose tissue (AT) (Miard and Picard 2008; Barzilai et al. 2012) and fat deposition in skeletal muscle (Slawik and Vidal-Puig 2006), which significantly affect insulin sensitivity. Changes in lifestyle of the elderly, as they enter retirement, may cause chronic positive energy balance state, leading to excess fat tissue accumulation, a condition that accelerates the development of age-related diseases (Tchkonia et al. 2010). It is becoming apparent that the

obese state leads to reduced life span and body health consequences, which are similar to those found in advanced ageing (Ahima 2009). Since fat is usually the largest organ in humans, age-related changes in AT function may result in profound systemic changes. In this review, we seek to show that the obesity state per se may affect the ageing process.

Ageing

Ageing is associated with the accumulation of changes in a person's physiology over time. The rate of ageing varies across species and is genetically based (Bowen and Atwood 2004). In humans, the ageing phenotype is characterized by hearing loss, visual impairment (Roth 2015), wrinkles and other skin conditions (Yosipovitch et al. 2007), a steady decline in many cognitive processes (Deary et al. 2009), a decrease in sex and growth hormones (Masternak and Bartke 2012), and increased inflammation (Starr et al. 2009). The elderly are the fastest-growing segment of the population, and it is estimated that by 2050, there will be two billion people over the age 60 and they will outnumber the children (Glatt et al. 2007). Even though scientists have shown that caloric restriction extends life expectancy (Harrison et al. 1984; Bartke 2000; Anderson et al. 2009), ageing remains the single largest risk factor for heart attacks, stroke, cancers, diabetes, and most chronic diseases. Another important aspect is that with age people become often less active, which contributes to reduced total energy expenditure and has effects on energy balance (Slawik and Vidal-Puig 2006). Usually, AT increases in middle age and declines at the end of life (Visser et al. 2003), and during the process of ageing, fat is redistributed from subcutaneous to abdominal depots and to liver, muscle, and other ectopic sites (Kuk et al. 2009). These features may per se determine organic failure through lipotoxicity. Moreover, AT of lean individuals is affected by age, i.e., decline in pre-adipocyte replication, decreased adipogenesis, and increased pro-inflammatory cytokines (Tchkonia et al. 2010). Thus, it is possible, equally for lean and obese individuals, that there are age-related changes in the phenotype of AT that can affect energy metabolism and systemic insulin resistance.

Data on age-related changes in obesity has led some researchers to postulate that obesity could be considered as a condition of premature metabolic dysfunction resembling ageing (Tchkonia et al. 2010; Burt Solorzano and McCartney 2010; Niemann et al. 2011). Other studies claim that molecular pathways of regulation involved in obesity and ageing are divergent and specific or at least not overlapping (Miard and Picard 2008). It is unclear how to describe or measure tissue age, but it is possible that obesity increases the biological age of some tissues and cell types or at least strongly influences the ageing process. The extensive literature on AT dysfunction in obesity may possibly unravel the mechanisms contributing to metabolic dysfunction linked to ageing. Importantly, aged rodents develop increased fat mass with close similarities to aged human (Huffman and Barzilai 2009). The identification of common functional genes and biomarkers for ageing and obesity obtained from several microarray studies conducted in different species, including humans, by comparing young versus old individuals may reveal metabolic relationships between obesity and ageing (Edwards et al. 2007; Ida et al. 2003).

Hypoxia, widely recognized as characteristic of pathological situations, such as wound healing or ischemic disorders, can also affect both AT and adipocytes (Trayhurn et al. 2008). This condition may play a role in tissue ageing as white AT in obese individuals has been shown to be hypoxic (Trayhurn et al. 2008; Ye et al. 2007; Hosogai et al. 2007) (reviewed by Trayhurn et al. 2008 (Trayhurn et al. 2008)). Research on human adipocytes has revealed that hypoxia induces the expression of certain inflammation-related adipokines, for example adiponectin, leptin, and interleukin-6. Additionally, it has been shown that macrophages respond to hypoxia with changes in the production of inflammatory mediators (Trayhurn et al. 2008; Lewis et al. 1999). Generally, hypoxia, which is thought to be partly responsible for inflammation in obesity (Trayhurn et al. 2008), might also affect the ageing process, since ageing itself is characterized by decrease in O_2 supply to tissues (Valli et al. 2015).

Adipose tissue and obesity

Humans have evolved to take advantage of rare periods of food abundance to store energy as AT for use during periods of food scarcity. Consequently, those human beings with greater AT mass had a greater chance to survive famine (Genne-Bacon 2014). The thrifty gene hypothesis

postulates that due to dietary insufficiency during evolution, humans, as well as animals, evolved a highly efficient metabolism that increased the risk of obesity during times of plenty. Presently, under the conditions of stable food supplies, which contribute to a positive energy balance, the costs of such adaptive mechanisms are weight gain and obesity (Genne-Bacon 2014).

The AT, apart from storing energy, also plays an important role in immune response, mechanical protection, endocrine function, and thermoregulation (Rosen and Spiegelman 2014). Studies on rodents and humans showed that the body of a healthy, lean individual is composed of approximately 15–28 % fat mass (Avram et al. 2005a) with low variance; however, a high-fat diet (HFD) induces obesity with a wide variability of fat mass accumulation as seen in some mouse genotypes (Moitra et al. 1998; Hausman et al. 2001; Koza et al. 2006). Similarly, a wide range of phenotypes occur at the metabolic and functional levels in obese individuals, where excessive AT accumulation may lead to the metabolic syndrome (Kirkland 2013). Nevertheless, certain AT levels have beneficial effects on growth, reproduction, and glucose metabolism (Moitra et al. 1998). Studies on mice have shown that life without white AT is possible, but it brings serious physiological consequences such as insulin resistance, diabetes, reduced leptin levels, and early death (Moitra et al. 1998). The importance of AT was shown with the use of a mouse model of lipoatrophic diabetes (Gavrilova et al. 2000). Fat tissue transplantation from healthy mice into lipoatrophic mice resulted in a dramatic reversal of the hyperglycemia, accompanied by improved muscle insulin sensitivity, lowered insulin concentrations, and decreased amounts of fat deposition in muscle. Moreover, studies on athletes have estimated that for a healthy physiology, the minimal AT amount is 3 % for men and 12 % for women (Measuring and Evaluating Body Composition). In conclusion, the absence of adipocytes is metabolically detrimental (Gavrilova et al. 2000).

Several mechanisms associated with longevity and age-related metabolic dysfunction take place in AT (Tchkonia et al. 2010). It has been shown that there is a strong negative effect of obesity on the life span of young adults, particularly white men (Fontaine et al. 2003). The authors of a study on over 9000 citizens of the USA have shown that 20–30-year-old severely obese men have a 10-year reduction in their life expectancy (Fontaine et al. 2003). Furthermore, people who exceed an optimal body weight by 20 % have an increased probability of suffering from obesity-related diseases (Avram et al. 2005a). This reflects the relevance of a balanced amount of AT for metabolic homeostasis and body function. Additionally, the localization of fat deposition is also important. Lean individuals with relatively greater amounts of intra-abdominal fat than subcutaneous fat are at increased risk for diabetes (Pischon et al. 2008). In humans, increased adiposity develops usually between the third and seventh decades of life and it is usually independent of changes in body weight (Pischon et al. 2008). It has been shown that regardless of the gender, subcutaneous fat decreases and abdominal fat increases with age (Kuk et al. 2009). Elevated visceral fat accumulation is strongly associated with ectopic fat deposition in skeletal muscle, heart, liver, pancreas, or blood vessels, a trend leading to lipotoxicity in aged individuals (Slawik and Vidal-Puig 2006; Tchkonia et al. 2010; Tchkonia et al. 2006). Non-subcutaneous fat accumulation is known to be strongly associated with insulin resistance and dyslipidemia (Kuk et al. 2009). Currently, the utility of BMI as a predictor of type 2 diabetes mellitus is questioned, essentially because many abdominally obese older individuals have normal BMI, whereas highly muscled athletes can have an abnormal BMI (Kuk et al. 2009; Jiang et al. 2015; Mathus-Vliegen 2012). Despite stable BMI or body weight, ageing is associated with an increase in percent body fat by approximately 1 % per decade (Kuk et al. 2009). Carter et al. (2013) suggested that the negative effect of obesity on health is supported by research on longevity and that obesity might be viewed as a global epidemic linked with ageing-like cellular processes (Carter et al. 2013).

Ageing and metabolic contributors to ageing

Ageing is the most universal contributor to the decline of metabolic and health and is a main risk factor for various diseases (Kirkland 2013). Insulin resistance, shown to be common in older adults (Arum et al. 2014), represents a major component of the metabolic syndrome. Increasing abdominal obesity, often observed in the process of ageing, is a major contributor to insulin resistance and metabolic syndrome (Folsom et al. 1993). Moreover, ageing is associated with higher levels of pro-inflammatory cytokines, which are known to alter insulin action. Here, we bring together evidence

that age-related changes in body fat distribution and metabolism are key factors in a vicious cycle that can accelerate the ageing process and the onset of age-related diseases.

Inflammation and ageing, inflammaging

It has been well documented that ageing is associated with a decline in immune system function (De Martinis et al. 2005; Franceschi et al. 2000) linked to numerous infections and frequently with chronic diseases (Deleidi et al. 2015). Ageing also affects innate and adaptive immune systems (Shaw et al. 2013). Furthermore, it has been shown that caloric restriction in old animals reduces the levels of pro-inflammatory cytokines to levels comparable to those of young animals (Spaulding et al. 1997). Chronically elevated levels of pro-inflammatory markers, such as interleukin 6 (IL-6) or tumor necrosis factor-α (TNF-α), are key features of ageing since low-grade inflammatory activity in the elderly is common (Starr et al. 2009; Bruunsgaard et al. 2001). This pro-inflammatory environment has been defined as "inflammaging." TNF-α and IL-6 have become frailty markers of ageing in humans (Hernandez-Bautista et al. 2014); however, the mechanisms that cause and preserve high levels of these markers in ageing are poorly understood.

Inflammatory molecules that promote systemic low-grade inflammation are secreted by both immune cells and hypertrophic fat cells (Starr et al. 2009). In an obese state, the AT actively secretes different pro-inflammatory molecules such as TNF-α and IL-6 (Bastard et al. 2006), which exert their effects on metabolism. Macrophage infiltration, present in AT of mice-sensitive to diet-induced obesity (DIO), depends more on cells in the stromal vascular fraction of AT than fat cells per se (Tchkonia et al. 2010; Weisberg et al. 2003). Since high levels of IL-6 were observed in obese states and its concentration decreased after weight loss (Ryan and Nicklas 2004), obesity has been linked to inflammation (Deleidi et al. 2015). Although AT may be inflamed in obesity, a relationship between adipocyte size and IL-6 and TNF-α messenger RNA (mRNA) levels was not found (Hoffstedt et al. 2010). It has been suggested that fat cell size did not determine inflammation; thus, AT morphology is not involved in the release of inflammatory markers (Hoffstedt et al. 2010). A recent study on bacterial challenge showed dysregulation in homeostatic networks counteracting inflammation as obesity develops (Amar et al. 2007). The authors associated DIO with a form of immune paralysis.

In general, fat mass redistribution and increased fat mass accumulation with age lead to a failure in regulation of adipokine secretion (adiponectin or leptin are described in "Adiponectin" and "Leptin" sections) and in insulin sensitivity that is linked to local and systemic inflammation. It is probable that increasing incidence of obesity among the elderly may intensify and accelerate the problem of age-related inflammation processes with an increasing risk of developing insulin resistance, heart attack, stroke, or even cancer.

Adiponectin

Adiponectin, an adipokine secreted only from AT into the bloodstream, is involved in the energy homeostasis and regulation of glucose metabolism (Kern et al. 2003). Relevantly, this adipokine mediates insulin sensitivity and shows anti-inflammatory properties (Barzilai et al. 2012). Adiponectin not only diminishes liver free fatty acid influx but also prompts a decrease in circulating free fatty acids by increasing fatty acid oxidation in skeletal muscle and the stimulation of glucose uptake by adipocytes (Li et al. 2014). In healthy subjects with normal body weight, circulating adiponectin levels have a cyclic rhythm with a decline of up to 30 % during the night (Whitehead et al. 2006). In humans, high levels of circulating adiponectin have been associated with a reduced risk of cardiovascular disease (Zoccali et al. 2002).

Current studies on adiponectin and ageing revealed contradictory results; Koh et al. (2008) reported plasma adiponectin levels increasing with age (Koh et al. 2008), other groups reported no age-related changes in its levels (Li et al. 2014; Takenouchi et al. 2009), whereas others reported that the plasma adiponectin level/visceral fat ratio was decreased between 6 and 24 months of age in mice (Li et al. 2014). Li et al. (2014) hypothesized that the relative insufficiency of adiponectin secretion per visceral fat during ageing may be associated with an increased risk in the progression of ageing or cardiovascular disease (Li et al. 2014; Stenholm et al. 2010). In agreement, longitudinal studies showed a genetic predisposition of centenarians to have higher adiponectin levels associated with longevity (Gulcelik et al. 2013). Dysregulation of adiponectin in older

individuals may be due to loss of function of circulating adiponectin or a response to increased chronic inflammatory processes.

Studies on obese subjects showed that adiponectin levels are inversely correlated with body fat percentage in adults (Ukkola and Santaniemi 2002). Lower adiponectin concentrations in obese animals were associated with chronic inflammation, increased TNF-α, and altered glucose and insulin homeostasis (Hernandez-Bautista et al. 2014). Plasma adiponectin levels, examined in humans, were not only decreased in obese and diabetic subjects but were also inversely associated with measures of insulin resistance (Gulcelik et al. 2013). Obese subjects lost diurnal variations in adiponectin (Whitehead et al. 2006); however, plasma adiponectin levels increase following weight loss (Kern et al. 2003) and restore its daily rhythms (Whitehead et al. 2006).

Undeniably, adipocyte function goes beyond simple fat storage. The AT represents an active endocrine organ that plays multiple roles in body function. Lean individuals with small adipocytes are metabolically homeostatic, but enlarged adipocytes in overweight or obese subjects promote inflammation due to macrophage recruitment. In parallel with fat mass enlargement, as the metabolic role of adipocytes changes, the secretion of various hormones, such as adiponectin, is affected (Ukkola and Santaniemi 2002; Frederich et al. 1995). Since adiponectin naturally decreases with age and obesity accelerates the decline in adiponectin levels, one may speculate that obesity alters the ageing process through adiponectin regulation.

Leptin

Leptin, an AT-secreted hormone, stimulates fat oxidation (Minokoshi et al. 2002), inhibits food intake, and acts as a long-term internal measure of energy balance by interacting with appetite and satiety centers in the brain (Scarpace and Tumer 2001; Ahima and Flier 2000). Fundamental knowledge on the effects of leptin on energy balance was obtained with studies on genetically obese mice (Zhang et al. 1994; Tartaglia et al. 1995). The lack of circulating leptin in *ob*/*ob* mice (Zhang et al. 1994) or mutations to its receptor in *db*/*db* mice (Tartaglia et al. 1995) result in hyperphagia and obesity. Leptin mRNA, protein, and serum levels not only correlate with each other (Ahima and Flier 2000; Maffei et al. 1995) but also its serum levels were highly correlated with body fat mass content (Sinha et al. 1996). Serum leptin levels change after fasting and refeeding and are associated with changes in body weight and body fat content (Ahima and Flier 2000). The circadian profile of leptin is characterized by an increase between midnight and early morning hours in lean, obese, and obese non-diabetic human subjects (Sinha et al. 1996). Studies on rats found that the lowest leptin levels occurred during the day cycle, with a peak at the beginning of the night cycle after the rats started eating (Saladin et al. 1995). Thus, the cyclicity of AT leptin mRNA levels was associated with diurnal changes in food intake. Leptin expression was observed to rise after the peak of insulin secretion during the feeding cycle (Saladin et al. 1995). Human studies revealed leptin and insulin levels to be correlated, leading to the suggestion that the increase in leptin might be predictive of insulin resistance (Ahima and Flier 2000; Segal et al. 1996). In AT, leptin is known to inhibit insulin-binding and insulin-mediated effects on glucose transport (Carter et al. 2013; Zierath et al. 1998). Also, its availability influences lipogenesis and lipolysis, and since this hormone was shown to modulate the T cell immune response, it is thought to function as a pro-inflammatory adipokine (Carter et al. 2013). Recent studies have shown that although the complete absence of leptin leads to obesity (Ahima and Flier 2000; Zhang et al. 1994), leptin at excessive levels does not prompt a lean phenotype (Ahima and Flier 2000; Myers et al. 2012). Leptin expression occurs at high levels in animal models of obesity (Frederich et al. 1995; Sinha et al. 1996) and in human obesity (Lonnqvist et al. 1995). This phenomenon is called leptin resistance and is described as a reduced sensitivity with respect to the anorectic response to exogenously administered leptin (Carter et al. 2013).

Older individuals have higher leptin mRNA levels than young ones (Carter et al. 2013), and high concentrations of serum leptin have been found in lean, aged rodents (Li et al. 1997) and humans (Carter et al. 2013; Sanchez-Rodriguez et al. 2000). Youth is associated with sensitivity to leptin, while ageing is linked with a failure in leptin action independently of obesity and body fat distribution (Carter et al. 2013; Scarpace et al. 2000a). Comparison of young and aged individuals showed a decrease in mRNA, and serum leptin was observed after fasting at all ages (Scarpace and Tumer 2001; Li et al. 1998); however, the magnitude of this decrease is blunted with age (Li et al. 1998). Indeed,

studies on resistance to leptin administration revealed that old rats (30 months of age) with elevated adiposity presented threefold greater endogenous serum leptin levels than young individuals (6 months of age) (Scarpace and Tumer 2001; Scarpace et al. 2000a). Scarpace et al. (2000) has shown that 7 days of subcutaneous leptin administration increased its serum levels and diminished food intake with greater significance for young rats (Scarpace et al. 2000a), leading to the conclusion that older individuals are resistant to the effects of leptin (Scarpace et al. 2000a). Conversely, recent work demonstrated that in old non-obese and calorie-restricted rats, 7 days of intra-cerebroventricular leptin infusion efficiently decreased food intake (Petervari et al. 2014). Petervari et al. (2014) suggested that ageing per se does not promote leptin resistance development; rather, early appearance of obesity leads to the progressive loss of the hypermetabolic effects of leptin (Petervari et al. 2014).

Typically, obesity is associated with increased circulating leptin concentrations (Ahima and Flier 2000). Obese individuals exhibit leptin resistance, and its elevated concentrations fail to control hunger and body weight (Myers et al. 2012). Myers et al. (2012) concluded that increased leptin levels in obese subjects might be functionally relevant, since even extremely obese individuals demonstrate beneficial changes in satiety and energy expenditure upon weight loss (Sinha et al. 1996; Wing et al. 1996), although these changes are inhibited by exogenous leptin administration (Myers et al. 2012). As mentioned, studies on rodents demonstrated that aged individuals show reduced responsiveness to externally derived leptin (Scarpace et al. 2000a; Scarpace et al. 2000b). Thus, it has been proposed that leptin signaling might be impaired due to an age-related elevation in obesity and serum leptin levels (Scarpace and Tumer 2001; Petervari et al. 2014; Scarpace et al. 2000b). Maintaining stable AT mass and its function seems to be crucial for physiological homeostasis during the ageing process, which may involve regular leptin signaling (Carter et al. 2013). Since the leptin resistance observed in obese state and ageing share common metabolic alterations, it has been suggested that this hormone is central to the dysregulations observed in ageing and obesity, and its putative role in morbidity is anticipated (Carter et al. 2013).

Leptin research has broadened our knowledge of obesity and ageing interactions. High leptin level was reported to act as chemoattractant for macrophages (Carter et al. 2013), and leptin synthesis can be stimulated by infection (Ahima and Flier 2000; Sarraf et al. 1997) indicating an important link between nutrition and the immune system (Ahima and Flier 2000; Lord et al. 1998). Moreover, epidemiological studies have revealed that low leptin levels were linked to the pathophysiology of neurodegenerative diseases, including Alzheimer's disease (Marwarha and Ghribi 2012). Therefore, the maintenance of normal leptin levels and homeostatic activation of its signaling pathway seem to be key factors for successful ageing.

Lean mass decrease

The ageing process is accompanied by a reduction of muscle, bone mass, and strength levels with a concomitant increase of whole-body fat mass, especially visceral fat mass (Jiang et al. 2015). Skeletal muscle mass usually contributes up to about 50 % of total body weight in young adults and decreases during ageing to approximately 25 % of total body weight by 75–80 years of age (Short et al. 2004). For example, quadriceps muscle decreases by up to 40 % between the ages of 20 and 80 years (Lexell 1995). Accordingly, diminishing lean mass and percent lean mass with age (Jiang et al. 2015) is a major biomarker of ageing. It represents an irreversible biological process, where physical function generally declines with age, not only for those with a sedentary lifestyle but even in people who participate in regular and demanding exercise throughout their lives (Latorre-Roman et al. 2015). Recent studies have shown that an increase in a sedentary way of life and deterioration of physical condition accelerates the ageing process (Latorre-Roman et al. 2015). Comparison of older adult sport practitioners to those with a sedentary way of life showed that sport helps to maintain strength levels throughout ageing, despite the loss of muscle mass (Latorre-Roman et al. 2015).

Forbes et al. (1983) reported that most obese individuals, children as well as adults, have increased lean weight and that DIO results in both fat mass and lean mass augmentation (Forbes and Welle 1983). This and other results showing stable lean mass during the development of obesity (Hulens et al. 2001) suggest that carrying greater weight may have physical training-like effects (Hulens et al. 2001). There is confusion on how to interpret changes in lean mass associated with muscle separately from non-muscle fat-free mass, that is, liver, intestine, kidney, and heart, which indeed might be enlarged with the development of obesity (Masgrau

et al. 2012). Studies on rodents demonstrated that muscle mass was not changed under conditions of DIO (Chanseaume et al. 2007), whereas reduced muscle mass was found in genetic models of obesity (Kemp et al. 2009). In a study of sequential changes of protein synthesis in two types of skeletal muscles during long-term DIO, Masgrau et al. (2012) showed that the muscle mass of rats increased in the initial phase (16 weeks fed HFD) and decreased in the second phase (from 16 to 24 weeks fed HFD) of obesity development (Masgrau et al. 2012). Chronic exposure to lipid overload in obese individuals leads to an infiltration of fat into muscle, which is also a characteristic of the ageing process. It has been shown that the amount of intra-myocellular lipid deposition is correlated with the percentage body fat used as a proxy measure of adiposity (Dube and Goodpaster 2006).

These observations highlight the characteristic features of muscle mass in both obesity development and ageing. Changes in skeletal muscle are important because muscle is essential for locomotion and is the major site of insulin-mediated glucose uptake (Alvim et al. 2015). Although physical exercise is considered to be an anti-ageing therapy, weight loss in obese older adults is still heavily debated due to the potential loss of skeletal muscle or bone mass. Moreover, data supporting improvements in weight loss treatment of obese older adults are limited (Mathus-Vliegen 2012). Studies on rodents showed that muscle mass repair mechanisms, such as activation of a quiescent population of myogenic cells, is dysfunctional in older individuals (Kalyani et al. 2014; Tidball 2011). It has been suggested that defects in repair mechanisms are related to the tendency of ageing satellite cells to achieve an "adipocytic" phenotype (Kalyani et al. 2014).

p53

Initially associated with the regulation of cell proliferation (Reich and Levine 1984), the p53 molecule has been identified as the first known tumor suppressor that is inactivated in most human cancers (Lane and Benchimol 1990; Vogelstein et al. 2000). In homeostatic cells, the level of p53 protein is downregulated via the binding of specific proteins that promote p53 degradation via the ubiquitin/proteasome pathway. Most of the genes that promote p53 degradation are upregulated by p53, which leads to a regulatory loop that keeps p53 at very low levels in regular cells (Vousden 2002). Interestingly, increased p53 activity in skeletal muscle of older animals was recently associated with the ageing phenotype (Edwards et al. 2007). Global gene analysis comparing young and old mice revealed the activation of a p53-mediated transcriptional program (Edwards et al. 2007). Transcript levels measured in mouse gastrocnemius muscle at 5-month intervals, from 5 to 30 months, showed that expression of p53 and its transcriptional target p21 (cyclin-dependent kinase inhibitor 1A) occur already at 10 months of age. Edwards et al. (2007) showed that transcripts that are activated by p53, or whose gene products are known to bind p53, increase significantly with age, while the expressions of genes that are known to inhibit p53 activity decline in old mouse and human muscle (Edwards et al. 2007; Welle et al. 2004).

The p53 molecule was also shown to be present in AT. Yahagi et al. (2003) demonstrated that p53 and its target genes are highly induced in adipocytes of *ob*/*ob* mice in a fed state, leading to the negative regulation of lipogenic genes (Yahagi et al. 2003). Moreover, disruption of p53 in *ob*/*ob* mice fully suppressed the p53-regulated genes to the levels of wild-type subjects and partially restored expression of lipogenic enzymes. The authors suggested that the activation of the p53 gene might develop a negative feedback loop against abnormal fat accumulation in adipocyte cells (Yahagi et al. 2003). Another study on rodents showed that p53 expression in AT is a key component in the development of insulin resistance, which underlies age-related cardiovascular and metabolic disorders (Minamino et al. 2009). Upregulation of p53 gene activity in AT caused an inflammatory response and led to insulin resistance, while its inhibition in AT significantly decreased the expression of pro-inflammatory cytokines and improved insulin resistance in mice with type 2 diabetes-like disease (Minamino et al. 2009). Furthermore, recent studies on mice skeletal muscle indicate that endothelial p53 regulates glucose metabolism by modulating mitochondrial biogenesis and glucose uptake in this tissue (Yokoyama et al. 2014). This work demonstrated the existence of a mechanism for a cycle in which upregulation of endothelial p53 induces metabolic

abnormalities that in turn promote cardiovascular dysfunction (Yokoyama et al. 2014).

Inhibition of endothelial p53 has been proposed as a novel therapeutic strategy for blocking the development of insulin resistance in obese patients (Yokoyama et al. 2014) as well as postponing skeletal muscle ageing-related processes (Edwards et al. 2007).

Growth hormone

Age-related decreases in hormones have been associated with the ageing process prompting studies characterizing the potential for hormone-replacement strategies to modulate features of ageing. The antagonistic pleiotropy theory of ageing postulates that one gene controls multiple traits, each with variable relevance, and it has been suggested that there are pathways evolutionarily favorable for facilitation of development and reproduction that can be antagonistic during ageing (Bartke 1998).

Reduced growth hormone (GH, called also somatotropin) level emerges as biomarker of ageing as well as a suspected causal factor in various symptoms and functional deficits associated with the ageing process (Masternak and Bartke 2012). The hormones, which have increasing levels at puberty, such as GH, strongly affect body composition and strength. After the third decade of life, there is progressive decrease in GH secretion by approximately 15 % per decade of adult life (Kargi and Merriam 2000). The main mediator for the trophic effects of GH is insulin-like growth factor 1 (IGF-1, also called somatomedin C), the levels of which also decline with age (Kargi and Merriam 2000). It has been suggested that the age-related decrease in IGF-1 production might be a direct consequence of decreases in GH levels, but there are no results to indicate the occurrence of increased "GH resistance" (Hersch and Merriam 2008). Studies on rats have shown that deficiencies in GH and IGF-1 may contribute to senescence, whereas GH or IGF-1 augmentation has led to improved cognitive function, increased brain glucose utilization, and increased cortical vascularity (Sonntag et al. 2005).

Ageing is a state of relative physiologic GH deficiency, is not considered a disease itself, and is definitely a condition separate from adult growth hormone deficiency (AGHD). However, similarities between ageing and AGHD, although not exact, have led researchers to consider administrating GH or stimulating its secretion. In one of the first studies, healthy older men (>60 years old) were treated with GH for 6 months, and they responded with significant lean mass increase, AT decrease, and increase in bone mineral density (Rudman et al. 1990). Moreover, these changes in body composition persisted after 1 year of GH treatment (Rudman et al. 1991). Other studies on GH treatment showed that the beneficial effects on body composition, which seemed to alter ageing (Rudman et al. 1990; Papadakis et al. 1996), are accompanied with a higher risk of experiencing soft tissue edema, arthralgias, an onset of diabetes mellitus, and an impairment in fasting glucose (Liu et al. 2007). Thus, chronological age is not an indication for GH therapy because of its serious side effects.

Obesity is correlated with blunted GH secretion (Lubrano et al. 2015). It has been proposed that in some patients with AGHD, a hypothalamic-pituitary structural lesion may contribute to GH deficiency (Lubrano et al. 2015). The close relationship between empty sella (observed frequently in obese individuals) and GH secretory capacity indicates the possibility of AGHD being natural state in obese humans (Lubrano et al. 2015). Consequently, it has been suggested that there is a great potential for GH treatment on the metabolic consequences of obesity. Currently, studies on rodents have shown that protein constructs based on a GH secretagogue receptor (GHS-R1a) decreased circulating levels of acylated ghrelin (Gagnon et al. 2015), therefore having the potential to reduce body weight gain. Experiments have shown that after a HFD challenge, mice treated with GHS-R1a have reduced weight gain compared with controls, which was associated with reduced fat mass accumulation, but no reduction of lean mass (Gagnon et al. 2015). The authors of this study proposed that in vivo expression of the GHSR-based fusion protein prevents diet-induced weight gain, modifying adipose gene expression and improving glucose tolerance. Therefore, as GH levels decrease with age, as well as in premature ageing (Schumacher et al. 2008), an obesity driven early decline in GH may accelerate the ageing process by affecting the most conserved ageing-controlling pathway, that is, the insulin and IGF-1 signaling pathways (Bartke 1998; Kargi and Merriam 2000).

Brown adipose tissue

There are two main types of adipose tissues, white adipose tissue (WAT) that contains a single large lipid droplet storing excess energy and brown adipose tissue (BAT) that is characterized by multiple lipid droplets and large numbers of mitochondria that use lipids to

generate heat (Cannon and Nedergaard 2004; Kozak et al. 2010a). The cold environment stimulates the sympathetic nervous system which releases norepinephrine into BAT to activate β-adrenergic receptors (β-AR). Brown adipose tissue cells contain uncoupling protein 1 (UCP1), localized in the inner mitochondrial membrane where it dissipates the membrane potential generated by respiration fuelled by beta-oxidation of fatty acids to produce heat (Ricquier 2011) (reviewed by Cannon and Nedergaard 2004 (Cannon and Nedergaard 2004)). Additionally, brown adipocytes, also called brite or beige cells, can be induced in WAT depots upon cold stimulation (Cannon and Nedergaard 2004; Wu et al. 2012).

Human BAT is maximally recruited in early infancy. Although novel findings have led to a consensus that metabolically active BAT is present in most children and many adult humans (Virtanen et al. 2009; Cypess et al. 2009), BAT deposits are often undetectable in people who live at thermoneutrality (23 °C) (Seale and Lazar 2009). Recent studies suggest that adult human BAT presents the molecular characteristics of rodent beige cells rather than classical BAT (Wu et al. 2012). Animal studies showed relatively stable *Ucp1* mRNA levels in adult mice (Xue et al. 2005; Chabowska-Kita et al. 2015); nonetheless, BAT activity was shown to diminish in ageing (Seale and Lazar 2009). It has been suggested that ageing may be associated with impaired thermogenesis as suggested by greater reduction of BAT activity in old men compared to young ones (Seale and Lazar 2009; McDonald and Horwitz 1999; Lin et al. 2014). Additionally, age-dependent loss of thermogenic capacity is associated with a decline in UCP1 activity but not in UCP1 protein (Valle et al. 2008). A study on the effect of age on BAT found active BAT in only 10 % of the subjects between 50 and 60 years of age (McDonald and Horwitz 1999; Yoneshiro et al. 2011). There are increasing numbers of papers with data interpreted as showing that decreased amounts of brown fat may contribute to thermal dysregulation and energy imbalance often observed in older individuals; however, it is still uncertain whether the methodology for quantifying the number of brown adipocytes and their thermogenic activity in individuals with variable levels of obesity is accurate (Muzik et al. 2013).

It has been demonstrated that during the process of ageing, there is an ageing-dependent accumulation of point mutations in mitochondrial DNA of most subjects analyzed. Cumulative molecular damage leads to mitochondrial impairment (Detmer and Chan 2007), and its functional decline is linked to an age-dependent increase in the pathogenesis of metabolic disorders and neurodegenerative diseases (Lin et al. 2014; Detmer and Chan 2007). On the other hand, it has been shown that lifelong dietary caloric restriction, which decelerates ageing, can attenuate the age-related decline in mitochondrial mass and uncoupling protein levels in BAT of rats (Valle et al. 2008). Although it has been proposed that changes in circulating levels of thyroid and sex hormones might contribute to the age-related decline in BAT activity (Mattson 2010), the main components underlying the dysfunction of BAT in ageing are still unknown (Lin et al. 2014).

BAT function is decreased not only during ageing but also in obese state. Experimental mouse and human obesity models evidence that additionally to diminished or defective BAT function (Himms-Hagen and Desautels 1978; Avram et al. 2005b; Vijgen et al. 2011; Claessens-van Ooijen et al. 2006; van Marken Lichtenbelt et al. 2009), obese individuals have blunted cold-induced thermogenesis and were proposed to have a larger insulative response (Wijers et al. 2010). Additionally, genetically obese *ob*/*ob* mice were shown to be cold sensitive, perhaps due to the fact that their BAT is usually thermogenically inactive, atrophied with low UCP1 levels (Carter et al. 2013), but also from defects in centrally controlled thermogenesis. Thus, *ob*/*ob* mice fail to maintain proper body temperature when subjected to cold treatment (Himms-Hagen and Desautels 1978). Studies on mice revealed that obesity-prone mouse strains possess less BAT than obesity-resistant mice (Collins et al. 1997; Guerra et al. 1998). Also, in transgenic mice with increased BAT activity due to overexpression of UCP1, there is enhanced energy expenditure and resistance to DIO (Kopecky et al. 1995). In morbidly obese human subjects, expression of UCP1 in BAT was shown to be significantly reduced in comparison to lean controls (Vijgen et al. 2011). It is speculated that the absence of adequate amounts of BAT could lead to a severe overweight condition (Vijgen et al. 2011; van der Lans et al. 2013). However, mice with an inactive *Ucp1* gene do not have increased susceptibility to DIO (Liu et al. 2003), leading to an alternative interpretation that overall, metabolic efficiency is reduced in individuals

with lower levels of UCP1-based thermogenesis (Butler and Kozak 2010). Other studies, with both genetic and surgically generated models of classical BAT insufficiency (Myf5-BMPR1A-KO), suggest the existence of a physiological mechanism to ensure thermoregulation by compensatory browning in WAT (Schulz et al. 2013). Schulz et al. (2013) showed that classical BAT is crucial during acute cold challenges, but compensatory brown cells induced in WAT in Myf5-BMPR1A-KO mice (with severe insufficiency of classical BAT) had a critical role in normal body temperature maintenance, particularly in long-term cold exposure (Schulz et al. 2013). The induction of brown adipocytes in the inguinal fat of mice with a deficiency in UCP1-based thermogenesis was originally shown by Liu et al. (Liu et al. 2003). The idea that brown adipocytes, which can be induced in white fat depots by adrenergic signaling, constitute a mechanism for reducing or preventing obesity is still not settled.

As mentioned, beige adipocytes can be induced in WAT depots (Cannon and Nedergaard 2004), and even mild cold increases heat production (Claessens-van Ooijen et al. 2006). It has been proposed that BAT has functional significance in humans and might be targeted as a source for the development of anti-obesity treatments. It has been shown that BAT exerts anti-type 2 diabetic effects associated with improvements of dyslipidemia and insulin secretion (de Souza et al. 1997; Peirce and Vidal-Puig 2013). Moreover, recent studies on rodents have showed that caloric restriction postpones the age-related decline in BAT mitochondrial function (Valle et al. 2008) and ghrelin ablation in older individuals prevents age-associated decline in *UCP1* gene expression (Lin et al. 2011). Therefore, it may be possible to prevent the age-related decrease BAT content and in consequence decelerate age-related fat mass accumulation and development of diabetes.

Adipose tissue expansion

Adipose tissue expansion (ATE) is an adaptive mechanism which allows an individual to remain metabolically healthy, because the adipose depot can accommodate caloric excess without displacement to ectopic sites like liver and skeletal muscle; however, expandability is not an unlimited process (Hersch and Merriam 2008). The expandability hypothesis states that when AT reaches its capacity to store fat, insulin sensitivity deteriorates (Tan and Vidal-Puig 2008). When adipose depot of an individual is not able to expand further to store excess energy, then ectopic lipid accumulation occurs, which as a consequence can lead to insulin resistance or cardiovascular complications. Since some relatively lean individuals are insulin resistant, whereas some very obese individuals are not, it was proposed that the maximal capacity for AT to expand is an individualize trait, perhaps determined by genetic background (Virtue and Vidal-Puig 2010). Moreover, rodent studies reported that mouse models on the *ob*/*ob* background with reduced capacity for ATE (due to partial lack of peroxisome proliferator-activated receptor gamma (PPARγ) function) presented reduced insulin sensitivity in comparison to the very obese *ob*/*ob* mice (Virtue and Vidal-Puig 2010; Medina-Gomez et al. 2007).

Spalding et al. (2008) showed that adipocyte number remains constant in adulthood for both lean and obese individuals, and the difference in cell number between lean and obese is established during childhood and adolescence (Spalding et al. 2008). Adipocyte turnover appears to be constant throughout adult life, and the life span of adipocytes is 10 years on average. Interestingly, the adipocyte number in AT depots in obese individuals declined between 45 and 65 years of age (Virtue and Vidal-Puig 2010; Spalding et al. 2008). Metabolic responsiveness decrease at the end of life (Slawik and Vidal-Puig 2006; Visser et al. 2003), and there is an age-related decline in expression of pro-adipogenic transcription factors such as PPARγ or C/EBPα (Karagiannides et al. 2001). As ATE may fail with advancing age, the need for increased storage of fat may lead to ectopic fat deposition, i.e., in muscle or bone marrow (Slawik and Vidal-Puig 2006; Rudman et al. 1991). The decline in adipocyte number in obese people after the age of 45 years can be expected to limit ATE, and the resulting lipotoxicity may contribute to pathogenesis of obesity and type 2 diabetes in later life. In general, DIO is associated with hypertrophy (increase in adipocyte size) (Avram et al. 2005a); nonetheless, there is sparse evidence indicating that ageing has any effect on the development of adipocyte hypertrophy. In individuals predisposed to develop hypertrophic obesity, ageing might facilitate early onset of metabolic disorders (Slawik and Vidal-Puig 2006). Aged individuals at the onset of obesity, when the adipocytes are growing larger, have an increased risk of metabolic syndrome in comparison to young (less than 20 years old) individuals in the same state of obesity (Brochu et al. 2001).

Longitudinal studies on obesity development are sparse, and WAT fat depots vary considerably in propensity to expand during diet-induced body weight gain (van Beek et al. 2015), which leaves many questions unsolved. A mouse model with chronic overexpression of adiponectin have an enormous increase in subcutaneous fat mass; however, they were protected against diet-induced insulin resistance (Kim et al. 2007). The interpretation is that an increase in AT storage capacity may prevent metabolic complications. The main caveat of this phenomenon is that unlimited ATE could lead to morbid obesity and cause health problems other than the metabolic syndrome (Virtue and Vidal-Puig 2010).

Most studies on expandability of AT focus on the development of WAT in neonatal mice or in young adults with DIO showing abnormal fat deposition process. Recent microarray studies on subcutaneous WAT comparing mice exposed to different nutritional conditions during early post-natal development and then in adult mice exposed to HFD identified a set of genes highly associated with ATE, including *mesoderm specific transcript* (*Mest*), *caveolin1* (*Cav1*), *caveolin2* (*Cav2*), and *secreted frizzled-related protein 5* (*Sfrp5*) (Koza et al. 2006; Voigt et al. 2013). The absence of MEST protein in the interscapular BAT in adult obese mice (Nikonova et al. 2008) indicates that *Mest* is one of the few genes known to be expressed at high levels only in WAT. Lack of *Mest* gene expression leads to reduced levels of adiposity, suggesting that MEST enhances the capacity for lipid storage in adipocytes (Nikonova et al. 2008). Moreover, high levels of *Mest* expression were linked to cellular mechanisms controlling fat mass expansion (Voigt et al. 2013; Kozak et al. 2010b; Takahashi et al. 2005) and *Mest* gene was suggested to control the initial phase of ATE by regulating adipocyte hypertrophy (Takahashi et al. 2005). *Mest* and caveola components, *Cav1* and *Cav2*, have a similar pattern of gene expression in time; they are highly expressed during early development at the time of nursing, they present low levels in mice with normal adiposity (0.22–0.25), and are highly expressed in WAT from adult mice in a positive energy status (Kozak et al. 2010b). Moreover, both *Mest* and *Cav1* KO mice have reduced DIO, suggesting that these genes are involved in the remodeling of cellular structures associated with the uptake and assembly of lipids into the lipid vesicles and might be co-dependent. In an obesogenic environment at adulthood, both *Mest* and *Sfrp5* genes are highly induced and show a strong positive correlation with adiposity index and with each other (Koza et al. 2006). Expression of these genes decreases when adiposity index reaches a plateau and animals reach a maximal capacity for fat mass storage (Jura et al. 2015). Furthermore, the majority of proteins synthesized in the endoplasmic reticulum undergo glycosylation (Rini et al. 2009), the process by which sugar is covalently attached to a target protein. It has been showed that *Mest* has a dominant effect in the processing of low-density lipoprotein receptor-related protein-6 (LRP6) and that the levels of both ectopically expressed and endogenous LRP6 localized in the plasma membrane were reduced by *Mest* overexpression (Jung et al. 2011). Based on these data, it was proposed that increased levels of *Mest* prevent cells from responding to Wnt signaling by inhibiting maturation and plasma membrane localization of LRP6 during angiogenesis (Jung et al. 2011). Although there is missing information on *Mest* and *Sfrp5* gene expressions and their regulation in the process of ageing, caveolae are currently being intensively studied. Recent research has shown that adipocytes from animals in a process of ageing presented a decrease in mean expression of caveolar proteins per unit cell surface (Hulstrom et al. 2013); in addition, *Cav1* was reported to be relevant for insulin signaling in AT (Gustavsson et al. 1999).

Adipose tissue expansion has also its mechanical limitations since adipocyte cells are embedded within extracellular matrix (ECM). During the AT enlargement, the ECM composed of many proteins often with signaling functions must undergo remodeling. The levels of ECM components reflect the balance between the rate of synthesis and degradation of matrix proteins. One of the most highly investigated components of the ECM is collagen VI (*col6*), the ablation of which allows a robust grow of adipocytes (Khan et al. 2009). Moreover, recent studies observed differences in caveolar structures between the *col6KO.ob*/*ob* and *ob*/*ob* mice and collagen-deficient mice had an accumulation of uninvaginated caveolae in their adipocytes, suggesting that the *col6KO.ob*/*ob* mice had reduced levels of shear stress in adipocytes due to lack of collagen VI. A few studies on ageing and ECM have shown that by the age of 60, all types of collagen are significantly below their youthful levels (Divoux and Clement 2011); thus, enlargement of the adipose cell is facilitated.

A prolonged positive energy balance state causes a myriad of changes in AT such as adipocyte hypertrophy, adipocyte proliferation, or accumulation of

inflammatory cells. Research focusing on the vasculature in AT function highlights the importance of microcirculation for this organ's metabolic function (Rutkowski et al. 2009). It has been proposed that fat mass expansion and contraction relies on blood circulation in AT, which being inefficient leads to local hypoxia and metabolic complications. Additionally, it has been shown that ECM is essential for AT architecture (Divoux and Clement 2011) and that these are potential biomarkers of ATE (Koza et al. 2006; Nikonova et al. 2008; Kozak et al. 2010b). The AT is a very plastic organ and is a key regulator of systemic energy homeostasis. Studies on genes controlling the size and enlargement of adipocytes and genes controlling their regulation may identify novel targets for prevention of excess body fat. The impact of dysregulation of genes linked to ATE or ECM components in AT on the systemic metabolic state is currently being unexplored.

Discussion and conclusions

For most of human history, mankind struggled with food insufficiency and short life expectancy; thus, obesity was viewed as a sign of wealth and privilege. With the increase in life expectancy in recent years, excess weight is often viewed as unattractive, and obesity is commonly associated with increased susceptibility to health problems, thereby becoming a leading cause of preventable death (Fontaine et al. 2003). During the past decades, two human conditions or states, that is the increase in longevity and obesity, have been converging to confound and exacerbate human physiology. An evolutionary process, called the thrifty genotype, has driven the development of an efficient metabolism and a centrally regulated behavior designed to minimize energy expenditure, while maximizing the storage of energy in the form of lipids in AT. The increase in longevity, due to natural ageing process, depends on many of the same processes that are associated with maximizing metabolic efficiency; in fact, longevity depends on efficient metabolism. Presently, owing to the dramatic increase in incidence of obesity, life expectancy may start to decline especially in developed countries.

The focal point of our review is a description of the adipocyte biology and how it is affected by the obese condition and the ageing process. We have sought to identify common sub-phenotypes that show interactions or confounding behavior when the obese condition is overlaid on the ageing condition. The attempt to identify a central regulatory mechanism inevitably leads to consideration of insulin resistance as a function of the obese and ageing conditions. Increasing visceral obesity, often observed during the ageing process, is a key contributor to insulin resistance and metabolic syndrome. Therefore, a major goal is to determine how insulin resistance arises and how it can be reversed.

The sub-phenotypes we have explored are

1. Inflammation induced in adipose tissue of obese and in the ageing tissue with effects on insulin resistance in both sites.
2. Adiponectin production and secretion suppressed with the progression of obesity and age, with evidence of a genetic disposition to high levels of endogenous adiponectin in centenarians.
3. Leptin, another secreted adipokine, determining the energy status of the animal through effects on food intake and lipid oxidation. Although its absence leads to obesity, excessive production leads to leptin resistance, analogous to insulin resistance. A possible link between leptin and ageing comes from evidence that older individuals often present leptin resistance.
4. Reduction of lean mass, which is an established biomarker of ageing. Although some studies show a reduced lean mass in genetic models of obesity, increased lean mass is routinely found in obese humans.
5. P53, a well-established tumor-suppressor gene, silenced by mutation in cancer but curiously upregulated in the adipocytes of *ob*/*ob* mice and in the skeletal muscle of ageing mice. Given the role of cell proliferation in obesity, p53 provides access to a key regulatory system in obesity and ageing.
6. A reduction in GH which is associated with the ageing process and obesity. Accordingly, treatment with GH has been tested as a way to reverse the ageing process, but serious side effects have prevented this as a feasible treatment. Perhaps, more promising is to explore the long-term effects of reduced GH secretion in obesity and on the progression of ageing in obese individuals.
7. Brown adipocyte induction and ATE, two opposing and reversible cellular phenomena that are driven by the ambient temperature in the former and the nutritional environment in the latter. Activation of these processes has major effects on the obese

condition. The stimulation of energy expenditure and the reduction of adiposity by BAT thermogenesis or the induction of adipocyte hypertrophy by a positive energy balance (mediated by a selective cohort of genes including *Mest* and *Sfrp5*) can improve insulin sensitivity. The activation of these processes may also impact the ageing process through interactions with the state of adiposity.

There is vast literature indicating that age-related changes in body fat distribution and metabolism are key factors of a vicious cycle that can accelerate the ageing process and the onset of age-related diseases. Recent substantial progress in understanding the interplay between metabolism and ageing has identified potential strategies to delay the onset of age-related diseases and improve health span. Studies on young animals with accelerated onset of conditions modeling human age-related diseases are not likely to answer all basic questions. To understand the impact of ageing on health span, it will be important to conduct studies on old animals. Use of old animals is more likely to phenocopy the systemic ageing context, in which chronic disease occurs in humans.

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