

# 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.*,<sup>1</sup> 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.<sup>2</sup> 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.<sup>3,4</sup> Although beneficial effects of glucose control on CVD risk have never been conclusively demonstrated,<sup>3</sup> 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.<sup>4</sup> 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.<sup>5,6</sup> Moreover, several studies have reported a stabilization or even fall in the T2D incidence.<sup>6</sup>

### 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.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9</sup> 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.<sup>7,10</sup>

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.<sup>11</sup> Oxidative stress and related chronic low-grade inflammatory state (inflamm-aging) are well known to develop with advanced age.<sup>12</sup> These conditions are, in turn, associated with faster aging<sup>13</sup> and with accelerated age-related attrition of telomere ends of chromosomes.<sup>14</sup> In addition, senescent cells which produce pro-inflammatory markers such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF- $\alpha$ ) were found to be characterized by critically short telomeres.<sup>15</sup> Therefore, leukocyte telomere length (LTL) is increasingly used as a biomarker of aging and age-related diseases.<sup>16</sup> However, despite well-established causal link between

inflammatory profiles and LTL, there is still little clinical evidence to support interaction and covariation among them.<sup>15</sup> Several studies also obtained consistent evidence that short LTL is associated with increased risk of aging-related disorders such as T2D<sup>17</sup> and associated CVD.<sup>18</sup>

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”<sup>19</sup> 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,<sup>20</sup> 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.<sup>21,22</sup> So, in meta-analysis of prospective, case-control, and cross-sectional studies (9 population cohorts; 5759 cases and 6518 controls) by Zhao *et al.*,<sup>21</sup> 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.*,<sup>22</sup> 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.<sup>22</sup> 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,<sup>23–25</sup> and also related chronic inflammation,<sup>26,27</sup> 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 glycaemic categories are obviously different: IFG being predominantly related to genetic factors, while IGT is predominantly related to physical

inactivity, unhealthy diet, and short stature.<sup>28</sup> 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.<sup>29</sup>

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.<sup>30</sup> 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.<sup>31</sup> 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),<sup>32</sup> while the fasting plasma glucose (FPG) data recommended by World Health Organization (1999) for categorization of prediabetes ( $\geq 6.1$  mmol/l and <7.0 mmol/l)<sup>33</sup> 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.<sup>28,34</sup> 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.<sup>35–37</sup> 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.<sup>35</sup> 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.<sup>35</sup>

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.<sup>35</sup> 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.<sup>36</sup> 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<sup>36</sup> 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.<sup>36</sup> 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.<sup>38</sup> This condition has been also shown to be associated with accelerated telomere attrition with age.<sup>39</sup> In our research,<sup>37</sup> 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.<sup>37</sup> 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<sup>40</sup> 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%),<sup>41</sup> a significant association with LTL was also repeatedly showed for life-style factors such as aerobic training<sup>42</sup> and diet.<sup>43,44</sup> For instance, adherence to high quality diet is associated to longer salivary telomeres in Spanish elderly population of the SUN study.<sup>43</sup> A higher daily intake of deep fried potato products was found to be associated with shorter LTLs.<sup>44</sup> Aerobic and interval training, on the contrary, resulted in an increase of both LTLs and telomerase activity.<sup>42</sup> In our recent study of the effectiveness of T2D prevention<sup>45</sup> 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.<sup>46</sup> 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.<sup>47</sup> 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.<sup>48</sup> As an  $\alpha$ -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.<sup>49</sup> 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.<sup>50</sup> 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.<sup>51–54</sup> 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.<sup>51</sup> Furthermore, postprandial plasma glucose (PPG) levels were shown to be more predictive of long-term glycemic control (reflected in glycated hemoglobin, HbA<sub>1c</sub>) in non-diabetic persons, suggesting that PPG response could be more indicative than FPG level for long-term glycemic maintenance.<sup>52</sup> Our research also points to the difference in the power of association of LTLs with FPG and 2hPG levels.<sup>35,36</sup> In particular, no association has been revealed between LTL and normal FPG levels.<sup>36</sup> Thereby, FPG and 2hPG levels can likely differently impact the associations between different aspects of MetS and LTLs. In the longitudinal CARDIA Study,<sup>55</sup> 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,<sup>55</sup> that does not coincide with conventional IDF-based MetS definition.<sup>38</sup> 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.<sup>38</sup> 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.<sup>56,57</sup>

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.<sup>24</sup> 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.<sup>24</sup> 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.<sup>58,59</sup> 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.<sup>60</sup> However, despite the importance of genetic contributions, both telomere length and the risk for T2D may be modified by life-style interventions,<sup>61</sup> including modulations in diet<sup>62,63</sup> and in physical activity.<sup>42,64</sup> These relationships may also be affected by antidiabetic drug administration.<sup>48</sup>

Collectively, these considerations may explain the controversies in epidemiological associations reported between LTL and T2D status, control and duration,<sup>21,22</sup> and also current trend of increased life expectancy observed in T2D patients.<sup>2,6</sup> 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<sup>65</sup>: 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.<sup>66</sup> 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,<sup>67</sup> these data can be viewed as the result of natural selection in accordance with James Neel’s ‘thrifty gene’ hypothesis.<sup>68</sup>

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.<sup>69,70</sup> 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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#### REFERENCES

1. Franco OH, Steyerberg EW, Hu FB, Mackenbach J, Nusselder W. Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. *Arch Intern Med* 2007;**167**:1145–51
2. Lutgers HL, Gerrits EG, Sluiter WJ, Ubink-Veltmaat LJ, Landman GW, Links TP, Gans RO, Smit AJ, Bilo HJ. Life expectancy in a large cohort of type 2 diabetes patients treated in primary care (ZODIAC-10). *PLoS One* 2009;**4**:e6817
3. Lorber D. Importance of cardiovascular disease risk management in patients with type 2 diabetes mellitus. *Diabetes Metab Syndr Obes* 2014;**7**:169–83
4. Nørgaard CH, Mosslemi M, Lee CJ, Torp-Pedersen C, Wong ND. The importance and role of multiple risk factor control in type 2 diabetes. *Curr Cardiol Rep* 2019;**21**: 35
5. Green A, Støvring H, Andersen M, Beck-Nielsen H. The epidemic of type 2 diabetes is a statistical artefact. *Diabetologia* 2005;**48**:1456–8

6. Magliano DJ, Islam RM, Barr ELM, Gregg EW, Pavkov ME, Harding JL, Tabesh M, Koye DN, Shaw JE. Trends in incidence of total or type 2 diabetes: systematic review. *BMJ* 2019;**366**:15003
7. Blackburn EH, Epel ES, Lin J. Human telomere biology: a contributory and interactive factor in aging disease risks and protection. *Science* 2015;**350**:1193–8
8. Aksenova AY, Mirkin SM. At the beginning of the end and in the Middle of the beginning: structure and maintenance of telomeric DNA repeats and interstitial telomeric sequences. *Genes* 2019;**10**:pii: E118
9. Bonfigli AR, Spazzafumo L, Prattichizzo F, Bonafè M, Mensà E, Micolucci L, Giuliani A, Fabbietti P, Testa R, Boemi M, Lattanzio F. Leukocyte telomere length and mortality risk in patients with type 2 diabetes. *Oncotarget* 2016;**7**:50835
10. Khan SS, Singer BD, Vaughan DE. Molecular and physiological manifestations and measurement of aging in humans. *Aging Cell* 2017;**16**:624–33
11. Koliada AK, Krasnenkov DS, Vaiserman AM. Telomeric aging: mitotic clock or stress indicator? *Front Genet* 2015;**6**:82
12. Chung HY, Kim DH, Lee EK, Chung KW, Chung S, Lee B, Seo AY, Chung JH, Jung YS, Im E, Lee J, Kim ND, Choi YJ, Im DS, Yu BP. Redefining chronic inflammation in aging and age-related diseases: proposal of the senoinflammation concept. *Aging Dis* 2019;**10**: 367–82
13. Fougère B, Boulanger E, Nourhashémi F, Guyonnet S, Cesari M. Chronic inflammation: accelerator of biological aging. *J Gerontol A Biol Sci Med Sci* 2017;**72**:1218–25
14. Chiriaco M, Georgiopoulos G, Duranti E, Antonioli L, Puxeddu I, Nannipieri M, Rosada J, Blandizzi C, Taddei S, Virdis A, Masi S. Inflammation and vascular ageing: from telomeres to novel emerging mechanisms. *High Blood Press Cardiovasc Prev* 2019;**26**:321–9
15. O'Donovan A, Pantell MS, Puterman E, Dhabhar FS, Blackburn EH, Yaffe K, Cawthon RM, Opreko PL, Hsueh WC, Satterfield S, Newman AB, Ayonayon HN, Rubin SM, Harris TB, Epel ES; Health Aging and Body Composition Study. Cumulative inflammatory load is associated with short leukocyte telomere length in the health, aging and body composition study. *PLoS One* 2011;**6**:e19687
16. Sanders JL, Newman AB. Telomere length in epidemiology: a biomarker of aging, age-related disease, both, or neither? *Epidemiol Rev* 2013;**35**:112–31
17. Wang J, Dong X, Cao L, Sun Y, Qiu Y, Zhang Y, Cao R, Covasa M, Zhong L. Association between telomere length and diabetes mellitus: a meta-analysis. *J Int Med Res* 2016;**44**:1156–73
18. Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P. Leukocyte telomere length and risk of cardiovascular disease: systematic review and Meta-analysis. *BMJ* 2014;**349**:g4227
19. Casagrande S, Hau M. Telomere attrition: metabolic regulation and signalling function? *Biol Lett* 2019;**15**:20180885
20. Alva ML, Hoerger TJ, Zhang P, Gregg EW. Identifying risk for type 2 diabetes in different age cohorts: does one size fit all? *BMJ Open Diabetes Res Care* 2017;**5**: e000447
21. Zhao J, Miao K, Wang H, Ding H, Wang D. Association between telomere length and type 2 diabetes mellitus: a meta-analysis. *PLoS One* 2013;**8**:e79993
22. Menke A, Casagrande S, Cowie CC. Leukocyte telomere length and diabetes status, duration, and control: the 1999–2002 national health and nutrition examination survey. *BMC Endocr Disord* 2015;**15**:52
23. D'Mello MJ, Ross SA, Briel M, Anand SS, Gerstein H, Paré G. Association between shortened leukocyte telomere length and cardio-metabolic outcomes: systematic review and meta-analysis. *Circ Cardiovasc Genet* 2015;**8**: 82–90
24. Tamura Y, Takubo K, Aida J, Araki A, Ito H. Telomere attrition and diabetes mellitus. *Geriatr Gerontol Int* 2016;**16**(Suppl 1):66–74
25. Kirchner H, Shaheen F, Kalscheuer H, Schmid SM, Oster H, Lehnert H. The telomeric complex and metabolic disease. *Genes* 2017;**8**:pii:E176
26. Kordinas V, Ioannidis A, Chatzipanagiotou S. The telomere/telomerase system in chronic inflammatory diseases. Cause or effect? *Genes* 2016;**7**: pii:E60
27. Zhang J, Rane G, Dai X, Shanmugam MK, Arfuso F, Samy RP, Lai MK, Kappei D, Kumar AP, Sethi G. Ageing and the telomere connection: an intimate relationship with inflammation. *Ageing Res Rev* 2016;**25**:55–69
28. Faerch K, Borch-Johnsen K, Holst JJ, Vaag A. Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and treatment of type 2 diabetes? *Diabetologia* 2009;**52**: 1714–23
29. Khalangot ND, Kravchenko VI, Okhrimenko NV, Pysarenko YM, Koliada OS, Kovtun VA, Gurianov VG, Tronko MD. Anthropometric differences of persons with various types of screen-detected hyperglycemia in rural Ukraine. *Zurnal NAMN Ukrainy* 2015;**21**:342–50
30. Tönjes A, Fasshauer M, Kratzsch J, Stumvoll M, Blüher M. Adipokine pattern in subjects with impaired fasting glucose and impaired glucose tolerance in comparison to normal glucose tolerance and diabetes. *PLoS One* 2010;**5**: e13911
31. Li CH, Wu JS, Yang YC, Shih CC, Lu FH, Chang CJ. Increased arterial stiffness in subjects with impaired glucose tolerance and newly diagnosed diabetes but not isolated impaired fasting glucose. *J Clin Endocrinol Metab* 2012;**97**:E658–62
32. Adaikalakoteswari A, Balasubramanyam M, Ravikumar R, Deepa R, Mohan V. Association of telomere shortening with impaired glucose tolerance and diabetic macroangiopathy. *Atherosclerosis* 2007;**195**:83–9
33. World Health Organization. *Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1. Diagnosis and classification of diabetes mellitus (No. WHO/NCD/NCS/99.2)*. Geneva: World health organization, 1999
34. Faerch K, Hulman A, Solomon T. Heterogeneity of pre-diabetes and type 2 diabetes. *Curr Diabetes Rev* 2015;**12**:30–41
35. Khalangot M, Krasniakov D, Vaiserman A, Avilov I, Kovtun V, Okhrimenko N, Koliada A, Kravchenko V. Leukocyte telomere length is inversely associated with post-load but not with fasting plasma glucose levels. *Exp Biol Med* 2017;**242**:700–8
36. Krasniakov DS, Khalangot MD, Kravchenko VI, Kovtun VA, Guryanov VG, Chizhova VP, Korkushko OV, Shatilo VB, Kukharsky VM, Vaiserman AM. Hyperglycemia attenuates the association between telomere length and age in Ukrainian population. *Exp Gerontol* 2018;**110**:247–52
37. Khalangot MD, Krasniakov DS, Chizhova VP, Korkushko OV, Shatilo VB, Kukharsky VM, Kravchenko VI, Kovtun VA, Guryanov VG, Vaiserman AM. Additional impact of glucose tolerance on telomere length in persons with and without metabolic syndrome in the elderly Ukraine population. *Front Endocrinol* 2019;**10**:128
38. Alberti KG, Zimmet MMP, Shaw J. Metabolic syndrome – a new worldwide definition. A consensus statement from the international diabetes federation. *Diabet Med* 2006;**23**:469–80
39. Kirchner H, Shaheen F, Kalscheuer H, Schmid S, Oster H, Lehnert H. The telomeric complex and metabolic disease. *Genes* 2017;**8**:176
40. Rentoukas E, Tsarouhas K, Kaplanis I, Korou E, Nikolaou M, Marathonitis G, Kokkinou S, Haliassos A, Mamalaki A, Kouretas D, Tsitsimpikou C. Connection between telomerase activity in PBMC and markers of inflammation and endothelial dysfunction in patients with metabolic syndrome. *PLoS One* 2012;**7**:e35739
41. Starkweather AR, Alhaeeri AA, Montpetit A, Brumelle J, Filler K, Montpetit M, Mohanraj L, Lyon DE, Jackson-Cook CK. An integrative review of factors associated with telomere length and implications for biobehavioral research. *Nurs Res* 2014;**63**:36–50
42. Werner CM, Hecksteden A, Morsch A, Zundler J, Wegmann M, Kratzsch J, Thiery J, Hohl M, Bittenbring JT, Neumann F, Böhm M. Differential effects of endurance, interval, and resistance training on telomerase activity and telomere length in a randomized, controlled study. *Eur Heart J* 2018;**40**:34–46
43. Ojeda-Rodríguez A, Zazpe I, Alonso-Pedrero L, Zalba G, Guillen-Grima F, Martinez-Gonzalez MA, Marti A. Association between diet quality indexes and the risk of short telomeres in an elderly population of the SUN project. *Clin Nutr* 2019. DOI: 10.1016/j.clnu.2019.11.003
44. De Meyer T, Bekaert S, De Buyzere ML, De Bacquer DD, Langlois MR, Shivappa N, Hébert JR, Gillebert TC, Rietzschel ER, Huybrechts I. Leukocyte telomere length and diet in the apparently healthy, Middle-aged asklepios population. *Sci Rep* 2018;**8**:6540



45. Khalangot MD, Kovtun VA, Gurianov VG, Pysarenko YM, Kravchenko VI. Evaluation of type 2 diabetes prevention through diet modification in people with impaired glucose regulation: a population-based study. *Prim Care Diabetes* 2019;**13**:535–41
46. Morell-Azanza L, Ojeda-Rodríguez A, Azcona-San Julián MC, Zalba G, Marti A. Associations of telomere length with anthropometric and glucose changes after a lifestyle intervention in abdominal obese children. *Nutr Metab Cardiovasc Dis* 2020; **30**:694
47. Østhus IB, Sgura A, Berardinelli F, Alsnes IV, Brønstad E, Rehn T, Støbakk PK, Hatle H, Wisløff U, Nauman J. Telomere length and long-term endurance exercise: does exercise training affect biological age? A pilot study. *PLoS One* 2012;**7**:e52769
48. Liu J, Ge Y, Wu S, Ma D, Xu W, Zhang Y, Yang Y. Association between antidiabetic agents use and leukocyte telomere shortening rates in patients with type 2 diabetes. *Aging* 2019;**11**:741–55
49. Zhang X, Fang Z, Zhang C, Xia H, Jie Z, Han X, Chen Y, Ji L. Effects of acarbose on the gut microbiota of prediabetic patients: a randomized, double-blind, controlled crossover trial. *Diabetes Ther* 2017;**8**:293–07
50. Frey N, Venturelli S, Zender L, Bitzner M. Cellular senescence in gastrointestinal diseases: from pathogenesis to therapeutics. *Nat Rev Gastroenterol Hepatol* 2018;**15**:81
51. Faerch K, Hulman APJ, Solomon T. Heterogeneity of pre-diabetes and type 2 diabetes: implications for prediction, prevention and treatment responsiveness. *Curr Diabetes Rev* 2016;**12**:30–41
52. Faerch K, Alssema M, Mela DJ, Borg R, Vistisen D. Relative contributions of preprandial and postprandial glucose exposures, glycemic variability, and non-glycemic factors to HbA1c in individuals with and without diabetes. *Nutr Diab* 2018;**8**:38
53. Meyer C, Pimenta W, Woerle HJ, Van Haeften T, Szoke E, Mitrakou A, Gerich J. Different mechanisms for impaired fasting glucose and impaired postprandial glucose tolerance in humans. *Diabetes Care* 2006;**29**:1909–14
54. Kantartzis K, Machann J, Schick F, Fritsche A, Häring HU, Stefan N. The impact of liver fat vs visceral fat in determining categories of pre-diabetes. *Diabetologia* 2010;**53**:882–9
55. Révész D, Verhoeven JE, Picard M, Lin J, Sidney S, Epel ES, Penninx BW, Puterman E. Associations between cellular aging markers and metabolic syndrome: findings from the CARDIA study. *J Clin Endocrinol Metab* 2018;**103**:148–57
56. Liu Y, Cao L, Li Z, Zhou D, Liu W, Shen Q, Wu Y, Zhang D, Hu X, Wang T, Ye J. A genome-wide association study identifies a locus on TERT for mean telomere length in Han Chinese. *PLoS One* 2014;**9**:e85043
57. Saxena R, Bjonnes A, Prescott J, Dib P, Natt P, Lane J, Lerner M, Cooper JA, Ye Y, Li KW, Maubaret CG. Genome-wide association study identifies variants in casein kinase II (CSNK2A2) to be associated with leukocyte telomere length in a Punjabi Sikh diabetic cohort. *Circ Cardiovasc Genet* 2014;**7**:287–95
58. Al Khaldi R, Mojiminiyi O, AlMulla F, Abdella N. Associations of TERC single nucleotide polymorphisms with human leukocyte telomere length and the risk of type 2 diabetes mellitus. *PLoS One* 2015;**10**:e0145721
59. Dato S, De Rango F, Crocco P, Passarino G, Rose G. Pleiotropic effects of UCP2-UCP3 variability on leukocyte telomere length and glucose homeostasis. *Biogerontology* 2017;**18**:347–55
60. Zhou Y, Ning Z, Lee Y, Hambly BD, McLachlan CS. Shortened leukocyte telomere length in type 2 diabetes mellitus: genetic polymorphisms in mitochondrial uncoupling proteins and telomeric pathways. *Clin Transl Med* 2016;**5**:8
61. Lin J, Epel E, Blackburn E. Telomeres and lifestyle factors: roles in cellular aging. *Mutat Res* 2012;**730**:85–9
62. Freitas-Simoes TM, Ros E, Sala-Vila A. Nutrients, foods, dietary patterns and telomere length: update of epidemiological studies and randomized trials. *Metab Clin Exp* 2016;**65**:406–15
63. Pérez LM, Amaral MA, Mundstock E, Barbé-Tuana FM, Guma Ftr Jones MH, Machado DC, Sarria EE, Marques E Marques M, Preto LT, Epifanio M, Meinem Garbin JG, Mattiello R. Effects of diet on telomere length: systematic review and meta-analysis. *Public Health Genom* 2017;**20**: 286–92
64. Arsenis NC, You T, Ogawa EF, Tinsley GM, Zuo L. Physical activity and telomere length: impact of aging and potential mechanisms of action. *Oncotarget* 2017;**8**:45008–19
65. Lumey LH, Khalangot MD, Vaiserman AM. Association between type 2 diabetes and prenatal exposure to the Ukraine famine of 1932–33: a retrospective cohort study. *Lancet Diabetes Endocrinol* 2015;**3**:787–94
66. Khalangot MD, Kovtun VA, Okhrimenko NV, Gurianov VG, Kravchenko VI. Glucose tolerance testing and anthropometric comparisons among rural residents of kyiv region: investigating the possible effect of childhood starvation – a community-based study. *Nutr Metab Insights* 2017;**10**:1–5
67. Diamond J. The double puzzle of diabetes. *Nature* 2003;**423**:599–602
68. Köbberling J, Tattersall R. *The genetics of diabetes mellitus*. New York: Academic Press, 1982, pp.283–93
69. Harding JL, Shaw JE, Peeters A, Guiver T, Davidson S, Magliano DJ. Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997–2010. *Diab Care* 2014;**37**:2579–86
70. Khalangot M, Gurianov V, Vaiserman A, Strele I, Fedash V, Kravchenko V. Diabetes in Eastern Europe. In: Dagogo-Jack S (ed) *Diabetes mellitus in developing countries and underserved communities*. Cham: Springer, pp.191–23