

# How Does Obesity and Physical Activity Affect Aging?: Focused on Telomere as a Biomarker of Aging

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Obesity is known to continuously increase systemic inflammation and oxidative stress, leading to shorter telomere length. However, research regarding the correlation between physical activity, exercise, obesity, and telomere length is not consistent. Therefore, this review aims to summarize the effects of obesity, physical activity, and exercise on telomere length. Our search for effects of obesity, physical activity, and exercise, on telomeres was conducted using three computerized databases: Medline, PubMed, and EBSCO. Keywords in the search were "physical activity, exercise and obesity," "physical activity, exercise and telomere," and "obesity and telomere." Improving chronic inflammation and oxidative stress levels can prevent telomere attrition due to obesity. In addition, differences in the anti-aging effects of physical activity and exercise are shown in the post-middle-age period, when telomere length changes, rather than in past exercise habits. Maintaining high cardiorespiratory fitness levels through regular exercise and physical activity in the post-middle-age period minimizes obesity-related diseases and helps maintain telomere length, which is an index of cell senescence.

**Key words:** Telomere, Obesity, Physical activity, Exercise, Cardiorespiratory fitness

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## INTRODUCTION

Obesity is a major risk factor that increases mortality and the prevalence of associated age-related diseases.<sup>1</sup> Obesity is known to continuously increase systemic inflammation and oxidative stress<sup>2</sup>, leading to shorter telomere length (TL).<sup>3</sup>

Telomeres are DNA protein complexes on the end of the chromosomes of human eukaryotic cells<sup>4</sup> and have been reported to generally shorten with age.<sup>5</sup> While inflammation and oxidative stress are major causes of aging, they also play an important role in telomere attrition<sup>6</sup>, and studies on the association of TL with chronic inflammation and oxidative stress have been reported.<sup>7</sup>

Recent systemic reviews have reported various results regarding the correlation between body weight status and TL, with some claiming an inverse correlation between obesity and TL<sup>8-10</sup> and

others indicating that there is no correlation.<sup>11,12</sup> However, a meta-analysis based on cross-sectional studies reported that body mass index (BMI) and TL have an inverse association.<sup>7</sup>

Telomeres are not only affected by oxidative stress and inflammation, but also by lifestyle habits such as smoking and sedentary behavior.<sup>13-15</sup> Recent reports have documented that physical activity is associated with TL in adults<sup>16-18</sup>, since physical activity reduces obesity, type 2 diabetes, the risk of hypertension and cancer and improves visceral fat, bone fitness, and insulin resistance.<sup>19,20</sup>

It is widely known that exercise improves cardiorespiratory function and weight loss and decreases the risk of early chronic diseases. Furthermore, the increase in oxygen consumption during exercise leads to the generation of active oxygen, which causes oxidative stress.<sup>21</sup> Studies have shown that high intensity exercise increases oxidative stress and cause cell damage.<sup>22</sup> Studies have also reported

that excessive physical activity and exercise can promote a decrease in TL.<sup>23</sup> Thus, the correlation between physical activity, exercise, and TL is still unclear. Moreover, research findings are not consistent in this area. Some studies report that physical activity reduces the prevalence of obesity-related diseases and that it is effective in weight loss, whereas other studies report that it is ineffective.<sup>24,25</sup> Therefore, the purpose of this review is to investigate the correlation between obesity and TL and to determine the effects of physical activity and exercise on obesity and TL through related studies.

## TELOMERE AND AGING

Telomeres are composed of hexanucleotide sequences (TTAGGG) at the ends of eukaryotic chromosomes. The TL of adult mitotic cells decrease due to certain parts not being replicated during every cell division.<sup>26,27</sup> When telomeres, which shorten after every cell division, reach a critical point, they cause arrest and malfunction of the cell cycle. This causes replicative senescence and potential genomic instability, leading to cell death.<sup>28</sup> Therefore, telomeres reflect divisional activity (loss and stability) of each cell and are used as indicators of biological aging.<sup>29</sup>

Telomeres are affected by tissue oxidative stress and inflammation<sup>30</sup>, and chronic inflammation promotes telomere attrition by increasing white blood cell replacement.<sup>31</sup> In addition, oxidative stress conditions promote TL attrition in cell replication by decreasing the activity of telomerase, which is the polymerase responsible for maintaining TL.<sup>3</sup>

People with cardiovascular disease (CVD) are reported to have shorter TL compared to healthy individuals.<sup>32</sup> TL is reported to have a negative correlation with factors that cause CVD such as age, BMI, waist-to-hip ratio (WHR), hypertension, triglycerides, fasting blood glucose levels, and body fat mass.<sup>33</sup> Hypertension causes continuous stress on blood vessels and endothelial cells and promotes remodeling, thereby increasing oxidative stress and decreasing TL.<sup>34</sup> It has been reported that diabetes also promotes cellular aging of tissues associated with glucose transport and metabolism, thereby affecting telomere attrition.<sup>35</sup> The accumulation of atherosclerotic plaques in blood vessels affects the aging of vascular endothelial and smooth muscle cells resulting TL reduction. Coronary artery disease is also reported to have a negative correlation

with TL.<sup>36</sup>

Many studies have also reported that shortened telomeres in leukocytes increase the prevalence and risk of disease due to aging.<sup>37,38</sup> Short telomeres are involved in disease pathogenesis because senescent cells increase the secretion of proinflammatory cytokines and extra-cellular matrix-degrading enzymes, which promotes disease progression.<sup>39,40</sup> Thus, telomere attrition may occur with risk factors and conditions that cause disease, and shortened telomeres may be responsible for promoting diseases caused by aging.

## OBESITY AND TELOMERE

### The association between obesity and TL

It is reported that obesity and TL reduction may be correlated because obesity increases oxidative stress and chronic systemic inflammation (Table 1). There is an inverse correlation between TL and BMI, WHR, total fat, and waist circumference (WC), and abdominal adipose tissue is directly related to TL attrition and promotes the aging process.<sup>8,9,15,16,41-49</sup> Njajou et al.<sup>9</sup> and García-Calzón et al.<sup>10</sup> also reported that higher WCs were associated with shorter telomeres, even after age adjustment. However, because many studies have used indirect anthropometric measurements, study results on the correlation between obesity, abdominal fat, and TL have not been consistent. Some studies have shown that telomeres correlate with obesity indices<sup>45-47</sup>, whilst some report no correlation in middle-aged people<sup>11,12</sup> or the elderly.<sup>50-52</sup>

TLs of adipose tissue are reported to have a negative relationship with WC and adipose tissue size regardless of age.<sup>44</sup> It has been reported that subcutaneous adipose tissue and visceral adipose tissue telomeres have a negative correlation with BMI, blood pressure, hyperlipidemia, and the size of adipose tissue. Thus, metabolic diseases associated with obesity seem to be correlated with the amount of fat tissue and TL attrition.<sup>42-44</sup>

### The effect of change of body weight or fat mass on telomere

Weight gain and obesity are reported to promote telomere attrition regardless of age (Table 2). Rapid weight gain since the age of 18 has been reported to promote telomere attrition.<sup>11</sup> A study of 2,912 Chinese women aged 40–70 years showed that TL was

**Table 1.** The studies of the association between the TL and obesity

Author (year)	Participant	LTL measurement method	Obesity marker	Association
Lee et al. (2011) <sup>8</sup>	8–80 yr, Adults (n=309, 52% women)	qPCR	BMI, WC, HipC, %fat, VAT	Negative
Njajou et al. (2012) <sup>9</sup>	70–79 yr, Adults (n=2,721, 51.6% women)	qPCR	%Body fat, SAT	Negative
Bekaert et al. (2007) <sup>11</sup>	35–55 yr, Adults (n=2,509, 51.5% women)	Southern blot for WBC TRF	Body weight, BMI, WC	No
Diaz et al. (2010) <sup>12</sup>	40–64 yr, Adults (n=317, 54.9% women)	qPCR	BMI, VAT	No
Valdes et al. (2005) <sup>15</sup>	18–76 yr, Women (n=1,122)	Southern blot for WBC TRF	BMI	Negative
Cherkas et al. (2008) <sup>16</sup>	18–81 yr, Twins (n=2,401, 89.6% women)	Southern blot for WBC TRF	BMI	Negative
Nordfjäll et al. (2008) <sup>41</sup>	26–75 yr, Adults (n=989, 48.0% women)	qPCR	BMI, body weight, WC, HipC in women	Negative
Moreno-Navarrete et al. (2010) <sup>42</sup>	31–61 yr, Obese women (n=21, waist 110–147 cm)	qPCR in adipocyte	WC, adipocyte size with TL of adipocytes	Negative
Monickaraj et al. (2012) <sup>43</sup>	34–56 yr, Obese, diabetic, and obese-diabetic subjects (n=59, 57.6% women)	qPCR in SAT	BMI	Negative
Jones et al. (2014) <sup>44</sup>	>35 yr, Obese, diabetic, and obese-diabetic subjects (n=61)	qPCR in SAT & VAT	Adipose hypertrophy	Negative
Kim et al. (2013) <sup>45</sup>	>60 yr, Women (n=129)	qPCR	BMI, WC	Negative
Cui et al. (2013) <sup>46</sup>	40–70 yr, Women (n=2,912)	qPCR	Body weight, WC, HipC, BMI, WHtR WHR, height	Negative or no
Al-Attas et al. (2010) <sup>47</sup>	5–12 yr, Children (n=148, 53.4% girls)	qPCR	WC in girls	Negative
Fitzpatrick et al. (2007) <sup>48</sup>	74.2±5.2 yr (Mean±SD), adults (n=419)	Southern blot for WBC TRF	Body size, age ≤73 yr	Negative or no
Gardner et al. (2005) <sup>49</sup>	21–43.5 yr, Adults (n=70, 57.1% women)	Southern blot for WBC TRF	BMI	Negative
Farzaneh-Far et al. (2010) <sup>50</sup>	55–78 yr, CAD (n=608, 17.9% women)	qPCR	BMI	No
Bischoff et al. (2006) <sup>51</sup>	79–101 yr, Elderly twins (n=812, 67.9% women)	qPCR	Obesity	No
Oliveira et al. (2018) <sup>52</sup>	65–74 yr, Women (n=83)	qPCR	Body weight, BMI, WC	No

TL, telomere length; LTL, leukocyte telomere length; qPCR, quantitative polymerase chain reaction; BMI, body mass index; WC, waist circumference; HipC, hip circumference; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; WBC, white blood cell; TRF, terminal restriction fragment; WHtR, waist to height ratio; WHR, waist to hip ratio; SD, standard deviation; CAD, coronary artery disease.

shorter when weight gain after age of 50 was more than 15%.<sup>46</sup> Furthermore, in a study of 2,721 elderly people aged 70 to 79 years, TL was reported to be shorter with increased body weight and adipose tissue.<sup>9</sup>

On the other hand, it was also reported that weight loss was correlated with TL elongation. TL elongation was positively correlated with weight loss, and the lengthening rate increased with increase in weight loss.<sup>53</sup> In a study of 521 adults aged 55 to 80 years and elderly subjects who underwent the Mediterranean diet intervention for 5 years, TL was inversely correlated with changes in fat tissue including body weight, BMI, WC, and WHR, and it was reported that TL underwent elongation.<sup>54</sup> These results suggest that weight loss prevented the decrease of TL and DNA damage.<sup>55</sup> Oxidative stress and chronic inflammation due to obesity accelerate telomere attrition<sup>56</sup>, and telomere DNA is very sensitive to oxidative stress damage. Oxidative stress plays an important role in the decrease of TL, because explicative senescence is considered a stress response blocking the growth of cells that have a high risk of mutation.<sup>22</sup> Therefore, it can be suggested that telomere lengthening is correlat-

ed with weight loss, decrease of inflammation and oxidative stress. Weight loss intervention not only prevents telomere shortening, but also plays an important role in telomere elongation.<sup>53</sup> Another study showed that TLs of severely obese subjects were significantly shortened at 3, 6, 9, and 12 months after bariatric surgery and additional attrition occurred immediately after surgery, likely because of their catabolic state.<sup>57</sup> However, there was a report that weight loss through dietary and exercise treatments for 12 months were not correlated with changes in TL.<sup>58</sup> Thus long-term studies are needed to observe changes in TL.

Taken together, obesity is correlated with TL decreases due to chronic inflammation and oxidative stress. Obesity-related indicators (WC, WHR, or fat mass) also seem to be correlated to TL. In addition, weight loss has the effect of elongating telomeres, but weight loss through bariatric surgery is considered a catabolic state that promotes TL reduction, indicating that further studies are needed.

**Table 2.** Summary of the association between the TL and weight change

Author (year)	Participant	Intervention	LTL measurement method	Change of body weight	Association
Njajou et al. (2012) <sup>9</sup>	70–79 yr, Adults (n=2,721, 51.6% women)	7-yr Follow-up	qPCR	BMI, %body fat loss	Positive
Bekaert et al. (2007) <sup>11</sup>	35–55 yr, Adults (n=2,509, 51.5% women)	Cohort study	Southern blot for WBC TRF	Fast weight gain since age of 18 yr	Negative
Cui et al. (2013) <sup>46</sup>	40–70 yr, Women (n=2,912)	Self-report (weight at enrollment, age 50)	qPCR	Loss (≥5%) Stable (≤5%) Gain (5%–15%) Gain (>15%)	Positive No No Negative
Carulli et al. (2016) <sup>53</sup>	31–52 yr, Obese subjects (n=37, 62.2% women)	Bioenteric intragastric balloon	qPCR	Loss (–18.66 kg)	Positive
O'Callaghan et al. (2009) <sup>54</sup>	55–80 yr, Adults (n=521, 55% women)	Mediterranean diet (5 yr)	qPCR	Loss (–1.09 kg) BMI (–0.47 kg) WC (–1.15 cm) WHR (–0.008) Adiposity	Positive Positive Positive Positive Positive
Latifovic et al. (2016) <sup>58</sup>	50–75 yr, Women (n=439)	Diet/AE/diet+AE/CON (12 mon)	qPCR	Diet (–8.5%) AE (–2.4%) Diet+AE (–10.8%) CON (–0.8%)	No

TL, telomere length; LTL, leukocyte telomere length; qPCR, quantitative polymerase chain reaction; BMI, body mass index; WBC, white blood cell; TRF, terminal restriction fragment; WC, waist circumference; WHR, waist to hip ratio; Diet, diet group; AE, aerobic exercise group; CON, control.

### The mechanism on association between obesity and TL

Obesity is generally caused by the accumulation of excessive fat tissue due to excessive dietary intake and lack of physical activity.<sup>59</sup> The accumulation of ectopic fat surrounding organs is directly correlated to insulin resistance, which is a major cause of metabolic syndrome and CVD.<sup>60</sup> Obesity also results in the formation of reactive oxygen species and cytokines which are increased in the inflammation processes. These processes are key factors that may explain the association between obesity and telomere shortening, because inflammation induces further inflammatory reactions causing DNA damage.<sup>30</sup> DNA migration was increased in the lymphocytes of overweight and obese.<sup>61</sup> These DNA damage responses are defined by the consequences of genomic instability. This is the reaction of cells to damaged DNA to prevent negative health conditions such as the initiation of mitotic senescence, arrest, repair, and cell death.<sup>62–64</sup>

Adipose tissue plays a key role in this reaction. Accumulation of visceral fat (abdominal fat) also increases fat cells and is associated with dysfunctional fat tissue.<sup>65</sup> Fat, or adipose tissue, plays an important role in the physiological processes of tissues. It plays a role in the production of inflammatory cytokines and chemokines as well as in host defense, immunity, and injury response.<sup>66</sup> The

mechanism of a proinflammatory state accompanied by obesity may be associated with hyperplasia and hypertrophy of adipocytes, which can induce adipose tissue hypoxia. Dysfunction of adipose tissue causes secretion of prostaglandins, C-reactive proteins (CRPs), and cytokines such as interleukin-6, tumor necrosis factor alpha, and leptin, and proinflammatory biomarkers.<sup>67,68</sup> It also lowers the level of adiponectin such as anti-atherosclerotic adipokines. This abnormal secretion of adipose tissue causes type 2 diabetes, hyperlipemia, and CVD.<sup>69,70</sup> Obesity, metabolic syndrome, and CVD prevent malignant transformation through the activation of processes that lead to senescence and programmed cell death. These response mechanisms play a key role in the increased of inflammation via DNA damage and the activation of transcription factors as well as telomere dysfunctions.<sup>62,64</sup>

A high fat ratio in muscle also causes metabolic dysfunction by increasing the circulation of free fatty acids. Increased circulating free fatty acids increase insulin secretion to control glucose metabolism, and hyperinsulinemia reduces insulin sensitivity and causes type 2 diabetes.<sup>71</sup> Chronic systemic inflammation also increases oxidative stress and reduces metabolic flexibility, leading to metabolic syndromes and a vicious cycle of disease<sup>72</sup> as well as shorter TL.

## PHYSICAL ACTIVITY AND TELOMERE

### Effect of physical activity on metabolic health independent from obesity

Several studies have reported a strong correlation between obesity and physical inactivity<sup>73-75</sup>, and metabolic syndromes have also been associated with sedentary lifestyles and low cardiorespiratory fitness.<sup>76</sup> Ostman et al.<sup>77</sup> used a systematic review and meta-analysis to conclude that exercise was inversely correlated to body composition, blood cholesterol, fasting plasma glucose, fasting insulin, blood pressure, and clinical outcomes. Hayashino et al.<sup>78</sup> also reported that exercise interventions affected insulin resistance, inflammatory markers/cytokines, and adipokines that cause metabolic syndrome and CVD and that there were measurable effects in the decrease of systemic inflammation as exercise duration and frequency increased.

Unlike the positive effects of exercise on disease, results of the effects of exercise on weight loss were somewhat inconsistent. According to a meta-analysis on weight loss effects by Votruba et al.<sup>79</sup>, six out of 11 studies reported weight loss in which exercise was performed without dietary control, whereas the other five studies reported no change in body weight. In another meta-analysis study, exercise alone resulted in 3 kg weight loss in men after 30 weeks and 1.4 kg weight loss in women after 12 weeks, suggesting that exercise-induced weight loss is limited.<sup>80</sup> In a meta-analysis of 16 studies, 11 studies showed a significant decrease in body weight after exercise, but the decrease in body weight was within the range of 0.1 to 5.2 kg and the difference in weight loss between the exercise group compared to a control group who did not exercise was 0.6 to 3.0 kg. The effect of weight loss for exercise alone without dietary control was very limited.<sup>81</sup>

The effect of exercise on weight loss varies according to the exercise volume. In a study that conducted high intensity ( $\geq 65\%$  maximum oxygen consumption [ $VO_{2max}$ ]) exercise 6 to 7 days per week for at least 30 minutes to 2 hours, a 10 to 20 kg weight loss was reported.<sup>82-84</sup> However, other studies have shown that weight loss was in the range of 0.2 to 1.5 kg despite high intensity training.<sup>85,86</sup> Such differences in study results exist because exercise volume and weight loss do not necessarily have a measurable correlation, and the threshold of weight loss with exercise is different according to

sex, individual differences, and the forms of exercise.<sup>87</sup> Furthermore, compensatory actions such as a decrease in basal metabolism is induced because as the intake is reduced by 7,700 kcal, the amount of body weight is reduced by 70% and the amount of fat is reduced by 30%.<sup>88,89</sup>

Although the weight loss effect of exercise was limited, the risk factors associated with being overweight and obese were reduced even with no change in body weight or a small weight loss of less than 5 kg.<sup>90,91</sup> Exercise, regardless of weight loss, has the effect of reducing abdominal obesity, and decreasing abdominal obesity has the effect of reducing systemic inflammation and risk factors for metabolic syndrome and CVD.<sup>92,93</sup> Exercise has anti-inflammatory effects regardless of weight loss because it reduces hypoxia in adipose tissue by increasing capillary blood flow.<sup>94</sup> In addition, exercise training reduces CRP levels and BMI; this has been observed even without a reduction in body weight.<sup>95</sup> The anti-inflammatory effect of exercise reduces oxidative stress, which improves glucose tolerance, insulin resistance, and fat metabolism, and has the effect of reducing blood pressure in people with metabolic diseases as well as in healthy people.<sup>96</sup>

Therefore, exercise induces a positive improvement in the prevalence of obesity and obesity-related diseases by reducing abdominal obesity, systemic inflammation, and oxidative stress, thereby reducing the risk factors of obesity-related diseases.

### Effect of physical activity on telomere in adults

It is well known that regular physical activity improves cardiorespiratory function, induces some weight loss, and lowers the risk of early chronic disease. However, it has been reported that the increase of oxygen consumption during exercise increases the oxidative stress by inducing active oxygen.<sup>21</sup> In particular, high intensity exercise greatly increases oxidative stress, resulting in cell damage. Thus, various results on the correlation between physical activity and TL have been reported.<sup>22</sup>

Many previous studies have reported that people with higher levels of physical activity have longer TLs than those who have a sedentary lifestyle (Table 3). Cherkas et al.<sup>16</sup> reported that people with the highest physical activity had longer TLs by 200 nucleotides (7.1 vs. 6.9 bp) than those with the lowest physical activity, suggesting that regular physical activity can prevent aging. It has

**Table 3.** Summary of the association between the TL and physical activity

Author (year)	Subject	LTL measurement method	Intervention or factor	Association
<b>Physical activity &amp; TL</b>				
García-Calzón et al. (2014) <sup>10</sup>	47 yr, Men (n=782)	Southern blot for WBC TRF	Low/moderate/high PA Moderate: walking, cycling, skiing, gardening, bowling, fishing, or other light Ex weekly	Proportion of shorter TRF was lowest in the moderate PA
Bekaert et al. (2007) <sup>11</sup>	35–55 yr, Adults (n=2,509, 51.5% women)	Southern blot for WBC TRF	PA (MET × time per wk)	No association
Cherkas et al. (2008) <sup>16</sup>	18–81 yr, Twin adults (n=2,401)	Southern blot for WBC TRF	Self-reported PA during the past 12 mon	Positive
Ludlow et al. (2008) <sup>17</sup>	50–70 yr, Adults (n=69, 50.7% women)	qPCR in mononuclear cells	Self-reported PA during the past month	Longer LTL of PBMC in 991–3,540 kcal/wk shorter LTL of PBMC in 9,351 kcal/wk
Latifovic et al. (2016) <sup>58</sup>	20–50 yr, Healthy adults (n=477, 57.2% women)	qPCR	Self-reported PA during the past 7 day	Positive
Edwards and Loprinzi (2016) <sup>97</sup>	>20 yr, Adults (n=1,868, 49.2% women)	qPCR	Self-reported PA during the past 30 day	Positive
Du et al. (2012) <sup>98</sup>	43–70 yr, Women (n=7,813)	qPCR	Self-reported PA during the past year	Positive
Song et al. (2010) <sup>100</sup>	18–80 yr, Healthy adults (n=80)	qPCR in T-lymphocytes	Self-reported PA	No association LTL & PA PA was negative associated with DNA damage.
Saßenroth et al. (2015) <sup>101</sup>	>61 yr, Adults (n=814, 51.3% women)	qPCR	Self-reported PA during the last month Longer period PA at least 10 yr	Positive association in unadjusted No association after adjustments such as CHD, medicine, BMI, and smoking etc. PA was associated with longer LTL at over 42 yr No association at 20–30 yr
Laine et al. (2015) <sup>102</sup>	599 Men (392 former athletes & 207 CON)	qPCR	Cohort study (1985, 1995 or 2001)	No difference in LTL in late life
Zhu et al. (2011) <sup>103</sup>	667 Adolescents (14–18 yr, 51% girls)	qPCR	Vigorous PA	Positive only in girls
<b>TL in exercise experience &amp; sedentary</b>				
LaRocca et al. (2010) <sup>18</sup>	18–32 yr vs. 55–72 yr (n=57, 59.6% women)	Southern blot for WBC TRF	Endurance Ex-trained vs. SED VO <sub>2max</sub>	Longer LTL in Ex vs. SED in older No difference in young and adults
Borghini et al. (2015) <sup>23</sup>	45.4 ± 9.2 yr (Mean ± SD), adults (n=62, 21% women)	qPCR in saliva	Athletes (n=20, 59.4 km/wk, 13.15 yr)	LTL in athletics was longer than CON
Silva et al. (2016) <sup>104</sup>	65–85 yr, Adults (n=61)	Southern blot for PBMCs TRF	Regular aerobic training for at least 5 yr	Longer T-cell TL in the trained group vs. CON
Østhus et al. (2012) <sup>105</sup>	66–77 yr, Men (n=20, 10 young, 22–27 yr; 10 older)	qPCR in skeletal muscle	Endurance athletes (EA, n=10, long distance & track running competitions) vs. moderate PA (MPA, n=10)	Longer LRL in older EA vs. MPA No difference of LRL in young EA vs. MPA
Denham et al. (2013) <sup>106</sup>	>30 yr, Men (n=123)	qPCR	Ultra-marathon runner (n=67, 40–100 km/wk, ≥2 yr)	Longer LTL in runners vs. CON
Mathur et al. (2013) <sup>107</sup>	15 yr, Boys (n=32)	qPCR in lymphocyte and granulocyte	Marathon runner (n=17) vs. CON (n=15)	No difference
Shin et al. (2008) <sup>108</sup>	47 yr, Obese women (n=16)	Southern blot for WBC TRF	AE (3 day/wk, 60 min, 6 mon)	No difference
Friedenreich et al. (2018) <sup>109</sup>	50–60 yr, Postmenopausal women (n=212; 99 Ex vs. 113 CON)	qPCR	AE (5 day/wk, 12 mon)	No difference

TL, telomere length; LTL, leukocyte telomere length; WBC, white blood cell; TRF, terminal restriction fragment; PA, physical activity; Ex, exercise group; MET, metabolic equivalent of task; qPCR, quantitative polymerase chain reaction; PBMC, peripheral blood mononuclear cell; CHD, chronic heart disease; BMI, body mass index; CON, control group; SED, sedentary; VO<sub>2max</sub>, maximum oxygen consumption; SD, standard deviation; EA, endurance athletes; LRL, long distance & track running competitions; MPA, moderate physical activity; AE, aerobic exercise.

also been reported that the higher the level of physical activity and the amount of physical activity per week, the longer the TL is.<sup>58,97,98</sup>

However, while physical activity of moderate intensity (991–3,540 kcal/wk) results in longer TLs, too much physical activity (9,351 kcal/wk) can result in shorter TLs.<sup>17</sup> In another study, the TL reduction rate of a moderate intensity exercise group was lower than that of the high intensity and control groups.<sup>99</sup> Some studies reported that physical activity was negatively correlated with levels of DNA damage, but not with TL<sup>100</sup>, whilst others reported that there was no correlation between TL and physical activity.<sup>11</sup> As such, study results are inconsistent. Regarding the different study results, the differences in TL and physical activity were found to be different according to age, periods of physical activity, lifestyles, and medical histories.<sup>101,102</sup> In teenagers, the correlation between physical activity and TL was only observed in female students.<sup>103</sup> Moreover, there was no difference in TL and physical activity in people aged 20 to 30 years, but there was a difference in people who were over 42 years old. In particular, it has been reported that there was a difference according to the presence of obesity, illness, and smoking when the period of physical activity was over 10 years.<sup>101</sup>

### The different effects of physical activity on telomere according to age

In studies where TL changes during long-term regular exercise were observed, many reported that TL was longer in the regular exercise group than in the non-exercise group (Table 3).<sup>23,104-106</sup> However, TL according to long-term exercise varied according to age. In

the 15-year-old group, there was no difference in TL between marathon runners and ordinary individuals<sup>107</sup>, and no difference in the young group (18–32 years). However, in the middle aged group (55–72 years) that exercised regularly, TL was reported to be 900 bp longer than that of the sedentary group. Thus, the study reported that exercise habits in the post-middle-age period were effective in preventing aging.<sup>18</sup> However, after premenopausal women exercised three times a week for 6 months, and menopausal women aged 50 to 60 years exercised five times a week for 12 months (supervised exercise, three times a week), no difference between the exercise group and the non-exercise group was reported. Thus, the correlation between exercise and TL differs among women depending on exercise training periods and menopause.<sup>108,109</sup>

In a study of the relationship between cardiorespiratory fitness and TL, it was reported that the maximum oxygen uptake and TL were significantly correlated (Table 4).<sup>110,111</sup> However, the positive correlation between cardiorespiratory fitness and TL also showed age-related differences such as a correlation with long-term regular exercise. There was no correlation between cardiorespiratory fitness and TL in the 15-year-old adolescent group<sup>106</sup> or in the young (18–32 years) group.<sup>18,97</sup> Differences were observed only in the middle-aged group (55–72 years).<sup>18</sup> In a study of 582 elderly people aged 60 years and older, TL was reported to be longer in persons showing good performance in sitting and standing, and the TL decrease was reported to be less than 0.9 bp each year for every 1 second decrease in performance.<sup>112</sup> In addition, a study correlating leg muscle strength and TL in adults over 50 years of age re-

**Table 4.** Summary of the association between the TL and cardiorespiratory fitness

Author (year)	Subject	LTL measurement method	Intervention or factor	Association
LaRocca et al. (2010) <sup>18</sup>	18–32 yr vs. 55–72 yr (n=57, 59.6% women)	Southern blot for WBC TRF	Maximal Ex test (VO <sub>2max</sub> )	LTL was positively associated with VO <sub>2max</sub> in older adults
Edwards and Loprinzi (2016) <sup>97</sup>	>20 yr, Adults (n=1,868, 49.2% women)	qPCR	Submaximal treadmill test (CRF)	No association
Mathur et al. (2013) <sup>107</sup>	15 yr, Boys (n=32)	Lymphocyte TL	Maximal Ex test (VO <sub>2max</sub> )	No association
Mason et al. (2013) <sup>110</sup>	50–75 yr, Postmenopausal women (n=439)	qPCR	Maximal Ex test (VO <sub>2max</sub> )	LTL was positively associated with VO <sub>2max</sub>
Krauss et al. (2011) <sup>111</sup>	944 Adults with CVD (20% women)	qPCR	Maximal Ex test (CRF)	High CRF (>7 METs) had two-fold longer LTL vs. low CRF
Soares-Miranda et al. (2015) <sup>112</sup>	73.5 yr, Adults (n=582, 62% women)	Southern blot for WBC TRF	15-ft walk (sec), grip strength (kg), chair stands (sec)	A better chair test performance in longer LTL Changes chair time was associated with changes in LTL

TL, telomere length; LTL, leukocyte telomere length; WBC, white blood cell; TRF, terminal restriction fragment; Ex, exercise; VO<sub>2max</sub>, maximum oxygen consumption; qPCR, quantitative polymerase chain reaction; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; METs, metabolic equivalent of task.

ported that telomere attrition was reduced by as much as 9% with every 50 N increase in leg strength<sup>113</sup>, with a possible explanation being that leg muscle strength and exercise performance ability are fitness factors that can be maintained or improved through regular physical activity and exercise, which affect cardiorespiratory fitness.

## CONCLUSION

Telomerase maintains TL according to age. The activity of telomerase gradually decreases between 4 and 39 years of age and, after the age of 40, telomerase activity is not observed in 35% of the population.<sup>114</sup> Furthermore, there is a more positive effect of regular physical activity in late middle age, when changes in TL are observed. In particular, considering that it was reported that past athletic experience does not affect TL after 10–20 years<sup>102</sup>, regular exercise at the time of telomere attrition could be an important precaution to prevent cell senescence.

## CONFLICTS OF INTEREST

The author declares no conflict of interest.

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