Medical Advances

Telomere Length and Insulin Resistance

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Abstract

In humans, telomeres are repeating strings of TTAGGG sequences that protect chromosomal ends and maintain genomic stability. Telomere length is considered a critical marker of biological aging because telomeric DNA progressively shortens in dividing somatic cells and contributes to cell senescence, apoptosis, or neoplastic transformation. Recent studies have associated telomere shortening with insulin resistance and various age-related pathological conditions. In this review, we summarized the current available evidence concerning the role of telomere length in the development of insulin resistance. *[N A J Med Sci. 2010;3(2):57-60.]*

Key Words: *Telomere length, insulin resistance, oxidative stress, chronic inflammation*

Telomeres are regions of highly repetitive TTAGGG DNA sequences extending over several kilobases at the ends of chromosomes in eukaryotes whose complete biological functions remain unclear. The gradual loss of telomeric DNA in dividing somatic cells is known to contribute to senescence, apoptosis, or neoplastic transformation,[1] indicating the critical importance of telomere length as a biomarker for somatic cell aging.[2] It is now increasingly recognized that telomere shortening also contributes to the pathogenesis of several age-dependent complex disorders,[1,3-27] including insulin resistance.[3,11,14,28-31]

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Insulin resistance is a state in which a given concentration of insulin produces a less-than-expected biological effect on target tissues that do not respond properly to insulin action. High plasma levels of insulin and glucose due to insulin resistance are believed to play a major pathogenic role in the development of metabolic syndrome, type 2 diabetes, and heart diseases. Aging and obesity have long been recognized as important causes of insulin resistance, and both are associated with a rise in systemic inflammation,[32,33] and oxidative stress.[34,35] Inflammation enhances the turnover rate of leukocytes, and oxidative stress heightens the loss of telomeric repeats per cell replication,[32] therefore oxidative stress and inflammation may accelerate telomere erosion in leukocytes. Cumulative burden of oxidative stress is considered the key element in age-related diseases,[3] including insulin resistance, and is considered a major determinant of lifespan. Oxidative stress also appears to be a major regulatory factor affecting the loss of telomeres[36] by increasing telomeric erosion with each replication,[37,38] thereby contributing to overall telomere shortening.[39] *In vitro*, von Zglinicki and colleagues have established that oxygen free radicals are a major cause of telomere shortening and that reduction in oxidative stress reduces the rate of telomere shortening.[40-44] *In vivo*, leukocyte telomere length is often used to represent an individual's telomere length at birth and telomere attrition thereafter.[3] Presumably, this attrition is determined not only by the replicative history of leukocytes, but also the cumulative oxidative stress in progenitor cells.[3] Thus, leukocyte telomere length could be regarded as a biological record of the cumulative burden of inflammation and oxidative stress over an individual's life span.[45]

Additionally, supporting data are now emerging to indicate a possible link between oxidative stress and telomere shortening in vascular cells.[46] Some studies have related changes in telomere length during growth and aging to changes in biomarkers of endothelial damage[47] and other bio-precursors of atherosclerosis like hyperhomo−cysteimia.[36,48] By inducing senescence, telomere erosion may also directly contribute to progressive endothelial dysfunction and atherosclerosis.[49] In practice, leukocyte telomere length could be used as a record representing the cumulative burden of exposures to oxidative stress and/or insulin resistance that pre-date the leukocyte collection.[32] In several cross-sectional analyses of human populations, leukocyte telomere length has been inversely associated with insulin resistance,[3,11,14,28-31,50] serum leptin, and body mass

index (BMI),[9] In the only prospective cohort available, accelerated leukocyte telomere attrition, was also associated with an increase in insulin resistance and BMI in a longitudinal study.[31]

The homeostasis model assessment (HOMA-IR) is most commonly used to quantify insulin resistance in population studies.[51] HOMA-IR, the product of basal glucose (mmol/L) and insulin levels (μU/mL) divided by 22.5, is a well-established simple biomarker for estimating the balance between hepatic glucose output and basal insulin secretion.[52,53] To date, there has been a total of eight cross-sectional studies that directly investigate the relation between telomere length and HOMA-IR (**Table 1**).

Table 1. Available Epidemiologic studies relating telomere length to insulin resistance in the published literatures.

Year	Author	Size	Race	Cell Type	Results
2005	Adaikalakoteswari et al[11]	40 non-diabetic controls	Asian Indian	Leucocyte	TRF length negatively correlated with insulin resistance (HOMA-IR) where r = -0.4, p = 0.01
2005	Gardner et al[31]	48 from two cross-sectional cardiovascular screenings of the Bogalusa Heart Study	22 white males, 28 white females, 8 black males, and 12 black females	WBC	relative changes in telomere length were correlated with the HOMA-IR ($r = -0.531$, $P < 0.001$)
2006	Dimissie et al[3]	327 from the Offspring cohort of the Framingham Heart Study	Caucasian men	leukocyte	age-adjusted TRF length was inversely correlated with the HOMA-IR ($r = -0.16$, $P = 0.007$)
2006	Sampson et al[14]	21 type 2 diabetic cases and 29 matched control	Caucasian males	monocytes	Telomere length was unrelated to insulin resistance (HOMA-IR, r = 0.08, p = 0.2)
2006	Nakajima et al[50]	44 patients with nonalcoholic fatty liver disease	Japanese Asian	liver tissue	HOMA-IR were significantly higher in low telomere length group (high vs low = 2.2 vs 3.7, p = 0.019)
2006	Aviv et al[30]	1517 Caucasian female twins from the St. Thomas' Adult Twin Registry	Caucasian	leukocyte	Telomere length was inversely associated with HOMA-IR in pre-menopausal women ($r = -0.149$, $p < 0.001$)
2009	Barbieri et al[29]	476 healthy, unrelated Caucasians (208 men and 268 women), aged 16–104 years	Caucasian (Italy)	leukocyte	LTL was correlated negatively with HOMA-IR (r = −0.123, P = 0.023) in individuals younger than 85 years. However, not significant after age-adjustment.
2010	Al-Attas et al[28]	69 boys and 79 girls, aged 5-12 years	Arabian	leukocyte	telomere length was not associated with insulin resistance

The majority of studies found that leukocyte telomere lengths were shorter in participants with insulin resistance and that telomere lengths were inversely associated with HOMA-IR in healthy participants. In a cross-sectional study of Asian Indian, Adaikalakoteswari et al[11] observed that telomere length was negatively correlated with HOMA-IR in 40 non-diabetic controls (r = -0.4, p = 0.01). Demissie et al[3] measured the leukocyte terminal restriction fragment length of 327 Caucasian males (mean age of 62.2 years) from the Framingham Heart Study Offspring Cohort and observed that age-adjusted TRF length was inversely correlated with the HOMA-IR (r = –0.16, p = 0.007) and urinary 8-epi-$PGF_{2\alpha}$ (r = –0.16, p = 0.005), an index of systemic oxidative stress. Similar findings were also reported in another cross-sectional study of apparently healthy Italians[29] aged < 85 years (r = –0.149, p < 0.001), although t the association was no longer statistically significant after the adjustment of age. However, no relation was found between insulin resistance and telomere length in Arab youth (aged 5-12 years).[14,28] Interestingly, there seems to be a sex-specific phenomenon regarding the telomere-HOMA-IR relation where the impact of menopause appears quite significant on both insulin resistance and telomere length in women. To evaluate the impact of menopause on the telomere-HOMA-IR relation, Aviv et al[30] studied 1,517 Caucasian female twins aged 18-79 who were enrolled in UK's adult Twin Registry, and observed that mean telomere length was 187 bp longer in low HOMA-IR pre-menopausal women (age ≤ 50) compared

to high HOMA-IR women, but 40bp shorter in low HOMA-IR postmenopausal women (age > 50).[30] Although these differences did not reach statistical significance at the conventional α=0.05 levels, the overall trend appeared to support the notion that menopausal status modified the association between telomere length and insulin resistance in women. In the only prospective study of Bogalusa Heart Study that analyzed changes in telomere length and changes in HOMA-IR,[31] Gardner and colleagues found that the relative changes in telomere lengths of the 48 individuals who participated in two cross-sectional screenings (1988-1991 and 2000-2001) were correlated with yearly change of the HOMA-IR between the two screenings (r=-0.531, p<0.001). These correlations were also independent of the relative change in BMI and other covariates.

In conclusion, available evidence, albeit limited, indicates that telomere length may be inversely associated with insulin resistance. The mechanisms that are potentially responsible for such an observation remain largely unknown but are thought to reflect the cumulative oxidative stress and chronic inflammation. Large and well-characterized prospective studies are needed to clarify the role of telomere biology in the development of insulin resistance in humans.

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