Dietary Restraint and Telomere Length in Pre- and Postmenopausal Women

Amy Kiefer, PhD, Jue Lin, PhD, Elizabeth Blackburn, PhD, and Elissa Epel, PhD

Background: Leukocyte telomere shortening can serve as a biomarker of aging, as telomere length (TL) can decline with age and shortening is positively associated with morbidity and mortality. It is therefore important to identify psychological and behavioral factors linked to accelerated telomere shortening. Stress and poorer metabolic health (greater adiposity, insulin resistance, and cortisol) correlate with shorter telomeres. Self-reported dietary restraint (DR), defined as chronic preoccupation with weight and attempts at restricting food intake, is linked to greater perceived stress, cortisol, and weight gain, when assessed in community studies (versus in weight loss programs). **Objective:** To test for an association between DR and TL in healthy women across a range of ages. **Methods:** We examined whether DR is linked to TL in two samples, one of premenopausal women (aged 20–50 years; $N = 36$) and one of postmenopausal women (aged 53–69 years; $N = 20$). **Results:** In both samples, higher levels of DR were associated with shorter leukocyte TL, independent of body mass index, smoking, and age. **Conclusions:** Chronic DR, as assessed by self-report (i.e. not caloric restriction), may be a risk factor for premature telomere shortening. Potential mechanisms are discussed. **Key words:** TL, dietary restraint, stress, aging, obesity.

DR = dietary restraint; **BMI** = body mass index; **TL** = telomere length; **DEBQ** = Dutch Eating Behavior Questionnaire.

INTRODUCTION

Obesity and obesity-related illnesses have increased in prevalence worldwide, especially in Western and other developed countries. Individuals in these countries are surrounded by an abundance of calorically dense food, the type of food that cues overeating and in the short run provides pleasure. For many individuals in Western societies, food has become a source of preoccupation and distress (1), with a concomitant increase in dietary restraint (DR). DR is defined as the desire to restrict food intake in order to lose or maintain weight. DR is not, however, consistently related to caloric intake or weight (2,3). In naturalistic studies, self-reported DR predicts weight gain rather than weight loss (4–6). In this context, it is thought to partly indicate unsuccessful attempts at weight loss or weight maintenance rather than active dieting behaviors (2,3,7). In contrast, participants enrolled in dietary interventions who have increased scores on DR have reduced calorie intake and weight loss (6,8). To explain discrepancies in findings, DR researchers have pointed out that measurement of self-reported DR indicates mainly intention to restrict rather than effective caloric restriction (9).

DR may act as a subtle but chronic psychological stressor in a variety of ways. DR can serve as a source of chronic disappointment and shame when one fails to meet unrealistic goals for food restriction and weight. Further, maintaining high DR requires mental effort and may be a form of cognitive load. High DR, or reporting being on a diet is related to lower performance on a wide range of cognitive tasks, including those tapping executive function, in part due to preoccupying thoughts about eating and weight (10–13). Preoccupation and poor executive function may in turn affect ability to cope with everyday stressors. Among women, DR has indeed been linked to greater perceived stress, as well as to physiological factors that are related to long-term stress, such as elevated salivary and urinary cortisol (14–18), reduced bone mass (15,19), and menstrual irregularities (18,19). One study found the association of DR with cortisol to be statistically independent of exercise, nutrient intake, and weight fluctuation (20). Given these apparent links between DR and indices of stress, we hypothesized that DR would be associated with telomere length (TL), a biological marker linked to stress.

Telomeres are nucleoprotein structures that cap and protect the ends of eukaryote chromosomes. They contain tracts of a simple repeat sequence (TTAGGG in humans) that bind protective telomeric proteins. Because telomeres shorten during mitosis, they are thought to reflect biological age. We and others have shown that indices of chronic stress, such as caregiving, high perceived stress, major depression, and elevated cortisol are negatively correlated with TL, in leukocytes (in either whole blood or in peripheral blood mononuclear cells (PBMCs) (21–23). Hence, we hypothesize that DR, by serving as a source of chronic psychological and possibly biochemical stress, may lead to greater wear and tear at the cellular level, in the form of telomere shortening.

Here we focus on leukocyte TL because shorter leukocyte TL is associated with cardiovascular disease and predicts overall mortality (24–29). Poor metabolic health—adiposity, high leptin, and insulin resistance—has also been associated with shorter leukocyte TL (14,15). Furthermore, within an individual, leukocyte TLs in different tissues tend to correlate with each other, leading some to suggest that leukocyte TL may be a marker of TL in other tissues (30).

Because DR appears to be associated with both psychological and physiological stress, we propose that DR may be linked to accelerated telomere shortening in leukocytes. We provide a preliminary test of this hypothesis using cross-sectional data. In two studies, we tested whether higher scores on DR are associated with shorter telomeres among healthy women who differ in age and menopausal status. We hypothesized that DR would accelerate telomere shortening over time, potentially by affecting perceived stress, cortisol, or insulin sensitivity. These studies represent an initial attempt to determine whether this relationship exists at a phenotypic

level. The University of California, San Francisco Investigational Review Board, approved both studies.

STUDY 1: PREMENOPAUSAL WOMEN
Participants and Recruitment

Participants were initially recruited through their child's health care professional in clinics in Bay Area hospitals or through public postings from 2000 to 2003 [for details, see Epel et al. (21)]. Participants completed a health examination including a blood draw. Participants were contacted 18 months after the examination and were asked to complete several mood and eating behavior questionnaires by phone. Sixteen participants in the original study had moved and/or could not be reached. Forty-five completed the questionnaire, resulting in a final sample of 36 women with no missing data. Of these women, three were current smokers. Twenty-seven were caring for a disabled child (caregivers), and nine were age-matched controls. The average body mass index (BMI) was 24.96 (SD = 4.15), with a range of 19.6 to 34.9. This included 61% normal weight, 22% overweight, and 17% obese. Their ages ranged from 20 to 50 years (M = 38.89, SD = 6.26).

Procedure

Blood draws were performed at the Oakland Children's Hospital Pediatric Clinical Research Center. Blood was drawn in a fasting state on a morning during the follicular stage of the menstrual cycle. PBMCs were isolated, DNA was extracted, and TL was measured by PCR method, as described previously (16,21).

Measures

DR was assessed using a shortened version of the restraint subscale of the Dutch Eating Behavior Questionnaire (DEBQ) (31). The DEBQ also includes subscales that assess external eating (eating in response to food cues, such as seeing others eat or seeing delicious food) and emotional eating (eating in response to negative emotions, such as feeling depressed, irritated, or lonely), which were used in secondary analyses. The DR subscale assesses desire and behaviors to control weight, with questions such as: "Do you try to eat less at mealtimes than you would like to eat?"; and "How often do you try not to eat between meals because you are watching your weight?" It measures relative deprivation, eating less than desired rather than less than needed (32). The DR subscale consisted of 6/10 items that assess DR (to keep the phone interview short, four items that were similar to others were not included). The short scale had high internal consistency (Cronbach's α = 0.81). All three factors on the DEBQ have high internal consistency and factorial validity across various samples (31).

Perceived stress was measured using the widely used 10-item Perceived Stress Scale (PSS) (33). This scale assesses cognitive appraisals of life stress over the last month, the extent to which situations are experienced as unpredictable and uncontrollable, and demands outweigh resources. It has

questions such as "In the last month, how often have you felt that you were unable to control the important things in your life?" The 10-item scale has good internal reliability (Cronbach's α = 0.78) and validity, relating to measures of life events in the past year life and perceived stress in an average week in a large population representative sample (33,34).

Results

Perceived stress scores ranged from 5 to 33 (M = 15.75; SD = 6.84). DR scores item mean was 2.68, SD = 0.81 (with a 1–5 range). Pearson correlations were examined to assess relationships between the variables of interest (Table 1). Age was negatively associated with BMI and percent body fat. DR was positively associated with being a smoker. As predicted, DR was negatively associated with TL (Figure 1). This relationship was not due to outlying values (i.e., not influenced by the person with the highest DR score). Hierarchical linear regression analyses were conducted to examine whether DR predicted TL beyond the effects of smoking, age, and BMI. Age, smoking status, and BMI were entered at Step 1. DR was entered at Step 2. In Step 1, age was marginally significantly associated with TL, β = −0.25, p = .06. Neither BMI, β = −0.09, p > .5, nor smoking β = −0.12, p > .3, predicted TL. In Step 2, as hypothesized, higher levels of DR predicted shorter telomeres, β = −0.45, p < .01, controlling for the effects of age, smoking, and BMI (Table 2).

STUDY 2: POSTMENOPAUSAL WOMEN
Participants and Recruitment

The second sample consisted of 20 healthy postmenopausal women, 13 of whom were caring for a family member with some type of dementia (caregivers), and 7 age-matched controls. The women were recruited through flyers in the community as well as from dementia clinics and elderly service providers in the Bay Area. Data were collected from 2005 to 2007. Women ranged in age from 52 to 79 years (M = 59.73, SD = 6.40). The average BMI was 27.9 (SD = 5.0), with a range of 17.7 to 36.3. This included 36% normal weight, 32% overweight, and 32% obese. None of the women were current smokers.

Procedure

Women underwent a fasting morning blood draw. Buffy coat was separated and frozen at −80°C. DNA was subsequently extracted and assayed for TL, following the procedure

TABLE 1. Pearson Intercorrelations Between Variables in Study 1

	1	2	3	4	5
1 Age	—				
2 Body mass index	−0.36*	—			
3 Smoking	−0.06	−0.16	—		
4 Restrained eating	0.02	0.14	−0.33*	—	
5 Telomere length	−0.20	0.18	−0.06	−0.38*(−0.45*)	—

Correlation within parentheses is adjusted for age, smoking, and BMI.
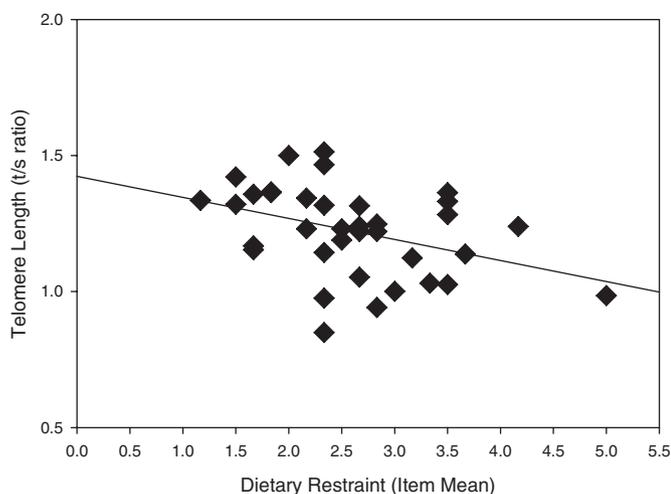* p < .05.

Figure. 1. Scatter plot of dietary restraint and telomere length for premenopausal women.

TABLE 2. Results of Hierarchical Linear Regression Analyses for Studies 1 and 2

	b	SE (b)	β	t	p
Study 1					
Step 1					
Age	−0.007	0.004	−0.252	−1.89	.06
Smoking	−0.056	0.084	−0.088	−0.67	.51
Body mass index	−0.004	0.004	−0.122	−0.92	.36
Step 2					
Restrained eating	−0.090	0.032	−0.450	−2.79	.009
Study 2					
Step 1					
Age	−0.006	0.019	−0.073	−0.32	.75
Body mass index	−0.028	0.022	−0.294	−1.28	.22
Step 2					
Restrained eating	−0.501	0.125	−0.702	−4.01	.001

described in Epel 2004, online supplement. The assessment of PSS and DEBQ are described in Study 1. In this study, however, women completed the full DEBQ. The restraint subscale had internal consistency, Cronbach's $\alpha = 0.91$, as did the PSS, Cronbach's $\alpha = 0.93$. These self-report questionnaires were completed during the same week as the blood draw.

Results

Perceived stress scores ranged from 2 to 27 (M = 17.19; SD = 7.33). DR scores had an item mean of 2.55, SD = 0.66. The sample was similar to Sample 1 in DR, with a slightly higher average perceived stress score, and greater BMI. Unlike Study 1, TL in Study 2 was not normally distributed. A log transformation was conducted to normalize its distribution. Pearson's correlations were conducted to examine the relationships between log TL, age, BMI, and DR (Table 3). BMI increased significantly with age and was used as a covariate in all analyses. As hypothesized, higher DR scores correlated with shorter TL (Figure 2). No other potentially confounding factors were related to TL. To examine whether

TABLE 3. Pearson Intercorrelations Between Variables in Study 2

	1	2	3	4
1 Age				
2 Body mass index	0.28	—		
3 Restrained eating	−0.01	−0.29	—	
4 Telomere length	−0.20	−0.26	−0.55*(−0.73**)	—

Correlation within parentheses is adjusted for age and BMI.
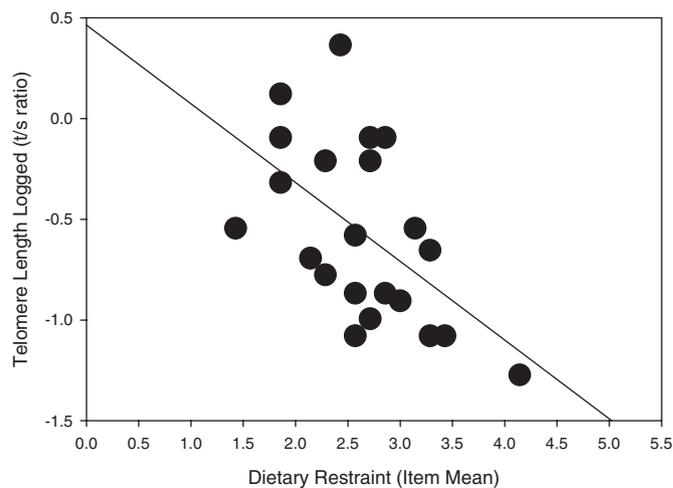* $p < .05$; ** $p < .01$.

Figure. 2. Scatter plot of dietary restraint and telomere length for postmenopausal women.

DR was associated with TL beyond effects of age and BMI, a hierarchical linear regression of TL on age, BMI, and DR was conducted. Age and BMI were entered at Step 1. DR was entered at Step 2. Neither age, $\beta = -0.04$, $p < .80$, nor BMI, $\beta = -0.29$, $p > .20$, significantly predicted TL in this sample. In contrast, in Step 2, as predicted, higher levels of DR predicted shorter telomeres, $\beta = -0.70$, $p < .001$, controlling for the effects of age and BMI (Table 2).

Post hoc Analyses for Studies 1 and 2

There are several potential competing explanations for these findings. Notably periods of overeating could lead to spikes in insulin and serve as a metabolic stressor. We therefore assessed two additional measures that might serve as proxies for overeating, to determine whether the tendency toward nonhomeostatic eating (eating for reasons other than caloric need) was related to TL. We first tested whether eating in response to external cues rather than hunger (external eating subscale) and eating in response to emotions (emotional eating subscale) from the DEBQ were associated with TL. In both studies, there were no significant associations of TL with either subscale (all p values >0.40). Second, given the association between perceived stress with TL, we also assessed whether DR was associated with TL when adjusting for perceived stress. In both studies, DR was still significantly associated with TL (p

values <0.05). We also examined whether controlling for caregiver status (using a dummy variable: 1 = Caregiver; 0 = Control) would affect our results; there were no effects. Hence, DR remained significantly associated with telomere shortness even after controlling for perceived stress scores and for caregiver status.

Finally, we conducted additional analyses combining the samples across Studies 1 and 2. Although TL was skewed in Study 2, it was not skewed in the combined sample; thus, results are reported for the untransformed variable. Controlling for age, $\beta = -0.68$, $p < .001$, smoking, $\beta = -0.02$, $p > .80$, and BMI, $\beta = -0.12$, $p > .10$, higher levels of DR predicted shorter telomeres, $\beta = -0.26$, $p < .01$. As in the uncombined analyses, the emotional eating and the external eating subscales neither predicted TL nor moderated the relationship between DR and TL (i.e., these scales did not interact with DR).

Because of the cross-sectional nature of the study, we did not test for mediation, which should be reserved for longitudinal data in which the mediator follows the target (35,36).

DISCUSSION

Across two samples, in both pre- and postmenopausal women, higher DR was linked to shorter leukocyte telomeres. In both samples, this effect was independent of BMI, age, perceived stress, and smoking. This report adds to the growing literature on the negative correlates of high DR. While DR may to some extent be necessary to maintain weight in the rich food environment of the modern United States, high levels of restraint may be unhealthy, as self-reported DR has been linked to aberrations in stress and reproductive hormones, greater adiposity, and in some studies, greater levels of life stress (14–18). Here we introduce the possibility that DR may also relate to accelerated aging of the immune system. Identification of lifestyle factors that are linked to telomere maintenance is a nascent field. It was notable that DR had an effect over and above other known effects, such as obesity and stress. Future research should examine whether DR predicts accelerated telomere shortening prospectively.

There are many potential explanations for why high DR would be negatively associated with TL. Given the cross-sectional nature of the study, it is possible that DR may have served as a proxy for an unmeasured third variable that leads to telomere shortening. This study tested several plausible third variables, including emotional eating, external eating, BMI, and perceived stress, none of which appeared to affect the relationship between DR and TL. Nonetheless, the relationship between DR and TL is likely an indirect relationship that involves a chain of behavioral or biochemical events. Future research should assess additional plausible third variables or mediators of this relationship, such as responsiveness to food cues, dietary habits, early life influences on nutrition, and personality or lifestyle variables.

One might wonder how these findings are related to the literature on caloric restriction. In animal studies, caloric restriction enhances longevity, and delays the onset of the diseases of aging (37–39). Caloric restriction may have similar effects on promoting longevity in humans, in that it improves biomarkers

that predict longevity (39–42). The relationship between TL and caloric restriction has not been studied in humans. Caloric restriction may promote TL maintenance by increasing insulin sensitivity, which has been linked to longer telomeres (43). On superficial examination, our results might appear to contradict the hypothesis that caloric restriction slows aging and telomere shortening in humans. However, caloric intake is not strongly related to DR. Self-reported DR assesses only the intention to reduce caloric intake, not actual restrictive behavior; DR is not consistently associated with weight loss or caloric intake (2,4–7,20,44). Rather, it appears to be related to eating less in controlled conditions, and overeating when self-control is challenged, especially if one scores high on the tendency to overeat in response to food cues or emotions (20).

The distinction between unhealthy and ineffectual attempts at weight loss, which are frequently reported by chronic dieters, and successful DR induced by behavioral interventions, which increase well-being and aid weight loss (6), is important for interpreting our results. We propose that behaviorally successful DR, and the consequent decreases in habitual caloric intake, lower glucose and insulin levels, distress, and therefore should slow rate of telomeric loss. Free (unrestrained) eaters tend to eat meals more regularly. Conversely, DR, as typically assessed by self-report, is associated with dysregulated patterns of eating (fasting, bingeing, and purging) (45). Frequent missed meals followed by overeating, may cause some 'metabolic strain,' in the form of more frequent and greater fluctuations in insulin and glucose levels, and such exposure is hypothesized to accelerate telomeric loss (46). These findings therefore call for assessment of eating behaviors in conjunction with self-reported DR, to distinguish "healthy" DR from "unhealthy" DR. Until this research is conducted, we can only speculate about the mechanisms to explain the relationship between self-reported DR and TL in humans.

Additional limitations of these studies include the small sample sizes and exclusive focus on women. Further, in the first study, a subset of the DEBQ was administered over the phone 18 months after the other assessments. Despite these limitations, the results of these two studies were consistent with each other and not explained by obvious confounding factors, such as BMI, age, or reported tendency to overeat in response to stimuli or emotions.

In conclusion, we find that self-reported DR is linked to shortened telomeres. Given the replication across two samples, among pre- and postmenopausal women, the relationship between DR and TL appears to exist at least phenotypically. Findings from this preliminary test of the hypothesis call for experimental and prospective assessment of this relationship to determine if the relationship is causal, and whether it is due to cognitive, behavioral, or physiological pathways.

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