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Short Leukocyte Telomere Length Predicts Albuminuria Progression in Individuals With Type 2 Diabetes

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Introduction: Telomere length, a marker for biological aging, is implicated with diabetic kidney disease (DKD); however, the association between telomere length and albuminuria progression among Asian patients with type 2 diabetes (T2D) is not well understood. Here, we aim to study whether leukocyte telomere length (LTL) may independently predict albuminuria progression in patients with T2D with preserved renal filtration function (estimated GFR >60 ml/min per 1.73 m^2 and urine albumin-to-creatinine ratio [uACR] <300 mg/g).

Methods: The baseline LTL was measured by real-time polymerase chain reaction in the SMART2D cohort (n = 691) with a median follow-up of 3 years. Albuminuria progression was defined as a change in albuminuria category to a higher category and at least 30% increase in uACR from baseline in 3 years.

Results: Progressors (n = 123) had significantly shorter median LTL compared with nonprogressors (n = 568) (0.58 [0.38–0.79] vs. 0.62 [0.45–0.88], P = 0.039). Compared with subjects with longer LTL (fourth quartile), subjects with shorter LTL (first quartile) had 1.93-fold (1.04–3.60, P = 0.038) increased risk for albuminuria progression after adjustment for traditional risk factors. The association of LTL with microalbuminuria to macroalbuminuria progression was stronger than its association with normoalbuminuria to microalbuminuria (odds ratio [OR]: 1.54; 95% confidence interval [CI]: 1.02–2.32; P = 0.042 vs. OR: 1.13; 95% CI: 0.91–1.40; P = 0.263 per 1-SD decrement in natural log-transformed LTL).

Conclusion: Therefore, our results demonstrated that in patients with T2D with preserved renal filtration function, LTL predicts albuminuria progression beyond traditional risk factors, suggesting LTL may be novel biomarker for DKD progression.

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Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease and cardiovascular mortality.[1,2] DKD is characterized by the presence of albuminuria and/or decline in glomerular filtration rate (GFR).[3] Although microalbuminuria is clinically the first indicator of incipient DKD, DKD is a heterogeneous disease, both in terms of its clinical manifestations and rate of decline in renal function.[4–8] Despite improved management of known risk factors, the residual risk for DKD still remains high, suggesting our incomplete understanding in the pathophysiology of DKD.[9]

Telomeres are tandem repeats made up of TTAGGG sequence and proteins found at the ends of chromosomes, and protects chromosomal stability.[10] Telomeres naturally shorten with each cell division, as conventional DNA replicative enzymes cannot fully replicate telomere ends. Critically short telomere length, termed the HayFlick limit, triggers cell senescence and apoptosis.[11–13] Several epidemiological studies have shown that short telomeres are associated with age-related disorders, such as cardiovascular and neurodegenerative disease, cancer,[14–16] and metabolic syndrome.[17] Therefore, decreased telomere length is suggested to be an indicator of biological age and has been extensively studied as a potential marker for disease risk and progression.[18–21] Accumulating evidence has begun to demonstrate the link between telomeres and pathogenesis of diabetes and renal disease. Experimental data from mouse models and humans have shown that short telomeres lead to beta cell dysfunction and defects in the insulin signaling pathway, increasing the susceptibility to and more severe diabetes than

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controls.[22,23] A series of prospective studies mainly in non-Asian cohorts have confirmed a clear association between short telomere length and incident type 2 diabetes (T2D).[24–26] Moreover, a recent study in Caucasians found that short leukocyte telomere length (LTL) is also associated with increased risk for all-cause mortality in patients with T2D.[27]

Telomere shortening is also accelerated by deregulated renin-angiotensin system, inflammation, and chronic exposure to hyperglycemia,[28–30] which are all risk factors associated with DKD.[31] Several lines of evidence have demonstrated the association of telomere length with renal disease.[32,33] Betjes *et al.*[34] found that telomeres in T cells were shorter in patients with end-stage renal disease compared with healthy individuals in a cross-sectional study. Increased expression of cellular senescence markers was also observed in renal tissue from patients with T2D with renal disease.[30] In agreement, a cross-sectional study found that telomere lengths were significantly shorter in patients with T2D with microalbuminuria as compared with patients with T2D with normal albuminuria.[35] Prospective association between LTL and renal disease progression in a Caucasian population with type 1 diabetes (T1D) by Fyhrquist *et al.*[36] demonstrated that short telomeres are associated with increased risk for albuminuria progression, whereas Raschenberger *et al.*[37] showed that association between short LTL and chronic kidney disease progression was stronger in individuals with diabetes. However, the latter study included individuals with impaired renal function.

The natural course of DKD is less understood in patients with T2D as compared with T1D, as diagnosis is delayed by many years, and the prevalence of DKD is approximately twofold to threefold higher in Asian compared with Caucasian individuals.[38] Given the roles of telomeres in aging, diabetes, and renal function, we hypothesized that LTL may be involved in deterioration of renal function in Asian patients with T2D with preserved renal function. Therefore, using a diverse sample with T2D and preserved renal filtration function, we investigated the association of LTL with DKD progression as measured by albuminuria progression in a prospective cohort in Asian patients with T2D.

METHODS

Study Population

This prospective study is nested within the Singapore Study of Macro-angiopathy and Micro-Vascular Reactivity in Type 2 Diabetes (SMART2D). Briefly, 2058 adult participants (21 years and older) with T2D were recruited from a regional hospital and a community medical center in the northern part of Singapore from August 2011 to March 2014. Three years after enrollment date, participants were recalled consecutively for the planned 3-year follow-up study. Given that this was an ongoing study, at the time the study commenced, we had 1066 patients' follow-up (censored at July 2016 for this study) (Figure S1). The exclusion criteria included the following: T1D, pregnant subjects, subjects with active inflammation (e.g., systemic lupus erythematosus) and cancer, subjects taking nonsteroidal anti-inflammation drugs on the same day of clinical/vascular/biomedical assessment, or subjects on oral steroids equivalent to >5 mg/d prednisolone, as described previously.[39,40] Subjects would be excluded when involvement of other causes of renal disease was suspected. The SMART2D study and the follow-up of patients complies with Helsinki Declaration, has been approved by our domain-specific ethical review board, and written informed consent was obtained from all participants.

Clinical and Biochemical Assessments

Detailed information on collection of baseline data and biological samples has been described previously.[40] Briefly, blood pressure was measured by a sphygmomanometer and average of 3 readings was used. Blood and urine (spot urine collected in the morning void) specimens were collected after overnight fast. HbA1c was measured by point-of-care immunoassay analyzer (DCA Vantage Analyzer; Siemens AG, Erlangen, Germany). Creatinine, triglycerides, and high-density lipoprotein and low-density lipoprotein cholesterol were quantified by enzymatic methods (Roche/Hitachi Cobas C System; Roche Diagnostic GmbH, Basel, Switzerland). Urinary albumin was measured based on a solid-phase competitive chemiluminescent enzymatic immunoassay (Immulite; Diagnostic Products Corp, UK). Albuminuria level was expressed as albumin-to-creatinine ratio (ACR, mg/g). The estimated GFR (eGFR) was calculated based on Chronic Kidney Disease Epidemiology Collaboration equation. Baseline and follow-up biochemical measurements were performed in the same clinical laboratory, which is accredited by the College of American Pathologists.

Definitions of Albuminuria Progression

Albuminuria status was categorized according to American Diabetes Association criteria as normal to mildly elevated (ACR <30 mg/g, "normoalbuminuria"), moderately elevated (ACR 30–299 mg/g, "microalbuminuria") or severely elevated (ACR >300 mg/g, "macroalbuminuria").[3] Progression of albuminuria was defined as changes from normoalbuminuria to microalbuminuria or macroalbuminuria or from microalbuminuria to macroalbuminuria[36] and more than 30%

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