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Hyperglycemia attenuates the association between telomere length and age in Ukrainian population

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ABSTRACT

Diabetes-related conditions such as chronic hyperglycemia and related oxidative stress and inflammation were repeatedly associated with accelerated telomere shortening in epidemiological studies, although some findings are inconsistent. In present study, we aimed to assess the impact of disturbances in glucose metabolism on association between age and leukocyte telomere length (LTL) in the Ukrainian population. The study was conducted on the 119 adult subjects aged between 43 and 87 years residing in the Kyiv region, Ukraine. LTL was determined by a quantitative PCR-based method. LTL was negatively correlated with the measure of abdominal obesity such as waist-hip ratio, as well as with both fasting plasma glucose (FPG) and two-hour post-load glucose (2hPG) levels. Consistently with previous studies, a significant negative association between LTL and age was observed in individuals with normal (< 5.6 mmol/L) FPG levels. Unexpectedly, however, no association was found in subjects with impaired glucose metabolism assessed by abnormal FPG or/and 2hPG levels. No association between LTL and age was observed in a logistic regression model; the association between LTL and age became significant after adjusting for FPG level. In the FPG-adjusted model, 1.6-time lower odds to have long telomere length were indicated for each 10 years increase in age. We hypothesize that the attenuation of association between LTL and age in hyperglycemic persons can likely be attributed to the interaction of multidirectional processes determining this relationship.

1. Introduction

Life expectancy has been significantly extended worldwide during the last century. Such increase of life expectancy is, however, not accompanied by corresponding improvement in health span as most present-day societies undergo rapid population aging (Vaiserman and Lushchak, 2017). Since aging is the main risk factor for most chronic disorders, the incidence of age-related pathologies including type 2 diabetes (T2D) rises to a large extent with increasing longevity. In recent decades, T2D is emerged as an epidemic worldwide. About 9% of the global adult population (around 415 million people in total) presently has diabetes; this number is expected to increase dramatically and will reach 642 million people over the next decade (Chatterjee et al., 2017; Jaacks et al., 2016). T2D, accounting for > 90% of all diabetes cases, is commonly referred to as typical age-related disease. Its age-specific incidence and mortality rates rise exponentially with age, starting at age 40 and doubling with each successive 6–8-year period. As a result, about 20% of people over the age of 65 have T2D (Perry 3rd, 1999; Samos and Roos, 1998). The risk factors involved in the etiology of this disorder include genetic predisposition, unhealthy dietary habits, inadequate physical activity and stresses. Pathophysiological mechanisms of T2D include impaired β-cell function, peripheral insulin resistance and disturbed glucose metabolism (Skyler et al., 2017). Hyperglycemia is a common feature of T2D. One of the most

Abbreviations: 2hPG, two-hour post-load glucose; ADA, American Diabetes Association; AFG, abnormal fasting glucose; BMI, body mass index; DiastBP, diastolic blood pressure; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HC, hip circumference; LTL, leukocyte telomere length; NFG, normal fasting glucose; NGT, normal glucose tolerance; RTL, relative telomere length; SystBP, Systolic blood pressure; T2D, type 2 diabetes; TERT, telomerase reverse transcriptase; WC, waist circumference; WHO, World Health Organization; WHR, waist-hip ratio

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important consequences of chronic hyperglycemia is oxidative stress leading, in turn, to chronic inflammation (Tangvarasittichai, 2015) and accelerated telomere shortening (Tamura et al., 2016a). Since all these processes are known to accompany aging, T2D is considered by several authors as a premature aging syndrome (Murillo-Ortiz et al., 2012).

Telomeres are DNA-protein complexes that cap and protect the ends of eukaryotic chromosomes (Blackburn et al., 2015). The length of telomeres is regulated by a specific RNA-dependent DNA polymerase complex, telomerase, which catalyzes the addition of telomeric repeats to the ends of chromosomes to preserve their integrity. In most somatic cells, telomeric regions shorten during successive cell divisions (a process referred to as "telomere attrition") due to insufficient telomerase activity. Therefore, cellular replication may go on until a critical threshold of telomere length is reached (Bonfigli et al., 2016). For this reason, the rate of telomere shortening is considered to be an indicator of replicative senescence, and telomere length, especially leukocyte telomere length (LTL), is widely used as a biomarker of organismal aging (Blackburn et al., 2015; Khan et al., 2017). Due to their chemical composition, telomeres are highly vulnerable to oxidative damage, and chronic oxidative stress, in particular that related to T2D and its complications, can accelerate telomeric shortening (Koliada et al., 2015). Based on the available data, it can be assumed that chronic hyperglycemia, oxidative stress, and telomere attrition in different tissues, including pancreatic beta cells and adipocytes, can be key components of a vicious cycle underlying the pathophysiology of T2D (Tamura et al., 2016a).

The association of T2D and related conditions with short telomere length has been observed in many epidemiological studies. For example, LTLs have been shown to be significantly lower in pre-diabetic subjects with impaired glucose tolerance (IGT), lower still in T2D individuals without atherosclerotic plaques and lowest in T2D patients with atherosclerotic plaques compared to control subjects (Adaikalakoteswari et al., 2007). Shortened telomeres were also found in β-cells from autopsy pancreas obtained from T2D patients compared to age-matched control individuals (Tamura et al., 2014). In this study, telomere lengths were negatively correlated with glycated hemoglobin levels and telomeres were substantially shorter in T2D patients who had been treated with hypoglycemic medications than in those who had been not, indicating that an association exists between T2D severity and telomere attrition rate. A relationship between T2D and telomere length was evident in recent meta-analyses on this topic (D'Mello et al., 2015; Wang et al., 2016; Willeit et al., 2014; Zhao et al., 2013). This relationship was, however, significantly influenced by age, sex, body mass index (BMI), region of residence and diabetes type (Wang et al., 2016). Moreover, reports on the association of telomere length with T2D and associated cardiometabolic risk factors are conflicting in the literature (Zhao et al., 2013). For example, leukocyte telomere length has not been associated with T2D status and duration, as well as with poor glucose control in diabetic patients in the US general population (Menke et al., 2015). In our previous study, LTL was inversely associated with two-hour post-load glucose (2hPG) levels but not with fasting plasma glucose (FPG) levels (Khalangot et al., 2017a, b). Due to such inconsistency in the results, further studies need to be conducted for better understanding of causal relationships and pathways involved in this association.

In present study, we aimed to assess the impact of disturbances in glucose metabolism on association between age and telomere length in Ukrainian population.

2. Methods

2.1. Participants

119 eligible participants were recruited for the study during the 2014 to 2016 timeframe. Among them, 37 persons were recruited from the clinic of Institute of Gerontology, Kyiv, Ukraine [for more sample details, see Shatylo et al., 2016]. 82 persons were recruited under the supervision of the Institute of Endocrinology and Metabolism from two local family medicine clinics of the Makariv rural district (Kyiv region) [for more sample details, see Khalangot et al. (2016, 2017a, b)]. The inclusion criteria were as follows: 1) middle-to-old age persons (minimal age: 43; maximum age: 87); 2) lack of previously diagnosed T2D. Thus, all participants involved in the study did not receive glucose-lowering drugs before the investigation started. This is an important point because treatment with such medications may likely influence LTLs, thereby biasing the results of the study [see, e.g., Ma et al., 2015]. The exclusion criteria were as follows: 1) residence in a region other than Kyiv; 2) inability to visit the clinic due to either chronic illness or disability; 3) refusal or inability to give informed consent.

2.2. Ethical aspects

The study protocol was approved by the Ethics Committees of the Institute of Endocrinology and Metabolism and Institute of Gerontology (both are part of the National Academy of Medical Sciences of Ukraine). All participants provided written informed consent. The Declaration of Helsinki (2000) and the applicable national standards as they relate to the involvement of human subjects in research were enforced.

2.3. Collection and storage of blood samples

For the FPG test, blood was collected from all volunteers after a 10 h fast. For the oral glucose tolerance test, blood was collected for 2 h after ingestion of glucose (75 g of glucose per 200 mL of water) in the morning after at least 10 h of fasting. Blood was collected in EDTA-coated tubes and centrifuged at 1000*g* for 10 min. For DNA extraction, blood was collected in EDTA-coated tubes and stored at −80 °C until DNA extraction procedure.

2.4. Measurement of baseline characteristics

BMI was determined as the body weight (in kg) divided by the height (in m) squared (kg/m^2). Waist circumference (WC) was measured at the point of noticeable waist narrowing using a flexible anthropometric tape, with the subject in a standing position. Hip circumference (HC) was measured at the maximum circumference over the buttocks. The waist-hip ratio (WHR) was calculated by the ratio between WC and HC. Systolic blood pressure (SystBP) and diastolic blood pressure (DiastBP) (mm/Hg) were measured twice with a standard sphygmomanometer in a sitting position after at least 5 min of rest. Plasma glucose levels were determined by a standard glucose oxidase method. Among all subjects studied, 32 were categorized as normal fasting glucose (NFG) persons (FPG < 5.6 mmol/L), and 87 were categorized as abnormal fasting glucose (AFG) individuals (FPG ≥ 5.6 mmol/L), among them, 68 had impaired fasting glucose (IFG) levels (5.6–6.9 mmol/L, prediabetic persons) and 19 had diabetic (DIAB) FPG levels (> 6.9 mmol/L). According to the 2hPG test, 90 subjects had normal 2hPG levels (< 7.8 mmol/L; normal glucose tolerance, NGT), while 29 were categorized as abnormal glucose tolerance (AGT) persons (≥7.8 mmol/L), among them, 22 had prediabetic (IGT; 7.8–11.0 mmol/L) and 7 had diabetic (> 11.0 mmol/L) 2hPG levels.

2.5. Telomere length assay

The relative telomere lengths (RTLs) were measured by monochrome multiplex polymerase chain reaction in real time (qPCR) following the method described by Cawthon (2009). DNA was extracted from the whole blood by the phenol-chloroform purification method (Greider and Blackburn, 1985). PCR reaction mix was prepared using a commercial reagent kit for RT-PCR (Syntol, Russia) with addition of betaine (Sigma, USA) at a final concentration of 1 M. For multiplex