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Original Article

The history of sleep apnea is associated with shorter leukocyte telomere length: the Helsinki Birth Cohort Study

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ABSTRACT

Objectives: Sleep apnea poses an elevated risk for chronic age-related diseases. Leukocyte telomere length (LTL), a biomarker and factor associated with accelerated cellular aging processes, may serve as a novel mechanism underlying these disease risks. We investigated if a history of clinician-diagnosed sleep apnea or primary snoring was associated with LTL in later adulthood.
Methods: Data on sleep apnea, primary snoring and LTL, were available for 1948 participants from the Helsinki Birth Cohort Study. Patients with sleep apnea ($n = 44$) and primary snoring ($n = 29$) severe enough to be recorded as an inpatient diagnosis for hospitalization were identified by their case records through the Finnish Hospital Discharge Register. The LTL was measured by using the realtime quantitative polymerase chain reaction (PCR) method at a mean age of 61.5 years (standard deviation [SD], 2.9).
Results: A history of sleep apnea was associated with shorter LTL ($P = .010$). Adjustment for a number of covariates did not alter the association.
Conclusions: Accelerated cellular aging reflected in shorter LTL in patients with a history of sleep apnea may partly explain their higher risk for age-related diseases. Future studies elucidating the impacts of long-term or successful treatment history of sleep apnea on the maintenance of LTL are warranted.

1. Introduction

Sleep apnea poses an elevated risk for cardiovascular disease [1] and type 2 diabetes mellitus (DM) [2,3]. However, the precise physiologic and biochemical mechanisms that underlie these risks are poorly understood. Telomere biology may serve as a novel mechanism underlying these associations. Telomeres are repeated protein complexes (TTAGGG) located at the end of chromosomes [4]. Their function is to preserve chromosomal integrity and prevent p53 activation and consequent cellular growth arrest and apoptosis [5].

Shorter leukocyte telomere length (LTL) has been associated with an increased risk for cardiovascular disease [6] and type 2 DM [7]. There also is evidence that sleep apnea is characterized by inflammation and oxidative stress [8,9] and that LTL is highly sensitive to these conditions [10,11]. Yet, to our knowledge only one study to date has examined the associations between sleep apnea and LTL in adulthood. This study showed that individuals with severe sleep apnea verified by polysomnography and further characterized by the apnea–hypopnea index had shorter LTL than individuals without a sleep apnea diagnosis [12]. This difference persisted after controlling for age, body mass index (BMI), cholesterol, triglycerides, glucose, uric acid, smoking, and hypertension status.

Our study adds to the literature by using a community sample, with a prospective diagnosis of sleep apnea obtained from comprehensive nationwide registers. We examined if a history of sleep apnea severe enough to be recorded as a hospital inpatient diagnosis was associated with LTL in a well-characterized cohort of adults with a mean age of 61.5 years. In addition, we examined if primary snoring, a classic symptom of sleep apnea most often appearing without fulfilling the diagnostic criteria for sleep apnea [13] severe enough to warrant hospitalization, was associated with LTL.

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2. Materials and methods

2.1. Participants

The participants of our study were part of the Helsinki Birth Cohort Study [14]. Relative LTL was available for 1964 participants at a mean age of 61.5 years (standard deviation [SD], 2.9; range, 56.7–69.8 years). The study sample comprised 900 men and 1048 women (n = 1948) and excluded 16 men and women who were hospitalized for sleep disorders other than sleep apnea and primary snoring (sleep disorder codes extracted from the Finnish Hospital Discharge Register [HDR] between 1987 and the clinical examination: 78060 (n = 1) from the *International Classification of Diseases*, eighth revision [ICD-8]; 3074A (n = 12) and 3074F (n = 1) from the ICD ninth revision [ICD-9]; and G471 (n = 1) and G479 (n = 1) from ICD 10th revision [ICD-10]). None of the participants had 30640 from the ICD-8; 3074F, 3471A, 3074A, 3074G, 3074H, 3471A, 3478X, or 3074A from the IDC-9; or F510, F511, F512, F513, F514, F515, F518, F519, G470, G472, G474, or G478 from the ICD-10. These individuals were excluded because sleep apnea often co-occurs with other sleep disorders such as insomnia [15]. There also is evidence that insomnia is associated with higher oxidative stress [16], and shorter sleep duration and poor sleep quality are associated with shorter LTL [17,18]. Thus disentangling the effects of sleep apnea and primary snoring from other sleep disorders becomes complicated without these exclusions; further, the small number of individuals with the other sleep disorders in our sample precluded tests focusing on comorbidity. The Helsinki Birth Cohort Study protocol was approved by the Ethics Committee of the National Public Health Institute. All study participants gave their written informed consent.

2.2. Telomere length measurement

Relative telomere length from peripheral blood DNA was determined as in Savolainen et al. [19] using a quantitative realtime polymerase chain reaction (PCR)-based method [20], as described in detail by Eerola et al. [21], with the following modifications. Based on O'Callaghan's method [22], a synthetic oligomer (Sigma) dilution series, a hgb-120-mer, and a tel14× (0.0002, 0.002, 0.02, 0.2, 1.0, 3.0, and 6.0 pg/μL) were included on every plate to create reaction specific standard curves. Plasmid DNA (pcDNA3.1) was added to each standard to maintain a constant 10 ng/μL of total DNA concentration per reaction. Samples and standard dilutions were transferred to 384-well plates as triplicates using a DNA Hydra 96 robot and dried for 24 h at 37 °C.

Quality control was performed with the Bio-Rad CFX Manager software v.1.6. All plates included four genomic DNA control samples for plate effect calibration and for the repeat measures correlation coefficient of variation (CV) monitoring. The quantities of the control samples were used for calculating CV values as the ratio of the SD to the mean, which gave means of 21.0% for the telomere reaction, 6.0% for the β-hemoglobin reaction, and 24.8% for their ratio (T/S). The plate effect was considered by normalizing the telomere signal and reference gene signal to the corresponding mean of four control samples, which were analyzed for every quantitative PCR plate before taking the T/S ratio. The original stock DNA concentration (mean, 157.9 ng/μL; SD, 103.8) prior to dilution to a constant 10 ng/μL was associated with LTL (P < .001); the effect was controlled by running all of the analyses adjusted for stock DNA concentration. However, the results did not significantly differ between the stock DNA concentration-adjusted and nonadjusted models.

2.3. Sleep apnea and primary snoring

Subjects with central or obstructive sleep apnea or primary snoring recorded as inpatient diagnoses were identified from the Finnish HDR between the year 1987 and the clinical examination. HDR data also were available between 1969 and 1986 based on ICD-8 criteria, but less clinical awareness existed about the importance of sleep apnea at that time; accordingly, there were no apnea diagnoses (code 783.21; no specific code for primary snoring) within our study population. Between 1987 and 1996, sleep apnea and snoring were coded by ICD-9 criteria (sleep apnea codes, 3472A and 3478X; primary snoring code, 7849C) and by ICD-10 criteria (sleep apnea code, G47.3; primary snoring code, R06.5) from 1996 onward.

From the 1948 participants, we identified 34 men (14 with snoring) and 10 women (four with snoring) who had been hospitalized with sleep apnea (2.3%). Sleep apnea was a primary diagnosis for hospitalization for 41 (93.2%) of these subjects. All of the 20 men and 9 women hospitalized for primary snoring without sleep apnea (1.6%) had this diagnosis as the primary diagnosis of hospitalization. Participants who had not been hospitalized for sleep apnea or snoring were included in the control group (n = 1875).

2.4. Covariates

Variables known to be associated with sleep apnea, snoring, or LTL were treated as covariates. These variables included: (1) sex; (2) age; (3) stock DNA concentration in the blood sample for telomere length measurement; (4) diagnoses according to ICD-8, -9, and -10 between 1969 and the clinical examination of mental disorders (for detailed diagnoses, see [23]); (5) coronary heart disease (codes 430–434 and 436–437 from the ICD-8 and ICD-9, 438 from the ICD-9, and I60–I69 from the ICD-10 [24]) and stroke derived from the Finnish HDR (codes 410–414 from ICD-8 and ICD-9 and I21–I25 from ICD-10 [25]); (6) diagnosis of type 2 DM based on an oral glucose tolerance test and BMI (kg/m^2), measured in conjunction with the clinical examination; (7) self-reported highest attained level of education (e.g., elementary school or less, vocational school, high school diploma, university degree); (8) leisure-time physical activity (<3 times/week vs ⩾3 times/week); (9) current smoking status (yes vs no); and (10) alcohol consumption (<3 times/week vs ⩾3 times/week).

2.5. Statistical analyses

Associations between sleep apnea, snoring, and LTL were examined using multiple linear regression analyses with relative LTL as the outcome. Sex, age, and stock DNA concentration were entered as covariates in model 1. Model 2 included all covariates and LTL was standardized to the mean of 0 and SD of 1 to facilitate interpretation.

3. Results

Table 1 shows that participants with sleep apnea and primary snoring more frequently were men. Participants with apnea also had a higher BMI than control participants. As previously reported [19], older age was associated with shorter LTL (β = −0.039 [95% confidence interval {CI}, −0.053 to −0.024]; P < .001) and men had shorter LTL than women (β = −0.147 [95% CI, −0.232 to −0.061]; P = .001). Participants with sleep apnea had shorter LTL than control participants (β = −0.375 [95% CI, −0.660 to −0.090]; P = .010 for model 1 and P = .015 for model 2), whereas participants with a history of primary snoring did not differ in LTL from control participants (P = .899) (Fig. 1). Participants with sleep apnea with and without primary snoring did not differ in LTL (P = .558). No significant interactions existed in sex × sleep apnea or sex × primary snoring (P > .128). Age at first hospitalization for sleep apnea or primary snoring was not associated with LTL (P > .393).