Telomere Attrition in Controlled & Un-Controlled Type –2 Diabetes Mellitus- Review

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Abstract— Type -2 diabetes mellitus (DM) is a disease characterized by dysfunction of various organs. Recent studies have shown a close relationship between DM and telomere attrition in leucocytes. In patients with DM or impaired glucose tolerance excessive oxidative stress induces damage to telomere and shortens their length. Furthermore, it is suggested that telomere length is a good surrogate marker for mortality and diabetic complications in DM patients. We recently found that telomere length in pancreatic beta –cells is also shortened in DM patients, potentially leading to an impaired capacity for proliferation and insulin secretion, and accelerated cell death. In contrast leukocyte telomere length has also been reported in patients with obesity or insulin resistance, both of which are frequently associated with type 2 DM. It also shown that telomere attrition in adipose tissue induces insulin resistance. The available data suggest that hyperglycemia, oxidative stress and telomere attrition in pancreatic beta cells and adipocytes create a vicious cycle that underlies the pathophysiology of type 2 DM. Inhibition of telomere attrition in various organs, including pancreatic beta cells, could be a new approach for preventing the progression of DM and its complications. (Geriatr Gerontol Int 2016; 16) (Suppl.1):66-74.

I. INTRODUCTION

In worldwide predominantly developed societies, there has been an explosive increase of patients with diabetes mellitus (DM). The International Diabetes Federation has shown that there were 387 million individuals with DM in 2014 and the figure is expected to raise 592 million by 2035. [1] Sustained hyperglycemia is a risk factor for various vascular complications such as diabetic retinopathy & nephropathy, which significantly compromise the quality of life. Furthermore medical care for DM is extremely costly; Diabetes Federation have reported that adult DM accounts for at least 12 billion or 11% of total health spending. Thus, from both an economic and public health viewpoint, Control of DM “epidemic” is vitally important.

Diabetes mellitus is divided into two clinical types.

1) Type-1 DM.
2) Type-2 DM.

T2 DM accounts for the majority of DM patients and is increasing rapidly in every country. In contrast to T1DM, in which pancreatic Beta cells are damaged by an autoimmune process and their insulin secretary capacity is depleted completely, T2DM develops through multiple pathophysiological processes. These include insulin resistance associated with excess adiposity caused by excess caloric consumption and insufficient exercise and a relative shortage of insulin secretion from beta cells that is insufficient for systemic demand.

The pathophysiology of DM shows an age-related aspect. First the prevalence of DM increases with age [2] second many deleterious events that are associated with aging, such as atherosclerosis and cognitive dysfunction are exacerbated and occur frequently in DM patients, transition to high risk category for cardiovascular diseases occurs approximately 15 years earlier than in individuals without DM. [3] Life expectancy in both the Framingham Heart Study cohort in USA and a Japanese cohort was shown to be shortened by 6-8 years. [4] Therefore, it is imperative. It clarify the mechanism where by DM accelerates age related dysfunction in various organs. [5]

Various key factors related to cellular aging have been identified. One of these is the telomere, a region of repetitive G-rich DNA at the end of eukaryote chromosomes that protects the chromosomes from attrition and damage. [6] Telomeres shorten with each cell division because of the end replication problem. Telomerase an enzyme that prevents telomere shortening, consists of telomere reverse transcriptase (TERT) and telomere RNA component (TR). Telomerase is abundant in cancer cells and germ cells, but limited in somatic cells [7] When Telomeres in a cell shorten beyond the critical threshold, the cell stops dividing. The telomere length of a cell represents how many times the cells has replicated, and thus can be regarded as marker of cellular senescence.

In the past decade many studies have shown that patients with DM have shorter white blood cell telomeres than non DM individuals [8, 9] In addition we prove that telomere length is more shorter in Uncontrolled T2DM patients than Controlled T2DM patients. These results strongly indicate a close relationship between pancreatic metabolic changes and telomere attrition. [10] In the present research paper we studied few parameters and its correlation with telomere length. These are a) HbA1c b) hs-crp. c) Microalbuminuria with obesity hypertension high lipid concentration (i.e. hyper cholesterol) in controlled & uncontrolled T2DM patients. In the final section, we propose some possible strategies for prevention or slowing of telomere shortening.

II. MECHANISM OF TELOMERE ATTENTION IN PATIENTS WITH CONTROLLED & UNCONTROLLED T2DM

It is known that oxidative stress plays the key role in telomere attrition in DM patients. In such patients, production
of reactive oxygen species (ROS) is increased. The causes of ROS overproduction are diverse. Hyperglycemia increases ROS from the mitochondrial electron transport chain. In addition, increased glucose auto-oxidation, activation of polyol pathway and protein kinase C pathway, and production of advance glycation end products also play roles in increasing the level of oxidative stress [11] such exacerbated oxidative stress accelerates the shortening of telomeres and in fact Sampson et al. have reported that LTL is negatively correlated with the level of 8-hydroxyguanosine, a marker of oxidative DNA damage, in patients with T2DM [8, 9].

In DM, oxidative stress is increased in not only leucocytes but also pancreatic beta cells, which could result in shortening of beta cell telomeres and subsequent dysfunction of insulin secretion, it is clear that oxidative stress is also increased in adipocytes and muscle cells in patients with DM which are characterized by excessive caloric intake resulting in obesity and DM have higher ROS levels in adipose tissue. Furthermore, another report has shown that oxidative stress in muscle fibers might induce telomere shortening. [7]

**Telomere attrition as a risk factor for onset of diabetes:**

LTL is already reduced in individuals with impaired glucose tolerance and this is recognized as a risk factor for the onset of DM. Three prospective cohort studies have investigated the degree to which LTL shortening is a risk being as high as two fold in two of the studies whereas the risk was fairly attenuated in post menopausal women Willeit et al. carried out meta-analysis of these three studies and concluded that the relative risk of T2DM onset in subjects who were in lowest quartile for telomere length was 1.31 relative to those in the top quartile. [21]

In contrast, Weischer et al. reported that the change in telomere length within a 10-year period was not associated with subsequent onset of DM. [15, 16,]

**Telomere attrition & diabetic complications:**

There are many studies examining the relationship between telomere attrition and mortality or progression of diabetic complications.

In our study it is clear that telomere length attrition in T2DM with microalbuminuria. It is also found that in patient with HbA1c in uncontrolled stage is more telomere attrition than controlled patients. It is also clear that inflammatory diabetic complication have more telomere attrition than non inflammatory complication. (i.e. Patient’s in High hs-CRP level have more telomere length attrition than normal patient’s.) [4]

In cross-sectional studies of T2DM patients showed that those with previous myocardial infarction or atherosclerotic plaques detected by carotid artery had more reduced LTL than without either. It is found that telomere attrition was recently shown to be associated with depression & periodontalitis which are now recognized as new complications of diabetes. [7]

III. **Beta cells distruction in T2DM patient & telomere attrition:**

Pancreatic Beta cells differentiate from precursor cells during the prenatal period, but after birth they are supplied mainly by auto replication. However, it has been shown that the replication capacity of beta cells decreases with aging possibly as a result of telomere shortening and in fact a previous report has shown that telomerase activity is associated with the proliferative capacity of beta cells Liew et al. reported that both TERT expression & telomerase activity were unregulated in liver-specific insulin receptor-knockout mice, which show an accelerated proliferative capacity of beta cells in contrast TERT expression and telomerase activity were reduced in cyclin D2-knockout and beta-cell-specific insulin receptor-knockout mice, which show a low beta cell proliferative capacity. Telomere length in beta cells are originally shorter in infancy and decrease more rapidly before adulthood, whereas the reduction speed according to age is fairly blunted in adulthood. This means that the effect of aging itself on telomere shortening of beta cells in elderly DM patients might be relatively small. [22, 23]

**Telomere attrition in obesity and uncontrolled T2DM:**

Most of the T2DM patients have associated obesity and insulin resistance, which play considerable role in the disease pathogenesis. Parameters, such as body mass index, waist–hip ratio and visceral fat accumulation is also play an important role in telomere attrition. Central obesity and high cholesterol & triglycerides also parameters for telomere length attrition. It is also prove that Microalbuminuria, higher level of HbA1c and high hs-CRP in T2DM patients have reduced telomere length. In controlled T2DM Patients have less telomere attrition than uncontrolled T2DM patients. It has been shown that ROS production in adipose tissue is increased in obesity and that could result in telomere shortening. [8]

Our study now show that subject which is uncontrolled T2DM have short telomere length than controlled T2DM subject. It is also prove that Patient’s having high level of Microalbuminuria, HbA1c & hs-CRP have reduced telomere length than controlled T2DM subject. (which having above parameters within normal limits.) we studied 25 Controlled & 25 Uncontrolled T2DM patients. For this study. Hear both controlled & Un controlled T2DM subjects taking hypoglycemic drougs. In this study Controlled T2DM subjects are control & Un controlled T2DM subjects are case we compare all above parameters with telomere length in above subjects. [13, 14]

**Relationships among DM, Obesity and Telomere attrition:**

A schematic diagram of the relationships among DM, obesity and telomere attrition is shown in below figure. Hyperglycemia induces systemic oxidative stress, including Beta cells and adipocytes whereas obesity induces oxidative stress in adipocytes. In both cell types, oxidative stress induces telomere attrition. Telomere attrition in Beta cells further induces senescence and loss of beta cells and impairment of insulin secretion. Which leads to hyperglycemia? Thus, two
vicious cycles are formed between hyperglycemia & telomere attrition and P53 plays a crucial role in both processes.

1) Glycosylated Hemoglobin (HB A1C) and Type II Diabetes Mellitus:-

Glycated hemoglobin is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed by non enzymatic glycation of hemoglobin by plasma glucose. [13]

In diabetes mellitus, higher amount of glycated hemoglobin indicates poor control of blood glucose levels and has been associated with cardiovascular disease, nephropathy and retinopathy. Glycprotein can also be formed by addition of carbohydrate residues without any of the complex enzymatic pathway of carbohydrate addition. [13] This process is known as non-enzymatic glycation proceeds by the condensation of a monosaccharide, usually glucose with certain reactive amino groups on the protein.

The initial liable Schiff base adduct slowly rearranged to the stable ketoamine or fructosamine form. Small fraction of hemoglobin A. The major hemoglobin of adult humans is present in the red blood cells as glycated hemoglobin. (HBA1C) The glycations of hemoglobin is a continuous process occurring throughout the 120 day life span of the red cell. In HBA1C glucose is incorporated via an N-Group of valine of each B-chain. Enhanced levels of HBA1C occur in individuals with diabetes mellitus. Measurement of glycated hemoglobin has been useful in monitoring the effect of therapy. Measurement of HBA1C concentration reflects integrated plasma glucose levels over a long period (2-3 months).

2) hs –CRP and Type II Diabetes Mellitus:-

The C-reactive protein derives from the fact that it reacts with capsule polysaccharides of Streptococcus pneumonia. It is an acute phase response protein markedly increased in both inflammatory and infectious disease plays an important role in innate immunity. It assists in complement binding to foreign and damaged cells and enhances phagocytosis. (Opsonization) [21] C-reactive protein is synthesized by the liver cells in response to the pro-inflammatory cytokines. Being a member of the pentraxin family of proteins CRP contains five non glycosylated subunits each comprising of 224 amino acids. hs-CRP levels in type II diabetes Mellitus

Hyperglycemia is associated with an increase of serum CRP levels in uncontrolled type II diabetic subjects. Several studies demonstrate that hs-CRP remained a significant predictor of diabetes even after adjusting with body mass index. [8] There have been certain evidences, suggesting the role of inflammation as a mediator in the pathogenesis of type II DM [28] CRP and interleukin -6 have been associated with insulin resistance in type II DM, metabolic factors like high glucose levels, adipokines, fatty acids etc. trigger increase in CRP production by endothelial and smooth muscle cells, hence local CRP production in atherosclerotic plaques of diabetic individuals could be higher as compared to non-diabetic subjects. [6]

3) Microalbuminuria and Type II Diabetes Mellitus

The term Microalbuminuria has been used to describe an amount of albumin in the urine which is cannot be detected by ordinary clinical tests, but is still associated with future disease. Microalbuminuria has been defined using different units of measurement. According to the Gento-Montecatini conversion, Microalbuminuria is present when the urinary albumin excretion rate (UAER) in 24hours.urine or short time collected urine during day-time is in the range of 30 to 300 mg/24-hrs. (20 to 200µg/min.)Which is equivalent to 0.46 to 4.6µmol/24-hrs. [37]

Diabetic Nephropathy

The development of diabetic nephropathy is characterized by a progressive increase in the excretion of protein, particularly albumin, an early and continuing rise in systemic blood pressure and a late decline in glomerular filtration rate leading eventually to end-stage renal failure. In diabetic patients with proteinuria the relative mortality is about 40 times higher than in diabetics without proteinuria. [23] Renal damage is a serious complication of diabetes mellitus (DM). It is estimated that death due to renal diseases is 17 time more common in diabetics then in nondiabetics. [19]

The relative risk of renal mortality in diabetic patients diagnosed after the age of 45 years is estimated to be twofold that in nondiabetic patients. It is now established that in type-I and type-II diabetes mellitus urinary excretion of small amounts of albumin (Microalbuminuria) is predictive of morbidity and mortality due to renal complications and cardiovascular disease.

Pathogenesis of Diabetic Nephropathy

Biochemical, hormonal, immunologic and rheological factors are important in the pathogenesis of diabetic nephropathy. A large number of human studies provide support for the concept that the micro vascular complications of diabetes mellitus are dependent on hyperglycemia. Polyol pathway, nonenzymatic glycation, glucose auto-oxidation and denovo synthesis of diglycerol leading to protein kinase c and phospholipase A2 activation are the 4 potential biochemical pathways linking hyperglycemia to the changes within the kidney. [14]
Microalbuminuria and renal outcomes in type II Diabetes

There have been several studies examining the relationship between microalbuminuria and renal outcomes in type 2 diabetes. Mogensen studied the predictive value of microalbuminuria in patients with type 2 diabetes. [3] It was predictive of the development of overt proteinuria as well as mortality. Patients with type 2 diabetes and albumin concentrations of 30-140 μg/ml at baseline were more likely to develop clinically detectable proteinuria.

Telomere

A region of repetitive nucleotide sequence at each end of the chromatid is known as telomere, it protects the end of the chromosome from deterioration or from fusion with neighboring chromosomes. Its name is derived from Greek nouns Telos – End and Meros -Part. For vertebrates the sequence of nucleotides in telomeres is TTAGGG. [1]

After each cell division the telomere ends become shorter, as the enzymes that duplicate DNA cannot continue their duplication all the way to the end of the chromosome. These ends are thus replenished by an enzyme, telomerase, a reverse transcriptase.

Correlation of Telomere & Diabetes Mellitus

Type II Diabetes is a chronic metabolic disease resulting from a combination of genetic susceptibility, environment, behavior, and as yet unexplained risk factors. Considerable increased prevalence and earlier age of onset have been observed in older people suggesting that genetic factors may influence both timing and prevalence with advance age.

We can find out the association of telomere and diabetes and its mechanism. Gardner et al. noted association between telomere length and diabesity. He also found that in disability telomere length is shorter. In addition, they also observed that, obesity at an earlier age increases the risk to develop diabesity, and these subjects have shorter telomeres. They suggested that, telomere is a biomarker and showed negative correlation of Leukocyte Telomere Length with development of diabesity. HbA1C were negatively correlated with Leukocyte Telomere Length.

Similarly, Tentolouris showed that patients with both T2DM and microalbuminuria (MA) have shorter telomere compared to patients with MA only. Tentolouris observed that T2DM patients have increased arterial stiffness.

Strategies to Reverse Telomere Attrition and its Deleterious Effects:

Normalization of the blood glucose level might prevent telomere attrition, Uziel et al reported that glycemic control attenuated LTL reduction in patients with both T1DM & T2DM our own study showed that patients with T2DM who used hypoglycemic agents show grater reduction telomere length. It is also prove that Uncontrolled T2DM patients have grater reduction of telomere length than controlled T2DM patients.

There are few important points for maintain Telomere Length
1) Avoid fast food.
2) Drink plenty of water
3) Eat less
4) Walk more

These points prevent telomere length attrition & also control diabetes. As obesity is another significant risk factor for telomere attrition, it is possible that lifestyle modification could prevent telomere attrition. Ornish et al. have reported that comprehensive lifestyle intervention, including changes in diet, exercise, stress management and social support resulted in higher LTL. A diet specific cross-sectional study showed that strict adherence to a Mediterranean diet is associated with longer LTL. Mediterranean diet is characterized by high intake of olive oil. Which has an anti-oxidative effect, and this might have contributed to the favorable outcome. With regard to exercise, although only a few studies have investigated its effect on telomere length, [4] a cross-sectional study between controlled & un controlled T2DM patients have shown that the older endurance-trained athletes have longer LTL than non-athletes, suggesting a positive effect of exercise on telomere length. Stress management also give positive effect, we research on two groups one group doing meditation and other group not doing such meditation, after 2 months it is clear that group who doing meditation daily have longer telomere length than non-meditation group. However, it is unclear whether these lifestyle modifications have same effects on beta cells and adipocytes. It is also clear that structured exercise. More effective than Non structured exercise for telomere length. [22]

The ultimate goal for treatment of disorders related to telomere attrition is direct modification of telomere related gene (TERT). [21]

REFERENCES


