Nutrition 66 (2019) 115–121

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review article

Obesity, weight loss, and influence on telomere length: New insights for personalized nutrition

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ARTICLE INFO

Article History:
Received 21 February 2019
Received in revised form 22 April 2019
Accepted 11 May 2019

Keywords:
Telomere length
Obesity
Shelterin complex
Biomarker
Weight loss
Nutritional intervention

ABSTRACT

Telomeres are structures located at the ends of chromosomes associated with proteins, from the shelterin complex, which are responsible for the protection and preservation of the genetic material. The telomere length (TL) progressively decreases with each cell division, and recent evidence suggests that lifestyle can lead to telomere shortening. In individuals with obesity, excess adipose tissue plays a key role in inducing a chronic and systemic inflammatory state, which can cause TL shortening. Thus, the aim of the present review was to show the relationship between obesity and TL in addition to the possible risk factors for its shortening and how the different strategies for weight loss can modulate TL. As the crucial result, we can consider the association between TL and weight loss, and adiposity changes after different interventions, showing that TL may be used as a biomarker of responses to obesity treatment.

Introduction

Obesity is characterized by abnormal or excessive fat accumulation in adipose tissue with deleterious effects on human health. It is classified by body mass index (BMI, weight in kg/height in m^2), and individuals with scores $\geq$ 30 kg/m^2 are defined as obese individuals [1]. Severe obesity is defined by BMI $\geq$ 40 kg/m^2, and these individuals have a serious chronic health condition. Prevalence of severe obesity has increased in last decades. Excess body weight is a condition that substantially increases the risk for developing a number of chronic diseases such as hypertension, type 2 diabetes mellitus, dyslipidemia [2], heart failure [3], osteoarthritis [4], sleep apnea [5], respiratory problems [6], and breast cancer [7]. Obesity results from an interplay between an at-risk genetic background and environmental aspects such as excessive caloric intake, sedentary lifestyle, intrauterine environment (epigenetic signatures), intestinal microbiota, and physiological and socioeconomic status [8].

Considering obesity and its genetics aspects, emerging studies have shown a bidirectional association between this disease and telomere length (TL). Some authors who compared the TL of eutrophic and obese women verified a lower TL among those with obesity [9–11]; however, the mechanisms that associate obesity with reduced TL are still not fully elucidated. This review aims to pinpoint the main shortening factors and presents current evidence of the association among obesity, weight loss, and TL, in addition to future perspectives in this area, considering personalized nutrition.

Telomeres and shelterin complex

Telomeres are structures located at the ends of the chromosomes associated with protective proteins and are constituted by non-coding genetic material. In mammals, the telomeric repeat TTAGGG double-stranded tandem repeats with a 50 to 400 nucleotide 3′ single-band protrusion, rich in guanine (G), called G tail [12,13]. In humans, telomeres have 10 to 15 kb and, for each cell division, there is a loss of telomeric repeats with an approximate reduction of 24 to 45 bases/y [14]. The non-coding DNA of the telomeres preserves the genetic information, protecting the DNA from damage during the replication. Indeed, it avoids the fusion of the ends of different chromosomes and protects from enzymatic DNA damage recognition and degradation [15].

CW, CNF, and MASP conceived of and designed the study. All authors generated, analyzed, and interpreted the data; drafted and revised manuscript; and approved the final version of the manuscript.

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https://doi.org/10.1016/j.nut.2019.05.002
0899-9007/

The telomere's three-dimensional structure with a protrusion of single-strand DNA is associated with a set of proteins called shelterin complex [16]. This hexameric nucleoprotein complex is responsible for maintaining the chromosome integrity by favoring the formation of G tail in a three-dimensional loop structure that helps to protect against excessive wear during cell division [17]. Therefore, such proteins have the function of protecting the chromosome terminations from all aspects of DNA damage response. Additionally, by physical proximity, the shelterin complex also regulates the activity of the enzyme telomerase on the telomeres [18].

Briefly, the shelterin complex is composed of six proteins called telomeric repeat-binding protein factor 1 and 2 (TRF1, TRF2), repressor/activator protein 1 (RAP1), TRF-1 interactin nuclear factor 2 (TIN2), trypeptidyl peptidase 1 (TPP1) and protection of telomeres 1 (POT1) [19]. TRF1 has been considered to be the main component of the complex because it is the key protein for attraction and formation of other proteins [20]. TRF1 binds to the double strand of telomeric DNA with high specificity. TRF2 also interacts with the double strand of telomeric DNA, protecting the 3′ strand and being responsible for the formation and maintenance of loop structures [21]. On the other hand, the RAP1 protein is recruited to the telomeres through its specific interaction with TRF2 [16,19].

Moreover, POT1 and TPP1 play important roles in the regulation of telomerase action [21]. The TTP1 protein promotes greater stability of POT1 on telomeric DNA and interacts directly with the telomerase catalytic subunit (telomerase reverse transcriptase [TERT]), being responsible for its recruitment [22]. Meanwhile, TIN2 forms a bridge between the two homodimers TRF1/TRF2 and the TPP1/POT1 heterodimer, stabilizing the whole complex [23].

Regulation of telomere length: the telomerase protein

Telomeres and mechanisms of telomeric regulation have been targeted by clinical studies because of their relationship to aging, cell immortalization, obesity, and cancer [24–26]. TL decreases progressively during successive cycles of cell division, which occur constantly with most human somatic cells [27,28]. As a result, telomere shortening is a natural process, but it can be accelerated by factors associated with oxidative stress and inflammatory processes [29,30], which are closely associated with obesity.

When telomeric region presents a critical length, signaling pathways transduce the signal to stop cell growth and induce senescence [31,32]. Cell senescence is characterized by the interruption of cell division, where telomeres can reach a size that does not respond to physiologic stimuli, which causes fusion of the chromosomes and apoptotic cell death [33]. In light of this, telomerase acts in response to telomere shortening associated with cell replication and DNA degradation events, recognizing telomere terminations and adding additional base pairs [34,35]. Telomerase is not expressed in most somatic cells [34,36]. Furthermore, in mature cells and in cells in differentiation process, such as blood cells, telomerase activity is generally low or non-existent [37,38]. In contrast, germ cells and most tumor cells express telomerase and thereby maintain TL over many cell divisions [39].

The major components of telomerase include a catalytic subunit of the enzyme TERT and a template RNA, telomerase RNA component (TERC). Telomerase is responsible for maintaining TL by adding new pairs of bases to chromosomes, guaranteeing their extension to each cell division [40]. In this context, TL has been considered to be a biological clock of cellular senescence and biological aging capable of predicting the replicative capacity of cells, being an important biomarker [41].

Factors associated with TL

It is estimated that the heritability of TL in humans varies from 30% to 80% [42]. Also, there is a substantial interindividual variation both in absolute TL and in the rate of telomere shortening [43]. However, recent evidence suggests that genetic factors are not enough to explain TL and telomerase activity, showing that lifestyle can lead to telomere shortening [44–46]. In light of this, many factors have been related to TL, such as sex, stress, physical activity, smoking, environmental pollution, BMI, alcohol consumption, dietary antioxidants, vitamins, trace elements, chronic inflammation, socioeconomic status, and paternal age [44–46] (Fig. 1).

As an example, it has been observed that women have higher TL than men, possibly owing to lifestyle and the protective effects of estrogen [47]. In addition, the association between stress and TL may be evidenced early in life. Newborns' TL is lower in proportion to the stress levels experienced by the mother during pregnancy [48].

In addition, TL has been shown to be associated with nutritional status and healthy lifestyles. Evidence shows that changes in diet and lifestyle may modulate telomerase activity in peripheral blood mononuclear cells [49], although it is not clear whether its translates into changes in TL. Some nutritional factors like vitamins (including folate, nicotinamide, vitamin A, B_{12}, C, D, and E), minerals (such as magnesium, zinc, and iron), and other bioactive dietary components (such as ω-3 fatty acids, polyphenols, and curcumin) can directly or indirectly influence TL through several mechanisms [50].

Telomere length and obesity

It is well established in the literature that obese individuals have shorter telomeres than eutrophic individuals [9,51,52]. In obese women, it is estimated that telomeres are 240 bp shorter [9]. Considering the main aspects that may explain why TL is shorter in the obese state, we point out the increased inflammatory processes and oxidative stress that accompany excess body weight [2,3].

The excess adiposity increases the production of an extensive range of adipokines, including hormones, cytokines, and immunologic factors that exhibit proinflammatory actions [53]. Adipose tissue in obese individuals is infiltrated by macrophages, and this recruitment is linked to systemic inflammation and insulin resistance [54]. This proinflammatory state appears to be associated with adipocyte hyperplasia and hypertrophy, which may be

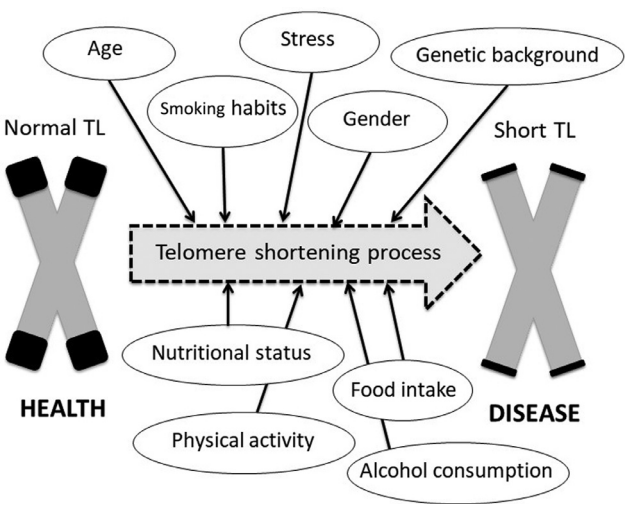

Fig. 1. Factors that influences telomere shortening process. TL, telomere length.

correlated with adipose tissue hypoxia [55]. These characteristics contribute to a chronic and low-grade inflammatory state and, consequently, to the appearance of metabolic imbalances beyond the acceleration of aging and the propensity for age-related diseases [56]. High levels of inflammation, including C-reactive protein, amyloid A, and interleukin (IL)-6 was previously associated with decreased leukocyte TL [57–59]. Furthermore, adipose tissue may promote inflammation through directly secreting leptin [60].

Leptin and adiponectin are among the most prominent adipocyte-derived protein hormones. Their origin in adipocytes and ability to affect the expression of various markers of systemic inflammation has led to the notion of both protein hormones as adipocytokines [1]. In this way, considering that high leptin levels contribute to inflammation, insulin resistance, glucose intolerance, and stress-induced cardiovascular disease, authors found consistent evidence for an inverse correlation between TL and leptin levels, in both sexes, which was independent of increased BMI or C-reactive protein levels [61].

The main mechanism explaining the telomere dysfunction induced by chronic inflammation seems to be oxidative stress, an imbalance between the production of reactive oxygen species (ROS) and cellular antioxidant defenses [62]. ROS are byproducts of aerobic metabolism and of adenosine triphosphate production in mitochondria, which can directly influence cell signaling and homeostasis [63]. Deregulation of ROS production can induce toxic effects via damage of cellular structures including proteins, lipids, and nucleic acids [64] (Fig. 2). Telomeres are highly sensitive to oxidative stress damage owing to their high content of guanines [65,66]. Consequently, short and dysfunctional telomeres are the starting point for cellular senescence, cell death, and DNA instability [67]. 8-Oxo-dG is the reactive species most prevalent in DNA and present in oxidized and senescent cells [68]. The generation of 8-Oxo-dG creates breaks in the single DNA strand, which can be unsatisfactorily repaired in some parts of the chromosome, such as in telomeres, causing genome instability [69].

Telomere length and weight loss strategies

Different strategies can be used to treat obesity, aiming at significant weight loss and improvement of comorbidities. Clinical treatment using restrictive diets, practice of physical activity, pharmacologic therapy, or surgical treatment are the most popular strategies adopted currently [70].

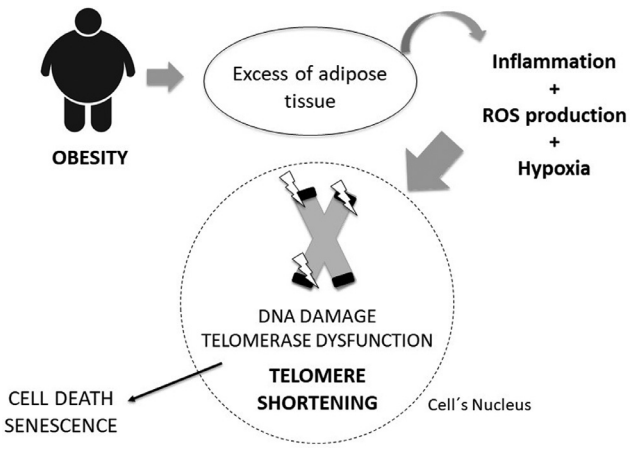

Fig. 2. Effects of obesity in telomere length. ROS, reactive oxygen species.

Several studies have shown a combination between the size of telomeres and obesity versus different types of weight loss' treatments [71–74]. Associations among weight loss, adiposity dynamics through life course, and TL were described [71]. Table 1 shows the main findings observed in this condition.

Dietary and physical activity interventions

Most studies report a significant effect of calore restriction and significant weight loss on the TL [72,73]. A 2-mo energy-restricted diet (30% of energy from fat, 15% energy from protein, and 55% energy from carbohydrates) study with overweight or obese adolescents demonstrated that the diet resulted in increased TL, mainly in those with the shortest telomeres at baseline [74].

On the other hand, a study with overweight and obese postmenopausal women submitted to dietary weight loss, aerobic exercise, or diet plus exercise intervention demonstrated that TL change was inversely associated with TL at baseline. More interestingly, no significant difference was found in TL regarding the magnitude of weight loss [75].

García-Calzón et al. [74], when studying individuals with excess body weight in a 5-y follow-up of the Mediterranean diet, observed that changes in TL were inversely associated with changes in anthropometric parameters. In addition, the risk for remaining obese after 5-y diet intervention was lower in those individuals with the longest telomeres at baseline and increased their TL after intervention.

A study that investigated the effect of weight loss induced by calorie-restricted diets on TL in the rectal mucosa of obese men founded that TL increased after intervention. Moreover, the increase of TL appeared to be positively correlated with weight and body fat loss. The authors concluded that calorie-restricted diets may contribute to the prevention of telomere shortening and DNA base damage [76].

Therefore, association of the consumption of specific foods and TL has been investigated [77–80]. Leung et al. [78] suggested that a diet rich in fruits, vegetables, whole grains, dairy, and vegetable proteins and low in red and processed meats, sodium, and sugars is related to higher TL. Also, intake of foods rich in antioxidants may lead to healthy cell aging, which can soften the telomeric friction [78]. Rafie et al. [77] showed that processed meat, cereals, and sugar-sweetened beverages may be associated with shorter telomeres. However, De Meyer et al. [79] found that carbohydrate consumption, such as white bread, pasta, rice, and potatoes, did not present a significant correlation with TL. Similarly, Kasielski et al. [77] also found no correlation between cereal consumption and TL, only an inverse correlation between red/processed meat consumption and TL.

In addition, a recent study published by our research group showed that obese women who underwent green tea supplementation for 8 wk had a significant increase in TL after supplementation (1.57 ± 1.1 to 3.2 ± 2.1 T/S ratio; $P < 0.05$) [81]. The antioxidant properties of green tea, especially of its major compound, epigallocatechin-3-gallate, are directly connected to the number and the position of the hydroxyl (-OH) groups distributed on aromatic ring in the molecule [82]. It has been shown that the hydroxyl group contributed to antioxidant activity. This effect was due to the electron-donating hydroxyl groups location, the presence of -OH in the position 5- and 7- in the A ring, and to the presence of the catechol group (3,4-dihydroxyl) in the B ring, that was directly associated with the antioxidant activity. Another effect that can strongly modulate the potential as free radical scavengers of the catechins is the presence of the gallate group linked in the ring C [83,84].

Table 1
Studies about telomeres length, obesity, and different types of treatment for weight loss

Authors	Year	N	Method	Association	Time	TL
Obesity vs TL studies						
Boccardi et al. [73]	2013	217	qPCR	Mediterranean diet	–	↑
Leung et al. [78]	2018	4758	qPCR	Unprocessed plant-based diet	–	↑
De Meyer et al. [79]	2018	2509	Southern blot	Diet composition	–	NA
Kasielski et al. [77]	2016	28	qPCR	Red meat	–	↓
Kiefer et al. [72]	2008	56	qPCR	Dietary restraint	–	↓
Weight loss intervention vs TL studies						
García-Calzón et al. [74]	2014	204	qPCR	Dietary restraint	2 mo	↑
Mason et al. [75]	2013	439	qPCR	Dietary restraint Aerobic exercise Diet + exercise	12 mo	NA
García-Calzón et al. [95]	2014	521	qPCR	Mediterranean diet	5 y	↑
O'Callaghan et al. [76]	2009	54	qPCR	Dietary restraint	12 wk	↑
Carulli et al. [86]	2016	37	qPCR	Bioenteric intragastric balloon	6 mo	↑
Formichi et al. [87]	2014	237	qPCR	Bariatric surgery (different techniques)	1 y	↓
Hohensinner et al. [88]	2018	58	qPCR	RYGB	24 mo	↑
Dershem et al. [89]	2017	50	qPCR	RYGB	3–5 y	↑
Laimer et al. [90]	2016	142	qPCR	Bariatric surgery (different techniques)	10 y	↑

NA, no association; qPCR, quantitative polymerase chain reaction; RYGB, Roux-en Y gastric bypass; TA, telomerase activity; TL, telomere length.
All measurements were done in blood cells except the study from O'Callaghan et al., 2009.

Bariatric surgery

Bariatric surgery is now recognized as the treatment of choice for severe obesity and is associated with improvement of metabolic dysfunction in addition to substantial weight loss [85]. The effect of different surgery techniques on TL is not yet fully elucidated, and the investigations show several divergent results.

In the recent postoperative period (6 mo) of intragastric balloon, Carulli et al. [86] demonstrated that individuals who obtained greater weight loss had greater telomere elongation. However, 1 y post-surgery, authors found a reduction of TL compared with baseline [87].

Hohensinner et al. [88] found an increase in TL 24 mo after Roux-en Y gastric bypass (RYGB), in which post-surgery TL doubled in relation to the initial length. After evaluating individuals between 3 and 5 y post-RYGB, Dershem et al. [89] observed increased TL, emphasizing that significant elongation occurred in patients with shorter baseline telomeres. However, the TL did not correlate with the percentage of weight loss. Also, in the late post-operative period (10 y), authors observed a relative increase in TL, possibly owing to improved metabolic characteristics [90].

Furthermore, increased telomerase activity was reported 3 to 5 y after RYGB, which was correlated to the change in dietary pattern and physical activity resulting from the surgical procedure and would be an explanation for the increase in TL [89].

Telomere length, genetic background, and obesity or weight loss

In addition to many studies that have shown that inflammation and oxidative stress are the main link between obesity and TL [91], in the personalized nutrition scope, genetic variables also should be considered. It is well known that individuals respond differently to interventions, which may be explained by genetic polymorphism [92]. In this way, genetic background also may help to explain some of the non-consistent relationship between obesity phenotype and TL [93].

Recent reviews have evidenced that *FTO* genotypes may be associated with genetic aging and shorter telomeres [93]. Indeed, authors reported that middle-aged women who are carriers of at least one *FTO* risky (rs17817449 G) allele had shorter telomeres [94].

García-Calzón et al. [95] also observed a difference in the response to the Mediterranean diet between *Ala* carriers and non-carriers for the *PPARγ2* gene (rs1801282); variants of this gene are commonly associated with insulin resistance and lipid metabolism. *Ala* carriers seems to shorten the TL less after 5 y compared with the *Pro/Pro* genotype and also had greater positive correlation of TL and reduction on carbohydrate intake. The same authors, when studying obese adolescents after a 2-mo weight loss program, showed that -174 G/C polymorphism (rs1800795) in the *IL-6* gene modulated the association between basal TL and changes in *IL-6*. Interestingly, longer telomeres were associated with an improvement in glucose tolerance and inflammation after weight loss [96].

Considering TERC single-nucleotide polymorphisms, it has been shown that CC genotype for rs16847897 polymorphism and GG genotype of rs12696304 polymorphism were significantly associated with shorter TL and lower hTERT levels. Indeed, together, those polymorphisms significantly increased the risk for type2 diabetes mellitus [97].

Conclusions and future prospects in personalized nutrition

The growing field of science regarding studies related to the biology of telomeres opens new pathways for understanding, at the molecular level, the mechanisms involved with human aging, tumorigenesis [98], obesity [93], oxidative stress [99], and numerous metabolic dysfunctions [100]. Elucidating such molecular mechanisms that regulate this telomere's dynamics can help to prevent DNA damage [101]. Therefore, considerable interest has developed around the effectiveness and utility of using TL as a clinical biomarker for disease or disease predisposition.

In this review we observed the intimate association between TL and obesity in the face of different interventions for weight loss. The main factors that may explain associations between obesity and shorter telomeres are increased oxidative stress and the inflammatory processes that accompany this disease (excess adipose tissue) [10].

On the other hand, as the crucial result of this review, we can consider the association between TL and weight loss and adiposity changes after different interventions, showing that TL may be used as a biomarker of response to obesity treatment. Substantial weight loss promotes improvement of chronic inflammation and adipose tissue oxidative stress and can lead to shorter telomeric attrition, promoting TL conservation and DNA repair. However, the effects of weight loss on TL can be dependent on the strategies used by achieve the weight reduction, which explains the divergent results.

In dietary and exercise interventions studies, positive effects on TL could be associated, in addition to weight loss, to a reduction in the amount of saturated fat and sugar consumed, as well as with an increase in vitamin and mineral (antioxidant) intake. However, bariatric surgery may be related to abrupt changes in food intake with an extensive and fast weight loss but differs according to the surgical technique used. Thus, some controversial results may be associated with the catabolic state observed in the immediate postoperative period, which may accelerate telomeric attrition [102]. The recent period after surgery is accompanied by changes in inflammation and the process of scarring, which may affect the telomere turnover process. Moreover, the metabolic improvement reached in the middle and late postoperative periods may reflect benefits in TL. Therefore, TL measurement or specific genetic variants could have clinical utility in the potential to avert significant morbidity and alter treatment decisions in a way that advances patient care outcomes.

In addition, psychological status should be evaluated. It is important to note that dietary restraint may act as a chronic psychological stressor and for this reason may accelerate telomere shortening in leukocytes. In this case, TL shortening potentially is due to perceived stress, cortisol, or insulin sensitivity [72]. To achieve better results in the analysis of TL, the more results that are analyzed for each patient, the more precise the diagnostic treatment will be.

Currently, there are several methods for studying TL as a clinical biomarker, especially for age-related disease risk [103]. In the obesity scenario, identification of dynamic biomarkers that may predict weight loss could help with obesity management and promote prescription of the most suitable strategy [104,105]. As some studies show different responses to clinical treatments, individuals may also present different responses to different treatments for obesity and TL may be used as a biomarker.

In this context, studies in the nutritional genomics area are promising because they may potentially contribute to the development of effective prognostic indicators, improve therapeutic treatment, and consequently, the extension of a healthy life, especially with regard to personalized nutrition in obesity treatment. However, inconsistent results concerning the effect of obesity treatments and weight loss on TL suggest the need for more studies before its clinical application in routine use as biomarker.

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