Article

Obesity and Telomere Length: Does the obesity paradox exist?

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Abstract: Telomere shortening is related to aging and unfavourable health outcomes. Obesity and metabolic diseases are important factors for accelerating aging. This study aimed to find out the association between obesity, metabolic disease, and leukocyte telomere length in metabolically healthy adults. A total of 130 metabolically healthy subjects were selected for final analysis. The subjects were divided into quartile groups according to the telomere lengths of their oral mucosal cells. The subjects consisted of 66 (50.8%) males with a mean age of 58.59 years. The body mass index (BMI, kg/m^2) increased significantly along with the quartile groups (P-for trend=0.008). Waist circumference (WC, P-for trend=0.022), waist-to-hip ratio (WHR, P-for trend=0.005), and waist-to-height ratio (WHtR, P=0.001) also increased along with the quartile groups. After adjusting for covariates, the ORs for each obesity markers increased as the telomere length increased; and the ORs of WHtR were especially meaningful (Q1, 1.00; Q2, 2.53; Q3, 2.97; Q4, 7.81; P-for trend = 0.001). There were no significant trends for metabolic syndrome and the prevalence of fatty liver disease. Obesity markers and telomere length had significant positive correlation despite the established theory. The obesity paradox may exist in metabolically healthy adults with regard to telomere length.

Keywords: Body mass index; Metabolic syndrome; Obesity; Obesity paradox; Telomere; Waist circumference; Waist-to-hip ratio; Waist-to-height ratio.

1. Introduction

Telomere is a repetitive sequence (5′-TTAGGG-3′) located at the end of chromosomes in eukaryotic cells. It maintains the stability of the chromosomal end from recombination, fusion, and attenuation, preserves genetic information, and regulates replication of cells. Telomeres decrease by 50-200 base pairs each time a cell undergoes division. When they become too short, the cells become senescent and can no longer divide and die. For that reason, telomere shortening has been known as a marker related to aging [1]. As the oxidative stress and inflammation increases due to various causes, telomere length is shortened, and aging accelerates. Previous studies have shown that telomere length is negatively correlated with high blood pressure, diabetes and cardiovascular disease [2-5]. In another study, it was also reported that the shorter the telomere length, the greater the risk of chronic disease associated with aging and the shorter the life expectancy [6-8].

Obesity is a risk factor associated with the above-mentioned unfavourable health outcome. Obesity is a major independent risk factor for accelerating aging, and it increases the risk of metabolic diseases such as hypertension, diabetes, cardiovascular disease, and malignancy. Furthermore, it increases the risk of death, particularly from cardiovascular disease and cancer [9-15]. However, on contrary, there are conflicting studies reporting the opposite results, this is known as the ‘obesity paradox’ and it suggests better health outcomes for overweight and mildly obese people. Several studies have shown that obese patients presented a better survival rate than underweight patients

among patients with a chronic disease, including heart failure, chronic obstructive lung disease, and cancer [15-21] .

In this regard, it is important to determine whether being overweight or mildly obese could be a protective factor for accelerating aging or not. To the best of our knowledge, there is no study regarding the relationship between obesity and telomere length in a metabolically healthy population. Thus, in this study, we investigated the association of obesity and telomere length, as a predictor of aging and life expectancy, in metabolically healthy adults.

2. Materials and Methods

2.1. Study design and population

This study was a cross-sectional study conducted from February 2014 to March 2015. The subjects, aged over 20 years, were enrolled from among the patients who visited a health promotion centre for health screening in a university hospital, Korea. The research was conducted with those who agreed to participate in this study and completed their medical examinations. The exclusion criteria for this study were as follows: (i) subjects who had been diagnosed with malignancy including stomach, colon, liver, breast, and thyroid cancer in the past or during their current health screening, (ii) history of major advanced cardiovascular events (myocardial infarction, unstable angina, heart failure, arrhythmia, heart valve disease, heart muscle disease, or stroke), (iii) recent history of acute infection such as pneumonia or gastroenteritis in a month, (iv) history of chronic hepatitis including chronic hepatitis B, chronic hepatitis C, and autoimmune hepatitis, (v) uncontrolled diabetic patients with serum fasting glucose ≥200 mg/dL, (vi) uncontrolled hypertension patients with systolic blood pressure ≥160 mmHg, (vii) morbid obesity with body mass index ≥35 kg/m^2 (stage III obesity based on the criteria of Korean Society for the Study of Obesity[22]), (viii) withdrawal of consent, and (ix) subjects who did not complete their medical records or examinations. This study was approved by an institutional review board (IRB) at a local hospital (protocol no. KNUH 2012-01-002).

2.2. *Health status and obesity assessments*

All participants underwent buccal swab for sampling (see below) and a health assessment including history taking, physical measurements, laboratory tests, and abdominal ultrasonography during their routine health screening.

The past history of the subjects was investigated through structured interviewing, including past medical history, past surgical history, past admission history, current medications such as blood pressure-lowering drugs, lipid-lowering drugs, and glucose-lowering drugs.

Anthropometric measurements were taken to evaluate participants obesity status and physical status. Height was measured by a height measuring scale with participants looking straight forward with heels touching and feet spread open 60 degrees, as well as having their head, scapula, buttocks and heels touching the wall. After 8 hours of fasting and urination, body weight was measured with minimal attire using a scale (InBody230, Seoul, Korea). Body mass index (BMI, kg/m^2) was calculated by dividing the body weight by the height squared. When measuring the waist circumference (WC), the weight was spread evenly by spreading the legs of the subject 25 to 30 cm, relaxing their breathing, and measuring the distance between the lowest position of the ribs and the highest position of the iliac crest with a tapeline. Hip circumference was measured horizontally at the most protruding part of the rear part of the hips from the side of the subject in the straight posture.

Blood pressure (mmHg) was measured using an automatic blood pressure monitor in a stable state. The laboratory analyses including haemoglobin, serum glucose, lipid profile (total cholesterol, triglyceride, high density lipoprotein cholesterol), liver function test (aspartate aminotransferase, alanine aminotransferase), and creatinine levels were analysed using blood samples after 8 hours of fasting by a chemistry autoanalyzer (Siemens' Advia 2120i, USA; Roche's Cobas c702, Switzerland).

Abdominal ultrasonography was performed by a skilled radiologist to assess participants for the risk of fatty liver disease (Aplio 500, Toshiba, USA). Fatty liver disease was classified into four

categories based on a picture archiving and communication system (PACS)-based quantitative grayscale ultrasound quantification: normal, mild, moderate, and severe [23].

Metabolic syndrome was defined according to the National Cholesterol Education Program's Adult Treatment Panel (ATP) III criteria[24]. A diagnosis can be made if three or more of the following five conditions are satisfied: (i) Central obesity: Waist Circumference ≥90 cm for men and ≥85 cm for women, (ii) Hypertriglyceridemia: triglyceride ≥150 mg/dL, (iii) Low high-density lipoprotein cholesterol (HDL-C): HDL-C <40 mg/dL in men and <50 mg/dL in women, (iv) Hypertension: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, and (v) Hyperglycaemia: serum fasting glucose ≥100mg/dL.

2.3 Obesity markers and their cut-off

The body mass index (BMI), waist circumference (WC), Waist-to-Hip Ratio (WHR), and Waist-to-Height Ratio (WHtR) were used as obesity markers. The BMI ≥ 25 kg/m^2, and the WC ≥90 cm for men and ≥85 cm for women, were used to define obesity based on the criteria recommended by the Korean Society for the Study of Obesity [22,25]. The WHR 〉 1.0 in men and 〉 0.85 in women, and the WHtR ≥0.5 were used to define obesity based on the WHO recommendation [26,27].

2.4 *Leukocyte telomere length*

Biological samples were collected using Buccal swabs. Buccal swabs were quick, simple, and highly sensitive to low-invasive samples. The subjects were in a fasting state and rinsed their mouth with clean water before sampling. The research assistants rubbed the subjects on each side of buccal mucosa 6 times, firmly using the sterilized side of a cotton swab. Since the manner of mucosal cells collection was exfoliation, in order to take the DNA, the cotton swab was pressed a little harder and the end of the swab should be covered by a little blood. To remove any liquid components collected by the cotton swabs, they were left at room temperature for about 2 hours, and then the DNA was extracted from the oral mucosal cells using QIAGEN QI Aamp DNA Mini Kit. Each cotton swab with oral membrane cells was put in a 1.5ml microtube with 400μL of saline and 20μL of QIAGEN protease stock solution. Next, 400μL of Buffer AL was added and the microtubes were immediately vortexed for 15 seconds. Thereafter, the microtube was allowed to stand in a water bath at 56℃ for 10 minutes and then centrifuged. After removing the swab, 400μL of ethanol was added and centrifuged by vortexing for 15 seconds, the prepared 700μL mixture was then carefully added to the QIAamp spin column in a 2ml tube and centrifuged at 6,000 x g for 1 minute. The collected filtrates were dumped and the remaining mixture was added to the same QIAamp spin column, and the steps were repeated. After replacing the 2ml tube with a fresh one, the lid of the QIAamp spin column was carefully opened, 500μL of Buffer AW1 was added and centrifuged at 6000 ×*g* for 1 minute. After replacing the 2ml tube with a fresh one, the lid of the QIAamp spin column was carefully opened, 500μL of Buffer AW2 was added and centrifuged at 20,000 ×*g* for 3 minutes. Next, the QIAamp spin column was transferred to a 1.5ml microtube, and 150μL of Buffer AE was added. The lid was closed, and the tube was left at room temperature for 1 minute and then centrifuged at 6,000 x g for 1 minute. The telomere length was measured using the monochrome multiplex quantitative PCR method. 1.5μL of primer telg, telc 0.9μL, primer albu, albd 1.0μL, and Betaine 1.0μL were added to each 1.5ml microtube, then 5.0μL of SYBR Green Master mix was added and the mixture was vortexed. 9.8μL of the above mixed solution was added to the capillary, 1.2μL of a DNA sample was added, and resultant was placed in the machine and the telomere length was measured. The length of the telomere was calculated by dividing the reference value by the difference from the albumin value and the multiplying by 1000.

2.5 Statistical analysis

The subjects were divided into quartiles according to telomere length. Statistical analysis was performed using IBM SPSS Statistics version 25.0. Pearson's Chi-square test and ANOVA were used to compare the baseline characteristics between the quartile groups. A logistic regression analysis was performed after adjusting for age, sex, hypertension, diabetes, and dyslipidaemia, using the Q1

group as a reference, to assess the relationship between each obesity marker and telomere length. The statistically significant level of P value was less than 0.05.

3. Results

3.1. Baseline characteristics

Out of the 237 people who enrolled and agreed to participated in this study during the period, 8 subjects who had cancer and 99 subjects who did not have complete medical records and who met the exclusion criteria were excluded. Accordingly, a total of 130 subjects were included for the final analysis. The mean age of the subjects was 58.59 years and 66 (50.8%) subjects were male. Their mean height, weight, and BMI were 163.49 cm, 64.24 kg, and 23.98 kg/m^2, respectively (Table 1).

Table 1. Baseline Characteristics of the total subjects.

		Total subjects (N=130)
Sex	Male	66 (50.8)
	Female	64 (49.2)
Age, years		58.59 ± 9.25
Height, cm		163.49 ± 8.32
Weight, kg		64.24 ± 10.46
Body mass index, kg/m^2		23.98 ± 3.06
Waist circumference, cm		80.92 ± 9.51
Hip circumference, cm		94.99 ± 5.89
Systolic Blood Pressure, mmHg		124.96 ± 14.92
Diastolic Blood Pressure, mmHg		74.27 ± 10.61
Glucose, mg/dL		104.25 ± 23.44
Total Cholesterol, mg/dL		194.00 ± 35.71
HDL cholesterol, mg/dL		57.05 ± 15.58
Triglyceride, mg/dL		116.38 ± 52.71
LDL cholesterol, mg/dL		113.68 ± 31.61
AST, U/L		24.86 ± 12.67
ALT, U/L		22.08 ± 14.05
GGT, U/L		31.17 ± 40.45
Haemoglobin, g/dL		14.11 ± 1.76
Creatinine, mg/dL		0.83 ± 0.19
Hypertension, n (%)		31 (23.8)

AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; GGT, Gamma-Glutamyl Transferase; HDL, High-density lipoprotein cholesterol; LDL, Low-density lipoprotein.

3.2. Clinical characteristics of the subjects according to the quartile groups

Table 2 represents the results obtained by dividing the subjects into quartiles according to telomere length (Q1–Q4). The mean age and WC showed significant differences between the quartile groups (Q1–Q4 respectively, age: 56.97, 57.03, 56.56, 63.70, P-for trend 0.006; WC: 78.37, 81.15, 79.48, 84.56, P-for trend=0.022). However, there was no statistically significant trend observed for the other indicators.

Table 2. Clinical Characteristics of the subjects according to quartile groups of telomere length

	Q1 (N=32)	Q2 (N=33)	Q3 (N=32)	Q4 (N=33)	P*	P-for trend
Telomere length (×10³)	≤777.19	782.49–940.32	941.64–1029.36	≥1037.14		
Age, years	56.97 ± 7.24	57.03 ± 9.53	56.56 ± 8.81	63.70 ± 9.60	0.003	0.006
Height, cm	165.03 ± 8.36	164.75 ± 7.82	162.76 ± 9.32	161.46 ± 7.59	0.257	0.051
Weight, kg	62.91 ± 9.95	65.26 ± 11.11	62.90 ± 10.56	65.80 ± 10.35	0.561	0.443
Waist circumference, cm	78.37 ± 9.42	81.15 ± 9.43	79.48 ± 9.31	84.56 ± 9.11	0.046	0.022
Hip circumference, cm	95.22 ± 5.83	95.30 ± 5.16	93.50 ± 5.78	95.88 ± 6.70	0.405	0.958
Systolic blood pressure, mmHg	125.38 ± 11.90	126.12 ± 16.76	122.75 ± 15.73	125.55 ± 15.25	0.810	0.812
Diastolic blood pressure, mmHg	77.53 ± 10.91	74.94 ± 12.23	71.50 ± 8.94	73.12 ± 9.58	0.125	0.047
Glucose, mg/dL	102.25 ± 16.13	101.79 ± 15.58	108.00 ± 37.70	105.00 ± 17.84	0.699	0.436
Total Cholesterol, mg/dL	199.78 ± 30.94	182.91 ± 34.77	188.19 ± 33.39	205.10 ± 40.04	0.043	0.429
HDL cholesterol, mg/dL	61.03 ± 12.97	55.66 ± 18.92	52.38 ± 12.34	59.01 ± 16.30	0.120	0.478
Triglyceride, mg/dL	113.84 ± 64.96	112.33 ± 42.35	109.94 ± 49.90	129.12 ± 51.73	0.449	0.288
LDL cholesterol, mg/dL	115.98 ± 32.23	104.79 ± 25.67	113.83 ± 29.38	120.18 ± 37.37	0.244	0.373
AST, U/L	24.38 ± 13.83	24.61 ± 9.08	24.34 ± 9.68	26.09 ± 16.94	0.937	0.622
ALT, U/L	21.53 ± 13.37	22.79 ± 13.35	21.88 ± 14.41	22.12 ± 15.57	0.987	0.941
GGT, U/L	29.58 ± 53.97	31.46 ± 28.03	29.25 ± 43.42	34.30 ± 33.85	0.957	0.706
Haemoglobin, g/dL	14.26 ± 1.61	14.61 ± 1.95	13.60 ± 2.00	13.95 ± 1.34	0.121	0.164
Creatinine, mg/dL	0.82 ± 0.20	0.86 ± 0.18	0.83 ± 0.20	0.81 ± 0.17	0.741	0.637

Hypertension, n (%)	7 (21.9)	8 (24.2)	7 (21.9)	9 (27.3)	0.950	0.678
Dyslipidaemia, n (%)	3 (9.4)	2 (6.1)	2 (6.3)	3 (9.1)	0.973†	0.982
Diabetes, n (%)	3 (9.4)	4 (12.1)	1 (3.1)	2 (6.1)	0.641†	0.367

AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; GGT, Gamma-Glutamyl Transferase; HDL, High-density lipoprotein cholesterol; LDL, Low-density lipoprotein.
*ANOVA for continuous variables and Pearson's Chi-square test for discrete variables. †Fisher's exact test

3.3 Obesity status according to the quartile groups

Table 3 compares the relationship between obesity index and telomere length. As the telomere length increased, the BMI (kg/m^2) increased (Q1, 23.00; Q2, 23.96; Q3, 23.70; Q4, 25.20; P-for trend 0.008) and the obesity rate that above the BMI of 25 kg/m^2 also increased (Q1, 21.9%; Q2, 33.3%; Q3, 31.3%; Q4, 51.5%; P-for trend 0.020). The WC also increased with increasing telomere length (Q1, 62.91; Q2, 65.26; Q3, 62.96; Q4, 65.80; P-for trend 0.022), and the proportion of central obesity of the WC ≥90 cm in men and ≥85 cm in women also increased (Q1, 12.5%; Q2, 21.2%; Q3, 15.6%; Q4, 42.4%; P-for trend 0.011). The WHR, increased statistically with increasing telomere length (Q1, 1.00; Q2, 0.85; Q3, 0.86; Q4, 0.89; P-for trend 0.005), and the proportion of the WHR over 1.0 in men and 0.85 in women tended to increase (Q1, 6.3%; Q2, 12.1%; Q3, 31.3%; Q4, 33.3%; P-for trend 0.002). The WHtR increased with increasing telomere length (Q1, 0.47; Q2, 0.49; Q3, 0.49; Q4, 0.52; P-for trend 0.001), and the proportion of the WHtR over 0.5 also tended to increase (Q1, 21.9%; Q2, 39.4%; Q3, 40.6%; Q4, 66.7%; P-for trend <0.001).

3.4 Metabolic syndrome, fatty liver disease and telomere length

We analysed the relationship between telomere length and metabolic syndrome, components of metabolic syndrome including hypertension, hyperglycaemia, hypertriglyceridemia, low high-density lipoprotein cholesterol, and abdominal obesity. However, no statistically significant correlation was observed between metabolic syndrome and telomere length, except for abdominal obesity using waist circumference. The severity of fatty liver disease according to the ultrasonographic finding showed no significant differences between the quartile groups of telomere length, either. (Table 4).

Table 3. The obesity markers and telomere length

	Q1 (N=32)	Q2 (N=33)	Q3 (N=32)	Q4 (N=33)	P*	P-for trend
Body Mass Index (BMI)						
BMI, kg/m²	23.00 ± 2.57	23.96 ± 2.99	23.70 ± 3.17	25.20 ± 3.19	0.031	0.008
BMI ≥25 kg/m²	7 (21.9)	11 (33.3)	10 (31.3)	17 (51.5)	0.084	0.020
Waist Circumference (WC)						
WC, cm	62.91 ± 9.95	65.26 ±11.11	62.90 ± 10.56	65.80 ± 10.35	0.046	0.022
WC ≥90 cm (M) or ≥85 cm (F)	4 (12.5)	7 (21.2)	5 (15.6)	14 (42.4)	0.018	0.011
Waist-to-Hip Ratio (WHR)						
WHR	1.00 ± 0.01	0.85 ± 0.08	0.86 ± 0.07	0.89 ± 0.07	0.035	0.005
WHR >1.0 (M) or >0.85 (F)	2 (6.3)	4 (12.1)	10 (31.3)	11 (33.3)	0.012	0.002
Waist-to-Height Ratio (WHtR)						
WHtR	0.47 ± 0.05	0.49 ± 0.05	0.49 ± 0.59	0.52 ± 0.06	0.004	0.001
WHtR ≥0.5	7 (21.9)	13 (39.4)	13 (40.6)	22 (66.7)	0.003	<0.001

*ANOVA for continuous variables and Pearson's Chi-square test for discrete variables.

Table 4. The Fatty liver disease, metabolic syndrome and telomere length

	Q1 (N=32)	Q2 (N=33)	Q3 (N=32)	Q4 (N=33)	P*	P-for trend
Fatty liver disease: Ultrasonographic result						
Normal	22 (68.8)	21 (63.6)	21 (65.6)	22 (66.7)	0.231	0.478
Mild	9 (28.1)	7 (21.2)	10 (31.3)	5 (15.2)		
Moderate-to-Severe	1 (3.2)	5 (15.2)	1 (3.1)	6 (18.2)		
Metabolic syndrome and its components†						
Hypertension	18 (56.3)	17 (51.5)	14 (43.8)	14 (42.4)	0.644	0.212
Hyperglycaemia	14 (43.8)	14 (42.4)	13 (40.6)	18 (54.5)	0.668	0.428
Hypertriglyceridemia	8 (25)	8 (24.2)	6 (18.8)	9 (27.3)	0.874	0.962
Low HDL cholesterol	2 (6.3)	13 (39.4)	10 (31.3)	8 (24.2)	0.017	0.193
Abdominal obesity	4 (12.5)	7 (21.2)	5 (15.6)	14 (42.4)	0.018	0.011
Metabolic syndrome	5 (15.6)	10 (30.3)	7 (21.9)	9 (27.3)	0.526	0.435

HDL, High Density Lipoprotein. *ANOVA for continuous variables and Pearson's Chi-square test for discrete variables. † Metabolic syndrome if three or more of the following: Hypertension, blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic, or currently on treatment; Hyperglycaemia, fasting glucose ≥100 mg/dL or currently on treatment; Hypertriglyceridemia, triglyceride ≥150 mg/dL or currently on treatment; Low HDL cholesterol, HDL cholesterol <40 mg/dL (M), <50 mg/dL (F) or currently on treatment; Abdominal obesity, waist circumference ≥90 cm (M), ≥85 cm (F).

2.5 Relationship between obesity markers and telomere length

The association of each obesity marker and telomere length revealed a significant trend and positive correlation by logistic regression analysis adjusted for covariates, using the Q1 group as reference. The adjusted odd ratios (aORs) of Q2–4 compared to Q1 for BMI ≥25 kg/m² were 1.96 (95% CI 0.62–6.21), 1.89 (95% CI 0.58–6.18), and 5.70 (95% CI 1.70–19.14), respectively, and its trend was statistically significant (P-for trend=0.020). The aORs of Q2–4 for WC ≥90 cm in men or ≥85 cm in women were 1.90 (95% CI 0.48–7.49), 1.41 (95% CI 0.33–6.10), and 5.87 (95% CI 1.49–23.05), respectively, and its trend was significant (P-for trend=0.017). The aORs of Q2–4 for WHR >1.0 in men or >0.85 in women were 2.58 (95% CI 0.38–17.50), 8.14 (95% CI 1.36–48.66), and 5.70 (95% CI 0.93–34.80), with a significant trend (P-for trend=0.026), respectively. The aORs for WHtR ≥0.5 were 2.53 for Q2 (95% CI 0.81–7.90), 2.97 for Q3 (95% CI 0.93–9.50), and 7.81 for Q4 (95% CI 2.31–6.45), which showed the highest OR amongst the obesity markers. The increasing trend of aOR for WHtR from Q1 to Q4 was also statistically significant (P-for trend=0.001). (Table 5)

Table 5. Relationship between the obesity markers and telomere length

	Q1	Q2	Q3	Q4	P-for trend
			aOR (95% CI)		
Body Mass Index (BMI)					
BMI ≥25 kg/m²	1.00	1.96 (0.62–6.21)	1.89 (0.58–6.18)	5.70 (1.70–19.14)	0.020
P-value*	-	0.255	0.292	0.005	
Waist Circumference (WC)					
WC ≥90 cm (M) or ≥85 cm (F)	1.00	1.90 (0.48–7.49)	1.41 (0.33–6.10)	5.87 (1.49–23.05)	0.017
P-value*	-	0.359	0.645	0.011	
Waist-to-Hip Ratio (WHR)					
WHR >1.0 (M) or >0.85 (F)	1.00	2.58 (0.38–17.50)	8.14 (1.36–48.66)	5.70 (0.93–34.80)	0.026
P-value*	-	0.333	0.021	0.060	
Waist-to-Height Ratio (WHtR)					
WHtR ≥0.5	1.00	2.53 (0.81–7.90)	2.97 (0.93–9.50)	7.81 (2.31–26.45)	0.001
P-value*	-	0.110	0.067	0.001	

aOR, adjusted odd ratio. * Logistic regression analysis adjusted for age, sex, hypertension, diabetes, and dyslipidaemia.

4. Discussion

This study conducted a cross-sectional analysis to examine what influences obesity has on the life expectancy of metabolically healthy individuals, by investigating the relationship between obesity and telomere length. The subjects in this study were relatively healthy in most cases, despite being overweight or mildly obese, with only a small number of cases displaying an underlying disease. Interestingly, the results of this study showed a positive correlation between telomere length and each obesity marker, and the higher the level of obesity, the longer the telomere length. The higher the length of telomere, the higher the body mass index, the waist circumference, the waist-to-hip ratio, and the waist-to-height ratio. These results were significant after adjustment for age, sex, underlying disease, or radiological outcome, factors that may affect telomere length. In addition, the correlation was most significant for the waist-to-height ratio among the obesity markers.

The fact that obesity is a major factor increasing the rate of mortality is well known from previous studies [15]. Recent estimates using mortality data from the National Health And Nutrition Examination Survey estimated that about 112,000 deaths among adults in 2,000 were associated with obesity [28]. Obesity is also known to shorten the telomere length through increased oxidative stress and inflammatory reactions, thereby inducing various metabolic diseases including hypertension, diabetes mellitus, dyslipidaemia, atherosclerosis, coronary artery disease, heart failure, metabolic syndrome, stroke, non-alcoholic fatty liver disease, chronic kidney disease and its progression to end-stage renal disease. This contradicts the results of this study where the telomere length increased with an increase in obesity, which was supported by uniformly significant statistical values across all obesity markers. Most of the previous studies showed that the higher the level of obesity, the higher the rates of mortality and morbidity, and what they equally reported was the correlation being more significant with overweight and obesity stages 1 and 2 rather than with obesity stage 3 [29-32]. In this respect, the findings of this study that disagree with previous studies may be explained first and foremost by the obesity paradox. The obesity paradox is a term for the phenomenon that shows a better prognosis in obese patients than in non-obese patients. For example, higher incidence of cardiovascular disease is associated with obesity, but when looking at chronic progression it has better morbidity and survival in obese patients [16,18,19]. The phenomenon has been reported for a variety of diseases, and the most representative case comes from a study of heart failure patients with obesity that showed the more obese, the higher survival rate [33]. However, few studies have been conducted on the population in Korea, and there is a lack of research that directly proves the relationship with obesity. In the meantime, there was a preceding study on the relationship between mortality and BMI in Korean men and women that supports this study's results [34]. In this previous study, the overweight group, at BMI's of 23-25 kg/m² had the lowest risk of death and the risk of

death from atherosclerotic cardiovascular disease was lowest in the overweight to first stage obesity range. This study showed a similar BMI distribution to that of the previous study's subjects. In addition to the aforementioned diseases, an identical relationship has been reported for various other diseases such as chronic obstructive pulmonary disease, renal disease, and cancer, in numerous studies [35-37]. A similar result has also been reported in a small set of studies on metabolically healthy obese people. Based on recent data, among metabolically healthy obese people with neither metabolic complications nor increased risks of cardiovascular morbidity and mortality, the individuals belonging to the overweight to mild obesity range are shown to have an advantage in survival from chronic disease including heart failure and chronic renal disease, with the tendency being stronger for those with higher BMI. The suggested hypothesis is that, despite larger muscle mass and somewhat favourable metabolic profile shown by the metabolically healthy obese people with higher BMI, the level of inflammatory cytokines from visceral fat is also shown to be higher [38-41].

The obesity paradox described so far, is observed to slightly differ by disease or country, and although a U shaped or linear association rather than a perfect match is found between the level of obesity and mortality, a common result of the lowest mortality for the BMI of the overweight-to-stage I obesity has been obtained. In other words, the subjects in this study correspond to the overweight or mildly obese people with average BMI of 23.98 kg/m^2, which provides the same context to the previous studies where obesity paradox was anticipated. As such, the evidence for the best health outcome in overweight or stage I obesity is known as follows.

The mechanism of obesity paradox is yet to be clearly identified, but it may be conjectured based on obesity pathophysiology. Most previous studies on the obesity paradox have relied on BMI as the marker to assess obesity. However, an analysis of BMI alone has recently been shown to have limitations as a marker that can accurately indicate the state of obesity in an individual. In fact, for chronic diseases or aging, muscle mass decreases while fat mass is still high or may even increase, resulting in BMI being lower than the actual level of obesity. Muscle mass is a crucial determinant of the state of health as it defines the inflammatory activity and immune function. Its role is also prominent as a functional parameter in such phenomena as healthy healing after surgical trauma, appropriate response to different treatments, recovery from an acute disease, and prediction of life expectancy.

Obesity is characterized by a low-grade inflammatory state and endocrine changes. The central or visceral fat produces a higher level of pro-inflammatory adipokines than subcutaneous fat to increase the inflammatory load. Low-grade inflammatory state induces a decrease in lean-body mass and reduced immune function, accelerated atherosclerosis as well as insulin resistance. In fact, it is known to reduce the muscle mass through the excessive production of inflammatory molecules such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). However, a large cohort study on patients with community-acquired pneumonia reported that distinct immune reactions indicated by higher body temperature and a substantial increase in C-reactive protein (CRP) are associated with a favourable long-term prognosis. Thus, it may be presumed that a strong inflammatory or immune response could help produce favourable long-term effects in overcoming an infectious episode. From a different perspective, obesity may be advantageous with respect to metabolic reserve in a cachexia state. The loss of appetite and the subsequent unintentional weight loss in various diseases has a negative influence on immune function and may cause malnutrition. In this respect, the fat reserves in obese patients may ensure resistance to the catabolic progression of a wasting disease [42-44].

In this study, all four obesity markers including BMI as well as WC, WHR, and WHtR, were used, and among them, the strongest association was exhibited by WHtR. This agreed with previous studies showing WHtR as the marker that best reflects the association with cardiovascular disease outcome. As reported by various studies involving systematic review and meta-analysis, WHtR can be seen as a more reliable variable predicting the risk of cardiovascular disease than WC. These studies were conducted for diverse populations around the world, and compared to other obesity markers, WHtR was reported to have more outstanding differentiating ability. Thus, for detecting various cardiovascular disease metabolic risk factors, WHtR has been shown as a significant marker

that can be used as an efficient screening tool in both Asian and non-Asian populations [26,45-49]. It is thus significant that the findings of this study coincides with the reports of previous studies.

One interesting finding of this study is that the severity of fatty liver disease and metabolic syndrome did not show a significant correlation with telomere length. Fatty liver disease and metabolic syndrome are the diseases showing the closest association with obesity, and since previous studies have also reported correlations among these factors [5,50,51], an association with telomere length had been anticipated; however, a significant correlation was not found. This may be attributed to the following: i) small number of subjects in this study; ii) exclusion of morbidly obese patients. It is possible that statistical significance was not obtained because of the small number of patients with moderate or severe fatty liver disease (13 individuals; 10%) and the small number of subjects that satisfied the metabolic syndrome criteria (31 individuals; 23.8%). To identify the relationship, a large-scale study should be performed for the subjects including patients with morbid or super obesity.

This study has the following limitations. First, the study targeted a small set of people of one ethnic origin and a single region, which prevents generalization to the entire population and race. Second, the inclusion criteria used in the study selected relatively healthy subjects so that the selection bias cannot be ruled out. In the process of selecting only the subjects satisfying the inclusion criteria, 107 subjects were excluded. However, this was inevitable since the purpose of the study was to investigate the metabolically healthy subjects. Third, as a cross-sectional study, sequential correlation could not be verified. Fourth, the study could not consider other variables associated with telomere shortening. The correction for such variables was not provided, while the factors with a known association with telomere length include alcoholic drinking, smoking, physical activity, and dietary habit.

Nevertheless, despite the limitations, it is of considerable significance that this study was the first to elucidate the relationship between telomere length and obesity markers in a metabolically healthy population. Furthermore, a strength of this study is that, to examine all potential variables, various research tools including laboratory tests and abdominal ultrasonography in addition to history taking and physical examination were used simultaneously with buccal swabs. This leads to another strength of the study, that the subjects were carefully selected and that all four different obesity markers were examined. Yet another strength comes from the fact that, despite increasing reports on the obesity paradox, there is still a general lack of studies on metabolically healthy obese people.

To conclude, obesity is considered to have defensive effects on telomere shortening in metabolically healthy overweight or mildly obese people. This is one other piece of evidence that obesity might be associated with good health outcomes, contrary to general belief, and evidence for the possibility of the obesity paradox. Among the four markers: BMI, WC, WHR, and WHtR, the strongest association with telomere length was shown by WHtR that can thus be considered as a marker that best reflects the health outcome. To prove the obesity paradox in the future, a large-scale prospective study involving patients with morbid or super obesity should be conducted.

5. Conclusions

In this study, a positive correlation was observed between obesity indexes and telomere length in metabolically healthy overweight or mildly obese population. This is contrary to previous research, and the results of this study increased the possibility of the obesity paradox being true. We could also suggest the possibility of obesity being a preventive factor for aging.

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