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Original Article

Physiology Section

Comparison of Levels of Telomerase, Oxidative Stress, Adiponectin, Leptin, and Interleukin-6 in First Degree Relatives of Diabetics, Prediabetics, and Diabetics: A Cross-sectional Study

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ABSTRACT

Introduction: Rapid beta-cell senescence caused by telomere shortening is associated with type 2 diabetes. Hence, studying telomere dynamics in prediabetic stages or First Degree Relatives of Diabetics (FDRD) is crucial. Telomere attrition is influenced by oxidative stress, which is prevalent in diabetics, prediabetics, and FDRD due to dyslipidaemia. The relationship between telomerase activity and glycaemic control, insulin resistance, oxidative stress, dyslipidaemia, adipocytokines, and inflammatory markers remains unclear and requires further investigation.

Aim: To assess and compare telomerase levels, oxidative stress (malondialdehyde), adipocytokines (leptin, adiponectin, and Interleukin-6 (IL-6), lipid profiles, and Body Fat Percentage (BF%) across the glycaemic spectrum in the Indian population.

Materials and Methods: This cross-sectional study was conducted at the Department of Physiology, JIPMER, Puducherry, from 2016 to 2018, involving four groups: Group I (control group, non diabetic, healthy, non FDRD, n=63), Group II (FDRD, non diabetic, n=63), Group III (prediabetics, n=63), and Group IV (diabetics, n=63). Participants aged 30-50 years, matched for age and gender, were recruited. Anthropometric variables, cardiovascular parameters, telomerase levels, Malondialdehyde (MDA), adiponectin, leptin, IL-6, and lipid profiles were assessed. Mean differences were analysed using one-way Analysis of Variance (ANOVA) or Kruskal-Wallis test, while Pearson's correlation analysis was performed to assess the correlation between telomerase levels, glucose concentration, and BF%.

Results: An increasing trend in circulating telomerase levels, lipid profiles, and BF% was observed across the glycaemic spectrum. Circulating leptin concentrations did not differ between the groups. However, there was a decrease in circulating adiponectin concentration as the glycaemic status progressed. Increased MDA levels were observed only in the diabetics group. Telomerase levels showed a significant association with circulating glucose concentration (fasting and postprandial) and BF%.

Conclusion: The circulating telomerase level increased along the glycaemic spectrum (non FDRD<FDRD<Prediabetics< Diabetics). The major finding was that telomerase level increases even in normoglycaemic FDRD. Oxidative and inflammatory parameters did not significantly differ in FDRD compared to non FDRD individuals. Notably, adiponectin, Tumour Necrosis Factor (TNF)-α, Low-Density Lipoprotein (LDL), and High-Density Lipoprotein (HDL) were the parameters that showed changes in FDRD.

Keywords: Adipocytokines, Diabetes mellitus, Prediabetic state, Type 2 diabetes

INTRODUCTION

Approximately 74 million people in India have diabetes, and it is projected to increase to 125 million by 2045 [1]. Engaging in regular physical activity, avoiding smoking, maintaining a healthy diet, and achieving a normal body weight can help delay the onset of diabetes [2]. However, age is a non modifiable risk factor for diabetes, and the prevalence of diabetes increases with age regardless of any modifiable risk factors [3]. Furthermore, diabetes is considered to cause accelerated ageing [4].

Telomeres, which are repetitive nucleotide sequences at the end of human chromosomes, shorten with each cell division, contributing to genomic stability [5]. Therefore, telomere length can indicate the age of a cell. The length of telomeres depends on the enzyme telomerase [6], which can replace lost telomere sequences during replication [7]. Consequently, shortened telomeres can result from a relative or absolute decrease in telomerase activity. Additionally, short telomeres have been associated with cardiovascular risk [8]. Telomerase activity is now recognised as an important cardio-metabolic biomarker, linked to the progression of Type 2 Diabetes Mellitus (T2DM) and its complications [9]. Decreased telomere length has even been reported in individuals with prediabetes [9,10]. However, the presence or absence of telomere attrition in FDRD is still a topic of debate [11,12]. A recent study suggests that the rapid progression of beta-cell senescence, due to accelerated telomere shortening, is a possible cause of type 2 diabetes [13], as short telomeres have been shown to interfere with B cell signaling and lifespan [14]. Hence, telomere attrition or disturbances in telomerase activity could have begun before the onset of diabetes, highlighting the importance of studying these parameters in the prediabetic stage and in FDRD.

Although telomere length and the rate of telomere shortening are genetically programmed, they are also influenced by external factors [15]. Specifically, oxidative stress contributes to telomere shortening in T2DM [16,17]. Individuals with diabetes, prediabetes [18], and FDRD [19] often have dyslipidaemia, which in itself can cause oxidative stress. Adipocytokines (adiponectin and leptin) [20] and inflammation are also implicated in the pathophysiology of diabetes. However, the association between telomerase activity and

glycaemic control, insulin resistance, oxidative stress, dyslipidaemia, adipocytokines, and inflammatory markers is not yet clear [9,21] or remains to be studied. Given these factors, the present study was designed to assess and compare telomerase levels, oxidative stress MDA, adipocytokines (leptin, adiponectin, and IL-6), lipid profile, and BF% across the glycaemic spectrum in the Indian population.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Physiology, JIPMER, Puducherry, India from June 2016 to November 2018. The data presented here are from a larger study conducted as a Ph.D. project. The publications of other parts of the project can be found elsewhere [22-24]. The study was approved by the Institute Scientific Advisory Committee (JSAC/34/7/2016) and the Institutional Human Ethics Committee (No.JIP/IEC2016/28/939).

Inclusion criteria: Individuals of either gender, aged between 30 and 50 years, who were of native Indian origin and residing in and around Puducherry, were included in the study.

Exclusion criteria: Participants with random blood sugar levels ≥200 mg/dL, or those with prehypertension/hypertension, were excluded and advised to visit a nearby hospital for further medical support. Smokers, pregnant women, morbidly obese participants, and participants with any known organic disorders were also excluded from the study.

Procedure

The study consisted of four groups to cover the glycaemic spectrum: Group I - normoglycaemic healthy volunteer non FDRD, Group II - normoglycaemic FDRD (either parent or sibling, not less than a year), Group III - prediabetics, and Group IV - diabetics. The American Diabetes Association (ADA) diagnostic criteria [25] were used to define the population for prediabetics and diabetics groups. Subject recruitment was mainly conducted during the prediabetes screening camp held in and around Puducherry (n=1,177). Participants were requested to report after an overnight fasting period. After obtaining consent for the screening camp, a family history of diabetes along with other relevant personal and medical history was collected. Blood pressure (BP) was measured using an automatic BP monitor (Model: CH432B, Citizen Systems Japan Co., Ltd., Tokyo, Japan) following the JNC-7 recommendations [26]. Capillary blood sugar levels were measured using a blood glucometer (OneTouch Verio Flex® Blood Glucose Monitoring System). Recruitment for the diabetic group mainly took place in the Medicine Outpatient Department (OPD) at JIPMER, Puducherry. Diabetics on insulin therapy or with any known complications were excluded. People accompanying diabetics in the Medicine OPD were also considered for enrollment as participants under the FDRD or prediabetics group.

The study was explained to all the individuals considered for participation, and their written consent to participate was obtained. They were instructed to report to the Physiology department after an overnight fasting period, around 8 AM. Upon arrival, participants were given 10 minutes of rest in a sitting position, and baseline blood pressure (BP) and heart rate were manually recorded. Five milliliters of blood were collected from the antecubital vein for biochemical measurements, and an additional 3 milliliters were collected two hours after consuming 75 g of oral glucose. Following that, basic anthropometric measurements were made and BF% was measured using bioimpedance analysis. The assignment of participants to each group was based on the blood sugar levels (fasting and postprandial) obtained in lab sample, and family history of diabetes as explained in study population section. Total 252 participants were recruited, 63 in each group. The sample size was calculated based on a vascular parameter ET-1 , which is described elsewhere [22].

Parameters measured: The anthropometric variables (height, weight, and Body Mass Index (BMI) which were measured by certified personnel using standardised stadiometers and weighing scales recommended by the International Society for the Advancement of Kinanthropometry (ISAK). BMI was calculated using the Quetelet index [27]. Heart rate and BP were measured for all participants. BP was recorded using a BP mercury sphygmomanometer (Model: Diamond Deluxe: BPMR 120, Industrial Electronic and Allied Products, Pune, Maharashtra, India), with participants in a seated position after sufficient rest, in the right arm. Two BP readings were taken with a five-minute interval by the same person. Pulse rate was manually recorded from the right radial artery. Body composition analysis was performed using bioelectrical impedance analysis, which involves measuring bioelectrical resistive impedance [28]. BF% was determined using the software connected to the Quadscan 4000 bodystat machine (Model QuadScan 4000®, Isle of Man, United Kingdom).

For biochemical analysis, the collected blood samples were centrifuged, and the serum was separated and stored at -80°C for further analysis. Blood glucose levels were analysed using the glucose oxidase-peroxidase (GOD-POD) method using an automated Olympus AU 400 Clinical Chemistry Analyser (USA). Telomerase activity was measured using an Enzyme Linked Immuno Sorbent Assay (ELISA) kit (Elabscience Biotechnology) based on the sandwich-ELISA principle. MDA levels were quantified using the thiobarbituric acid reactive substances assay (QuantiChromTM TBARS Assay Kit, DTBA-100, Bioassay Systems, USA) according to the manufacturer's guidelines. Adiponectin (RayBio Human Acrp30 ELISA kit, Norcross, GA), leptin (DBC Diagnostics Biochem Canada Inc., Canada), and IL-6 (Quantikine, R&D Systems, USA) concentrations were measured using ELISA kits according to the manufacturer's instructions. Lipid profiles were analysed using the automated Olympus AU 400 Clinical Chemistry Analyser (USA). Total cholesterol was measured using an enzymatic colorimetric method (Diagnostic kit from Beacon Diagnostics, Navsari, India). High-Density Lipoprotein-Cholesterol (HDL-C) was directly measured using an enzymatic colorimetric method (Diagnostic kit from Agappe Diagnostics, Kerala, India). Triglycerides (TG) were quantified using an enzymatic colorimetric method (Diagnostic kit from Beacon Diagnostics, Navsari, India). LDL cholesterol and Very Low-Density Lipoprotein (VLDL) levels were calculated using Friedewald's formula [29].

STATISTICAL ANALYSIS

Telomerase, MDA, adiponectin, leptin, IL-6, and TNF-α did not follow a normal distribution and were expressed as median (interquartile range). A comparison of these variables across groups was conducted using the Kruskal-Wallis test, followed by the Mann-Whitney U test for post-hoc analysis. Lipid profile and its derived parameters followed a normal distribution and were expressed as mean and standard deviations (SD). The mean difference was calculated using one-way ANOVA, followed by a post-hoc test. The correlation coefficient was determined using the Spearman correlation test. The analysis was performed using Statistical Package for the Social Sciences (SPSS) version 19.0 (SPSS, Inc., Chicago, IL).

RESULTS

Data on age, gender, BMI, heart rate, BP, fasting insulin, and insulin resistance are presented elsewhere. Authors have summarised the results, and kindly request readers to refer to the previous publications for further details.

[Table/Fig-1] shows a comparison of telomerase, MDA, adiponectin, leptin, IL-6, and TNF-alpha across the glycaemic spectrum. Telomerase levels increase along the glycaemic spectrum. On post-hoc analysis, there was no significant difference in telomerase

Parameters	Control (Group I) (n=63) Median (IQR)	FDRD (Group II) (n=63) Median (IQR)	Prediabetics (Group III) (n=63) Median (IQR)	Diabetics (Group IV) (n=63) Median (IQR)	Kruskal Wallis test	Post-hoc analysis I vs II	I vs III	I vs IV	II vs III	II vs IV	III vs IV
Telomerase											
Telomerase (ng/mL)*	5.75 (2.19)	6.52 (4.59)	7.13 (7.36)	7.36 (4.28)	0.001	0.083	0.005	<0.001	0.220	0.037	0.535
Oxidative stress											
MDA (µM)	1.32 (4.49)	1.23 (3.21)	1.36 (5.54)	7.04 (2.04)	<0.001	0.723	0.633	<0.001	0.493	<0.001	<0.001
Adipocytokines											
Adiponectin (pg/mL)	35578.99 (47122.19)	6203.00 (2649)	279.44 (20046.89)	191.29 (4430.11)	<0.001	<0.001	<0.001	<0.001	0.063	<0.001	0.066
TNF-α (pg/mL)	7.83 (8.96)	8.54 (12.21)	11.96 (19.73)	24.03 (21.18)	<0.001	0.411	0.002	<0.001	0.014	<0.001	0.002
Inflammatory markers											
IL-6 (pg/mL)	6.30 (9.11)	5.99 (4.22)	6.03 (7.67)	14.49 (32.68)	<0.001	0.612	0.195	<0.001	0.124	<0.001	0.002
Leptin (ng/mL)	8.32 (18.21)	13.61 (25.89)	13.19 (24.6)	14.01 (25.49)	0.117	0.052	0.048	0.045	0.897	0.944	0.959

[Table/Fig-1]: Comparison of telomerase, adipocytokines, inflammatory markers and oxidative stress across the groups.
Comparison was done using Kruskal-Wallis test and post-hoc analysis using Mann-Whitney U test. The significance was set at p-value <0.05. (Group I)-Non first degree relatives of diabetes; FDRD (Group II)-First degree relatives of diabetes. MDA: Malondialdehyde; *Comparison was done using One-way ANOVA and post-hoc analysis by LSD

levels between non FDRD and FDRD, FDRD and prediabetes, and prediabetics and diabetics. Compared to non FDRD, prediabetics and diabetics had higher telomerase levels. Compared to FDRD, diabetics (p=0.037) had higher telomerase levels.

MDA was significantly higher in diabetics compared to non FDRD, FDRD, and prediabetics. Adiponectin was significantly lower in FDRD, prediabetics, and diabetics compared to the control group. Leptin remains comparable along the glycaemic spectrum. IL-6 was significantly higher in the diabetics group compared to all the other groups, while it is comparable among the other groups. TNF-alpha increases along the glycaemic spectrum. Prediabetics and diabetics have significantly higher TNF-alpha levels than the control and FDRD groups. Diabetics have significantly higher TNF-alpha levels than prediabetics.

[Table/Fig-2] shows a comparison of lipid profiles across the glycaemic spectrum. Lipid profile values (TC, TG, LDL, VLDL, TC/HDL, TG/HDL, AIP) increase along the glycaemic spectrum, while HDL values decrease along the glycaemic spectrum. Prediabetics and diabetics have significantly higher lipid profile values (except HDL, which was significantly lower) compared to the non FDRD group. Diabetics had significantly higher lipid profile values (except HDL, which was comparable) compared to FDRD.

[Table/Fig-3] shows the correlation between telomerase and glucose and BF%. There was a significant positive association between telomerase levels and fasting blood glucose, postprandial blood glucose, and BF%.

DISCUSSION

The objective of this study was to assess telomerase levels and associated parameters across the glycaemic spectrum. The major finding of this study was an increase in circulating telomerase levels along the glycaemic spectrum (non FDRD<FDRD<Prediabetics <Diabetics).

The groups were comparable based on age (p=0.132), gender (p=0.456), and BMI (p=0.495). BF% increased significantly in the three groups compared to group I. However, all the other three groups were comparable based on BF% [24]. Heart rate increases along the glycaemic spectrum as we move from group I to group IV. Post-hoc analysis showed that the heart rate was significantly higher in group II, III, and IV compared to group I, while it was comparable between group II, III, and IV. Both systolic and diastolic blood pressure were comparable along the glycaemic spectrum. Fasting insulin and insulin resistance (HOMA-IR) increase along the

Parameters	Control (Group I) (n=63) Mean±SD	FDRD (Group II) (n=63) Mean±SD	Prediabetics (Group III) (n=63) Mean±SD	Diabetics (Group IV) (n=63) Mean±SD	ANOVA	Post-hoc analysis I vs II	I vs III	I vs IV	II vs III	II vs IV	III vs IV
TC (mg/dL)	165.57±15.61	164.00±16.13	174.54±27.71	179.00±26.47	<0.001	0.692	0.024	0.001	0.008	<0.001	0.261
TG (mg/dL)	124.60±8.3	123.84±9.39	149.43±18.52	152.54±17.35	<0.001	0.763	<0.001	<0.001	<0.001	<0.001	0.218
HDL (mg/dLl)	47.52±4.59	44.24±6.45	44.33±6.53	44.60±6.27	0.005	0.002	0.003	0.007	0.929	0.734	0.801
LDL (mg/dL)	85.44±15.38	106.49±12.19	108.94±13.06	112.37±12.72	<0.001	<0.001	<0.001	<0.001	0.307	0.015	0.152
VLDL (mg/dL)	24.92±1.66	24.77±1.88	29.89±3.7	30.51±3.47	<0.001	0.763	<0.001	<0.001	<0.001	<0.001	0.218
TC/HDL	3.51±0.45	3.78±0.65	4.05±0.97	4.10±0.87	<0.001	0.048	<0.001	<0.001	0.054	0.020	0.684
TG/HDL	2.65±0.3	2.86±0.47	3.46±0.75	3.49±0.66	<0.001	0.038	<0.001	<0.001	<0.001	<0.001	0.730
AIP	0.42±0.05	0.45±0.07	0.53±0.09	0.54±0.08	<0.001	0.021	<0.001	<0.001	<0.001	<0.001	0.636

[Table/Fig-2]: Comparison of lipid profiles and derived parameters.
Comparison was done using One-way ANOVA and post-hoc analysis using LSD test; The significance was set at p-value <0.05; TC: Total cholesterol; TG: Triglycerides; HDL: High density lipoprotein; VLDL: Very low-density lipoprotein; LDL: Low density lipoprotein; AIP: Atherogenic index of plasma

Parameters	Telomerase level r-value	p-value
Fasting plasma glucose (mg/dL)	0.141	0.025
Postprandial glucose (mg/dL)	0.206	<0.001
Body fat (%)	0.230	<0.001

[Table/Fig-3]: Correlation coefficient between blood glucose levels and body fat percentage (BF%) with telomerase level.
Correlation was done using Spearman rank correlation.The significance was set at p-value <0.05

glycaemic spectrum. There is no significant difference in fasting insulin level and insulin resistance between non FDRD vs FDRD and prediabetics vs diabetics. However, fasting insulin levels and insulin resistance in prediabetics and diabetics are significantly higher compared to non FDRD and FDRD [23].

Telomere length is influenced by hereditary factors [30,31], with oxidative stress considered the primary cause of telomere shortening. Additionally, various factors such as higher BF% [32], dyslipidaemia [33],

high insulin levels [34], insulin resistance [35], increased inflammatory markers [36], decreased adiponectin levels [37], and high leptin levels [38] have been associated with reduced telomere length.

Diabetes is known to accelerate the ageing process [4] and induce a reduction in DNA unwinding rate [39], decrease Na+K+ATPase activity, increase collagen cross-linking, and oxidative damage [40]. Oxidative stress has been shown to accelerate telomere attrition during DNA replication [41]. Oxidative stress-induced single-strand breaks in telomeres can lead to faster telomere loss by stalling the replication fork [42-44]. It can be hypothesised that decreased telomere length due to oxidative damage may trigger a compensatory increase in telomerase levels to limit telomere shortening for genomic stability.

Similar observations have been made in rats, where chronic stress increased telomerase levels [45]. A study on depressed individuals has reported shorter telomere length accompanied by a compensatory increase in telomerase activity [46]. Therefore, increased telomerase activity could be considered an indirect measure of decreasing telomere length [46]. In this study, it was observed that telomerase levels showed a gradual increase across the glycaemic spectrum, with significant positive correlations between fasting and postprandial blood glucose levels and telomerase levels. However, studies on diabetic subjects with angiopathy or foot ulcer have shown decreased telomerase activity [47,48]. This discrepancy may be attributed to the exclusion of diabetics with complications and insulin therapy in this study. It can be proposed that telomerase levels increase as a compensatory mechanism in the early stages of diabetes and decrease in the late stages, leading to diabetic complications.

Based on the findings of this study, the increase in telomerase levels in diabetics can be attributed to higher oxidative stress, BF%, insulin levels, insulin resistance, dyslipidaemia, and low adiponectin levels observed in this group. However, the increase in telomerase levels in prediabetics could not be solely explained by oxidative stress levels, as MDA levels were not significantly different from the control group. It has been suggested that rapid T cell proliferation during conditions such as exacerbation of psoriasis or Chronic Obstructive Pulmonary Disease (COPD) can lead to short telomeres, overriding the compensatory increase in telomerase levels [49,50]. Hyperglycaemia-induced T cell activation and proliferation, mediated by oxidative stress [51], could potentially contribute to telomere shortening in prediabetics. Furthermore, higher insulin levels, insulin resistance, BF%, dyslipidaemia, and lower adiponectin levels observed in the prediabetics group could lead to telomere shortening through mechanisms other than oxidative stress.

Oxidative stress levels, glucose levels, insulin levels, and insulin sensitivity were comparable between the non FDRD control group and the FDRD group. With the exception of higher LDL and lower HDL, the lipid profiles of both groups were similar. The only significant difference from the control group was lower adiponectin levels and higher BF% in the FDRD group. These observations do not fully explain the non significantly higher telomerase levels in the FDRD group. Maternal stress during pregnancy has been associated with shorter telomere length in offspring of diabetic mothers [52]. Therefore, it can be hypothesised that FDRD individuals may have initially had shorter telomere length, and T cell dysregulation and proliferation in later life may have accelerated telomere attrition. However, this hypothesis does not apply to all FDRDs, prompting us to consider an alternate hypothesis proposed by Yi HS et al., [53]. They suggest that senescent T cells may serve as precursors of abnormal glucose homeostasis rather than being a result of hyperglycaemia. They observed increased CD4 T cell proliferation enhancing inflammation through TNF-α in prediabetic subjects, which aligns with this study's observation of increased inflammatory markers in prediabetics [53]. It can be noted that inflammatory markers and telomerase levels show an increasing trend across the glycaemic spectrum in this study. Therefore, it can be proposed that senescence in T cells (indicated by increased telomerase levels) precedes abnormal glucose homeostasis in this study as well.

Limitation(s)

One limitation of this study is that telomere length was not measured directly. Additionally, T cell function was not measured, and the sub-classification of T cells with reduced telomere length was not studied, which would be the logical extension of this study.

CONCLUSION(S)

The circulating telomerase level increased along the glycaemic spectrum (non FDRD<FDRD<Prediabetics<Diabetics). The major finding was that telomerase levels increase even in normoglycaemic FDRD. Oxidative parameters (MDA) and inflammatory parameters (IL6, Leptin) were not altered in FDRD compared to non FDRD. Adiponectin, TNF-α, LDL, and HDL were the parameters that showed changes in FDRD. This necessitates revisiting various parameters that contribute to the development of diabetes to identify an earlier marker of derangement.

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