Cathy E. Elks and Robert A. Scott

The Long and Short of Telomere Length and Diabetes

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Aging is a major risk factor for a number of complex diseases including cancers, cardiovascular disease, and type 2 diabetes, yet the biological processes linking aging and disease risk are poorly understood. A potential mediator of age-related increases in disease risk may lie in repetitive sequences of DNA known as telomeres. Telomeres represent the genome's defense mechanism against the biological conundrum that the tail ends of chromosomes cannot be replicated when cells divide (1). During mitosis, telomeric DNA is sacrificed in return for protecting the protein coding and regulatory elements of the genome, and as a result they become shorter with cellular aging (2). The enzyme telomerase helps to guard against this telomere loss by making additional copies of the hexanucleotide repeats that make up these protective chromosomal caps (3). However, when a critical threshold of shortening is reached (the "Hayflick limit"), cell senescence follows (4).

While telomeres are shorter in older age (5), the rate of telomere shortening varies among individuals (6). The association of shorter telomeres with disease and mortality (7) implicates telomeres as a biomarker of biological aging (8). Telomere shortening is influenced by a range of cellular stressors (9) such that telomere length may lie on the causal pathway between lifestyle exposures and risk of disease. Previous studies have highlighted the role of health behaviors in the apparent acceleration of aging (10); it will be of interest to investigate the role of telomeres as potential mediators of the association between lifestyle and behavioral factors and age-related disease. Indeed, a number of lifestyle and metabolic risk factors (including obesity [11], insulin resistance [6], and physical inactivity [12]) have been shown to be associated with shorter telomeres.

There is a growing body of evidence in support of an association between short telomeres and type 2 diabetes (13). However, most studies have been cross-sectional in nature, precluding causal inferences: Do the metabolic perturbances of type 2 diabetes cause telomere attrition, or do shorter telomeres lead to type 2 diabetes? Plausible biological hypotheses support both scenarios (Fig. 1). Short telomeres may lead to premature β-cell senescence, resulting in reduced β-cell mass and subsequent impaired insulin secretion and glucose tolerance. Indeed, experimental evidence suggests that telomerase is important in maintaining glucose homeostasis in mice (14). Conversely, elevated blood glucose levels increase oxidative stress, potentially interfering with telomerase function and resulting in shortened telomeres (15).

In this issue, Zhao et al. (16) address this uncertainty by demonstrating that short telomere length is associated with future development of type 2 diabetes independently of known type 2 diabetes risk factors. In the Strong Heart Family Study (16), Zhao et al. investigate the association of leukocyte telomere length at baseline with future risk of diabetes over an average follow-up period of over 5 years. The authors found that individuals in the lowest quartile of leukocyte telomere length were at almost twice the risk of developing diabetes compared with those with longer telomeres. Notably, they highlight a nonlinear association between telomere length and diabetes risk in which the increased risk is largely confined to those with the shortest telomere length. This apparent threshold effect is consistent with the hypothesis that there is a critical limit of telomere length that induces cellular senescence. A key strength of the study is the prospective design, which should minimize the possibility of reverse causality. However, there are some important caveats, particularly given the long latency that can precede diabetes diagnosis (17). Even with a 5.5-year follow-up period, many of those who went on to develop type 2 diabetes were likely to be experiencing subclinical metabolic derangements at baseline. A previous prospective study reported a weak association between telomere length and type 2 diabetes, which was attenuated after adjustment for prominent risk factors (18). However, while Zhao et al. found associations of

MRC Epidemiology Unit, University of Cambridge, Cambridge, U.K.

Corresponding author: Robert A. Scott, robert.scott@mrc-epid.cam.ac.uk.

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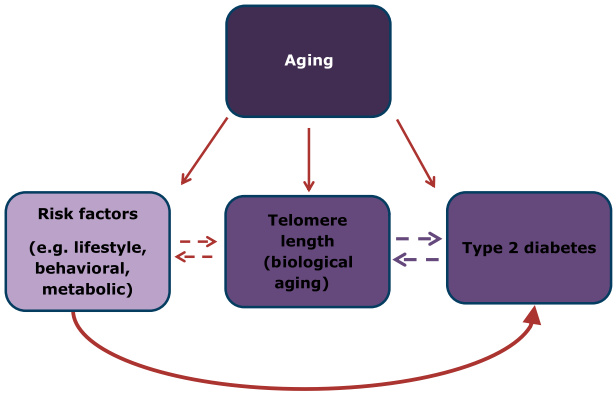

Figure 1—Conceptual framework relating telomere length and type 2 diabetes risk. While telomere length may have a direct and causal influence on type 2 diabetes, it may serve as a causal mediator of other risk factors or may be altered as a result of metabolic processes associated with diabetes.

telomere length with prominent risk factors at baseline (including fasting glucose and BMI), the association of telomere length with type 2 diabetes was independent of these risk factors. The discordant conclusions of these studies are difficult to reconcile, and it is clear that further large-scale prospective studies are required.

While prospective studies help to clarify the direction of causality between associated traits, it remains possible that confounding factors, either unmeasured or imperfectly adjusted for, may be responsible for the observed association. To make further inference on the causal nature of association between telomere length and diabetes, alternative approaches may be useful. For example, it is possible to use genetic variants as unconfounded instruments to make causal inference about observed associations. Telomere length has been shown to have a genetic basis (5), and a number of specific genetic variants have been associated with telomere length (19). You et al. (18) tested associations between single nucleotide polymorphisms in genes involved in telomere regulation and type 2 diabetes, but concluded that there was no evidence for a causal relationship between short telomeres and diabetes. However, specific genetic variants associated with telomere length explain only a small fraction of the variance in this measure. In turn, the variability in telomere length explains only a small portion of the variance in diabetes risk, suggesting that vast sample sizes would be required to resolve this question with any certainty. Nevertheless, this approach has shown promise in demonstrating the potentially causal nature of associations between telomere length and cardiovascular disease (19).

The work of Zhao et al. (16) provides additional evidence for a role of short telomeres in type 2 diabetes and is a promising basis for further investigation into whether telomere length is in the causal pathway for the etiology of type 2 diabetes. This is particularly important in light of a recent small study reporting that adherence to a lifestyle intervention is a predictor of telomere lengthening (20), which warrants further investigation. The opportunity to identify the causal pathways through which lifestyle behaviors alter risk of disease may allow the development of preventive interventions and provide further support for optimizing individual and population lifestyle behaviors as the cornerstone of diabetes prevention.

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