

Association of leukocyte telomere length with metabolic syndrome in type 2 diabetes mellitus

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Background: Leukocyte telomere length (LTL) has been revealed to be associated with aging-related diseases such as metabolic syndrome (MetS) and Type 2 diabetes mellitus (T2DM). We aimed to investigate the correlation of LTL with MetS and its components in T2DM patients in this cross-sectional study. **Materials and Methods:** A total of 344 T2DM patients were enrolled into this study. LTL was measured by Southern blot-based terminal restriction fragment length analysis. MetS was clinically defined by 2007 Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults. **Results:** Of 344 T2DM patients, 53% had MetS. T2DM patients with MetS had significantly longer LTL than those without MetS (6451.95 ± 51.10 base pairs vs. 6076.13 ± 55.13 base pairs, $P < 0.001$), especially when T2DM patients had poor glycemic control (hemoglobin A1c $\geq 7\%$). Meanwhile, the trend of longer LTL was associated with the increased components of MetS in T2DM patient. Finally, LTL had a significant association with MetS (odds ratio [OR]: 2.096, 95% confidence interval [CI] 1.337–3.285, $P = 0.001$), low levels of high-density lipoprotein-cholesterol (HDL-C) (OR: 2.412, 95% CI 1.350–4.308, $P = 0.003$) in T2DM patients. **Conclusion:** T2DM patients with MetS had a significantly longer LTL than those without MetS. The longer LTL was especially evident in T2DM patients with poor glycemic control. Longer LTL was positively associated with MetS, particularly low levels of HDL-C in T2DM patients.

Key words: Metabolic syndrome, telomere, type 2 diabetes mellitus

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by hyperglycemia and insulin resistance, which is becoming a severe global public health problem due to extremely high prevalence and harmful effects.^[1] Metabolic syndrome (MetS), characterized by a cluster of insulin-resistance-related disorders, including central obesity, hypertension, hyperglycemia, and dyslipidemia, is also a growing public health problem with a worldwide distribution.^[2] There is a close relationship between MetS and T2DM. Individuals with MetS have an increased risk of T2DM, and MetS has been reported to increase the risk of coronary atherosclerosis in T2DM patients.^[3]

Telomeres are repetitive structures at the end of chromosomes and together with associated proteins, and

they can protect chromosome ends from degradation. Mean leukocyte telomere length (LTL) is considered as a marker for cellular aging, and increased oxidative stress is considered to lead to telomere shortening.^[4] The association of MetS and its individual components with LTL has been explored in several previous studies, but the observations are controversial. Recently, Cheng *et al.* reported that increasing MetS components were associated with shorter telomere length in general Chinese populations, but only triglycerides (TGs) and waist circumference were related to decreased LTL with gender difference.^[5] A cross-section study identified that LTL was only associated with high-density lipoprotein-cholesterol (HDL-C) in men and body mass index (BMI) in women in general Sweden populations.^[6] Furthermore, Bekaert *et al.* even found that there was no correlation between LTL and classical MetS components such as obesity, blood lipid, and blood pressure in Belgian populations.^[7] Recent studies

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found impaired glucose tolerance affected the association between LTL and MetS in Ukrainians and physical activity also affected this relationship in Navarra area.^[8,9] Based on the above findings, the relationship between LTL and MetS and its components are still not clear. The potentially association of LTL with MetS is possibly largely affected by the genetic background and character of study population. Therefore, this study aimed to investigate LTL in relation to MetS in T2DM patients. In the present study, we discovered a new association of LTL with MetS in T2DM patients. T2DM patients with MetS had significantly longer LTL, especially in T2DM patients with poor glycemic control. Moreover, LTL had a significant association with MetS and low levels of HDL-C in T2DM patients.

MATERIALS AND METHODS

Ethics

This study was approved by the Ethics Committee of Tongji hospital (IRB ID: TJ-C20160206). The procedures complied with the provisions of the *Declaration of Helsinki*. All patients provided informed consent.

Selection and description of participants

Participants enrolled in our study were T2DM patients from Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, between January 2013 and May 2018. Patients were excluded under the following criteria: (1) acute cardiovascular and cerebrovascular events, (2) acute-chronic infectious disease, (3) malignant neoplasm, (4) exposure history of radioactive substances, (5) pregnancy, (6) secondary diabetes, and (7) patients refused to provide informed consent. After excluding 51 patients, a total of 344 Chinese Han ethnicity patients at the age of 14–83 years were ultimately enrolled in this study, which consisted of 184 T2DM patients with MetS and 160 age-matched T2DM patients without MetS.

Terminal restriction fragment length

AxyPrepBloodGenomicDNAMiniprepkit (Axygen, Corning, Inc, NY, USA) was applied in blood genomic DNA extraction. The concentrations of DNA samples were determined through Nanodrop spectrophotometer (NanoDrop2000, Thermo Scientific, USA). Genomic DNA was digested by Hinf I (R0155 L, New England Bio Labs, Beverly, MA, USA) and RsaI (R0167 L, New England BioLabs). Agarose gel electrophoresis was used to isolate the digested DNA. Then, the gel was denatured, followed by neutralization after drying. Afterward, the gel was prehybridized with prehybridization solution. Telomeres were detected using a ³²P-labeled telomeric probe. Finally, the gel was washed which was then exposed to a phosphor imager (Storm 860 Molecular Dynamics, Sunnyvale, CA, USA) and scanned with a Typhoon scanners (FLA 9500, GE Healthcare, USA).

The weighted mean telomere length was calculated. These were based on a previous study.^[10]

Clinical diagnosis for metabolic syndrome

According to the criteria established by JCDCC,^[11] MetS was defined as three or more of the following: (1) central obesity (waist circumference ≥ 90 cm for men and ≥ 85 cm for women); (2) elevated TG (TG ≥ 1.7 mmol/L) or specific treatment of lipid abnormalities; (3) reduced HDL-c (HDL-C < 1.03 mmol/L); (4) hypertension – systolic blood pressure (SBP)/diastolic blood pressure (DBP) $\geq 130/85$ mmHg or treatment of previously diagnosed hypertension; and (5) hyperglycemia – fasting plasma glucose ≥ 6.1 mmol/L and/or 2-h plasma glucose ≥ 7.8 mmol/L or previously diagnosed with Type 2 diabetes.

Statistical analysis

SPSS (version 22.0, IBM Corp., Armonk, NY, US) was used for statistical analyses. Differences were considered to be significant when $P < 0.05$. Student's *t*-test was applied to test the difference between means of normally distributed data. Distribution of the continuous variables was performed through Kolmogorov–Smirnov test. Mann–Whitney test was used to analyze nonnormally distributed data. Chi-square test was used to examine categorical data. Pearson's correlations as well as linear regression analysis were carried on to explore the association between LTL and other parameters. Multiple logistic regressions were conducted with relevant variables which were significantly different between T2DM patients with and without MetS. The ANOVA trend analysis with polynomial contrast was conducted to evaluate the association between the LTL and MetS score.

RESULTS

Characteristics of patients

General characteristics of the study subjects were shown in Table 1. No statistical difference was observed in age, sex, and diabetes duration between T2DM patients with or without MetS. T2DM patients with MetS had higher BMI and abdominal circumference than those without MetS (all $P < 0.001$). Similarly, SBP, DBP, total cholesterol, TG, HDL-C, uric acid, fasting plasma C-peptide, postprandial 2 h c-peptide, and homeostasis model assessment of insulin resistance (HOMA-IR) in T2DM patients with MetS were significantly higher compared with solely T2DM subjects (all $P < 0.001$). Moreover, T2DM patients with MetS had lower HDL-C ($P < 0.001$) and higher HOMA of β -cell function ($P = 0.003$).

Leukocyte telomere length in type 2 diabetes mellitus patients with or without metabolic syndrome

LTL in T2DM patients with MetS (6451.95 ± 51.10 bp) was significantly longer than those without MetS

(6076.13 ± 55.13 bp) ($P < 0.001$) after adjustment for age [Figure 1a]. Moreover, MetS also had longer LTL in both male and female groups in T2DM patients [Figure 1a]. In addition, MetS had longer LTL within all age groups when the T2DM patients were stratified by age (20–39 years, 40–59 years, and >60 years) [Figure 1b]. All T2DM patients were further stratified into four subgroups by diabetes duration to explore its effect on LTL. It turned out that T2DM patient with MetS had significantly longer LTL in all diabetes duration-related subgroups [Figure 2].

The effect of metabolic syndrome components as well as glycemic control on leukocyte telomere length

We next investigated the association between LTL and MetS components consisting of 1, 2, 3, and 4 components [Figure 3a]. Notably, we observed that the trend of longer LTL was associated with the

increased number of MetS components in T2DM patients (P for trend = 0.001).

In order to further explore the effect of MetS on LTL, both T2DM patients and T2DM patients with MetS were stratified into two subgroups by glycemic control (cutoff points for hemoglobin A1c [HbA1c] is 7%). Surprisingly, T2DM patient with MetS only had significantly longer LTL when HbA1c was more than 7% but not in T2DM patients with good glycemic control [Figure 3b].

Leukocyte telomere length was an independent factor of metabolic syndrome in type 2 diabetes mellitus patients

Explanatory factors of MetS in T2DM patients were identified using multiple logistic regressions [Table 2]. In model 1, after adjustment for age, LTL was significantly associated with MetS in T2DM patients (odds ratio [OR]:

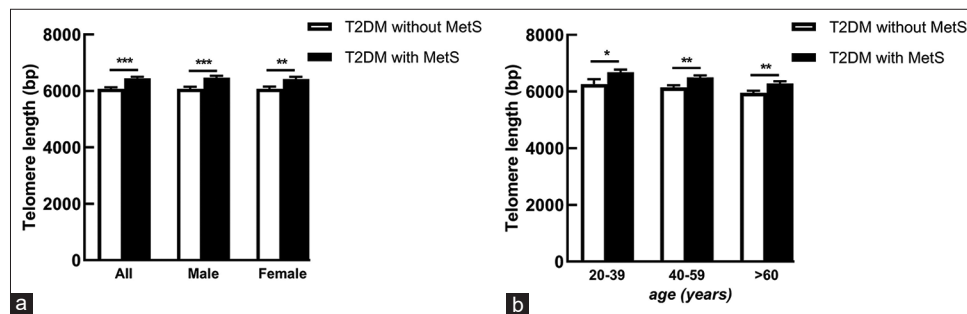


Figure 1: Leukocyte telomere length (bp) in T2DM with MetS and T2DM without MetS. (a) Telomere length between T2DM and T2DM + MetS patients when stratified by gender. (b) Telomere length between T2DM and T2DM + MetS patients when stratified into three subgroups by age. Means ± standard error of leukocyte telomere length are displayed. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$. bp = Base pairs; MetS = Metabolic Syndrome; T2DM = Type 2 diabetes mellitus

Table 1: Anthropometric and biochemical characteristics of participants

Variables	T2DM without MetS (n=160)	T2DM with MetS (n=184)	P
Diabetes duration (years) [†]	5.00 (0.87-10.00)	5.00 (0.62-10.00)	0.830
Male/female, n	84/76	106/78	0.385
Age (years)	55.11±12.87	53.01±13.54	0.143
BMI (kg/m ²)	22.47±2.74	26.84±3.39	<0.001
Abdominal circumference (cm)	85.58±8.81	95.17±9.27	<0.001
SBP (mmHg)	124.53±20.40	136.82±20.06	<0.001
DBP (mmHg)	75.78±11.75	82.51±11.84	<0.001
TC (mM)	4.38±1.23	4.98±1.46	<0.001
TG (mM)	1.57±1.17	3.54±2.32	<0.001
HDL-C (mmol/L)	1.15±0.35	0.90±0.24	<0.001
LDL-C (mmol/L)	2.58±0.84	2.76±1.05	0.111
Uric acid (umol/L)	290.98±108.37	369.33±155.19	<0.001
FPG (mmol/L)	8.38±3.38	8.77±3.24	0.302
2hPG (mmol/L)	17.13±6.19	17.70±7.41	0.479
FC-P (ug/L)	1.91±1.18	2.97±1.81	<0.001
2HC-P (ug/L)	4.95±3.09	6.98±4.08	<0.001
HOMA-IR	68.15±46.47	115.17±78.90	<0.001
HOMA-β [†]	8.09 (4.27-13.75)	10.20 (7.17-15.97)	0.003
HbA1c (%)	9.37±2.73	8.95±2.23	0.125

[†]Log transformed before analysis. Data are means±SD or median (interquartile range). BMI=Body mass index; SBP=Systolic blood pressure; DBP=Diastolic blood pressure, TC=Total cholesterol; TG=Triglyceride; HDL-C=High density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol; FPG=Fasting plasma glucose concentration; 2hPG=2-h plasma glucose concentration; FC-P=Fasting plasma C-peptide; 2hC-P=Postprandial 2h c-peptide; HOMA-IR=Homeostasis model assessment of insulin resistance; HOMA-β=Homeostasis model assessment of β-cell function; HbA1c=Hemoglobin A1c; T2DM=Type 2 diabetes mellitus; MetS=Metabolic syndrome; SD=Standard deviation

Table 2: Odds ratios (95% confidence interval) for metabolic syndrome and its individual components by leukocyte telomere length

	Model 1		Model 2	
	OR (95% CI)	P	OR (95% CI)	P
MS	2.096 (1.337-3.285)	0.001		
Obesity	1.493 (0.941-2.366)	0.089	1.199 (0.684-2.102)	0.526
Hypertension	1.090 (0.697-1.705)	0.706	1.117 (0.654-1.910)	0.685
Hypertriglyceridemia	2.217 (1.364-3.603)	0.001	1.660 (0.918-3.002)	0.094
Low levels of HDL-C	2.421 (1.466-3.999)	0.001	2.412 (1.350-4.308)	0.003

Model 1 was adjusted for age. Model 2 was further adjusted for other components of MetS. MetS=Metabolic syndrome; HDL-C=High-density lipoprotein cholesterol; OR=Odds ratio; CI=Confidence interval

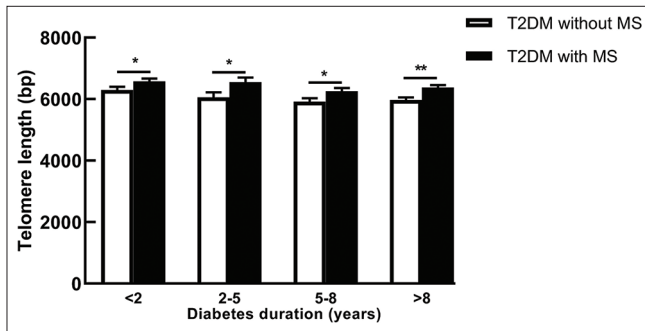


Figure 2: Leukocyte telomere length (bp) in T2DM with MetS and T2DM without MetS when stratified into four subgroups by diabetes duration. Means ± standard error of leukocyte telomere length are displayed. ***P* < 0.01, **P* < 0.05. bp = Base pairs; MetS = Metabolic Syndrome; T2DM = Type 2 diabetes mellitus

2.096 [95% confidence interval (CI) 1.337–3.285]; *P* = 0.001). Moreover, LTL was also positively associated with hypertriglyceridemia (OR: 2.217 [95% CI 1.364–3.603]; *P* = 0.001) and low levels of HDL-C (OR: 2.421 [95% CI 1.466–3.999]; *P* = 0.001) but not obesity and hypertension. In model 2, after adjustment for age and other MetS components, LTL was only positively associated with low levels of HDL-C (OR: 2.412 [95% CI 1.350–4.308]; *P* = 0.003).

DISCUSSION

This current cross-sectional study demonstrated that T2DM patients with MetS had significantly longer LTL in T2DM patient, especially when those patients had poor glycemic control. The trend of increasing LTL was associated with the increased number of MetS components in T2DM patients. In addition, LTL was significantly associated with the MetS status in T2DM patients.

Gender difference was found in the association between LTL and MetS components in the previous study.^[6] Therefore, we conducted analysis to examine the association of LTL with MetS in male and female T2DM patients separately. We found that there was no significant difference with gender in the association between LTL and MetS. Similarly, this relationship between longer LTL and MetS in T2DM patients existed even when stratified by diabetes duration and age.

Increasing MetS components were reported to be associated with shorter telomere length in general,^[5,12] while other publications did not observe an association between the changing MetS with changes in LTL,^[13,14] which seemed to be contrary to our findings. One explanatory reason may be that the participants are T2DM patients in our study; another possible reason is that the correlation between LTL and MetS components is indeed controversial based on previous studies which did not fully confirm this association.

Unexpectedly, our results indicated that MetS only had significantly longer LTL in T2DM patients. We might expect LTL to shorten at a quicker rate under the circumstance of increased oxidative burden such as T2DM and MetS due to oxidative damage being repaired less well in telomeric DNA than elsewhere in the chromosome.^[15] However, previous studies seeking to clarify the relationship between LTL and MetS were controversial. For example, Révész *et al.* showed that the presence of MetS was associated with shorter LTL,^[12] but this study was conducted in people who did not have T2DM in Netherlands, and the LTL was measured by quantitative polymerase chain reaction. Iglesias Molli *et al.* also observed lower LTL in subjects with MetS, while this study was only conducted in obese women in the Province of Santa Fe.^[16] However, there were studies showing that LTL was not associated with metabolic status including BMI, lipid profile, blood pressure, and glucose.^[6,17] One previous study even indicated that LTL could increase with time in obese people with impaired glucose metabolism.^[18]

The mechanism linking longer LTL with MetS in our study was still disputable. There are several explanations for the longer LTL in relation to MetS. First, the persisting inflammation under the coexistence of MetS and T2DM can likely induce telomerase activity, thereby leading to telomere elongation. For instance, in cultured B and T cells, telomerase activity could be induced through activation signals including cytokines and costimulatory signals.^[19,20] Supporting evidence comes from the study that observed an elevated telomerase activity, elevated markers of inflammation as well as endothelial dysfunction in circulating peripheral blood mononuclear cells of

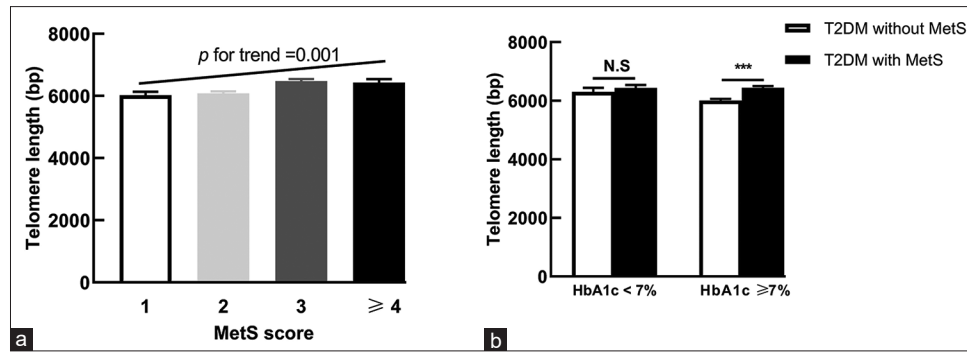


Figure 3: The effect of MetS components as well as glycemic control on leukocyte telomere length. (a) Telomere length between T2DM and T2DM + MetS patients when stratified into four subgroups according to the number of MetS components. (b) Leukocyte telomere length (bp) in T2DM with MetS and T2DM without MetS when stratified into four subgroups by HbA1c. Means \pm standard error of leukocyte telomere length are displayed. *** $P < 0.001$, NS indicates $P > 0.05$. bp = Base pairs; MetS = Metabolic Syndrome; T2DM = Type 2 diabetes mellitus

patients with MetS.^[21] Second, both shorter and longer LTL were shown to be associated with increased risk of dementia and over-elongated telomeres tended to be fragile and accumulate DNA damage.^[22,23] Furthermore, patients with longer LTL seem to have an increased risk of various kinds of cancers.^[24,25] Therefore, we may speculate that the occurrence of longer LTL might not be a good thing but a sign of the aggravation of these two diseases. Finally, the relationship between LTL and MetS is likely to be affected by the presence of T2DM. One previous study showed that hyperglycemia could attenuate the association between LTL and age,^[26] another study found that obese subjects with T2DM had longer LTL compared with merely obese subjects,^[27] both of which give support to the assumption that T2DM status contributes to longer LTL in MetS patients.

With respect to glycemic control, interesting, we found that T2DM patients with MetS only had significantly longer LTL when they had poor glycemic control (HbA1c $\geq 7\%$). As poor glycemic control was related to oxidative stress,^[28] the explanatory reason for this result may be that poor glycemic control in T2DM patients made the feature of oxidative stress in MetS more notable and thus widened the gap between patients with or without MetS.

We found that LTL was not associated with all the MetS components but part of them, which was in line with a previous study which also suggested an association between serum uric acid with some components of MetS.^[29] Our results indicated that longer LTL was positively associated with MetS state, hypertriglyceridemia, particularly low levels of HDL-c in T2DM patients. Controversial studies showing the association between lipid profile (HDL-C, LDL, TGs, and cholesterol) with LTL have been published,^[14,30,31] and some of them also showed the positive association between LTL with HDL-C, giving support to our findings.^[30,31] In terms of MetS state, LTL was positively correlated with MetS state in T2DM patients, further supporting the result

in the current study which linked the longer LTL with MetS in T2DM patients.

This study has the following strengths. First, our study is the first one to unravel the association between LTL and MetS in T2DM patients. Second, we also analyzed this association through stratifying by the number of MetS components as well as the glycemic control as this method was relatively rare in previous studies. Third, the southern blot-based method was applied in our study to estimate LTL, which is considered as the gold standard for measuring LTL. However, there are also some limitations in our study. First, the sample sizes were not large enough. Second, we only measured the baseline LTL and had no dynamic monitoring of LTL. Third, as the study population was Chinese people, we diagnosed MetS based on the criteria established by JCDG instead of the International Diabetes Federation diagnostic criteria.^[32] Finally, the underlying mechanism is indeed controversial and needs to be further elucidated.

CONCLUSION

Our findings indicated that T2DM patients with MetS had a significantly longer LTL than those without MetS. The longer LTL was especially evident in T2DM patients with poor glycemic control. In addition, longer LTL was positively associated with MetS, particularly low levels of HDL-C in T2DM patients. Further investigation and larger studies are warranted to explore the exact mechanism underlying these results.

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Conflicts of interest

There are no conflicts of interest.

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