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Review

"Is obesity linked to aging?" Adipose tissue and the role of telomeres

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ABSTRACT

Obesity is a condition in which excess or abnormal fat accumulation may present with adverse effects on health and decreased life expectancy. Increased body weight and adipose tissue accumulation amplifies the risk of developing various age–related diseases, such as cardiovascular disease, Type 2 Diabetes Mellitus, musculoskeletal disorders, respiratory diseases and certain types of cancer. This imbalance in body composition and body weight is now recognized as a state of increased oxidative stress and inflammation for the organism.

Increasing oxidative stress and inflammation affect telomeres. Telomeres are specialized DNA-protein structures found at the ends of eukaryotic chromosomes and serve as markers of biological aging rate. They also play a critical role in maintaining genomic integrity and are involved in age-related metabolic dysfunction. Erosion of telomeres is hazardous to healthy cells, as it is a known mechanism of premature cellular senescence and loss of longevity. The association of telomeres and oxidative stress is evident in cultured somatic cells in vitro, where oxidative stress enhances the process of erosion with each cycle of replication.

Shorter telomeres have been associated with increasing body mass index, increased adiposity, and more recently with increasing waist to hip ratio and visceral excess fat accumulation. Furthermore, many of the metabolic imbalances of obesity (e.g. glycemic, lipidemic, etc.) give rise to organ dysfunction in a way that resembles the accelerated aging process.

This article is a non-systematic review of the evidence linking obesity and accelerated aging processes as they are regulated by telomeres.

1. Introduction

Obesity is defined by the body mass index (BMI = weight (kg)/[height (m)^2], Overweight BMI: 25–29.9 kg/m^2, Obese BMI: ≥30 kg/m^2) and is closely related to both percentage of body fat and total body fat (WHO, 2011; Haslam and James, 2005). It is the leading, preventable cause of death globally (WHO, 2011). In 2008, the World Health Organization indicated that approximately 1.5 billion adults (>20 years) were overweight globally (WHO, 2011). Future projections show that by the year 2015, approximately 2.3 billion adults will be overweight while more than 700 million will be obese (WHO, 2011). Today, overweight and obesity are dramatically increasing (Ogden et al., 2008), especially in low- and middle-income countries (Haslam and James, 2005; Barness et al., 2007; Woodhouse, 2008).

Further to increasing the onset of metabolic imbalances, obesity leads to reduced life span and accelerated cellular processes similar to those of aging (Ahima, 2009), such as deterioration of the structure and function of organs associated with oxidative stress, genetic instability and disturbance of homeostatic pathways (Russell and Kahn, 2007). Increased weight and abnormal accumulation of fat tissue lead to detrimental health consequences, partly because fat is frequently the largest organ in humans. It constitutes over half of the body's composition in an alarmingly high number of people and thus the extent of the consequences is amplified (Ahima, 2009).

Key markers of cellular and biological aging are telomeres. Telomeres are non-coding double-stranded repetitive structures (TTAGGG in humans) at the ends of mammalian chromosomes [5′-(TTAGGG)$_n$-3′] (7). They become shortened with each cell division (Harley et al., 1990) due to incomplete replication of the lagging

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strand (von Zglinicki and Martin-Ruiz, 2005), and, together with associated proteins, they protect chromosome ends (Wong and Collins, 2001). With increasing age, a slow and gradual loss of telomere length (telomere length) in human peripheral blood has been reported (Slagboom et al., 1994; Martens et al., 2002).

Besides the physiological aging related telomere loss, shorter telomeres in peripheral blood have been described in cancer patients (Ju and Rudolph, 2006; Risques et al., 2007), diabetic patients (Brouilette et al., 2003; Sampson et al., 2006; Adaikalakoteswari et al., 2007; Balasubramanyam et al., 2007; Mulder, 2010), and in individuals with the metabolic syndrome (MetS) and increased cardiovascular disease (CVD) risk factors (Samani et al., 2001) such as increased blood pressure (Jeanclos et al., 2000), obesity (Valdes et al., 2005), high fasting glucose levels (Adaikalakoteswari et al., 2007; Balasubramanyam et al., 2007), smoking (Valdes et al., 2005), and in response to psychosocial stress (Epel et al., 2004), (Table 1). Therefore, telomere length can serve both as a biological marker for age and for stress-related conditions.

Oxidative stress and inflammation have been suggested as the underlying mechanisms for the association between obesity and shorter telomeres (Valdes et al., 2005). Oxidative stress is responsible for single strand breaks in the DNA (von Zglinicki, 2002). The G-rich telomeric sequence is more susceptible to acute oxidative damage, compared with genomic DNA. In addition, telomeric DNA has a reduced capacity for DNA repair. This causes accelerated telomere loss and replicative senescence during each cell cycle (von Zglinicki, 2002). The effect is enhanced in obesity, since increasing adiposity aggravates oxidative stress processes and the release of inflammatory cytokines (Furukawa et al., 2004).

The production of reactive oxygen species (ROS) is increased in the adipose tissue of obese mice; increased oxidative stress in fat has been proposed as the key mechanism underlying the occurrence of insulin resistance related to obesity (Furukawa et al., 2004).

These data suggest that obesity is an abnormality characterized by increased oxidative stress, inflammation, short telomeres and a hastened aging process. The aging pace and body weight balance are therefore interconnected.

In this review we conducted a search of the literature in Pub Med and Medline electronic databases using the search terms “telomere” with “obesity,” “adipose tissue”, “weight,” “BMI,” or “Aging”, “Oxidative stress and inflammation” for dates spanning from 1990 to 2011; and articles obtained from personal archives. We will review findings of these studies regarding the association of telomeres in obesity and its age-related pathologies.

1.1. Obesity

In obesity, excess adipose tissue accumulates. Depending on the extent of adipose tissue accumulation, this may cause adverse effects on health (Gray and Fujioka, 1991). Obesity can be further evaluated in terms of fat distribution via the waist hip ratio and total CVD risk factors (e.g. serum lipid levels) (Sweeting, 2007).

The causes of such profound accumulation of adipose tissue in an organism are primarily a combination of excessive caloric intake and a lack of physical activity (Lau et al., 2007). A limited number of obesity cases are primarily due to genetic abnormalities, medications, hormonal imbalances or psychiatric illnesses (Bleich et al., 2008). In contrast, increasing rates of obesity are primarily due to an increased consumption of easily accessible and palatable high fat and sugar diets (Drewnowski and Specter, 2004) decreased physical activity rates in everyday life (Nestle and Jacobson, 2000; James, 2008). Other possible contributors to the observed increase in the prevalence of obesity are: insufficient sleep or disruption of the circadian rhythm and melatonin levels (Korkmaz et al., 2009), endocrine disruptors (environmental pollutants that interfere with lipid metabolism) (Desvergne et al., 2009), population rise of the ethnic groups and age groups that tend to be heavier (El-Sayed et al., 2011), pregnancy at a later age which is associated with susceptibility to childhood obesity (Viner et al., 2006), epigenetic risk factors (Heerwagen et al., 2010), selective mating leading to increased concentration of obesity risk factors and fetal environmental influences and exposures to risk factors leading to obesity development in later life (Schmidt and Salahudeen, 2007). While there is substantial evidence linking these mechanisms to the increased prevalence of obesity, this evidence is still inconclusive.

1.2. Adipose tissue and health

Fat or adipose tissue is important in many physiological processes of an organism, such as host defense, immunity, injury response, as well as production of inflammatory cytokines and chemokines. Considerable variability is reported in regional fat distribution, even among individuals with similar total body fat content. Fat cells that have been isolated from different fat depots vary in size and responses to insulin and lipolytic agents, lipoprotein binding, fatty acid transfer and production of secreted proteins (Alessi et al., 1997; Montague et al., 1997; Berman et al., 1998; Dusserre et al., 2000; Tchkonia et al., 2001; Bastelica et al., 2002).

The regional variation of fat cell characteristics has been described for pre-adipocytes originating from various depots from the same individuals cultured under identical conditions and refers to their replicative potential, specific fatty acid transfer, cell differentiation and susceptibility to apoptosis (Hauner and Entenmann, 1991; Niesler et al., 1998; Zierath et al., 1998; Caserta et al., 2001; Tchkonia et al., 2001; Niesler et al., 2001; Tchkonia et al., 2002). This may well be a result of influences extrinsic to adipose cells, such as the hormonal and paracrine environments, local nutrient availability, innervation and anatomic constraints, but also due to inherent regional differences in inherent properties of adipose cells still under investigation.

In rats, the surgical removal of visceral or intra-abdominal fat is associated with increased hepatic insulin sensitivity and decreased hepatic glucose production (Weber et al., 2000), while removal of subcutaneous fat from hamsters results in insulin resistance (Gabriely et al., 2002). Indeed, increased central adiposity and accumulation of abdominal fat is associated with MetS and related risks for DM, atherosclerosis, dyslipidemia, hypertension, and malignancies (Despres, 2006; Pou et al., 2007).

Although the negative health consequences of obesity in the general population are well-evidenced, health outcomes in certain subgroups appear to be improved at increased BMIs; this phenomenon is known as the obesity-survival paradox (Habbu et al., 2006; Schmidt and Salahudeen, 2007). This paradox was first described in 1999 in overweight and obese people undergoing hemodialysis (U.S. Preventive Services Task Force, 2003). In people with heart failure, those with a BMI of 30.0–34.9 had lower mortality than those with a normal weight (U.S. Preventive Services Task Force, 2003). This, however, can be attributed to the fact that people often lose weight as they become progressively more ill and thus health outcomes deteriorate. In addition, the improved health outcomes observed in the high-BMI population have not been investigated in terms of biological and cellular aging rates.

2. Telomeres and aging

Telomere attrition depends on aging-related exposure to both physiological and patho-physiological environments, as well as epigenetic effects (Epel, 2009). The main cellular processes that contribute to aging and its related diseases are oxidative stress and inflammation; these also play an important role in accelerated telomere attrition (Hwangbo et al., 2004; Aviv et al., 2006;

Table 1
Chronic diseases/conditions and their correlation to telomere length.

Chronic disease/condition	Telomere length change	Publication
Cardiovascular disease (CVD)	In leukocytes Shortened	Epel et al., 2006 Fitzpatrick et al., 2007
Coronary disease	In leukocytes Without correlation	Kurz et al., 2006
Cardiovascular causes, infectious diseases	In peripheral blood With no difference	Martin-Ruiz et al., 2005
Atherosclerosis	In white blood cells and carotid artery atherosclerotic plaques Shortened	Benetos et al., 2004
Hypertension and diabetes mellitus	In white blood cells Shortened	Balasubramanyam et al., 2007
Type 1 diabetes	In white blood cells Shortened	Jeanclos et al., 1998
Type 2 diabetes mellitus	In leucocytes Shortened	Adaikalakoteswari et al., 2007
	In lymphocytes No difference	Sampson et al., 2006
Chronic gastroesophageal reflux disease	In esophageal squamous epithelium Shortened	Souza et al., 2007
Nonalcoholic fatty liver disease	In liver biopsy Shortened	Nakajima et al., 2006
Chronic obstructive pulmonary disease	In alveolar epithelial Shortened	Tsuji et al., 2006
Types of cancer (liver, lung, breast, prostate, colon, brain, pancreas and head and neck, as well as malignancies of the hematopoietic system)	In various types of biologic samples Shortened	Ju and Rudolph, 2006
Mature B-cell lymphoproliferative disorders	In B-cells Shortened	Ladetto et al., 2004
Chronic psychological stress	In peripheral blood mononuclear cells Shortened	Epel et al., 2004
Obesity	In white blood cells Shortened	Valdes et al., 2005

Hotamisligil, 2006; Herbert et al., 2008; Starr et al., 2008; Minamino et al., 2009). These processes seem to accumulate a "stress" burden with advanced age to an organism.

Telomerase ribonucleoprotein enzyme, a telomere length regulator has also a significant effect on cellular aging and its rate (Flores and Blasco, 2010; Mason et al., 2011). Its normal function is the elongation of the telomere sequence – in order to "fight" against the end-replication problem of telomere shortening – by addition of nucleotides to their ends which is regulated by genetic, epigenetic and environmental factors (Zhu et al., 2011a,b).

The telomere theory of aging has been argued since it fails to inversely correlate residual telomere lengths and donor age. Indeed, telomere lengths of very old individuals differ only slightly from those in cells of young donors (Cristofalo et al., 2004). However, an inverse correlation between telomere lengths and donor age cannot be expected in all cells of an organism. Cells in different tissues divide at different rates and according to different stimuli and programming (Mikhel'son, 2001).

Another puzzling finding is that telomeres in mouse cells are ten times as long as those in human cells, although their lifespan is limited to three years (Prowse and Greider, 1995). While it is not yet clear why telomeres are longer in white mouse cells than in human; this is a known characteristic only of white mice. Other experimental lines of mice found in the wild field have telomere lengths that correspond to their lifespan (Hemann and Greider, 2000; Manning et al., 2002). Moreover, the presence of long telomeres per se does not contradict the distinct correlation between telomere shortening and replicative aging.

It is unknown whether birth leukocyte telomere length or its age-dependent attrition explains the associations between telomere dynamics and aging. A clear distinction between leukocyte telomere length during early development vs. telomere shortening in later life, from animal studies, would provide information on whether an individual's longevity is regulated by either one or both factors (Benetos et al., 2011).

Telomere shortening seems to have a definite role in aging even in the absence of oxidative stress. Indeed, even if oxidative damage is absent, telomeres will nevertheless shorten with each mitotic cycle, since this is the mechanism of DNA replication. It known that aging would also progress even in the presence of antioxidants (Mikhel'son and Gamalei, 2010). Indisputably, ROS accelerate natural aging both in vitro and in vivo, but the mechanism by which ROS can cause aging has yet to be revealed. The only known mechanism is telomere shortening acceleration which is induced by telomere DNA damage caused, in turn, by various factors one of which is ROS (Forsyth et al., 2003).

2.1. Obesity and mechanisms of aging

Populations with shorter leukocyte telomere length show greater incidence of all-cause (Cawthon et al., 2003) and CVD-specific mortality (Jeanclos et al., 2000; Benetos et al., 2001) and greater risk of developing atherosclerosis (O'Donnell et al., 2008), coronary artery disease (Brouilette et al., 2008; Maubaret et al., 2010; Wang et al., 2011), and specific cancers (McGrath et al., 2007; Risques et al., 2007).

When considering the role of obesity and abdominal adiposity, in the development of chronic diseases such as the ones mentioned above (Festa et al., 2000; Despres and Lemieux, 2006), then it is likely to come to the conclusion that individuals with greater total and abdominal adiposity and lower lean body mass may exhibit shorter telomeres (Nordfjäll et al., 2008).

Indeed, studies in humans show that high total and abdominal adiposity are directly related to decreased telomere length, suggesting that obesity may accelerate the aging process (Lee et al., 2011). Telomere length is inversely associated with BMI, waist to

hip ratio, independent of sex, age, fasting glucose and insulin, lipid and lipoprotein concentrations, habitual physical activity, smoking status, and other metabolic risk factors (Lee et al., 2011).

This association between BMI and telomere length differs in younger compared with older individuals (Lee et al., 2011). The inverse relationship between health status and adiposity is thus further affected by aging, which in turn influences the structure and function of adipose tissue (Wehrli et al., 2007; Zafon, 2007). The extent of the changes is not only dependent upon age but also lifetime exposures to obesity and related risk factors (Lee et al., 2011).

Furthermore, obesity is regarded as the main determinant in the deposition and regulation of adipose tissue aging along with metabolic alternations such as increased pro-inflammatory cytokines, insulin resistance, and finally diabetes mellitus and CVD (Epel, 2009; Scaglione et al., 2010). An example is the tumor suppressor protein 53 (p53) with its primary role being conserving stability by preventing genome mutation. The p53 pathway in adipose tissue, which is the key in the aging process of adipose tissue and increased inflammation, may play an important role in obesity and obesity-mediated aging (Minamino et al., 2009).

An in vitro study demonstrated the differences in adipose tissue in individuals with or without obesity (Moreno-Navarrete et al., 2010). This study showed that telomere length measured from subcutaneous adipocytes in formerly obese patients was significantly lower than in never-obese patients. Since oxidative stress is thought to affect telomere attrition, this relationship may be partially responsible for the observed inverse association. However, multiple different mechanisms produced by adiposity may affect telomere attrition and length (Epel, 2009).

Animal studies show that aging signals generated from adipose tissue are crucial in regulating the lifespan of various species, such as *Drosophila melanogaster* and mice (Blüher et al., 2003; Hwangbo et al., 2004).

Adipose tissue senescence may increase local inflammation and thus the production of pro-inflammatory cytokines and other molecules, which promotes a systemic inflammation and profound insulin resistance. Low circulating insulin concentrations are on the other hand associated with longevity, and longevity signals seem activated in adipose tissue that has lower circulating insulin levels (Blüher et al., 2002). A possible mechanism is the inhibition of p53 activity in adipose tissue which improves insulin resistance and decreases plasma insulin levels. Thus, p53 activation in adipose tissue may be a pro-senescence signal with negative effects on longevity and the development of age-related diabetes mellitus and other associated diseases (e.g. CVDs).

Others have also observed an inverse association between telomere length and levels of C-reactive protein (Aviv et al., 2006). Obesity is associated with chronic systemic inflammation (Gardner et al., 2005; Hotamisligil, 2006), which affects telomere length, regardless of age, by increased cellular proliferation.

2.2. Telomeres, dietary/caloric restriction and aging

Other environmental factors affecting aging and telomere length include dietary caloric restriction (CR), a dietary regimen that restricts caloric intake. The baseline for the restriction varies, usually being the previous unrestricted intake of the subjects. CR without the presence of malnutrition improves age-related disease risk and slows the overall aging process in a range of animals (Anderson et al., 2009).

Despite CR's reducing effect on all biochemical stressors such as insulin, inflammatory factors, and oxidative stress it increases cortisol (Epel, 2009). In rhesus monkeys, CR has not been found to significantly affect telomere length dynamics despite an age-dependent shortening of telomere length in leukocytes and skin (Smith et al., 2011). Furthermore, chronic dietary restriction (DR), as assessed by self-report (i.e. not CR), may even be a risk factor for organic stress and premature telomere shortening (Kiefer et al., 2008).

There is evidence in rodents that a reduction in the aging processes and consequently a life span extension is affected by dietary intake and genetic determinants of fat accumulation (Barzilai and Gupta, 1999; Masoro, 2006). This can be triggered by CR leading to reduced visceral fat accumulation in the fat cell insulin receptor (FIRKO), insulin receptor substrate-1 (IRS-1) and S6 kinase-1 knockout mice (Barzilai and Gupta, 1999; Masoro, 2006). These animals exhibit limited fat development (Blüher et al., 2003; Selman et al., 2008). A reduced rate of aging is also seen in growth hormone receptor knockout (GHRKO) mice which have reduced insulin-like growth factor-1 (IGF-1), and thus have a delayed increase in the ratio of visceral to subcutaneous fat (Berryman et al., 2008). The same effect is seen with rapamycin treatment, which is known for minimizing fat tissue development (Chang et al., 2009; Harrison et al., 2009) and after surgical removal of visceral fat (Muzumdar et al., 2008). The effects, as well as the mechanisms of dietary habits and genetic determinants in the aging process remain to be unraveled.

3. Discussion

The literature regarding the relationship of telomere length to adiposity is not yet clear. There have been both positive, as well as negative relationships between adiposity measures and telomere length (Table 2). It is not apparent whether the reason for these inconsistencies is a difference in methods of measurements (quantitative Polymerase Chain Reaction vs. Southern blot) of telomere length, sample characteristics in the study, or simply there is no relationship between adiposity and telomere length. It is possible that telomere shortening, is unlikely to contribute to the aging of poorly proliferative tissues (Spalding et al., 2005, 2008) such as adipose tissue. On the other hand, studies have found a significant inverse association between adiposity and telomerase activity (Epel et al., 2006; Ren et al., 2010).

Few studies to date have focused on the role of total body and abdominal adiposity in telomere length since most have relied almost exclusively on BMI or other indirect anthropometric measures. The way adiposity, chronic stress, insulin resistance, diet, systemic inflammation and adipose-tissue derived hormones interact with telomere length, particularly in younger populations needs further clarification.

In terms of chronological age, accumulated damages due to inflammatory and oxidative stress resulting from obesity or other unfavorable risk factors may be greater in the elderly. Certain older healthy individuals may also differ from others, for example those who have a history of chronic diseases and environmental burdens (e.g. smoking) during youth and adulthood may have reduced telomere length while, others may have had low exposure to chronic disease risks and thus appear with longer telomeres compared with their age-matched counterparts (Valdes et al., 2005). This would result in a diminished association between telomere length and age.

In young and healthy populations, a measurement of the average bulk telomere length may not be sensitive enough to detect very early changes, such as single strand DNA breaks in the telomere. The measurement of telomerase activity in these samples is important, especially since it may be an earlier indicator of cellular aging than telomere length. Telomerase deficiency can have detrimental effects on telomere shortening.

Furthermore, gender may have a differential effect on telomere length independently of other factors such as obesity and chronic

Table 2
Summary of the main study findings regarding the association of telomeres in obesity and accelerated aging.

Positive or negative association	Main findings	Methodology of measurements	Sample characteristics	Other clinical and/or laboratory variables	Publication
Positive	Childhood obesity corresponds to shorter leukocyte telomere length, in boys but not in girls. The significant predictor of leukocyte telomere length in girls is waist circumference.	Quantitative RT-PCR for average telomere length in leucocytes	148 children of which 69 boys and 79 girls aged 5–12 years.	Serum insulin, leptin, adiponectin, resistin, tumor necrosis factor-α and active plasminogen activator inhibitor-1 quantified using multiplex assays.	Al-Attas et al., 2010
Negative	Leukocyte telomere dynamics in women younger than 50 years are influenced by elevated insulin resistance, leptin and CRP levels but not by body mass.	Southern blot for peripheral leukocyte TRF length measurement	1517 Caucasian female twins aged 18–79 years. From the St. Thomas' (Twins UK) Adult Twin Registry.	Fasting insulin determined by immunoassay, insulin resistance using the HOMA-IR, plasma leptin concentration using a radioimmunoassay and C-reactive protein using an ELISA assay.	Aviv et al., 2006
Negative	No association between telomere length and BMI defined obesity. Shorter telomere length is associated with increased levels of inflammation and oxidative stress.	Southern blot for peripheral leukocyte TRF length measurement	2509 Caucasians of which, 1291 women and 1218 men aged 35–55 years. From the Asklepios cohort.	2-year inclusion period. TLs experimentally determined while blinded for subjects ID.	Bekaert et al., 2007
Negative	No negative correlation between telomere length and obesity.	Southern blot for peripheral leukocyte TRF length measurement	812 subjects aged 73–101 years of which 652 twins. From population-based surveys of the Danish Civil Registration System.	Participants were followed up until January 2005, at which time 412 (51%) were dead.	Bischoff et al., 2006
Positive	A reduction of fat mass without caloric restriction is associated with increased longevity in mice.	Measurement of mice life span	250 male and female mice and 40 FIRKO mice and 60 control littermates for the 3 genotypes produced.	Adiposity estimated by perigonadal fat pad weight and by total-body triglyceride content.	Blüher et al., 2003
Negative	Telomere length is related to elevated stress hormones but not adiposity. Low telomerase activity is associated with greater abdominal adiposity and increased catecholamine and cortisol excretion.	Quantitative PCR for telomere length measured from PBMC DNA; telomerase repeat amplification protocol for telomerase	62 healthy women aged 20–50 years of which 40 mothers of children with chronic disorders and 22 mothers of healthy children free of any acute or chronic health conditions.	All sessions occurred during the first 7 days of the menstrual cycle follicular phase. 12 h nocturnal urine sample assayed for stress hormones.	Epel et al., 2006
Negative	Inverse associations of telomere length with body size, IL-6 and CRP are modified by gender and age, and are evident only in men aged 73 years or younger.	Southern blot for peripheral leukocyte TRF length measurement	419 randomly selected Caucasians (81.9%) and African Americans, aged ≥65 years 58.9% females. From the Cardiovascular Health Study.	Each sample analyzed twice for telomere length (on different gels on different occasions), and the mean was used.	Fitzpatrick et al., 2007
Positive	Weight gain and obesity is associated with chronic systemic inflammation and accelerated telomere attrition regardless of age.	Southern blot for WBC TRF length measurement	22 white males, 28 white females, 8 black males, and 12 black females aged 21.0–43.5 years. Sample from the Bogalusa Heart Study.	2 sequential blood samples at a time interval of at least 10 years.	Gardner et al., 2005
Positive	High total and abdominal adiposity are related to decreased telomere length.	Quantitative PCR for average TRL measurement	309 non-Hispanic white participants aged 8–80 years, 52% female. Sample from the "Fels Longitudinal Study".	DXA used for quantifying total body fat and fat-free mass.	Lee et al., 2011

Table 2 (*Continued*)

Positive or negative association	Main findings	Methodology of measurements	Sample characteristics	Other clinical and/or laboratory variables	Publication
Positive	Tert mice with shorter telomeres in adipose tissue have increased expression of pro-inflammatory cytokines and p53 protein leading to insulin resistance. Shorter telomeres promote the infiltration of macrophages into adipose tissue.	Q-FISH analysis of the telomere length in adipocytes	Tert deficient mice 4th generation G4 mice ($n = 1321$) on a high fat–high sugar diet and Wild-type mice ($n = 831$).	Double immunostaining for Mac3 and tumor necrosis factor-a in adipose tissue. Measured expression of p53, Cdkn1a, and cytokines.	Minamino et al., 2009
Positive	Adipose tissue cells from obese and formerly obese subjects show shorter telomere lengths than never obese subjects.	Quantitative PCR for average TRL measurement	72 Caucasian participants: of which 21 non-obese subjects and 51 obese subjects of similar age, sex and BMI.	Telomere length measured from subcutaneous adipocytes.	Moreno-Navarrete et al., 2010
Negative	Little evidence of expected associations between telomere length and dietary intake of specific food groups and dietary patterns related to obesity.	Quantitative PCR for leukocyte telomere length measured	840 total of which, 157 white, 434 women; 406 men, 228 African American, and 455 Hispanic adults aged 45–84 years. From the Multi-Ethnic Study of Atherosclerosis.	Computed 120-item food-frequency questionnaire.	Nettleton et al., 2008
Positive	Gender specific correlation exists between telomere length and obesity parameters.	Quantitative RT-PCR for average TRL	989 individuals of which 476 aged 48–68 years from a part of the MDCC study and 513 aged 26–75 years from the Northern Sweden MONICA 2004 survey.	All samples tested in triplicates.	Nordfjäll et al., 2008
Positive	Inverse association between leukocyte telomere length and the ICA-IMT in obese men but not in women.	Southern blot analysis for leukocyte telomere length measurement	1062 individuals of which 496 men and 566 women aged 33–86 years. From the Framingham Offspring Study.	Carotid artery IMT measured by B-mode ultrasonography.	O'Donnell et al., 2008
Positive	BMI-dependent obesity is associated with shortened WBC telomere length in women. Telomere length is inversely correlated with serum leptin concentration.	Southern blot for WBC TRF length measurement	1122 white women, twins (45 monozygotic and 516 dizygotic pairs) aged 18–72 years. From the TwinsUK Adult Twin Registry.	Leptin concentration in serum measured with a Radioimmunoassay.	Valdes et al., 2005
Negative	Obese adults have shorter telomeres than their normal-weight counterparts. Obese and normal children show no difference in their TRF lengths.	Southern blot for WBC TRF length measurement	76 Caucasian subjects, of which, 53 children aged 8.2 ± 3.5 years (12 obese) and 23 adults aged 40.5 ± 8.4 years (10 obese).	Estimation of body composition with BIA.	Zannolli et al., 2008

BIA = bioelectrical impedance analysis; DXA = dual energy X-ray absorptiometry; FIRKO mice = fat insulin receptor knockout mice; HOMA-IR = homeostasis model assessment – insulin resistance; ICA-IMT = internal carotid artery – intimal medial thickness; Q-FISH = quantitative fluorescent in situ hybridization; MDCC = Malmö diet and cancer cohort; PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction; RT-PCR = real time – PCR; Tert mice = mice deficient in telomerase reverse transcriptase; TRL = telomeric repeat lengths; TRF = terminal restriction fragment; WBC = white blood cells.

disease (Nordfjäll et al., 2008). The "obesity phenotype" has been associated with shorter telomeres but only in women (Nordfjäll et al., 2008). Certain investigators reported that telomere length in females is significantly longer than males (Jeanclos et al., 2000; Benetos et al., 2001; Bekaert et al., 2007; McGrath et al., 2007), while others did not reveal any significant difference between the telomere length of male and female adults (Das et al., 2009). In younger individuals the effect of sex on telomere length is controversial. In a cross sectional study in obese and non-obese Saudi children, differences were shown in the telomere length of obese boys compared to their non-obese counterparts but not in girls (Al-Attas et al., 2010). Therefore, it is essential to stratify for gender in studies investigating causal relationships between telomere length and chronic states of ill health.

A documented factor affecting telomere length is quality of life and exposure to environmental determinants of aging, such as smoking (Benetos et al., 2001). In addition, over-nutrition and sedentary lifestyles cause elevation of cortisol and insulin, and

suppression of certain anabolic hormones; this metabolic imbalance promotes abdominal adiposity and thus induces accelerated biological aging (Epel, 2009; Al-Attas et al., 2010). These factors should therefore be thoroughly recorded and assessed when measuring telomere length in humans.

Psychological stress – both perceived stress and chronicity of stress – may increase indicators of accelerated cellular and organismal aging such as oxidative stress, hormones, inflammatory factors, telomere length, and telomerase activity (Irie et al., 2003; Epel et al., 2004; Epel, 2009). It is often not taken into account although, it may be an important confounding factor of studies assessing cellular aging. When chronic stress co-exists with abdominal obesity it may systemically affect cell aging through biochemical stressors such as insulin, glucose, and inflammation from adipose tissue thus completing the recipe for accelerated cellular aging.

The effect is amplified considering the consequences of psychological stress and its effects on food consumption and abdominal obesity. Studies that investigate the association of aging and obesity should consider a more holistic approach incorporating the stress factor.

On the same note, few studies investigate obesity related hormonal imbalances and their effect on telomere length. An inverse association between telomere length and insulin resistance has been described in premenopausal women (Aviv et al., 2006), but possibly due to the effect of increased estrogens or antioxidant capacity (von Zglinicki et al., 2000; Balasubramanyam et al., 2007; Adaikalakoteswari et al., 2007).

It is argued that use of medications and vitamins that increase antioxidant capacity in humans are unable to modify the relationship between BMI and telomere length (Kim et al., 2009). In contrast, treatment with L-buthionine sulfoximine (an inhibitor of γ-glutamyl cysteine synthase) decreases the antioxidant capacity and may lead to increased oxidative stress in animals, which in turn decreases the telomere length in several tissues (Podhaisky et al., 1997).

In patients with atherosclerosis the expected accelerated rate of telomere length attrition may not reflect shortened leukocyte telomere length. This condition may arise since individuals with very short birth leukocyte telomere length probably have a relatively short telomere length as adults, despite of the rate of age-dependent and disease-influenced leukocyte telomere length shortening (Berman et al., 1998).

Poor epidemiological and laboratory methodology may compromise the integrity of data describing telomere length and aging related diseases. This confounding factor not only weakens true findings but also leads to confused conclusions regarding telomere biology (Nordfjäll et al., 2008). It is thus imperative that the major methods (i.e. Southern blots, flow-FISH and quantitative Polymerase Chain Reaction) currently used to measure telomere parameters are impartially evaluated.

Telomere length maintenance is a complex process involving a large number of interacting factors. Increased telomere attrition and reduced telomere length may, in some cases, serve as a mechanism for protecting against chronic age-related disease development and progression. Genetically modified mice with short and dysfunctional telomeres are protected from diet-induced atherosclerosis in apolipoprotein E-null mice, indicating that telomere attrition restricts atheroma progression (Cattan et al., 2008).

The above findings indicate that obesity may affect telomere dynamics and accelerate the aging process in more than one ways. This fact emphasizes the need for human and animal studies identifying traits of aging in obesity and weight loss. These data may lead to timely prevention and novel therapeutic guidelines regarding obesity and its impact on aging.

3.1. Future perspectives

There is still no widely accepted consensus as to the normal telomere length and its age-dependent attrition, probably due to the abovementioned wide range of inter-individual variation and a multitude of confounding variables (heredity, sex, race/ethnicity, socioeconomic status, paternal age at conception and environmental exposures) (Kaszubowska, 2008; Poch et al., 2004).

Longitudinal studies may clarify this relationship, as well as the way adiposity, obesity-derived chronic stress, accumulation of visceral fat causing insulin resistance, diet, systemic inflammation, and adipose-tissue derived hormones interplay in telomere length as well as in the attrition of telomeres, even in very early life, causing accelerated cellular aging.

Obesity therapies such as diet, medicine and bariatric surgery and their effect on telomere dynamics remains an underresearched field. It would also be interesting to investigate the effect of lifetime exposures specific nutrients, with telomere dynamics in large cohorts. Acquiring this information requires monitoring an individual over their entire life course.

Studies should have well defined sample size, birth telomere length data, telomere length shortening inter-individual variation, method of telomere length assessment and subject's sex in matched age populations to report significant relationships between telomere dynamics and adiposity quantity and type.

Large-scale epidemiological studies comparing all the methods currently used to measure telomere dynamics, in a number of laboratories, will limit biases and strengthen our understanding of aging-related diseases (Aviv et al., 2011).

These findings suggest an urgent need for studies that will elucidate the association between the telomere hypothesis of aging and obesity. Thorough screening for short telomere lengths, increased attrition rates and decreased telomerase activity in high risk or obese populations may unravel important mechanisms underlying longevity and eventually elucidate novel targets for age-related disease personalized medical interventions.

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