Minireview

Telomere length in different metabolic categories: Clinical associations and modification potential

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Impact statement

Metabolic disorders are known to be associated with accelerated telomere attrition. Their pathophysiological heterogeneity suggests the importance of multiple tests in examining these associations. However, oral glucose tolerance test (OGTT) has rarely been performed in such studies to date. There are few studies aimed at determining leukocyte telomere length (LTL) in different categories of impaired glucose tolerance (IGT), and those that do exist do not take into account the impaired fasting glucose (IFG)/IGT categorization. Therefore, we believe our study, when the OGTT was used, is important to the field. This testing made it possible to determine whether LTLs are associated with glucose levels in different hyperglycemic categories. Our data indicate that relationships between LTLs and IFG/IGT levels are not the same. This distinction can potentially be used in categorization of metabolic disorders and in determining the effectiveness of interventions aimed at treating diabetes and other metabolic abnormalities.

Abstract

Cardio-metabolic disorders, including type 2 diabetes, are known to be associated with accelerated attrition of telomeres, recognized as genetic and biological markers of aging. Some common genetic characteristics were found regarding the presence of shorter telomeres and the development of type 2 diabetes. However, there are conflicting epidemiological reports regarding the association of leukocyte telomeres lengths with type 2 diabetes: not only the causality of such a link remains unclear, but not all researchers acknowledge its existence. The link between current trends in life expectancy of people with type 2 diabetes and the increase in the number of people with type 2 diabetes raises interest in the question of the possibility of drug or life-style-related modification of leukocyte telomeres length. To address the question how leukocyte telomeres lengths are associated with glucose levels in hyperglycemic categories, we examined the correlations between leukocyte telomeres length and fasting plasma glucose and 2 h post-load plasma glucose levels (2hPG). Our data indicate that leukocyte telomeres length is negatively related to 2hPG and the relationship with increasing of fasting plasma glucose may be non-linear. Remarkably, the negative association between leukocyte telomeres length and age was demonstrated in our research only for individuals with normal fasting plasma glucose levels, but not for those with high fasting plasma glucose levels. The nonlinear nature of interactions between age and 2hPG level has been demonstrated by artificial neural networks modeling when investigating the links between leukocyte telomeres length and metabolic syndrome. Thus, it can be assumed that relationships between leukocyte telomeres length and FPG/2hPG levels are not the same, and this distinction can potentially be used in categorization of metabolic disorders. It is possible that these data along with reports of the possibility of modifying leukocyte telomeres length can improve the understanding of present-day epidemiological trends in type 2 diabetes incidence and mortality.

Keywords: Leukocyte telomeres lengths, fasting plasma glucose, glucose tolerance, metabolic syndrome, age, diabetes mellitus

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Introduction

The age-related cardio-metabolic conditions are commonly believed to be associated with shortened life expectancy. For example, in the study by Franco *et al.*,[1] diabetic men and women 50 years and older were shown to live on average 7.5 and 8.2 years less, respectively, than their non-diabetic counterparts. Some subsequent analyses, however, failed to support this association. A normal life expectancy, for instance, was observed in a cohort of primary care type 2 diabetes (T2D) patients when compared to the general

population in the Netherlands.[2] This trend toward an improvement of survival is commonly thought to reflect the progress in efficient pharmacological interventions and more stringent regimes for the treatment of hyperglycemia, dyslipidemia, hypertension, and other cardiovascular disease (CVD) risk factors among T2D patients.[3,4] Although beneficial effects of glucose control on CVD risk have never been conclusively demonstrated,[3] it has been shown in a recent Swedish population-based study that optimal risk status in T2D patients is associated with a CVD risk similarly to that in general population.[4] In this regard, many authors suggest that T2D "epidemic" is rather a statistical artifact primarily related to the decrease in diabetes deaths in developed countries driven by improved medical treatment than a real epidemiological phenomenon.[5,6] Moreover, several studies have reported a stabilization or even fall in the T2D incidence.[6]

Age-related telomere attrition: A potential role in aging and metabolic disease

One more possible explanation of this ambiguity may be derived from the assumption that association between T2D and mortality is more complex than previously thought. In particular, this association may be affected by confounding factor such as telomere attrition, known to accompany both aging and metabolic disease states. Telomere is the DNA-protein complex that caps and protects the end of eukaryotic chromosome.[7] The telomeric repeats of DNA play a central role in chromosome stability, preventing end-to-end fusions and also precluding the recurrent DNA loss during replication.[8] The telomere lengths are regulated by a specific RNA-dependent DNA polymerase complex, called telomerase, that adds telomeric repeats to chromosome ends to preserve their integrity. In somatic cells, telomeric DNA regions shorten during each successive cell division (a process commonly referred to as "telomere shortening") owing to inadequate telomerase activity. Therefore, cellular replication can be carried out until a critical threshold of telomere shortening is reached.[9] For this reason, the rate of telomere shortening (attrition) is generally regarded as an indicator of replicative senescence, and telomere length, in particular, leukocyte telomere length (LTL), is commonly used as a biomarker of aging.[7,10]

Due to their chemical composition, telomeres are highly vulnerable to oxidative damage, and chronic oxidative stress, in particular that is related to T2D and its complications, and can accelerate telomeric shortening.[11] Oxidative stress and related chronic low-grade inflammatory state (inflamm-aging) are well known to develop with advanced age.[12] These conditions are, in turn, associated with faster aging[13] and with accelerated age-related attrition of telomere ends of chromosomes.[14] In addition, senescent cells which produce pro-inflammatory markers such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-a) were found to be characterized by critically short telomeres.[15] Therefore, leukocyte telomere length (LTL) is increasingly used as a biomarker of aging and age-related diseases.[16] However, despite well-established causal link between inflammatory profiles and LTL, there is still little clinical evidence to support interaction and covariation among them.[15] Several studies also obtained consistent evidence that short LTL is associated with increased risk of aging-related disorders such as T2D[17] and associated CVD.[18]

Meanwhile some biologists suggest viewing telomere length not only as a biomarker for cumulative damage but also as a determinant of organismal condition, integrating the impacts of both past and current lifetime experiences. In accordance with their "metabolic telomere attrition hypothesis"[19] during energy shortages, cells may induce salvage pathways to gain ready-to-use nucleotides through telomere shortening, as a beneficial short-term strategy to avoid the costs of the replicative stress response.

Epidemiological data: Contradictions and some explanations

Since the risk of developing the most significant category of chronic hyperglycemia such as T2D is well known to increase with age,[20] it seems logical to predict that LTLs and glucose levels in blood must be negatively associated. However, epidemiological findings on the association between LTL and chronic hyperglycemia are rather controversial.[21,22] So, in meta-analysis of prospective, case-control, and cross-sectional studies (9 population cohorts; 5759 cases and 6518 controls) by Zhao *et al.*,[21] evidence was provided that shortened LTLs are associated with T2D risk, but this association was revealed to be moderate only (OR: 1.117; 95% CI: 1.0–1.2; $P = 0.045$) and reached statistical significance after excluding three out of nine studies that were determined as the key contributors to heterogeneity. Menke *et al.*,[22] when studying U.S. general population, did not find any association between LTL and either T2D status, control or duration after the age, sex, and race-ethnicity adjustment, so the authors concluded that telomere attrition is not a consequence or a cause of T2D.[22] Thus, even despite the fact that there is a lot of evidence confirming that accelerated telomere attrition mediates many age-related pathological conditions such as metabolic abnormalities, including impaired glucose tolerance (IGT), insulin resistance, obesity, and T2D,[23–25] and also related chronic inflammation,[26,27] the question of causality for an association between telomere shortening and T2D development remains unanswered.

Given this uncertainty, it seems important that in most studies devoted to examining association between LTL and risk for T2D, no oral glucose-tolerance testing (OGTT) was performed. Thus, the association between LTL and IGT was not studied. This may be important in the context of the topic discussed, because over the past decade a growing body of evidence has been accumulated for the pathophysiological heterogeneity of pre-diabetic categories of hyperglycemia. According to current classification, these categories include isolated impaired fasting glycaemia (i-IFG), isolated impaired glucose tolerance (i-IGT), and a combined category (IFG and IGT). The etiology and some mechanisms underlying these glycemic categories are obviously different: IFG being predominantly related to genetic factors, while IGT is predominantly related to physical

inactivity, unhealthy diet, and short stature.[28] Our study of anthropometric risk factors in elderly residents of rural Ukraine revealed that men and women of i-IGT category had the lowest height and body mass index, whereas neck, waist, and hip circumferences did not differ from persons of normal fasting and glucose tolerance glycemic category and were lower compared to corresponding indicators in i-IFG and combined groups.[29]

The level of some adipokines was significantly different in patients belonging to the category of IGT, compared with i-IFG. Higher chemerin and progranulin serum concentrations in the IGT compared to the IFG group suggest a specific role of adipose tissue in the pathogenesis of IGT, but not IFG.[30] In addition, increased arterial stiffness was found in patients with IGT and newly diagnosed T2D but not with isolated impaired fasting glucose in the Li *et al.* study.[31] Such differences in pathogenetic pathways can probably be explained by higher levels of oxidative stress and inflammation in T2D or i-IGT patients compared to i-IFG individuals. This difference may likely influence both the degree of metabolic impairment and LTL.

It should be noted that there are still very few studies that specifically compare LTL in different categories of impaired glycemia, and those that do exist do not take into account IFG/IGT categorization. For example, the Indian study by Adaikalakoteswari *et al*. revealed that telomere shortening was seen "even at the stage of IGT", without announcing any comparison with IFG. OGTT data were applied to categorize patients as those with normal glucose tolerance (2 h post-glucose load glycemia (2hPG) level <7.8 mmol/l) and those with IGT (2hPG >7.8 mmol/l and <11.1 mmol/l),[32] while the fasting plasma glucose (FPG) data recommended by World Health Organization (1999) for categorization of prediabetes (≥ 6.1 mmol\l and <7.0 mmol/l)[33] were not considered. Thus, it can be assumed that Adaikalakoteswari *et al*. compared the combined category (both subjects with normal fasting glucose levels and IFG individuals) with the subjects from IGT category.

The hyperglycemic categories are being currently considered as pathophysiologically different conditions of insulin resistance (mainly liver resistance in i-IFG and mainly muscle and adipose tissue resistance in i-IGT) that require different approaches to T2D prevention and treatment.[28,34] So involvement of telomeric biology in these pathogenetic pathways may be different as well. Many clinicians acknowledge that T2D is multifactorial and heterogeneous disease in terms of clinical presentation and outcomes, but neither prevention nor treatment is systematically stratified. This requires a more in-depth study of molecular pathophysiological pathways involved in the onset and progression of metabolic dysfunctions.

LTL in different hyperglycemic conditions

To address the question whether LTL is similarly associated with glucose levels in different hyperglycemic categories, we examined the correlations between LTLs and fasting and post-load glucose levels, and also several other metabolic characteristics in persons who did not receive glucose-lowering treatment in Ukraine.[35–37] In our research conducted in randomly selected rural residents of Kyiv region, an increase in telomere length (according to LTL quartiles) was found to be associated with better glucose tolerance according to OGTT 2hPG data ($P = 0.03$) and only with a tendency to decrease fasting plasma glucose (FPG) levels.[35] In different glycemic categories (normal, prediabetes, and T2D), LTL was inversely associated with glucose tolerance (according to 2hPG) in all categories, but with FPG in the T2D category only.[35]

Thus, our data indicate that LTL is negatively related to glucose tolerance and the relationship with increasing of fasting glycaemia may be non-linear. The pattern of association remained the same after adjusting for gender, age, and some anthropometric indices in studied population.[35] Remarkably, the negative association between LTL and age which has been repeatedly reported in many previous studies, was clearly demonstrated in our research only for individuals with normal FPG levels, but not for those with high FPG levels.[36] Thus, both the phenomena of a closer association between LTL and IGT levels (as expressed in increasing 2hPG) compared to that between LTL and FPG levels, and also absence of association between LTL and age in hyperglycemic patients observed in our study[36] need to be explained. It can be assumed that both of these phenomena can be partly explained in terms of the threshold level in the negative association between FPG and telomere shortening. Indeed, in our research, a linear negative association was detected between LTLs and 2hPG levels regardless of the presence of normal glucose tolerance or IGT, whereas a similar relationship occurred only by elevated but not by normal FPG levels.[36] It seems also significant that the threshold we have found coincides with the upper limit of normal fasting glycemia, thereby confirming the physiological nature of this limit. For glucose tolerance, according to the standard test, the association with LTL was independent of adherence to the criterion of normal or impaired glucose tolerance adopted today. So, the lack of association between LTL and FPG levels in normoglycemic category can partly contribute to both a stronger relationship between LTL and age, as well as to a weaker relationship between LTL and FPG levels as compared to 2hPG levels. Thus, it can be assumed that relationships between LTLs and FPG and 2hPG levels are not the same, and this distinction can potentially be used in categorization of metabolic disorders.

LTL in patients with and without metabolic syndrome

Metabolic syndrome (MetS) is commonly defined as a cluster condition of cardiovascular risk factors. These factors include impaired FPG, hypertension, abdominal obesity, as well as high triglyceride and/or low high-density lipoprotein (HDL) levels.[38] This condition has been also shown to be associated with accelerated telomere attrition with age.[39] In our research,[37] we studied LTLs in the sample from adult population of Kyiv region, Ukraine depending on presence or absence of MetS and examined the impact of age and glucose tolerance on this association. MetS was

identified in majority (69%) of study participants according to the IDF criteria. MetS has been found to be associated with 3-fold higher risk of having shorter telomeres, and this risk remained significant after adjusting for gender, age, and 2hPG levels. FPG levels and other components of MetS did not affect the power of this relationship; so, no evidence was obtained for an independent impact of these factors. 2hPG levels, on the contrary, demonstrated a significant relationship with LTL (OR = 1.3 CI 1.0–1.6 per 1 mmol/l; $P = 0.04$) regardless of the presence or absence of MetS. The interactions between age, gender, and 2hPG levels were mostly non-linear, as shown by neural network modeling.[37] To our knowledge, such non-linearity of associations of LTL with age, glucose tolerance, and MetS has never been reported previously. Perhaps an increase in telomerase activity in individuals with the MetS subtype, which is characterized by a strong dyslipidemic profile along with the lack of hyperglycemia[40] could be the possible explanation for this phenomenon.

Telomere length modification: Lifestyle and medication factors

Although telomeres are known to be genetically determined (heritability estimates ranging from 44% to 80%),[41] a significant association with LTL was also repeatedly showed for life-style factors such as aerobic training[42] and diet.[43,44] For instance, adherence to high quality diet is associated to longer salivary telomeres in Spanish elderly population of the SUN study.[43] A higher daily intake of deep fried potato products was found to be associated with shorter LTLs.[44] Aerobic and interval training, on the contrary, resulted in an increase of both LTLs and telomerase activity.[42] In our recent study of the effectiveness of T2D prevention[45] performed on the same cohort of rural Ukraine residents as our telomere research, we were unable to confirm the relationship between the physical activity level and the risk of developing T2D. This result is perhaps due to the lack of differentiation between aerobic and resistive loads in our study. In a recent Spanish study, significant improvement of anthropometric parameters and glucose metabolism indices was observed after a lifestyle intervention in children with abdominal obesity. Telomere length did not change but was a predictor for changes in blood glucose levels after this lifestyle intervention.[46] When discussing these results, it is necessary to note that it has not been indicated what kind of exercise was used in the study. In addition, in the Norwegian study, longer telomeres were obtained in older endurance trained athletes compared to those in older people with a medium activity level, while telomere length of young endurance trained athletes was not different than young non-athletes.[47] That is, the impact of physical activity on telomere length can only become noticeable in older adults.

In the context of understanding the relationship between telomeres and blood glucose, research of the dynamics of LTL under the influence of medicines seems appropriate. In China, antidiabetic pharmacological treatments without acarbose led to significant LTL lengthening, while treatment with acarbose resulted in shortened LTLs in T2D patients, independently of the level of glycemic control.[48] As an α-glucosidase inhibitor, acarbose is effective in lowering blood glucose level by reducing the digestion of complex carbohydrates. Gut microbiota composition was found to change significantly by acarbose.[49] This seems important in the context of the topic under discussion, as gut microbiota was demonstrated to influence senescence in various organs, thereby influencing the telomere erosion.[50] Thus, the telomere shortening following the treatment with acarbose may likely be a consequence of microbiota modification.

Conclusions

Overall, associations found in our research can be discussed in the context of current debates about pathophysiological backgrounds of different hyperglycemia categories determined by either FPG or 2hPG levels.[51–54] Fasting hyperglycemia is well known to be caused by increased glucose production in the liver, while IGT (2hPG hyperglycemia) is primarily related to insulin resistance in skeletal muscle.[51] Furthermore, postprandial plasma glucose (PPG) levels were shown to be more predictive of long-term glycemic control (reflected in glycated hemoglobin, HbA_{1c}) in non-diabetic persons, suggesting that PPG response could be more indicative than FPG level for long-term glycemic maintenance.[52] Our research also points to the difference in the power of association of LTLs with FPG and 2hPG levels.[35,36] In particular, no association has been revealed between LTL and normal FPG levels.[36] Thereby, FPG and 2hPG levels can likely differently impact the associations between different aspects of MetS and LTLs. In the longitudinal CARDIA Study,[55] low levels of HDL cholesterol were associated with short LTLs and increase in waist circumference during the 10-year period was associated with significant telomere attrition. In addition, enhanced FPG levels and MetS predicted significant 10-year decrease in leukocyte mitochondrial DNA copy numbers (alternative marker of cellular aging) but not in LTLs. In the CARDIA Study, however, an increase in waist circumference was not included as a mandatory criterion in MetS definition,[55] that does not coincide with conventional IDF-based MetS definition.[38] So, it can be assumed that difference in indices selected to define MetS can influence the association of this metabolic category with different markers of cellular aging.

Current definition of MetS proposed by International Diabetes Federation (IDF) does not include 2hPG as a mandatory criterion in clinical practice. IDF consensus, however, included OGTT (2hPG data) in the list of the additional metabolic criteria in the scientific investigation of MetS.[38] In our study, we tested the hypothesis that IGT may affect the relationship between MetS and LTLs. It has been shown that 2hPG levels, but not FPG levels affect the relationship between MetS and LTLs, which can be indicative of pathophysiological differences in these categories of hyperglycemia. Based on the results obtained, we suggest that testing the 2hPG (but not the FPG only) may provide an opportunity for a more accurate MetS diagnostics and estimating the biological age rate in subjects with MetS. More in-depth

studies, however, are needed to verify this assumption. Indeed, the sample size was too small to draw any definite conclusion from the findings obtained. This is the most obvious limitation of our study. From this, our findings should be considered as preliminary and suggestive only, and need to be confirmed using larger samples in further research. Another potential limitation of our study is that we used cross-sectional design that precludes causal inferences. Therefore, longitudinal follow-up studies are needed to be further performed in order to verify our findings. In addition, the association of 2hPG with LTLs should be further investigated in context of insulin resistance, and also aging of key metabolic organs, including the pancreatic islets, liver, adipose tissue, and skeletal muscle. The causal mechanisms for the discovered association between LTLs and increased fasting glycemia and glucose tolerance, which may manifest regardless of the normality or non-normality of the latter, are unclear. This association may be driven, at least in part, by genetic factors. Indeed, in several studies it has been shown that genes involved in the regulation of telomeres could be also implicated in the T2D development.[56,57]

Several assumptions can be proposed to explain the association between LTL and impaired glucose metabolism and T2D development. It has been shown in an animal model, that telomere attrition in adipose tissue may induce insulin resistance.[24] These data are indicative of a causal role of telomere shortening in T2D etiology. From this, it has been 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.[24] Evidence from some studies indicates that particular gene loci may exert pleiotropic effects on both telomere length and risk for impaired glucose homeostasis and T2D.[58,59] In particular, the genetic heterogeneity within the mitochondrial uncoupling proteins pathway was suggested to affect the oxidative stress level, thereby influencing the fine balance of telomere length regulation, control of cell cycle, and the risk for metabolic disease progression.[60] However, despite the importance of genetic contributions, both telomere length and the risk for T2D may be modified by life-style interventions,[61] including modulations in diet[62,63] and in physical activity.[42,64] These relationships may also be affected by antidiabetic drug administration.[48]

Collectively, these considerations may explain the controversies in epidemiological associations reported between LTL and T2D status, control and duration,[21,22] and also current trend of increased life expectancy observed in T2D patients.[2,6] The "metabolic telomere attrition hypothesis", where telomere reduction in the face of a significant energy deficit contributes to survival, may be one of the explanations for the long-term effects of mass starvation recorded in Ukraine through the analysis of diabetic databases[65]: a dose–response positive relation between famine severity during prenatal development and odds of T2D in later life. Another one of our studies shows that individuals who starved during famines of 1932 to 1933 and/or 1946 in Ukraine had a decreased screening-detected diabetes mellitus prevalence several decades after the famine episodes.[66] Similar to the explanation of the dynamics of T2D incidence among Nauruan residents (rising and falling over the last 40 years) provided by Jared Diamond,[67] these data can be viewed as the result of natural selection in accordance with James Neel's thrifty gene' hypothesis.[68]

One limitation of this review is that only relationship between LTL and type 2 diabetes and related conditions (impaired glucose regulation or metabolic syndrome) has been discussed. A comparative investigation of such relationships in patients with type 1 diabetes (T1D) and T2D can be very promising, in particular given significant differences in mortality rates between T1D and T2D patients, which persist despite an overall decreasing trend of mortality in patients with diabetes.[69,70] We are planning to conduct such comparative studies in the future.

In conclusion, study of LTLs in relation with T2D can provide an important key to understanding present-day epidemiological trends in T2D incidence and mortality, and also give hope for developing LTL as a novel powerful marker of effectiveness for interventions aimed at prevention and treatment of this disease.

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