The significance of telomeres in clinical practice

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Telomeres have received significant attention over the past few decades due to their role as primary gatekeepers of the genome[1]. Protective DNA-protein complexes at the ends of linear chromosomes ensure genome stability and integrity. Telomeres shorten with each cell cycle since the 3′ ends of telomeric deoxyribonucleic acid (DNA) cannot be fully replicated. Insufficient replication of telomeric DNA leads to either senescence or cell death[1]. Cells with critically short telomeres trigger a DNA damage response (DDR), resulting in senescence and contributing to a higher incidence of age-related disorders and cancer[1].

The rate of cell aging is mainly genetic-dependent but also affected by environmental inputs and lifestyle habits. Lifestyle factors such as smoking, excessive alcohol consumption, and chronic stress have been shown to increase systemic inflammation and oxidative stress, which, in turn, accelerate telomere shortening, leading to premature cellular aging and senescence[1,2]. Due to its high guanine content, telomeric DNA is sensitive to reactive oxygen species (ROS) damage, reducing telomere length values and integrity1. In contrast, healthy lifestyle factors (diet, exercise, sleep, and stress management) are critical in ameliorating telomere length dynamics. In particular, regular aerobic exercise, a Mediterranean diet rich in antioxidants, and stress reduction techniques can help maintain or even lengthen telomeres, reducing the risk of age-related diseases[1,2].

The leucocyte telomere length has been widely validated as a robust biomarker of biological aging[3]. A recent study has highlighted that the telomere length of blood cells is a biomarker of human aging and disease, confirming a strong link between the telomere length of whole blood and the telomere length of different organs[4].

Various studies have been focused on the importance and impact that telomeres have, especially on public health within the clinical practice. Tsatsakis[5] analyzed the importance of telomere shortening in each disease, highlighting how telomere homeostasis promotes healthy aging.

When it comes to cancer, genome instability is a key factor that induces both the onset and progression of the disease[6]. The molecular mechanism underlying genome instability is impaired telomere function[7]. In particular, shorter telomeres in tumor tissues have been associated with advanced disease states, faster progression, and poorer survival. Short telomere length values are associated with an increased risk of premature death after cancer but not with cancer risk[8].

Telomere length has been suggested as a potential prognostic marker for breast, colon, and prostate cancer[9]. In colorectal cancer, shorter telomeres serve as an independent prognostic indicator, correlating with increased risk of disease onset and progression[10], as well as a 2.43-fold higher mortality risk[11]. In prostate cancer, telomere length can provide insights on disease progression and surgery, even after surgery, regardless of their pathological signs[12]. Overall, telomere length values can hold a potential prognostic value across multiple cancers, guiding therapeutic decisions[13].

Telomeres can also play a crucial role in leukemias, particularly in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). In AML, high-risk patients with FLT3-ITD mutations and short telomeres have significantly lower life expectancy than those with longer telomeres[14]. In childhood and adolescence ALL, short telomeres combined with increased telomerase activity are associated with a higher risk of disease progression and relapse[15]. Lymphoblasts in ALL patients exhibit telomere shortening compared to B and T lymphocytes, with median telomere lengths of 4.3 kb in children and 2.3 kb in adults, compared to 8.0 kb and 6.3 kb in B-lymphocytes,

respectively[15]. Furthermore, studies indicate that telomere length is shorter at leukemia diagnosis than at remission[16]. Vakonaki et al.[17] confirmed that telomere length in lymphocytes at remission is twice that in lymphoblasts at diagnosis, highlighting accelerated telomere shortening as a characteristic of high-risk ALL. Thus, lymphoblast telomere length can serve as a potential prognostic marker for ALL progression and treatment response.

Prospective cohort studies have demonstrated that individuals with low leukocyte telomere length have an increased risk of cardiovascular diseases, including myocardial infarction, heart failure, and stroke[18]. The WOSCOPS (West of Scotland Primary Prevention Study) trial reported that individuals with the lowest leukocyte telomere length were 44% more likely to experience coronary artery disease events within five years compared to those with the highest telomere length, even after adjusting for coronary artery disease risk factors[19]. Additionally, patients with heart disease exhibit accelerated telomere shortening relative to healthy individuals, as confirmed through quantitative fluorescence *in situ* hybridization (Q-FISH) analysis at both the cellular and chromosomal levels[20].

In metabolic disorders, leukocyte telomere length has been identified as a potential prognostic marker for type 2 diabetes. A meta-analysis revealed significant telomere shortening in young patients with type 2 diabetes, independent of age-related effects[21]. Another meta-analysis demonstrated that individuals with accelerated telomere shortening had higher hazard ratios for developing type 2 diabetes over a 15-year follow-up period[22]. Furthermore, a two-sample Mendelian randomization analysis showed that a 1-unit genetic decrease in telomere length was associated with a 1.38-fold increase in type 2 diabetes progression[23]. Additionally, patients with type 2 diabetes and short leukocyte telomere length, face a higher risk of cardiovascular complications[24]. These findings highlight the strong link between telomere length and cardiovascular disease markers, suggesting its potential as an early indicator of vascular aging and related complications in type 2 diabetes patients.

In recent years, impaired telomere length has been associated with various autoimmune disorders[25]. Mendelian randomization analysis has shown that longer telomeres reduce susceptibility to rheumatoid arthritis[26]. The potential of telomere length as a prognostic marker in rheumatoid arthritis has been suggested since individuals are more susceptible to developing rheumatoid arthritis by inheriting the rheumatoid arthritis disease risk haplotype *HLA-DR-B1*04*[27]. Additionally, *HLA-DR-B104* is linked to increased vulnerability to type 1 diabetes[25]. Similarly, a two-sample Mendelian randomization study using inverse-variance weighted regression demonstrated an inverse relationship between leukocyte telomere length and systemic sclerosis (SSc) risk[28]. These findings suggest that telomere length may play a crucial role in autoimmune disease susceptibility and progression.

In vitro fertilization (IVF) is a widely used fertility treatment for female-related factors (e.g. age, ovulation disorders, blocked fallopian tubes, endometriosis), male-related factors (e.g. low sperm quality or quantity), or unexplained infertility. Emerging research suggests a strong relationship between telomere length, telomerase activity, and IVF success, supporting their potential as predictive biomarkers for IVF outcomes. Since telomere length and telomerase analysis are relatively simple and cost-effective, they could be incorporated into IVF procedures to assess embryo quality and predict pregnancy success, offering a valuable tool for improving assisted reproductive technologies[29].

Telomere shortening is a natural part of aging and contributes to age-related fertility decline. Advanced maternal and paternal age, often linked to reproductive challenges, may be influenced by telomere dynamics in reproductive cells[29]. Telomere length plays a crucial role in fertility, affecting both oocyte and sperm quality. Shorter telomeres in egg cells indicate cellular aging and reduced fertility, while in sperm cells, shorter telomeres are associated with decreased sperm quality and potential impacts on offspring health[30]. Additionally, telomere length influences pregnancy outcomes by affecting fertilized egg development and embryo health, ultimately impacting implantation success and pregnancy viability[31].

Last but not least, the usefulness of leukocyte telomere length as a potential predictive marker and its potential to monitor disease progression has also been proven in the context of Huntington's and Alzheimer's disease[32].

Various techniques have been developed to measure TL, each with advantages and limitations. Quantitative polymerase chain reaction (qPCR) identifies the mean telomere length. The advantage of quantitative polymerase chain reaction (qPCR) relies on the measurement of the average telomere length in the blood cell population in absolute terms[33]. The qPCR can be used in high-throughput, large-scale studies with limited initial high-quality and integrity genetic material[34]. Furthermore, another shortcoming of qPCR is its inability to accurately identify the percentages of short and very short telomeres[33]. Metaphase quantitative fluoresce in situ hybridization (Q-FISH) method accurately identifies telomere length values in a single cell and at a chromosome-specific level at high resolution allowing for the detection of chromosome instability, including 'telomere-free' ends that lead to chromosome fusions[35]. In particular, the median value, the percentages of critical short and long telomeres, and the elongated telomeres can provide accurate and highly reliable information for estimating each patient's biological age and susceptibility to disease.

The telomere length measurement is not yet widely adopted in routine clinical practice, but it holds promise. Initially, one can regularly monitor and tailor lifestyle to the

individual's biological age by evaluating telomere length values. Second, one can detect telomere length values that offer valuable insights into the susceptibility to increased disease risk, since telomere length can be a prognostic tool for several diseases (cardiovascular disease, diabetes, solid cancer types, leukemias, neurodegenerative diseases, autoimmune diseases). In particular, the mean, the median, and the percentages of the critical short and long telomeres can provide the potential susceptibility to different diseases. Then, one can optimize preventive healthcare strategies, improving outcomes in cancer and enhancing longevity. As a result, telomere length measurement shows clinical utility in diagnosing and managing diseases.

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The views and opinions expressed in this article are those of the authors.