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Leukocyte Telomere Length and Serum Levels of High-Molecular-Weight Adiponectin and Dehydroepiandrosterone-Sulfate Could Reflect Distinct Aspects of Longevity in Japanese Centenarians

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Abstract

Leukocyte telomere length and serum levels of high-molecular-weight adiponectin and dehydroepiandrosterone-sulfate (DHEA-S) were assessed in association with nutrition and performance status (PS) in Japanese centenarians. Twenty-three centenarians (five men, 18 women) were classified according to their PS 1 (nearly fully ambulatory, $n = 2$), 2 (in bed less than 50% of daytime, $n = 10$), 3 (in bed greater than 50%, $n = 6$), and 4 (completely bedridden, $n = 5$). Leukocyte telomere length was determined by the hybridization protection assay, and the adiponectin and DHEA-S levels were measured by chemiluminescent enzyme immunoassay. Among variables of PS, body mass index (BMI), albumin, adiponectin, DHEA-S, and telomere length, there were significant correlations between PS and albumin ($r = -.694$, $p < .01$), between telomere length and BMI ($r = .522$, $p < .05$), between adiponectin and BMI ($r = -.574$, $p < .01$), and between DHEA-S and albumin ($r = .530$, $p < .01$). When excluding two cancer-bearing centenarians with short telomere, telomere length significantly correlated with PS ($r = -.632$, $p < .01$). It was indicated that the short leukocyte telomere was associated with poor PS and cancer development and that the adiponectin or DHEA-S was associated with adiposity or nutritional status. Despite a small number of subjects, these biomarkers seemed to reflect distinct aspects of longevity in Japanese centenarians.

Keywords

leukocyte telomere length, high-molecular-weight adiponectin, dehydroepiandrosterone-sulfate, longevity, centenarians

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Introduction

Telomeres consist of 500 to 2,000 tandem repeats of a hexanucleotide (TTAGGG) in the 5′-strand of DNA at the ends of linear chromosomes in human cells. The associated proteins coating the telomeric DNA sequence prevent the cellular DNA repair machinery from mistaking telomeres for double-stranded DNA breaks, potentially leading to chromosomal deletions, inversions, and translocations (de Lange, 2005; Young, 2010). Telomeres progressively shorten with each cell division in cultured somatic cells, reaching to a critically shortened length with replicative senescence. Telomere shortening is considered a biomarker of cellular aging, and telomere length in leukocytes is usually measured to assess its inverse association with age-related morbidity and mortality (Brouilette, Singh, Thompson, Goodall, & Samani, 2003; Cawthon, Smith, O'Brien, Sivatchenko, & Kerber, 2003; Demissie et al., 2006; Honig, Schupf, Lee, Tang, & Mayeux, 2006). However, such associations have not clearly been demonstrated in centenarians or the oldest old (Bischoff et al., 2006; Martin-Ruiz, Gussekloo, van Heemst, von Zglinicki, & Westendorp, 2005). While centenarians who have generally been spared major age-related diseases had better maintenance of telomere length (Arai et al., 2015; Terry, Nolan, Andersen, Perls,

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Table 1. Clinical Characteristics and Laboratory Data of Centenarians Classified by PS (PS 1-4).

	PS			
	PS 1	PS 2	PS 3	PS 4
n	2	10	6	5
Male/female	1/1	1/9	2/4	1/4
Age (years)	101 (1)	101 (2)	101 (1)	103 (3)
Height (cm)	143 (11)	143 (9)	142 (8)	142 (8)
Weight (kg)	41 (2)	41 (8)	39 (8)	36 (5)
Body mass index	20.2 (4.0)	19.7 (1.7)	19.2 (2.8)	17.5 (1.6)
Comorbidities				
Hypertension (*n*)	1	8	4	1
Diabetes mellitus (*n*)	0	1	0	0
Hypercholesterolemia (*n*)	0	1	0	0
Heart failure (*n*)	0	3	2	0
Cerebral infarction (*n*)	0	2	0	3
Dementia (*n*)	0	2	2	2
Cancer (*n*)	1	1	0	0
Laboratory data				
Total protein (g/dl)	7.2 (0.4)	6.9 (0.7)	6.2 (1.0)	6.0 (0.4)
Albumin (g/dl)	4.4 (0.1)	3.8 (0.5)	3.0 (0.6)	3.0 (0.6)
LDL-chol (mg/dl)	123 (47)	109 (28)	73 (24)	88 (21)
HDL-chol (mg/dl)	45 (23)	48 (17)	41 (8)	45 (17)
Triglyceride (mg/dl)	165 (129)	127 (59)	79 (41)	91 (18)
Glucose (mg/dl)	94 (34)	83 (20)	90 (22)	86 (32)
Creatinine (mg/dl)	0.9 (0.2)	0.9 (0.3)	0.7 (0.2)	0.5 (0.2)

Note. The values represent *M* (*SD*); heart failure, excluding NYHA Class I; cerebral infarction, excluding silent lacunar infarction. PS = performance status; LDL-chol = low-density lipoprotein cholesterol; HDL-chol = high-density lipoprotein cholesterol; NYHA = New York Heart Association.

& Cawthon, 2008), healthy centenarians had longer telomeres (Atzmon et al., 2010). Studies on telomere length in centenarians are still scarce.

We made a field survey on health status of Japanese centenarians and reported on breath hydrogen gas in the previous study (Aoki, 2013). In the present study, leukocyte telomere length was assessed in association with nutrition and performance status (PS) of the centenarians whose telomere length could be determined in the stored DNA samples extracted from the peripheral blood. Serum levels of high-molecular-weight adiponectin and dehydroepiandrosterone-sulfate (DHEA-S), which are also known to be associated with aging or longevity (Arai & Hirose, 2012; Gulcelik, Halil, Ariogul, & Usman, 2013; Nair et al., 2006; Sanders et al., 2010; Yen, 2001), were simultaneously assessed in the Japanese centenarians.

Method

Subjects

As described in the previous report (Aoki, 2013), people aged 100 years and above (centenarians) during the fiscal year 2010 in Matsumoto city (135 people out of 242,000 citizens) and Shiojiri city (35 people out of 68,000 citizens) were asked by post whether they would agree to participate in the study, which was approved by the Ethical Review Board of National Hospital Organization Matsumoto Medical Center. The written consent was obtained from 39 centenarians by return of post, but we were able to visit only 28 centenarians in their own homes or nursing homes due to their inconvenience to our schedule. Because the amount of DNA stored was not enough for the assay used in this study, telomere length could not be determined in five out of 28 DNA samples. And then, 23 centenarians were studied in this report.

In Table 1, clinical characteristics and laboratory data of 23 centenarians, who were all nonsmokers (including three ex-smokers) and nondrinkers (including five occasional drinkers), were shown when classified according to the Eastern Cooperative Oncology Group scale of PS (Sorensen, Klee, Palshof, & Hansen, 1993): PS 0 means normal activity ($n = 0$); PS 1 means some symptoms, but still nearly fully ambulatory ($n = 2$); PS 2 means less than 50% of daytime in bed ($n = 10$); PS 3 means greater than 50% of daytime in bed ($n = 6$); and PS 4 means completely bedridden ($n = 5$). Two centenarians who bore prostatic cancer (hormone therapy) and skin cancer (liquid nitrogen therapy) belonged to PS 1 and 2, respectively. Three centenarians survived cancers in the past: gastric cancer in PS 2, tongue cancer in PS 3, and breast cancer in PS 4 (not shown).

Telomere Measurement

From the whole blood samples, DNA was extracted by using a AxyPrep Whole Blood Genomic DNA Miniprep kit (Axygen, CA, USA) according to its instruction, and stored at −20°C until used. Total telomeres were measured by MiRTeL Co. Ltd. (Hiroshima, Japan) using the hybridization protection assay (HPA; Hirashio et al., 2014; Nakamura et al., 1999). Briefly, the extracted DNA was adjusted to 40 ng/µl, and after the DNA solution was heat denatured for 5 min at 95°C, a telomere HPA probe labeled with acridinium ester (AE; 5′-CCC TAA CCC TAA CC*C TAA CTC TGC TCG AC-3′, where * indicates the AE position) was added and incubated at 60°C for 20 min. After hydrolyzation of unhybridized probe, chemiluminescence of AE was measured by a luminometer. Total telomeres are represented as luminescence signals in relative light units (rlu) per 400 ng genomic DNA.

Other Measurements

Blood samples were taken between 11:00 and 18:00 after meals, and stored in serum at −20°C until used. Serum high-molecular-weight adiponectin and DHEA-S levels were measured with chemiluminescent enzyme immunoassay. Serum levels of total protein, albumin, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, glucose, and creatinine were measured by an automated analyzer. All these measurements were performed by a referee laboratory (SRL Inc., Tokyo, Japan).

Statistical Analysis

Data are expressed as the mean (*SD*). Linear associations among continuous variables were assessed by Pearson's correlation coefficient, and those between PS (categorical variable) and other variables were assessed by Spearman's rank correlation coefficient, with a significance level at $p < .05$.

Results

In Association With PS

As shown in Table 1, centenarians with better PS had higher mean levels of body mass index (BMI), serum total protein, albumin, LDL cholesterol, triglyceride, and creatinine. Figure 1 shows leukocyte telomere length, serum albumin, adiponectin, and DHEA-S in PS 1 to 4, respectively. The telomere length was 18,948 (14,047) rlu in PS 1, 47,217 (20,041) rlu in PS 2, 41,051 (18,893) rlu in PS 3, and 14,540 (6,127) rlu in PS 4 (Figure 1A). The levels of albumin, adiponectin, and DHEA-S (Figure 1B-1D) were 4.4 (0.1) g/dl, 6.7 (6.8) µg/ml, and 50.5 (13.4) µmol/L in PS 1; 3.8 (0.5) g/dl, 10.7 (5.3) µg/ml, and 38.4 (19.2) µmol/L in PS 2; 3.0 (0.6) g/dl, 10.6 (3.2) µg/ml, and 21.0 (14.8) µmol/L in PS 3; and 3.0 (0.6) g/dl, 10.6 (4.4) µg/ml, and 29.8 (12.3) µmol/L in PS 4. The albumin and DHEA-S levels appear to decrease with PS worsening. A symbol '†' denotes a cancer-bearing centenarian whose leukocyte telomere length was apparently short (9,015 and 6,478 rlu). The measurements of telomere length in leukocytes from three centenarians who survived cancer in the past were 38,333, 36,978, and 22,920 rlu (not specified in Figure 1).

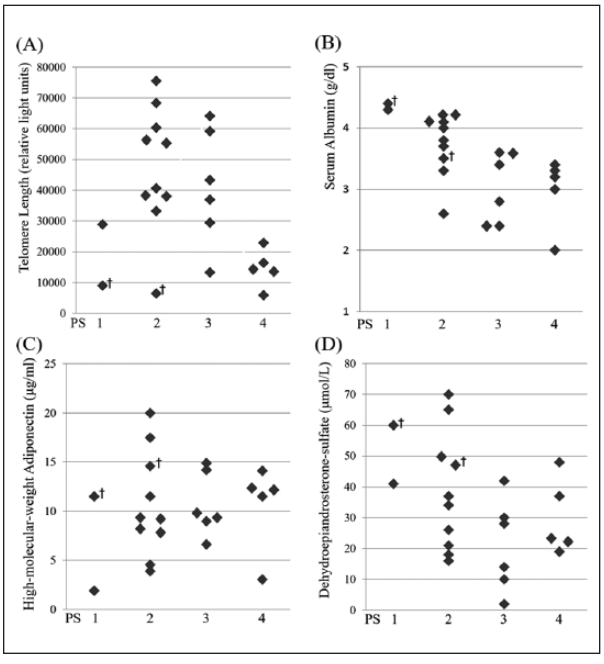

Figure 1. Associations of (A) leukocyte telomere length, (B) serum albumin, (C) serum high-molecular-weight adiponectin, and (D) serum dehydroepiandrosterone-sulfate with performance status (PS 1-4) in 23 centenarians as shown in Table 1.
Note. PS = performance status.
†Centenarian bearing cancer.

Correlation Matrix Among Aging-Related Variables

Table 2 shows correlation coefficients among variables of PS 1 to 4, BMI, albumin, adiponectin, DHEA-S, and telomere length in 23 centenarians. PS (PS 1-4) significantly ($p < .01$) correlated with serum albumin level ($r = -.694$). There were significant correlations between telomere length and BMI ($r = .522$, $p < .05$), between adiponectin and BMI ($r = -.574$, $p < .01$), and between DHEA-S and albumin ($r = .530$, $p < .01$). When excluding two cancer-bearing centenarians, telomere length significantly correlated with PS ($r = -.632$, $p < .01$).

Discussion

It has been demonstrated that serum albumin levels affected by nutritional and inflammatory status were

Table 2. Correlation Matrix Among Aging-Related Variables.

	PS	BMI	Albumin	Adiponectin	DHEA-S	Telomere
PS scale	1.000	−.365	−.694**	.137	−.329	−.391
BMI		1.000	.270	−.574**	−.020	.522*
Albumin			1.000	−.260	.530**	.270
Adiponectin				1.000	.070	−.208
DHEA-S					1.000	−.179
Telomere						1.000

Note. Calculated using BMI and data in Figure 1. PS = performance status; BMI = body mass index; DHEA-S = dehydroepiandrosterone-sulfate.
*$p < .05$. **$p < .01$.

correlated with PS (Han, Huang, Li, Hou, & Wu, 2015). The present study on centenarians also showed a significant correlation between serum albumin and PS. Unexpectedly, the leukocyte telomere length was not found to be significantly correlated with PS, although healthier centenarians have been demonstrated to have longer telomeres (Atzmon et al., 2010). Interestingly, however, the correlation between telomere length and PS became significant when two cancer-bearing centenarians were excluded. Most observational studies have demonstrated that people with inactive and unhealthy lifestyles had shorter telomeres potentially related to stress hormones, inflammation, and oxidative stress (Cherkas et al., 2008; Crous-Bou et al., 2014; Lin, Epel, & Blackburn, 2012; Sen et al., 2014; Starkweather et al., 2014). Telomere shortening seems to reflect age-related oxidative stress rather than mitotic clock, as discussed by Koliada, Krasnenkov, and Vaiserman (2015).

With regard to telomere attrition and cancer, Calado and Young (2009) describe that telomere shortening can modestly contribute to oncogenesis in general and may be the critical factor in promoting the development of cancer in some specific inflammation and immune diseases. Although telomere length is commonly measured only in circulating blood leukocytes, the telomere length has been documented to be inversely correlated with cancer incidence and mortality (Willeit, Willeit, Kloss-Brandstaetter, Kronenberg, & Kiechl, 2011; Willeit et al., 2010). The authors speculate that aging of leukocytes reflected by short telomere length may impair immune surveillance and reduce the clearance of tumor cells (Willeit et al., 2010). In our study, two cancer-bearing centenarians had short leukocyte telomeres in spite of better PS. Three other centenarians who had survived cancers did not have short leukocyte telomeres, but their leukocyte telomeres might have been lengthened due to telomere dynamics in leukocytes (Broccoli, Young, & de Lange, 1995; Epel, 2012; Ornish et al., 2013; Willeit et al., 2010).

In the present study, no significant correlation was found between leukocyte telomere length and serum high-molecular-weight adiponectin or DHEA-S level. Large-scale studies (Broer et al., 2014; Diaz, Mainous, Player, & Everett, 2010) showed no significant correlation between telomere length and adiponectin, but one study (Al-Attas et al., 2010) demonstrated its positive association with adiponectin as well as negative association with BMI (27.1 [4.9] in males, 29.6 [6.2] in females) in middle-aged obese Arabs. In our study, a positive association was found between telomere length and BMI (19.1 [2.2] in total) in lean Japanese centenarians, suggesting a potential role of nutritional status rather than adiposity on telomere length. Still, serum adiponectin level was found to be inversely correlated with BMI, as is commonly shown (Guenther et al., 2014; Lara-Castro, Luo, Wallace, Klein, & Garvey, 2006). Although age-related decline in serum DHEA-S (Nair et al., 2006) and age-related telomere attrition (Young, 2010) are noted, no association between them has been demonstrated (Li et al., 2014; Vasunilashorn & Cohen, 2014). In our study on centenarians, serum DHEA-S level was not correlated with leukocyte telomere length but was positively correlated with serum albumin level. Because DHEA-S is bound to serum albumin, serum DHEA-S level is affected by serum albumin level (Carlstroem, Karlsson, & Von Schoultz, 2002). Both the serum DHEA-S and albumin levels were presumed to reflect nutritional status in the centenarians studied.

The present study showed that short leukocyte telomere length was associated with poor PS and cancer development, as is regarded in general. Serum levels of adiponectin and DHEA-S were indicated to reflect adiposity and nutritional status, respectively. Despite a small number of subjects, these biomarkers, leukocyte telomere length and serum levels of high-molecular-weight adiponectin and DHEA-S, seemed to reflect distinct aspects of longevity in Japanese centenarians. As leukocyte telomere may be lengthened by nutrition and lifestyle interventions (Boccardi, Paolisso, & Mecocci, 2016) or some small molecules (Townsley et al., 2016), leukocyte telomere length could be a feasible and encouraging biomarker for aged people who wish to be healthier centenarians.

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The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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