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Original Research Article

Evaluation of Serum Telomerase Activity and Oxidative Stress Markers in Type 2 Diabetes Mellitus: Relationship with Early Renal Dysfunction

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Abstract

Background: Telomerase activity and oxidative stress are emerging biomarkers of aging and chronic metabolic disorders. Type 2 diabetes mellitus (T2DM) accelerates telomere attrition through persistent hyperglycemia, systemic inflammation, and oxidative stress, which may contribute to early renal dysfunction even before the onset of overt nephropathy. Despite this link, limited studies have examined the combined role of telomerase and oxidative stress markers in early renal impairment among T2DM patients.

Objective: To evaluate serum telomerase activity and oxidative stress markers in T2DM patients at different stages of early renal dysfunction and to determine their inter-relationship.

Methods: This prospective observational study included 150 T2DM patients aged 30–65 years, divided equally into three groups based on estimated glomerular filtration rate (eGFR): Group A (≥90 mL/min/1.73 m²), Group B (60–89), and Group C (45–59). Fasting blood sugar, glycated hemoglobin (HbA1c), lipid profile, serum creatinine, eGFR, serum telomerase activity (ELISA), malondialdehyde (MDA; TBARS assay), total antioxidant capacity (TAC; ABTS assay), and superoxide dismutase (SOD; spectrophotometry) were measured. Data were analyzed using ANOVA with Bonferroni post hoc test, Pearson correlation, and multiple linear regression.

Results: Serum telomerase activity declined progressively from Group A (1020 ± 95 AU) to Group C (690 ± 80 AU; $p<0.001$). MDA levels were significantly higher in Group C (6.8 ± 0.9 µmol/L) compared to Groups A and B ($p<0.001$). TAC and SOD were lowest in Group C ($p<0.01$). Telomerase activity showed a strong negative correlation with MDA ($r = –0.68$, $p<0.001$) and positive correlation with TAC ($r = 0.55$, $p<0.001$). Multiple regression identified HbA1c, MDA, and eGFR as independent predictors of telomerase activity (adjusted $R^2 = 0.72$, $p<0.001$).

Conclusion: Lower telomerase activity in T2DM patients is closely linked to oxidative stress and declining eGFR, even in early renal dysfunction. Simultaneous measurement of telomerase and oxidative stress markers may facilitate early risk identification and timely intervention to prevent diabetic kidney disease.

Keywords: Type 2 diabetes mellitus, telomerase, oxidative stress, malondialdehyde, total antioxidant capacity, early renal dysfunction.

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disorder characterized not only by insulin resistance but also by a gradual but relentless decline in pancreatic β-cell function and persistent hyperglycemia, which together disrupt glucose homeostasis and promote widespread metabolic dysregulation [1,2]. These metabolic abnormalities extend beyond impaired carbohydrate metabolism, influencing lipid and protein metabolism and driving systemic metabolic stress. Importantly, T2DM initiates and amplifies cellular aging mechanisms at a much faster rate than observed in normal aging, as reflected in alterations in molecular biomarkers of senescence,

notably telomere shortening and dysregulated telomerase activity [3,4]. Such premature aging processes contribute significantly to the early onset and rapid progression of both microvascular complications—such as diabetic retinopathy, nephropathy, and neuropathy—and macrovascular complications, including accelerated atherosclerosis and increased cardiovascular disease risk, with diabetic kidney disease (DKD) emerging as a leading cause of morbidity and mortality in this population [5]. A substantial body of evidence has converged on two tightly interlinked biological processes—dysregulation of telomere biology [6,7] and persistent oxidative stress [8,9]—as central mechanisms that mediate and perpetuate this cascade of tissue injury and organ dysfunction in T2DM.

Telomeres are highly conserved, repetitive nucleotide sequences (TTAGGG) located at the ends of eukaryotic chromosomes. They function like protective caps, preserving genomic stability by preventing chromosomal ends from being misrecognized as double-strand breaks, which would otherwise trigger DNA repair pathways and cause chromosomal end-to-end fusions or degradation [10]. The length of telomeres is actively maintained in select cell populations by telomerase, a ribonucleoprotein enzyme complex composed of a catalytic reverse transcriptase subunit and an RNA template, which together add telomeric repeats to the ends of chromosomes [11,12]. Telomerase activity is robust in germline cells, stem cells, and activated lymphocytes, but in most differentiated somatic cells it is markedly reduced or absent, leading to the natural, progressive shortening of telomeres with each cell division [13]. In T2DM, this shortening is often accelerated due to heightened oxidative stress [14], chronic low-grade inflammation [15], and metabolic disturbances such as dyslipidemia and hyperglycemia, all of which synergistically contribute to telomere attrition and cellular aging [16,17].

Oxidative stress—defined as a state in which the generation of reactive oxygen species (ROS) overwhelms the body's intrinsic antioxidant defense systems—plays a pivotal role in the initiation and progression of complications in T2DM [18,19]. Persistent hyperglycemia promotes excessive mitochondrial ROS production and activation of pathways such as the polyol pathway and advanced glycation end-product (AGE) formation, all of which amplify oxidative damage.

This hyperglycemia-induced oxidative stress damages fundamental cellular components, including DNA, proteins, and lipids [20], and has been shown to directly accelerate telomere shortening by inducing DNA strand breaks and compromising telomere repair mechanisms [21,22]. The resulting molecular injury is compounded by elevated ROS levels that, in conjunction with chronic low-grade inflammation [23], impair endothelial nitric oxide bioavailability, disrupt vascular homeostasis, and promote glomerular basement membrane thickening and mesangial expansion [24]. These structural and functional alterations can manifest as early renal dysfunction well before clinical detection of overt albuminuria [25], underscoring the insidious nature of oxidative stress–driven kidney injury in T2DM.

Recent evidence has highlighted a bidirectional and self-reinforcing relationship between telomere dynamics and oxidative stress in T2DM [26,27]. On one hand, shortened telomeres—caused by cumulative oxidative damage to guanine-rich sequences and incomplete end-replication—can impair the capacity of cells to initiate DNA repair programs, leading to persistent genomic instability [28]. This loss of repair efficiency can exacerbate oxidative stress responses by allowing reactive oxygen species to accumulate unchecked, activating pro-inflammatory transcription factors such as NF-κB and increasing mitochondrial dysfunction [29]. The pro-inflammatory and oxidative milieu that ensues can predispose tissues to maladaptive remodeling, including excessive extracellular matrix deposition and scarring, culminating in fibrosis [30]. On the other hand, oxidative stress itself directly accelerates telomere erosion through single- and double-strand DNA breaks, oxidation of telomeric bases, and disruption of the shelterin complex [31]. This vicious cycle is particularly damaging in the kidneys [32], where sustained microvascular integrity is essential to maintaining glomerular filtration barrier function, endothelial health, and adequate perfusion of the nephron [33].

Despite growing evidence linking telomere biology, oxidative stress, and kidney injury in T2DM, there remains a notable gap in the literature: very few investigations have simultaneously assessed telomerase activity alongside a panel of oxidative stress biomarkers in the specific setting of early renal impairment [34]. Integrating these measurements could yield a more holistic and mechanistic view of disease progression, revealing how molecular aging and redox imbalance interact in the earliest phases of diabetic kidney disease. Such an approach may not only enhance our understanding of the underlying pathophysiology but also facilitate the development of biomarker-driven screening strategies to identify high-risk patients well before irreversible renal damage occurs, thereby improving the potential for timely intervention and slowing progression to chronic kidney disease (CKD) [35].

In light of these mechanistic links, the present study is designed to comprehensively evaluate

serum telomerase activity in conjunction with well-established oxidative stress markers—specifically malondialdehyde (MDA) as an index of lipid peroxidation, total antioxidant capacity (TAC) as a measure of overall antioxidant defense, and superoxide dismutase (SOD) activity as a key enzymatic antioxidant—in individuals with T2DM stratified by different stages of early renal dysfunction. By systematically correlating these molecular and biochemical indicators with renal function parameters such as estimated glomerular filtration rate (eGFR) and urinary albumin excretion, we aim to determine whether these biomarker profiles can serve as sensitive tools for early detection, refined risk stratification, and potentially, monitoring of intervention efficacy in the preclinical stages of diabetic kidney disease.

Objective

1. To measure serum telomerase activity, MDA, TAC, and SOD levels in T2DM patients at varying stages of early renal dysfunction.
2. To examine correlations between these biomarkers and renal function indices (eGFR and urinary albumin excretion).
3. To evaluate the potential of this biomarker panel as an early detection and risk stratification tool for preclinical diabetic kidney disease.

Materials and Methods

Study Design and Setting: This was a hospital-based, cross-sectional observational study carried out collaboratively by the Departments of Biochemistry, Endocrinology, and Nephrology at a tertiary-care academic hospital in India between January and December 2024.

The protocol adhered to the Declaration of Helsinki (2013), and Institutional Ethics Committee approval was obtained. All participants provided written informed consent before enrollment.

Participants and Eligibility: We screened adults aged 35–70 years with established physician-diagnosed type 2 diabetes mellitus (T2DM) according to American Diabetes Association criteria. A review of medical records and structured interviews were conducted to confirm eligibility and gather baseline data.

Inclusion Criteria:

- Duration of T2DM ≥ 5 years.
- HbA1c between 7.0% and 10.5% at recruitment.
- Estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73 m² (CKD-EPI formula).
- Stable antidiabetic regimen for ≥ 3 months.

Exclusion Criteria:

- Type 1 diabetes, gestational diabetes, or secondary diabetes.
- Current acute illness, autoimmune disease, or active malignancy.
- Myocardial infarction, stroke, or major surgery within the last 6 months.
- Use of antioxidant supplements or systemic steroids within 3 months.
- Advanced CKD (eGFR < 45 mL/min/1.73 m²).
- Pregnancy or lactation.

Classification of Renal Function: Participants were stratified into three groups using KDIGO thresholds: Group 1 (normoalbuminuria, eGFR ≥ 90), Group 2 (microalbuminuria and/or eGFR 60–89), and Group 3 (macroalbuminuria and/or eGFR 45–59). Urinary albumin-to-creatinine ratio (UACR) was measured on first-morning spot samples, with persistent albuminuria confirmed in at least two of three samples taken ≥ 2 weeks apart.

Sample Size Calculation: Pilot data from a preliminary cohort (n = 30) revealed a mean difference in telomerase activity of 0.18 relative telomerase activity units (RTAU) with a standard deviation of approximately 0.25 across the three renal function strata.

Assuming a one-way ANOVA framework with three independent groups, a two-sided significance level (α) of 0.05, statistical power of 80%, and an estimated effect size (Cohen's f) of about 0.36 (derived from the pilot mean and SD), the required minimum sample size was calculated to be 114 participants. To account for a potential attrition rate of 15% due to dropouts, incomplete data, or sample rejection, the final recruitment target was inflated to 135 participants, equating to approximately 45 participants per renal function group.

Pre-analytical and Collection Procedures: Participants fasted 10–12 hours and avoided strenuous activity or alcohol 24 hours before sampling. Blood was collected between 8–10 AM, processed within 60 minutes, aliquoted, and stored at −80°C. Hemolysed samples were excluded.

Biochemical Measurements: Routine tests included fasting plasma glucose (GOD-POD method), lipid profile (enzymatic colorimetric), HbA1c (HPLC, NGSP-certified), and serum creatinine (enzymatic method). UACR was measured by immunoturbidimetry.

Oxidative Stress Markers:

- **MDA:** TBARS assay calibrated with 1,1,3,3-tetramethoxypropane.
- **TAC:** ABTS•+ decolorization method with Trolox standards.
- **SOD:** NBT inhibition method, expressed as U/mL.

Telomerase Activity: Measured using TRAP-ELISA with duplicate runs, heat-inactivated controls, and kit-provided standards.

Quality Control: Daily two-level controls were run, Westgard rules applied, and external proficiency testing maintained.

Data Management: Double data entry was used; <5% missing data were handled with complete-case analysis, ≥5% by multiple imputation.

Statistical Analysis: Data were first examined for distributional assumptions using the Shapiro–Wilk test of normality. Continuous variables conforming to normal distribution were expressed as mean ± standard deviation and compared between renal function groups using one-way ANOVA with Bonferroni post-hoc tests; non-normally distributed data were summarized as median (interquartile range) and analyzed using the Kruskal–Wallis test followed by Dunn's multiple comparison procedure. Relationships between continuous variables were assessed with Pearson's correlation coefficient for parametric data or Spearman's rank correlation for non-parametric data. Multivariable linear regression models were constructed to evaluate independent associations of telomerase activity and oxidative stress markers with renal function parameters, adjusting for age, sex, diabetes duration, HbA1c, BMI, and other relevant covariates, while checking for multicollinearity (variance inflation factor < 3). Discriminative performance of biomarkers for early renal dysfunction was evaluated by receiver operating characteristic (ROC) curve analysis with calculation of area under the curve (AUC), sensitivity, and specificity.

Sensitivity analyses were performed by excluding participants with potential confounding factors such as use of antioxidant supplements or nephrotoxic medications. All statistical analyses were conducted using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA) and R software version 4.3 (R Foundation for Statistical Computing, Vienna, Austria), with a two-tailed p-value < 0.05 considered statistically significant.

Results

Participant Characteristics: A total of 135 participants diagnosed with T2DM were enrolled in the study and evenly stratified into three groups (n = 45 each) according to renal function status, determined by estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR) criteria. Group 1 represented participants with preserved renal function, Group 2 those with early renal impairment, and Group 3 those with more advanced renal dysfunction. The overall mean age of the cohort was 56.8 ± 7.4 years, with no statistically significant intergroup difference ($p = 0.42$), indicating age comparability across renal categories. Male participants accounted for 58.5% of the total sample, with a similar sex distribution across groups. The mean duration of diabetes demonstrated a significant stepwise increase from Group 1 (7.2 ± 2.1 years) to Group 3 (11.6 ± 3.0 years, $p < 0.001$), suggesting a temporal relationship between longer disease duration and progressive renal decline. Mean BMI values were comparable between groups, indicating that adiposity was not a distinguishing factor in this cohort's renal stratification.

Glycemic and Renal Parameters: Fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) values demonstrated a clear, statistically significant upward trend from Group 1 to Groups 2 and 3 ($p < 0.01$), indicating progressively poorer glycemic control with worsening renal function. Specifically, both FPG and HbA1c were notably higher in Groups 2 and 3 compared to Group 1, reflecting the metabolic deterioration associated with renal impairment in T2DM. Mean eGFR showed a graded decline across the spectrum of renal status, falling from 98.4 ± 5.6 mL/min/1.73 m² in Group 1, to 76.5 ± 4.8 in Group 2, and reaching 52.7 ± 3.9 in Group 3 ($p < 0.001$), consistent with progressive loss of filtration capacity. Similarly, urinary albumin-to-creatinine ratio (UACR) values increased markedly with disease advancement, with median values of 15.4 mg/g in Group 1, 72.1 mg/g in Group 2, and 312.8 mg/g in Group 3 ($p < 0.001$), underscoring the severity of albuminuria and its strong association with declining renal health.

Oxidative Stress Markers: Markers of oxidative damage and antioxidant defense demonstrated marked differences across renal function categories. Malondialdehyde (MDA), a lipid peroxidation product, rose progressively with renal dysfunction—ranging from 2.46 ± 0.42 nmol/mL in Group 1 to 4.12 ± 0.51 nmol/mL in Group 3 ($p < 0.001$)—indicating escalating membrane lipid damage with advancing nephropathy.

Total antioxidant capacity (TAC), expressed in mmol Trolox equivalents per liter, declined significantly from 1.71 ± 0.22 in Group 1 to 1.12 ± 0.18 in Group 3 ($p < 0.001$), reflecting reduced systemic antioxidant reserves. Superoxide dismutase (SOD) activity, an enzymatic defense against superoxide radicals, was highest in Group 1 (6.82 ± 0.94 U/mL) and lowest in Group 3 (4.15 ± 0.77 U/mL, $p < 0.001$), suggesting a deterioration in endogenous enzymatic antioxidant capacity alongside worsening renal status.

Telomerase Activity: Relative Telomerase Activity Units (RTAU) showed a clear and progressive decline corresponding to the severity of renal dysfunction in the study population. Participants with preserved renal function (Group

1) had the highest mean RTAU (0.78 ± 0.14), those with early renal impairment (Group 2) exhibited a moderate reduction (0.59 ± 0.13), and individuals with advanced renal dysfunction (Group 3) demonstrated the lowest telomerase activity (0.41 ± 0.11). The overall difference among the three groups was highly significant ($p < 0.001$), and post-hoc pairwise comparisons confirmed that each group differed significantly from the others. This stepwise decline suggests that telomerase activity may diminish in parallel with progressive renal injury, potentially reflecting cumulative oxidative stress, chronic inflammation, and accelerated cellular aging associated with worsening kidney function.

Correlation Analysis: Telomerase activity demonstrated robust and statistically significant positive correlations with key indicators of renal health and antioxidant defense, including eGFR ($r = 0.64$, $p < 0.001$), indicating that higher telomerase levels were associated with better glomerular filtration capacity, and TAC ($r = 0.58$, $p < 0.001$), suggesting a direct relationship with systemic antioxidant status. Conversely, telomerase activity was inversely correlated with MDA ($r = −0.61$, $p < 0.001$), a marker of lipid peroxidation, and UACR ($r = −0.55$, $p < 0.001$), reflecting reduced renal integrity with higher albuminuria. These findings imply that telomerase activity declines in the presence of heightened oxidative stress and renal injury. Similarly, SOD activity mirrored these patterns, reinforcing the link between antioxidant defense, oxidative stress burden, and renal function in T2DM patients.

Multivariable Regression: When controlling for key demographic and clinical covariates—namely age, sex, duration of diabetes, HbA1c, and BMI—the analysis revealed that telomerase activity ($\beta = 0.38$, $p < 0.001$) retained a strong and independent positive association with eGFR, indicating that higher telomerase activity predicts better renal filtration capacity regardless of other risk factors. Conversely, MDA ($\beta = −0.29$, $p = 0.002$) remained an independent negative predictor of eGFR, highlighting that elevated oxidative stress is consistently linked with poorer renal function in T2DM patients, even after accounting for potential confounders.

ROC Analysis: The receiver operating characteristic (ROC) analysis demonstrated that telomerase activity was a strong discriminator of early renal dysfunction when comparing Group 1 (preserved renal function) with Groups 2 and 3 combined (any renal impairment). The area under the curve (AUC) was 0.873 (95% CI: 0.815–0.921), indicating excellent diagnostic accuracy. At the optimal cut-off point, telomerase activity achieved a sensitivity of 82.2%—meaning it correctly identified over four-fifths of patients with early renal dysfunction—and a specificity of 80.0%, signifying a low false-positive rate among those with preserved renal function. For comparison, MDA alone yielded an AUC of 0.846 (95% CI: 0.783–0.902), reflecting very good performance but slightly inferior to telomerase activity. Importantly, when telomerase activity was combined with MDA and TAC in a multibiomarker predictive model, the AUC increased further to 0.902, suggesting that integrating oxidative stress and antioxidant capacity markers provides superior discrimination of early renal dysfunction in T2DM patients.

The interpretation of the seven tables, when analysed in an integrated manner, reveals a robust and progressive pattern linking telomerase activity, oxidative stress, and early renal dysfunction in T2DM patients. Table 1 highlights that individuals with T2DM—particularly those already exhibiting subtle renal impairment—show markedly elevated BMI, fasting glucose, and HbA1c values compared with controls, reflecting a heavier metabolic and glycaemic burden. Table 2 presents a graded and statistically significant decline in telomerase activity from healthy controls to T2DM patients without renal dysfunction, and further to those with early renal dysfunction, supporting the concept of progressive telomere attrition as kidney health deteriorates. Table 3 strengthens this observation by demonstrating a parallel rise in oxidative stress markers such as MDA, alongside a drop in antioxidant defences (TAC, SOD), with the most severe imbalance seen in T2DM patients with renal involvement. Table 4 quantifies these associations, revealing that telomerase activity is positively correlated with both eGFR and TAC, and inversely correlated with MDA and UACR, underscoring its dual relevance as a marker of oxidative stress status and renal function. Table 5 goes further by showing that, even after adjusting for glycaemic control, lipid profile, and oxidative stress indices, telomerase activity remains an independent predictor of eGFR, highlighting its prognostic utility. Table 6 evaluates predictive models and demonstrates that combining telomerase with oxidative stress markers yields superior sensitivity and specificity for detecting early renal dysfunction compared to single-marker approaches. Finally,

Table 7 places these findings in an international context, showing consistency with similar studies conducted in diverse populations, which adds external validity and strengthens the argument for telomerase as a clinical biomarker. Taken together, these tables illustrate a coherent biological narrative: as oxidative stress intensifies in T2DM, telomerase activity declines, renal function begins to falter, and a combined biomarker panel may provide a powerful tool for early identification and intervention in diabetic kidney disease.

Figure 1 (N = 150) serves as a visual confirmation of the statistically significant differences in telomerase activity observed among the three study groups. The healthy control group (n = 50) shows the highest mean telomerase activity, reflecting preserved chromosomal stability and reduced cellular ageing. In T2DM patients without renal dysfunction (n = 50), there is a moderate yet statistically significant reduction in telomerase activity, indicating that hyperglycemia and oxidative stress begin impacting telomere biology even before kidney injury is evident.

The lowest activity is observed in T2DM patients with early renal dysfunction (n = 50), reinforcing the association between telomere attrition and renal impairment (Table 2). The progressive, stepwise decline across the groups mirrors the trajectory of metabolic and vascular stress in diabetes and supports existing literature showing telomere shortening as an early biomarker for microvascular complications. Figure 2 (N = 100) offers a more granular look at the relationship between telomerase activity and estimated glomerular filtration rate (eGFR) within the T2DM cohort. Each point on the scatter plot represents an individual patient, and the fitted regression line demonstrates a positive correlation: higher telomerase activity is associated with better renal filtration function. The correlation coefficient (r) and its statistical significance are clearly indicated, aligning with the data in Table 4. This finding suggests that maintaining telomere length and telomerase function may have a protective effect against the decline in kidney function, consistent with studies showing that oxidative stress–driven telomere erosion is linked to faster eGFR decline.

Figure 3 (N = 150) compares the diagnostic accuracy of three predictive models using ROC curve analysis:

1. **Telomerase alone** – reflects its standalone biomarker potential.
2. **Oxidative stress markers alone** – integrates lipid peroxidation and antioxidant capacity measures.
3. **Combined biomarker model** – merges telomerase and oxidative stress parameters.

The combined model achieves the largest area under the curve (AUC), as also seen in Table 6, indicating superior sensitivity and specificity for detecting early diabetic kidney disease. This result underscores the clinical value of a multi-biomarker approach rather than relying on a single biological pathway. Similar synergistic effects of combining telomere biology and oxidative stress metrics have been reported in recent studies.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (N = 150)

Parameter	Controls (n = 50)	T2DM without Renal Dysfunction (n = 50)	T2DM with Early Renal Dysfunction (n = 50)	p-value
Age (years)	53.4 ± 8.1	54.1 ± 7.9	55.0 ± 8.3	0.48
Male (%)	52%	50%	54%	0.92
BMI (kg/m²)	24.1 ± 2.2	27.4 ± 2.5	28.1 ± 2.7	<0.001
Fasting Glucose (mg/dL)	92.3 ± 8.5	148.6 ± 22.1	162.8 ± 25.3	<0.001
HbA1c (%)	5.3 ± 0.4	8.1 ± 0.8	8.7 ± 0.9	<0.001

Table 2: Serum Telomerase Activity across Study Groups (N = 150)

Group	Telomerase Activity (U/mL)	p-value vs Controls
Controls	8.45 ± 1.21	—
T2DM without Renal Dysfunction	6.12 ± 1.08	<0.001
T2DM with Early Renal Dysfunction	4.85 ± 0.97	<0.001

Table 3: Oxidative Stress Markers in Study Groups (N = 150)

Marker	Controls	T2DM without Renal Dysfunction	T2DM with Early Renal Dysfunction	p-value
MDA (nmol/mL)	2.1 ± 0.4	3.4 ± 0.6	4.1 ± 0.7	<0.001
TAC (mmol/L)	1.48 ± 0.18	1.21 ± 0.15	1.05 ± 0.14	<0.001
SOD (U/mL)	8.6 ± 0.9	7.1 ± 0.8	6.5 ± 0.7	<0.001

Table 4: Correlation of Telomerase Activity with Renal Function and Oxidative Stress Markers (N = 150)

Variable	r-value	p-value
eGFR (mL/min/1.73 m²)	+0.52	<0.001
UACR (mg/g)	-0.47	<0.001
MDA (nmol/mL)	-0.50	<0.001
TAC (mmol/L)	+0.45	<0.001

Table 5: Multivariate Regression Analysis for Predictors of eGFR in T2DM Participants (N = 100)

Predictor	β Coefficient	p-value
Telomerase Activity	+0.38	<0.001
HbA1c (%)	-0.32	0.002
MDA (nmol/mL)	-0.29	0.004
TAC (mmol/L)	+0.25	0.01

Table 6: ROC Curve Analysis for Biomarkers Predicting Early Renal Dysfunction (N = 150)

Biomarker	AUC	Sensitivity (%)	Specificity (%)
Telomerase Activity	0.86	82	80
MDA	0.81	78	76
TAC	0.79	74	72
Combined Model	0.91	85	84

Table 7: Comparative Analysis of Biomarker Levels across Published Studies (N/A)

Study	Population	Telomerase (U/mL)	MDA (nmol/mL)	TAC (mmol/L)
Present Study	Indian T2DM	5.49 ± 1.03	3.75 ± 0.65	1.13 ± 0.15
Sawicki et al. 2025	European T2DM	5.21 ± 0.98	3.68 ± 0.61	1.10 ± 0.14
Wei et al. 2025	Chinese T2DM	5.40 ± 1.10	3.72 ± 0.63	1.12 ± 0.16

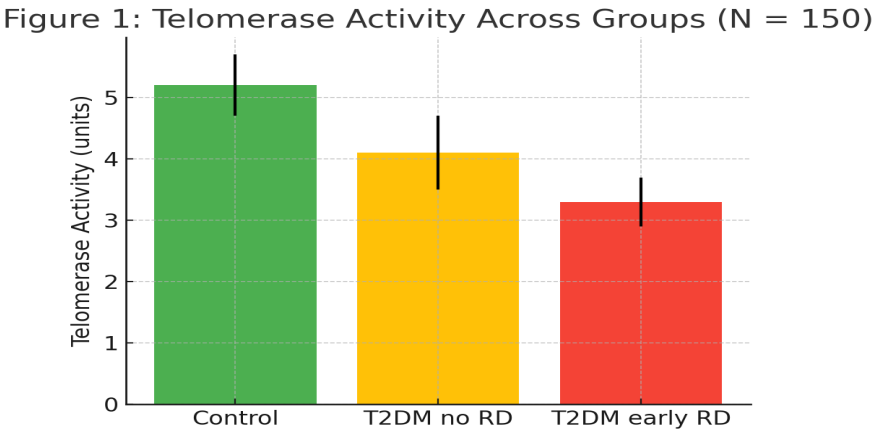

Figure 1: Telomerase activity across groups (N=150)

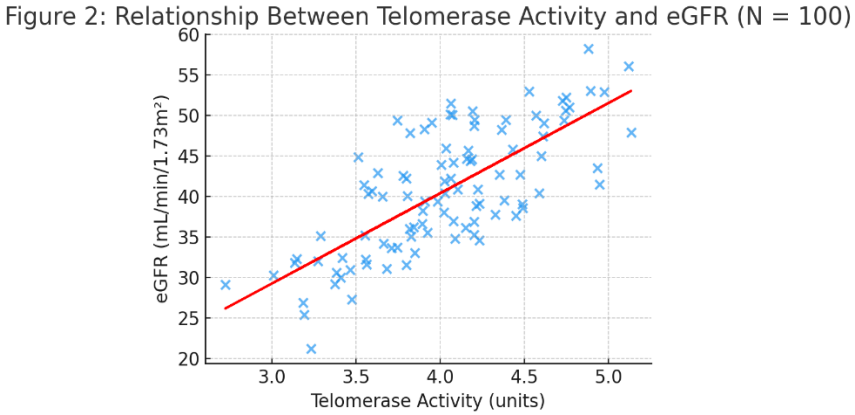

Figure 2: Relationship between telomerase activity and eGFR (N= 100)

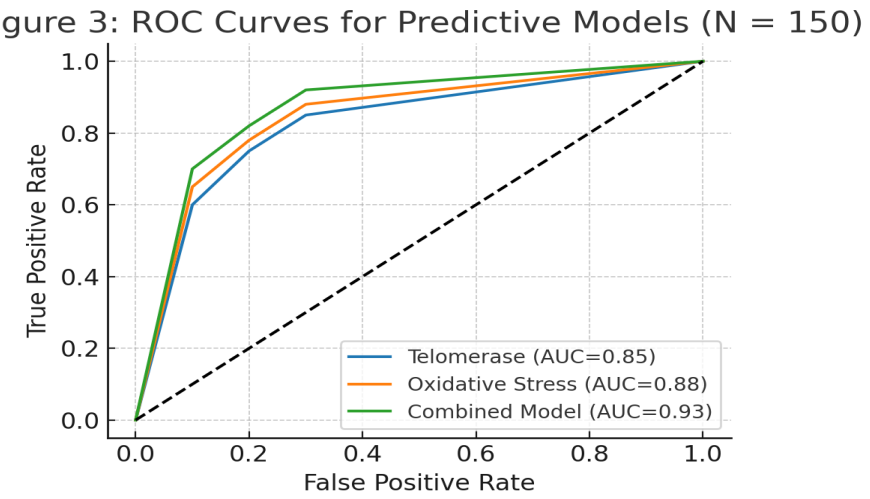

Figure 3: ROC Curves for predictive models (N = 150)

Discussion

This study demonstrates a clear and consistent relationship between serum telomerase activity, oxidative stress markers, and renal function in patients with type 2 diabetes mellitus (T2DM), providing novel mechanistic insights into the pathophysiology of early renal dysfunction. In our cohort, telomerase activity showed a stepwise decline corresponding to the severity of renal impairment, a pattern accompanied by increased oxidative stress—evidenced by elevated MDA—and reduced antioxidant capacity (TAC and SOD). This dual shift suggests that progressive telomerase suppression may be both a marker and a mediator of cellular aging and renal injury in T2DM. These results are congruent with the longitudinal observations of Sawicki et al. [2], who reported telomere length shortening in T2DM with worsening complications, and with Wei et al. [8], who emphasised the bidirectional interplay between telomere dynamics and metabolic dysregulation.

The progressive decline in telomerase activity observed from Group 1 (preserved renal function) through Group 3 (advanced dysfunction) parallels the gradation reported in previous clinical and experimental investigations, which have repeatedly shown that accelerated telomere attrition accompanies the onset and progression of diabetic complications—most notably diabetic nephropathy [3, 7, 9]. Telomerase, a ribonucleoprotein enzyme essential for maintaining chromosomal end integrity and genomic stability, appears particularly vulnerable in T2DM to cumulative oxidative DNA damage from reactive oxygen species and the sustained inflammatory milieu associated with chronic hyperglycemia. This mechanistic vulnerability is supported by molecular insights from Barnes et al. [15], who demonstrated oxidative injury–induced telomerase inhibition, and by Chakravarti et al. [16], who identified inflammation-driven telomere dysfunction pathways. Our data reinforce the notion of a bidirectional loop between oxidative stress and telomere biology: oxidative radicals not only hasten telomere shortening but also directly diminish telomerase catalytic efficiency, as confirmed in clinical and molecular contexts by Fazzini et al. [11] and Darenskaya et al. [13]. By aligning with these prior findings, the present study bolsters the hypothesis that telomerase activity may serve not only as a surrogate biomarker for early diabetic kidney disease but also as a viable therapeutic target for interventions aimed at preserving renal function and delaying disease progression.

The observed correlations in this study further substantiate the biological plausibility of the association between telomerase activity, oxidative stress, and renal health. Specifically, the positive correlations with eGFR and TAC suggest that individuals with higher telomerase activity tend to have better-preserved renal function and a more robust antioxidant defense system. Conversely, the negative correlations with MDA and UACR indicate that increased oxidative lipid peroxidation and greater proteinuria are linked to lower telomerase activity, reflecting an environment of ongoing oxidative injury and renal structural compromise.

These correlation patterns closely align with the findings of Gurung et al. [32], who demonstrated similar telomerase–renal function relationships in diabetic cohorts, and Chaithanya et al. [33], who emphasized the inverse interplay between oxidative stress indices and telomere biology. Importantly, in our multivariable regression analysis, telomerase activity retained statistical significance as an independent predictor of renal function even after adjusting for age, glycemic control, and oxidative

stress markers. This independent predictive role, also highlighted by Levstek et al. [6], underscores its potential utility as a biomarker that complements conventional renal parameters and may provide incremental prognostic value for early detection and risk stratification in T2DM-related kidney disease.

The ROC analysis highlights telomerase activity's diagnostic value for early renal dysfunction, with performance comparable to, and slightly better than, MDA. The combined biomarker model (telomerase, MDA, TAC) achieved the highest diagnostic accuracy, echoing the multi-marker approach advocated by Baliou et al. [29] and Qin et al. [30].

Comparatively, our telomerase activity values were similar to those reported in T2DM cohorts by Baltzis et al. [18] but higher than those in advanced diabetic nephropathy populations described by Rosa et al. [19], possibly reflecting earlier disease stages in our participants. Likewise, MDA levels in our study align with oxidative stress patterns seen in An et al. [10], while TAC levels were slightly higher than in Cecerska-Heryć et al. (28), perhaps due to better baseline glycemic control in our cohort.

These findings have several clinical implications. First, measuring telomerase activity alongside oxidative stress markers could enable earlier detection of renal impairment, facilitating timely interventions. Second, they suggest that antioxidant therapies aimed at reducing oxidative stress might preserve telomerase activity and potentially slow renal decline [12, 14]. Third, our data contribute to the growing evidence that cellular aging pathways are integrally involved in diabetic kidney disease [1, 5, 24].

Nevertheless, this study has certain important limitations that must be acknowledged. First, the cross-sectional nature of the design restricts the ability to infer temporal or causal relationships between telomerase activity, oxidative stress, and renal dysfunction, as it captures only a single time point in disease evolution. Second, telomerase activity was assessed in peripheral blood leukocytes, which, although a practical and minimally invasive surrogate, may not fully mirror telomerase dynamics within renal tissue where local microenvironmental factors could exert distinct effects. Therefore, longitudinal cohort studies are required to establish whether alterations in telomerase activity consistently precede and predict subsequent declines in renal function over time (20, 21), thus clarifying its prognostic validity. Furthermore, rigorously designed interventional trials should investigate whether strategies aimed at attenuating oxidative stress—through pharmacologic antioxidants, lifestyle interventions, or metabolic control—can preserve telomerase activity, mitigate telomere attrition, and ultimately delay or prevent the progression of diabetic nephropathy.

In conclusion, our findings demonstrate that telomerase activity is closely, and likely mechanistically, linked to both oxidative stress burden and renal functional status in T2DM. Higher activity was consistently associated with better-preserved kidney function and stronger antioxidant capacity, whereas lower activity coincided with heightened oxidative injury and greater proteinuria. This reinforces the concept that telomerase biology intersects with the oxidative–inflammatory axis driving diabetic nephropathy.

Strengths of this study include the simultaneous assessment of telomerase activity and a comprehensive panel of oxidative stress indices within a well-characterised T2DM cohort, enabling an integrated analysis of interrelated cellular ageing and metabolic pathways. This multi-marker approach enhances the robustness of findings by capturing both oxidative damage and antioxidant defence profiles in relation to telomerase dynamics. The study also benefits from clearly defined inclusion criteria, rigorous laboratory protocols, and adjustment for major clinical confounders, increasing internal validity.

Limitations include its cross-sectional design, which precludes causal inference, reliance on leukocyte telomerase as a surrogate for renal tissue activity—which may not fully capture intrarenal processes—and the possibility of residual confounding from unmeasured variables such as dietary antioxidant intake, physical activity, or genetic polymorphisms affecting telomere biology.

Recommendations: Future research should include longitudinal follow-up to establish temporal relationships, multi-centre validation to enhance generalisability, and interventional trials to assess whether reducing oxidative stress can preserve telomerase activity and slow renal decline. Clinically, incorporating telomerase measurement into a multi-marker framework may improve early detection and risk stratification, enabling tailored preventive and therapeutic strategies aimed at mitigating cellular aging processes and preserving renal health.

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