Telomerase Activity in Diabetic Patients with Angiopathy

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Abstract: Background: Diabetes mellitus (DM) is associated with damage to target organs and premature aging and telomeres serve as a mitotic clock and biological marker of senescence. **Aim of study:** was to A) evaluate telomerase activity in both type 1 and type 2 diabetic patients with microangiopathy and macroangiopathy, B) to study the possible factors that affect the activity of this enzyme in these patients. **Subjects and Methods:** Study was carried out on 40 patients from those attending diabetes clinics of Banha University Hospital, they were divided into three groups: **Group I:** 10 type 1 diabetic patients with angiopathy (4males & 6 females). **Group II:** 10 type 2 diabetic patients with angiopathy (3males & 7females). **Group III:** 20 apparently healthy age & sex matched volunteers serving as a control group**.** The following laboratory investigations were performed to all patients: Plasma glucose (fasting and post prandial), Glycated hemoglobin, Lipogram (Total cholesterol, LDLc, HDLc and Triglycerides), Serum creatinine, Urinary microalbumin and Study of telomerase activity in whole blood. **Results:** Our results showed: that (HBA1C, microalbumin, creatinine, LDL, TG, TCH, PPBS and FBS)are significantly higher in diabetic patients compared to control group where (telomeraseand HDL) are significantly lower in diabetic patients compared to control group. Also, Telomerase activity was significantly low in diabetic patients with HbA1C (≥7%)**,** LDL-c (>100mg/dl), HDL-c (<45mg/dl), TG (>150mg/dl), TCH (>200mg/dl), microalbuminuria (>30mg/ml) respectively compared to diabetic patients with HbA1C (<7%), LDL-c (<100mg/dl), HDL-c (>45mg/dl), TG (<150mg/dl), TCH (<200mg/dl), and normoalbuminuria (<30mg/ml). There was significant relation between telomerase activity and macroangiopathic complications, There was non significant correlation between telomerase activity and each of creatinine level and age in the case group. Statistical analysis showed that 80% of diabetic patients (16 patients) were telomerase negative (lower than cut off value ≤49.20), whereas 20% of diabetic patients (4 patients) were telomerase positive (higher than cut off value > 49.20). **Conclusion:** it was concludedthat telomerase enzyme activity decreased in both type 1 and type 2 diabetic patients with angiopathy, There was a relation between telomerase activity and both micro & macroangiopathic complications.

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Key words: telomerase, diabetic patients, angiopathy (micro- or macroangiopathy).

1. Introduction:

Diabetes mellitus (D.M) is a syndrome of disordered metabolism, associated with damage to target organs and premature aging[1].Usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia)[2].

Telomerase enzyme is a ribonucleoprotein maintaining the length of the telomeres (telomeres serve as a mitotic clock and biological marker of senescence) by adding G-rich repeats to the end of the eukaryoticchromosomes**.** Normal human somatic cells, cultured in vitro, have astrictly limited proliferative potential undergoing senescence after about (50-70) population doublings. In contrast, most of the tumor cells haveunlimited replicative potential[3].

Telomeres are composed of telomeric DNA and multiple bindingproteins that together act as a protective cap on the end of chromosomes.

The length of telomeres is maintained by a dynamic equilibrium betweenprocesses that shorten and lengthen telomeric DNA. Telomere shorteningserves as a checkpoint for the initiation of cell cycle arrest, which leads tocellular senescence (aging) and apoptosis (death). In healthy human somatic cells that lack telomere-lengthening by telomerase, the size oftelomeres decreases with each cell division and thus the cells have a finitecapacity for replication[4].Telomere shortness in humans is emerging as a prognostic marker of disease risk, progression, and premature mortality as in diabetes[5]**.** It was found that telomerase activity decreases in both type 1 andtype 2 diabetic patients and,since both types of diabetesdiffer in several aspects, including pathogenesis, severity, participation ofimmune system and other biological parameters, the difference intelomerase activity between them may be of interest[6]. The exact mechanism of low telomerase activity in diabeticpatients is still

controversial and may be explained by hyperglycemia, theproliferative stress imposed on the relevant cells or by the effect of theoxidative and metabolic stress[7].

Apart from replicative senescence, other exogenous factors e.g., oxidative stress, hypertension, hypercholesterolemia, and hyperglycemia, may be associated with low telomerase activity and telomere attrition. Reduced replicative capacity has been observed in cells harvestedfrom diabetic subjects and this finding has been correlated with some ofthe degenerative complications of poor glucose control in diabeticsubjects[8&9].

2. Subjects and Methods:

This study was carried out on forty patients selected from those attending diabetes clinics of Banha University Hospital. Patients were divided into three groups**: Group I:** included 10 type 1 diabetic patients with angiopathy(4males & 6females),**Group II:** included 10 type 2 diabetic patients with angiopathy (3males & 7females), **Group III:** Included 20 apparently healthy age & sex matched volunteers serving as a control group**.**.Any patient without micro- or macroangiopathic complications was excluded from the study.

I- All patients were subjected to a thorough history and clinical examination with stress on Mode of therapy, Microangiopathy (nephropathy, retinopathy, and neuropathy), Macroangiopathy (coronary, cerebral, and peripheral atherosclerosis) and Duration of diabetes.

II- Specimen collection: After 12 hours fasting, 10 ml venous blood sample was collected from all subjects by veni-puncture and divided as follow:

1. 1.5 ml of blood was delivered into a tube containing 1.2 mg/mlK3EDTA used for glycosylated hemoglobin (HBA1C).

2. The remainder was transferred into a plain tube, allowed to clot at37°C followed by centrifugation at 3000 r.p.m for 15 minutes. The serum was collected and used for determination of lipogarm, fasting serum glucose level and determination of telomerase activity (white blood cells are the most readily available source of normal human cells in which to measure telomerase activity directly).

3. Another blood sample was withdrawn postprandial for determination of post prandial serum glucose level.

III- The following laboratory investigations were performed to every subject:

A) Fasting and two hours post prandial serum glucose (glucose oxidase) and lipogarm(total cholesterol, triglyceride, HDLcholesterol) and **serum creatinine (jaffé method)** by Dimension RXL MAX auto analyser (Siemens Medical Solution Diagnostics, UL, USA) with estimation of LDL cholesterol by Fridwald equation LDLc= TCH – (TG/5 + HDLc).

B) Glycated hemoglobin (HbA1C): was assessed by BioSystems reagent kit provided by BioSystems, S.A. Costa Brava 30, Barcelona (SPAIN).

C) Microalbumin: was measured by BioSystems reagent kit provided byBiosystems, S.A. Costa Brava 30, Barcelona (SPAIN).

D) Specific study (Telomerase activity): was assayed in mononuclear cells extract using (Telomerase PCR ELISA PLUS) kit by Photometric Enzyme Immunoassay for Quantitative Determination of Telomerase Activity, Utilizing the Telomeric Repeat Amplification Protocol (TRAP),[10]**, (developed by Roche Applied Science), (Cat. No. 12 013 789 001).**

Statistical analysis:

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. Data were presented as range, mean ±SD and number (%). An explanation of logistic regression begins with an explanation of the logistic function, which, like probabilities, always takes on values between zero and one**.**

3. Results:

Table(1): shows that (HBA1C, microalbumin, creatinine, LDL, TG, TCH, PPBS and FBS) are significantly higher in diabetic patients compared to control group where (telomerase and HDL) are significantly lower in diabetic patients compared to control group. **Fig (1):** Statistical analysis showed that 80% of diabetic patients (16 patients) were telomerase negative (lower than cut off value ≤49.20), whereas 20% of diabetic patients (4 patients) were telomerase positive (higher than cut off value >49.20). **Fig (2)** shows the value of telomerasein case group & control group. **Table (2) and Figs (3,4,5,6,7,8.9,10)** shows that there was significant negative correlation between telomerase activity and each of HBA1C level, microalbumin level, , LDL level, TG level and TCH level, FBS level, PPBS level, while there was significant positive correlation between telomerase activity and HDL. There was nonsignificant correlation between telomerase activity and each of creatinine level and age in the case group. **Table(3)** shows that telomerase activity was significantly low in diabetic patients with HbA1C (≥7%) compared to diabetic patients with HbA1C (<7%). **Table(4)** shows that telomerase activity was significantly low in diabetic patients

with microalbuminuria (>30mg/ml) compared to diabetic patients with normoalbuminuria (<30mg/ml). **Table(5)** shows that telomerase activity was significantly low in diabetic patients with LDL-c (>100mg/dl) compared to diabetic patients with LDL-c (<100mg/dl). **Table(6)** shows that telomerase activity was significantly low in diabetic patients with HDL-c(<45mg/dl) compared to diabetic patients with HDL-c (>45mg/dl). **Table (7)** shows that telomerase activity was significantly low in diabetic patients with TG (>150mg/dl) compared to diabetic patients with TG (<150mg/dl). **Table(8)** shows that telomerase activity was significantly low in diabetic patients with TCH (>200mg/dl) compared to diabetic patients with TCH (<200mg/dl). **Table (9)** shows that there is non significant difference between telomerase activity and creatinine level. **Table (10)** shows that there was non significant correlation between telomerase activity and duration of diabetes. **Table (11)**: Logistic Order Regression analysis table, it provided the order of values of patient parameters (HBA1C, lipid profile, microalbumin, Creatinine) for telomerase activity inwhich HBA1C was the most important parameter(score=21.3 & P=<0.001), followed by LDL (score=20 & P =<0.001), followed by TCH (score=8.23 & P =<0.001), followed by HDL (score=6.55 & P =<0.001), then microalbumin (score=5.3 & P =<0.05) but creatinine was non significant. **Table(12)** shows that there was significant relation between telomerase activity and macroangiopathic complications. Mean ± SD of telomerase activity in patients with macroangiopathic complications (7coronary atherosclerosis &1cerebral atherosclerosis &3peripheral atherosclerosis) (N=11, 55%) Vs patients without macroangiopathic complications (N=9, 45%) was (35±1.6) Vs(75.8±41.4).

Table (1): Comparison between case and control group regarding (telomerase, HBA1C, microalbumin, creatinine, lipid profile, PPBS, FBS, duration and age):

		N	Mean	Std. Deviation	t	P
AGE / y	CASE	20	39.6	5.2	-0.7	NS
	CONTROL	20	40.7	4.7		
DURATION / y	CASE	20	13.5	7.2	----------	----------
	CONTROL	0*	.	.		
Telomerase	CASE	20	53.3	34	4.03	<0.05
	CONTROL	20	90.9	62.7		
HBA1C%	CASE	20	8.7	1.5	9.9	<0.001
	CONTROL	20	5	0.62		
MICROALBUM	CASE	20	31.1	15.6	5.4	<0.001
Mg/ml	CONTROL	20	11.1	4.1		
CREATININE	CASE	20	0.9	0.2	4.9	<0.001
Mg/dl	CONTROL	20	0.74	0.1		
LDL	CASE	20	127	19.8	7.1	<0.001
Mg/dl	CONTROL	20	92.3	9		
HDL	CASE	20	42.8	3.6	-9.7	<0.001
Mg/dl	CONTROL	20	56.9	5.3		
TG	CASE	20	149.7	37.5	7.5	<0.001
Mg/dl	CONTROL	20	84.4	9.7		
TCH	CASE	20	222.7	60.8	5.5	<0.001
Mg/dl	CONTROL	20	143.5	20.3		
PPBS	CASE	20	366.25	153.4	7.5	<0.001
Mg/dl	CONTROL	20	105.6	10.5		
FBS	CASE	20	243.6	126	5.6	<0.001
Mg/dl	CONTROL	20	84.6	9.4		

Table (2): Correlation of Telomerase Activity with HBA1c, Microalbumin, Creatinine, lipidprofile, FBS, PPS and Age in Case Group:

CASE	HBA1C (%)	r	-0.58
		P	<0.05
	Microalbum (Mg/ml)	r	-0.51
		P	<0.05
	Creatinine (Mg/dl)	r	-0.34
		P	NS
	LDL-c (Mg/dl)	r	-0.72
		P	<0.001
	HDL-c (Mg/dl)	r	0.51
		P	<0.05
	TG (Mg/dl)	r	-0.67
		P	<0.001
	TCH (Mg/dl)	r	-0.81
		P	<0.001
	PPBS (Mg/dl)	r	-0.47
		P	<0.05
	FBS (Mg/dl)	r	-0.45
		P	<0.05
	AGE / y	r	-0.1
		P	NS

Area Under the Curve

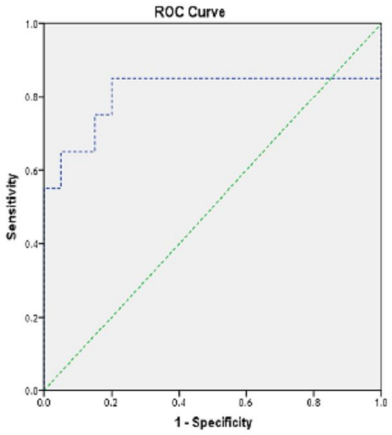
Test Result Variable(s): telomerase

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.810	0.080	0.001	0.653	0.967

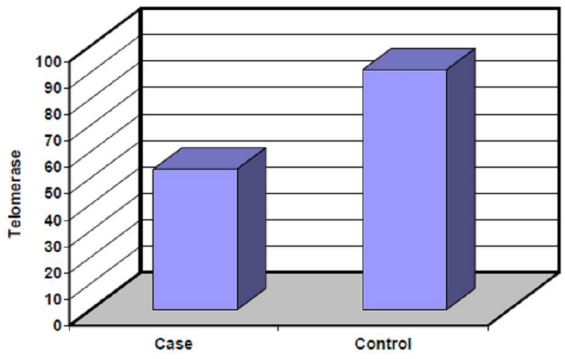
a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

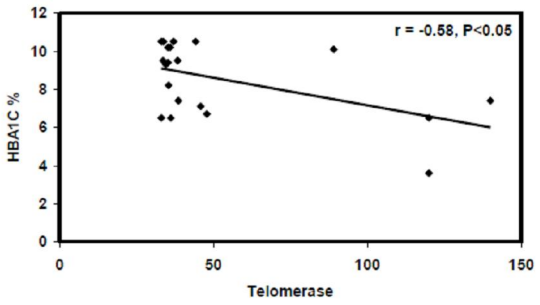
Cut Off	Sensitivity	Specificity	+Ve Predictive	-Ve Predictive	Accuracy
≤49.20	85%	80%	80.9%	84.2%	82.5%



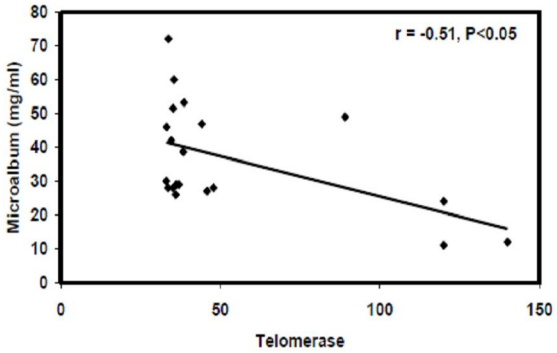
Fig(1) ROC Curve



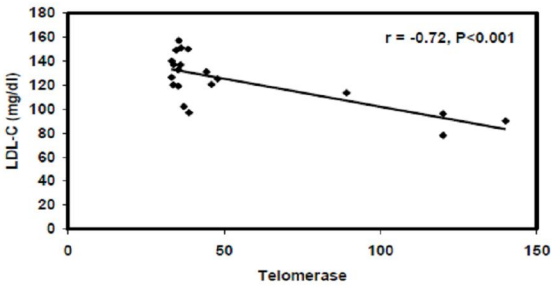
Fig(2): Histogram for Telomerase Value in Control and Case group.



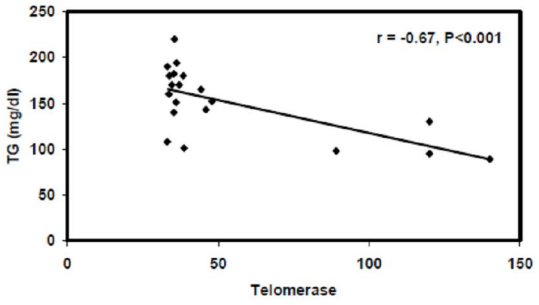
Fig(3): Scatter diagram for correlation between Telomerase activity and HBA1cin case group:



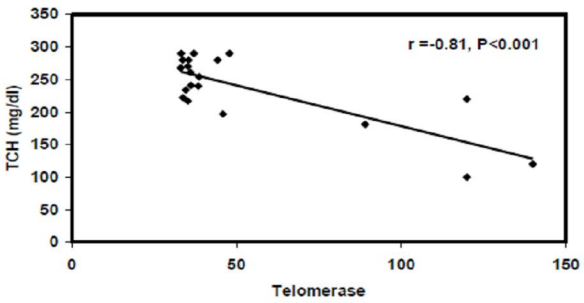
Fig(4): Scatter diagram for correlation between Telomerase activity and Microalbumin in case group.



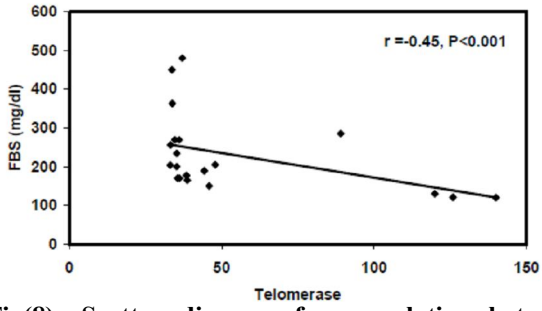
Fig(5): Scatter diagram for correlation between Telomerase activity and LDL-C in case group.



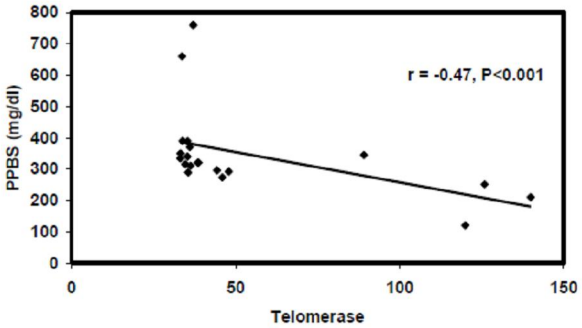
Fig(6): Scatter diagram for correlation between Telomerase activity and Triglycerides in case group.



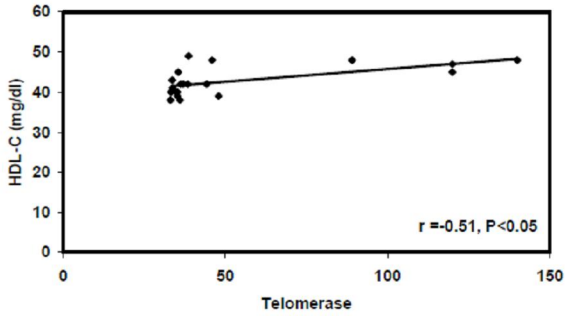
Fig(7): Scatter diagram for correlation between Telomerase activity and Total Cholesterol in case group.



Fig(8): Scatter diagram for correlation between Telomerase activity and FBS in case group.



Fig(9): Scatter diagram for correlation between Telomerase activity and PPS in case group.



Fig(10): Scatter diagram for correlation between Telomerase activity and HDL-C in case group.

Table(3):Comparison of telomerase activity in patients with HBA1C(<7%)versus patients with HBA1C>7%).

Telomerase activity	HbA1C <7 %	≥7%	t	P
Mean ± SD	89.2±47.7	43.1±26	2.6	<0.05

Table(4): Comparison of telomerase activity in patients with Microalbumin(<30mg/ml)versus patients with Microalbumin(>30mg/ml).

Telomerase activity	Microalbumin <30 mg/ml	>30mg/ml	t	P
Mean ± SD	58.3±39.3	34.5±1.1	-2.1	<0.05

Table(5): Comparison of telomerase activity in patients with LDL-C(<100mg/dl)versus patients with LDL-C(>100 mg/dl).

Telomerase activity	LDL-c <100mg/dl	>100mg/dl	t	P
Mean ± SD	106.2±58.4	42.9±20.5	-3.6	<0.05

Table(6): Comparison of telomerase activity in patients with HDL-C(<45 mg/dl)versus patients with HDL-C(>45 md/dl).

Telomerase activity	HDL-c ≥45mg/dl	<45mg/dl	t	P
Mean ± SD	81.3±41.8	36.8±4.4	-3.8	<0.001

Table(7): Comparison of telomerase activity in patients with Triglycerides(<150mg/dl)versus patients TG(>150mg/dl).

Telomerase activity	TG <150mg/dl	>150mg/dl	t	P
Mean ± SD	87.9±73.6	37.1±4.4	-3.1	<0.05

Table(8): Comparison of telomerase activity in patients with Total Cholesterol(<200 mg/dl)versus patients with TC(>200 mg/dl).

Telomerase activity	TCH <200mg/dl	>200mg/dl	t	P
Mean ± SD	77.7±45.4	42.9±22.5	-2.3	<0.05

Table(9): Comparison of telomerase activity in patients with Creatinine(<1.5mg/dl)vrsus patients with Creatinine(>1.5mg/dl).

Telomerase activity	Creatinine ≤1.5mg/dl	>1.5mg/dl	t	P
Mean ± SD	52.8±36.3	47.9±0.00	-0.2	NS

Table(10): Correlation between Telomerase activity and Duration of Diabetes(Persons correlation).

Correlations		
		telomerase
Duration/y	r	-0.17
	P	NS

Table(11):Logistic Order Regression.

	Score	P
1-HbA1C	21.3	<0.001
2-LDL	20	<0.001
3-TCH	8.23	<0.001
4-TG	6.56	<0.001
5-HDL	6.55	<0.001
6-MICROALB	5.3	<0.05
7-CREATININE	0.18	NS

Table(12):Correlation between Telomerase activity in patients with macroangiopathic complications versus patients without macroangiopathic complications.

Telomerase activity	Macroangiopathy -ve (N=9)	+ve (N=11)	t	P
Mean ± SD	75.8±41.4	35±1.6	-3.2	<0.05

4. Discussion

Telomerase enzyme is a ribonucleoprotein maintaining the length of the telomeres (telomeres serve as a mitotic clock and biological marker of senescence) by adding G-rich repeats to the end of the eukaryotic chromosomes[3].

Activation of telomerase by extracellular factors may have significant implications in activating and mobilizing stem cells, for tissue repair, organ regeneration and anti-aging regimes[11]. inactivation of telomerase has been demonstrated to be critical to stem cell renewal and potentially to incur aging diseases e.g. type 2 D.M[12].

There are several reasons why we studied telomerase activity in diabetic patients: firstly, to gain an objective measurement of disease activity as regard angiopathy in type 1 & type 2 patients; and secondly, trying to find a tool for prediction and management of CVD.

Our study was conducted on forty persons: 10 type 1 diabetic patients with angiopathy, 10 type 2 diabetic patients with angiopathy& 20 age and sex matched apparently healthy volunteers serving as control.

Our study showed that 80% of diabetic patients (16 patients) were telomerase negative, whereas 20% of diabetic patients (4 patients) were telomerase positive, **fig.(1).** Among 16 telomerase negative diabetic patients, 9 patients (56.25%) were type 1 D.M and 7 patients (43.75%) were type 2 D.M.

Our work showed that in comparison to control group, telomerase activity was significantly low in diabetic patients. This is in agreement with other studies who reported that telomeres serve as a mitotic clock and biological marker of senescence[1].

Our results showed that the state of glycemic control had a significant impact on the telomerase activity in diabetic patients. This could be inferred from the following:

1.Telomerase activity was significantly low in diabetic patients withHbA1C **(≥7)** compared to diabetic patients with HbA1C **(<7)**, **table(3).**

2.A significant negative correlation was found between telomeraseactivity and each of HBA1C level, FBS and PPBS in diabetic patients, **table (2), figs. (3, 8, 9).**

3.In Logistic Order Regression analysis: HbA1C greatly affectedtelomerase activity in which HbA1C

Score = (21.3), *P*= (<0.001), **table (11),** but there was no relation between telomerase activityand duration of diabetes according to Pearson"s correlation **table (10).** So, telomerase activity depends on glycemic control rather than duration of diabetes. This is in agreement with other studies who reported that there was inverse correlation observed between (leukocyte telomere lengths, telomerase activity) and Hb1AC & glucose level (F.B.S & P.P.B.S) influenced by several factors, including oxidative stress consequent toglycemic control, seems to confirm the association between accelerated telomere attrition, decreased telomerase activity and increased oxidativestress[13]**.** About the 70% of elderly Type2DM patients enrolled in this study show HbA1C levels higher than 7%, a value indicative of a poor glycemic control [13].

Previous studies have shown that Type2DM patients with well controlled diabetes did not have statistically

Significant shorter telomeres than controls, denoting the protective effect of efficient glycemic control on damage and premature senescence of these cells [1]**.**

In our study all cases had microangiopathic complications and most of them had decreased telomerase activity. So, we can conclude that there is relation between telomerase activity and microangiopathic complications. Also, there was 11 cases (55%) had macroangiopathic complications (7 coronary atherosclerosis & 1cerebral atherosclerosis & 3 peripheral atherosclerosis). Our results showed that macroangiopathic complications had a significant impact on telomerase activity in diabetic patients. This could be inferred from that telomerase activity was significantly low in diabetic patients with macroangiopathic complications (N=11, 55%) compared to diabetic patients without macroangiopathic complications (N=9, 45%), **table (12).** This is consistent with other studies who reported that patients with diabetes are at high risk of macro- and microangiopathic complications development. Macroangiopathic complications in diabetes are considered to be as symptoms of premature aging [14]**.**

Our results showed that microalbuminuria had a significant impact on the telomerase activity in diabetic patients. This could be inferred from the following:

1. Telomerase activity was significantly low in diabetic patients with microalbuminuria **(≥30)** compared to diabetic patients with normoalbuminuria **(<30**), **table (4).**

2. A significant negative correlation was found between telomerase activity and microalbumin in diabetic patients, **table (2), fig.(4).**

3. In Logistic Order Regression analysis: microalbumin also, affected telomerase activity in which microalbumin Score = (5.3), *P*= (<0.05), **table (11).**

This is in agreement with other studies who reported that some Type2DM complications, such as microalbuminuria (a urinary albumin excretion rate >30 mg/24 h.) and MI, are associated with lower telomerase activity &shorter telomere length [15-19].

Also, in our results we found that there was no relation between telomerase activity and age, **tables (1 & 2).**

This may be due to narrow age range in our study with (Mean ± SD) =(39.6±5.2) years. Although there is confirmed relation betweentelomerase and aging as reported in researches in the past two decades that points to a link between organismal aging and aging-related diseases and cellular senescence caused by telomere shortening. Several lines of evidence strongly suggest that the resulting telomere dysfunction could have a causal role in some aging and aging-related diseases[20].

Also, in our results we found that there was no relation betweentelomerase activity and creatinine, **tables (2&9&11).** This is in agreement with that plasma creatinine concentration isinversely related to GFR but GFR can decrease by 50% before plasmacreatinine concentration rises beyond the normal range. Plasma creatinineconcentration doubles for each further 50% fall in GFR. So, normalplasma creatinine doesn't necessarily imply normal renal function, andalso, raised plasma creatinine doesn't usually indicate impaired renalfunction. This may be due to that changes in plasma creatinine can occurindependently of renal function, due to changes in muscle bulk, thus a decrease can occur in starvation, wasting diseases, immediately aftersurgery and in patients treated with corticosteroids. our results showed that lipid profile (HDL-c, LDL-c, T.G, and T.CH) had a significant impact on the telomerase activity in diabetic patients. This could be inferred from the following:

1.Telomerase activity was significantly low in diabetic patients with LDL-c (≥100), TG (>150), TCH (>200), HDL-c (<45) compared to diabetic patients with LDL-c (<100), TG (<150), TCH (<200), HDL-c (>45), **tables (5,6,7,8).**

2.A significant negative correlation was found between telomerase activity and (LDL-c, T.G, T.CH) in diabetic patients, **table (2), figs.(5, 7, 8).**

3.A significant positive correlation was found between telomerase activity and HDL-c in diabetic patients, **table (2), fig.(6).**

4. In Logistic Order Regression analysis: LDL-c affected telomerase activity in which Score = (20), *P*= (**<0.001**), HDL-c affected telomerase activity in

which Score = (**6.55**), *P*= (**<0.001**), T.G affected telomerase activity in which Score = (**6.56**), *P*= (**<0.001**), and also, T.CH affected telomerase activity in which Score = (**8.23**), *P*= (**<0.001**); **table (11)**. This is in agreement with other studies who reported that diminished levels of high-density lipoprotein cholesterol (HDL-C) are associatedwith an increased risk for atherosclerosis[21,22].,a disease that is marked by chronic, low grade, inflammation and increased burden of oxidative stress[23,24].

It was found that there is positive correlation between HDL-C and telomerase activity in many[25,26]. Low levels of HDL cholesterol are considered as one of the components of, atherogenic dyslipidemia[25]and low HDL cholesterol phenotypes have been recently shown to display elevated oxidative stress, attenuated antioxidative activity[27]and accelerated senescence[28].

Conclusions:

From the previous results it was concluded that telomerase enzyme activity decreased in both type 1 and type 2 diabetic patients with angiopathy. There was a strong and significant relation between telomerase activity and the occurrence and presence of both micro & macroangiopathic complications. Telomerase activity and telomere length may be a possible new marker in the prediction of cvd and diabetes representing the contribution of tissue aging, atherosclerosis and their linked pathology, also we recomend that this trial must be done on a large number in diabetic patients to assess, compare and confirm these results.

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