Review article

Metabolic Syndrome, telomere length and Aging- A review of literature

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Abstract
Metabolic syndrome is reportedly one of the key health concerns worldwide. It is defined as a group of conditions including hypertension, dysglycemia, and abdominal obesity. The wear and tear of telomeres is known to be a major incident not only in mammalian aging, but also in distressed nutrient sensing, which may contribute to a number of metabolic dysfunctions. The metabolic syndrome was linked to the growing prevalence of obesity, which is at rise invariably in all age groups including elderly. The existing literature review focuses on the relationship of shorting of telomere and metabolic syndrome. As the shortening of telomeres influence cellular senescence and eventual stoppage of cell division. It is reviewed that the increasing number patients of the metabolic syndrome significantly affecting aging process by early diminishing the telomere lengthening.

Key words: Metabolic Syndrome, Telomere Length, Aging

Introduction

The metabolic syndrome (MetS) is a group of metabolic derangements resulting in acluster of clinical presentations including hypertension, diabetes mellitus and hypercholestrolemia. In 2005, a meeting planned by the International Diabetes Federation (IDF) put forward the first united agreement on the definition of Metabolic Syndrome. The IDF criteria for MetS was, central obesity with specific values according to ethnicity (ie waist circumference (WC) for European males must be greater than 94 cm and females must be greater than 80 cm; Japanese, Chinese and South Asian males must be greater than 90 cm and females must be greater than 80 cm. For Sub-Saharan Africans and Middle East and Eastern Mediterranean populace, European criteria is being used, for Central and South Americans, South Asian criteria is being used) with presence of any two from the following four characteristics:

1. HDL-cholesterol in males below 40 mg/dl and in females below 50 mg/dl,

2. Triglycerides equal to or greater than 150 mg/dl,

3. Fasting glucose equal to or greater than 100 mg/dl,

4. BP equal to or greater than 130/85 mmHg

Obesity is measured by using the Body Mass Index (BMI) and WC, which is stated as a key causative factor. Besides abdominal obesity, other factors are also required to be considered in the diagnosis of metabolic syndrome include the assessment of triglycerides, blood pressure, fasting blood glucose, or reduced lipoprotein cholesterol levels.(1) The pathophysiology of the metabolic syndrome is very complex and yet uncertain. A considerable number of patients have a sedentary life style, with advanced age, usually showing insulin resistance. The influencing factors include advancing age, genetics, increase weight, excess caloric intake and lifestyle.(2) Though, in spite of the significance of obesity people may not show signs of insulin resistance, occasionally others with normal weight can be resistant to insulin eventually ending up with metabolic syndrome.(3) The Adult Treatment Panel-III, according to the commonly inferred definition, is used to diagnose a metabolic syndrome when no less than 3 out of 5 of the following variants were found:

1. Visceral obesity (waist circumference of more than 102 cm in males or greater than 88 cm in females);

2. Dysglycemia (fasting blood glucose > 100 mg dL);

3. Elevated blood pressure (more than 130/85 mm Hg);

4. Elevated levels of blood lipids.(4,5)

It is established that metabolic syndrome accounts for a significant pathophysiological combinations to study metabolic process within animal models and humans. This results in an increased risk of cardiovascular disease as a peripheral or coronary atherosclerosis or heart dysfunction if metabolic syndrome is present. Furthermore, metabolic syndrome correlates with a few further systemic complications, which affect various systems and organs, for example osteoarticular disease, respiratory disease, fatty liver disease, and malignancy. Consequently, patients with metabolic syndrome have a reduced lifespan and raised all-cause mortality contrasted to the general people.(6, 7)Therefore, it is sequentially accepted that metabolic syndrome is associated with early ageing, which is of primary importance given the increasing global epidemic of metabolic syndrome. With this environment, it is very remarkable to understand biochemical processes associated with variations in metabolic syndrome with lifespan.(8)

Metabolic Syndrome in Pakistan Metabolic disorders resulting in chronic illness and end organ damage have remained research focus for a long time. Regardless of the nature of the syndrome, the truth remains that all its constituent anomalies have been repeatedly and independently presented with an increased risk of both diabetes mellitus and cardiovascular disease.(9) For practitioners, metabolic syndrome can only act as an indicator of amplified cardio- metabolic risk, leading to any interventional endeavors, a function that can be offered most effectively by

the easiest way to measure abnormality of the component alone. The prevalent elevation and availability of carbonated drinks and fast foods influence children in particular. This requires a deep understanding of people's health status with respect to cardio metabolic risks.(10)

Oxidative stress and Metabolic Syndrome Oxidative stress is a well-known mechanism that significantly contributes to several pathological conditions, and several human disorders have been strongly correlated with oxidative stress. Many cell functions seem to be controlled by free radical molecules, which can function as well as intracellular signals.(11, 12)Likewise, the protein redox state is associated with regulating a number of cellular activities, along with cell variation and stimulation of specific metabolic pathways.(13, 14)

Aging and Oxidative Stress

Aging is a biological process, characterized by a gradual wear and tear in metabolic functions and physiological activities resulting in morbidity and mortality. In line with the production of endogenous free radicals, reactive oxygen species and reactive nitrogen species as a result of different cellular mechanisms, which normally get neutralized, however with the ageing and obesity the production keep on rise while neutralization reduces. It is important to maintain A balance for proper physiological work between free radicals and antioxidants. In situations when free radicals production increases to override the body's capacity to neutralize them oxidative stress ensues. Free radicals adversely alter lipids, proteins, and DNA function and metabolism thus trigger a number of human diseases, causing cumulative and casual oxidative degradation of macromolecules stimulating loss with aging and ultimately cell death. Mitochondria tends to play pivotal role in the senescence process, as they are thought to be the primary intracellular source of anti-oxidants. Respiratory chain impairment causes reactive oxygen species (ROS) to induce mitochondrial components, including mitochondrial DNA, lipids, and proteins.(15) Progressive accumulations of oxidant- provoked somatic mutation in human mitochondrial DNA (mt DNA) resulting in wear and tear in the mitochondrial bioenergetics functions and play a part in aging process. Under physiological conditions, ROS low levels are produced in the course of mitochondrial respiration. Gradual oxidative impairment with age to mitochondrial (mt) DNA may cause DNA strand breaks and somatic mitochondrial DNA mutations.

The aggregation of these mt DNA variants result in disruption to the complexes of the respiratory chain contributing to a vicious cycle of decreased mitochondrial ROS synthesis and consequent production of additional mitochondrial DNA mutations. This chain reaction was suggested to include increased oxidative impairment during ageing, which triggers a gradual decline in tissue and cellular functions due to insufficient energy supply and/or increased susceptibility to apoptosis.(16) Ageing induced oxidative impairment of proteins, lipids and DNA has been well reported, and thus provide an evidence to suggest mitochondrial dysfunction.(17) Pathophysiology Telomere length (18) is a fresh indicator of cellular aging, usually evaluated in leukocytes, and has been correlated with increased mortality

and morbidity risks. Telomeres, consisting of mammalian DNA tandem repeats (TTAGGG) and associated proteins, are nucleoprotein complexes that are located at the ends of eukaryotic chromosomes. They contribute significantly to preserving the stability and integrity of the chromosome, forming an essential factor for cell survival. Telomeric DNA wears away whenever the cells divide, through partial "During DNA synthesis, replication of the lagging strand, referred to as the "end- replication problem." Through this method, each telomeric end reduces peripheral blood lymphocytes by about 20–60 base pairs (bp)/year. In vitro studies have shown that if telomeres turn out to be extremely small, cell division stops and encourages replicative senescence, leading to aging and consequent somatic cell death. Cellular impairment because of raised oxidative stress can additionally speed up the reduction process of TL. Thus, TL can be taken as an ageing biomarker, where elevated biological age could be seen by shorter TL. Certainly, metabolic disorders for example metabolic syndrome, which relates to aging, exhibit functional deterioration in tissues and major organs where pancreas and heart are particularly affected by ageing. A few studies have exhibited considerable correlations between central adiposity and shorter TL. Likewise, the TL was shorter as per the worsening of the metabolic conditions in demonstrative specimen of females. It is evident that a complex relation is present between metabolic syndrome components and TL with obesity. However, it is not yet known that the effect of TL in specific obesity groups such as metabolically healthy obesity (MHO). In this setting, the main objective of the current literature review was to explore the scientific evidence regarding absolute telomere length (aTL) in MHO people who were contrasted with a control group consisting of non-obese people with no metabolic syndrome and a cohort of obesity and metabolic syndrome patients.

Metabolic Syndrome and Correlation with Ageing

Metabolic syndrome directly correlated with raised mortality & atherogenesis due to MI as well as visceral adiposity accumulation during middle age correlated to exercise reduction & overeating. Moreover, there seems to be a genomic tendency to acquire metabolic syndrome.(19) Aging is taken into account as biological course of action typified by a gradual decline in metabolic course of actions as well as decline in physiological functions which results in mortality & morbidity.(20) Consistent with the aging theory “free radical”, reactive oxygen species, produced as biological oxidations byproducts, stimulate cumulative & unintentional oxidative impairment to large molecules provoking the cellular abnormality with age then finally the cell dies.(20) Metabolic syndrome is usually reflected to stimulate precocious aging even though the system which is responsible for it is not fully recognized. It is turning out to be evident that involvement of longevity genes can possibly be there. Trials in over stimulation or disturbance of major lifecycle factor routes, for example mTOR, p66Shc, and Sirtuins result in expression of MS features in mice. Further routes are concerned in relating longevity and accessibility of nutrients, together with IGF-1 signaling and insulin, in addition to factors of FOXO transcription.(21) Free radicals are continuous produced during metabolic disorder which is thus believed to generate stipulations in which oxidative

variations of cellular components increase, which consecutively results in dysfunction of mitochondria and finally loss of homeostasis of the cell. This motive has been convincingly applied as a factor of age- related decline in physiological processes, thus resulting in mitochondrial sense of "biological clock" for aging of the cell.(22) According to this concept a survey by Passos et al.(23) exhibited that the cellular senescence had greater ROS levels, mitochondrial dysfunction, further double-strand breakdowns of DNA as well as shorter telomeres, moreover it was exhibited that ROS of mitochondria increased telomere- reliant senescence. Lately, a few authors exhibited the association amid metabolic disorder & TL proposing raised cellular regeneration rate and thus speeding cellular aging.(24)

Telomere shortening is mostly the result of "end-replication" issue, caused by DNA polymerase inability to completely replicate the lagging strand's identical end.(25) One more factor taking part in telomere shortening encompasses the telomere ends processing to reconstruct projections of 3' single-strand, and telomere shortening because of the DNA restoration system, especially for lone-stranded DNA impairment, are fewer effective within telomeric DNA as compared to other places within genome. The subsequent growth of single-strand breakdowns besides telomeres results in DNA impairment-reliant shortening while copying.(25) Therefore, shortening of telomere can possibly function as a marker of history of replication and cumulative genetic impairment of somatic cells.

These shorter telomeres can either accredited to shorter length at childbirth liable to diabetes or to augmented telomere loss in the course of cell division due to raised oxidative stress within prediabetes conditions, or both. It has been noticed that shorter telomeres are present in circulating epithelial originator cells in cases suffering from metabolic syndrome and in other conditions of high oxidative stress.(26) Several studies stated significant link between shorter TL and metabolic syndrome components, while other studies did not manage to confirm this.(27) Whether TL predicts a wide range of metabolic disorder such as lipid profile derangements, glucose, or hypertension ranges over a wide period is unknown.

Table 1 shows findings of several researches for association of telomere shortening with aging, organ damage and metabolic syndrome

TABLE 1: FINDINGS FROM DIFFERENT RESEARCHES

Association of metabolic syndrome with telomere length

S.no.	Author	Year	Study sample	Findings
1	Yang Z et al.[28]	2009	767 subjects; Cases: 388 essential hypertension patients, 379 healthy controls	Hypertensive subjects have shortened telomeres, and the occurrence of coronary artery disease was linked with shorter telomeres in hypertensive subjects (P<0.05)
2	Demanelis K et al.(30)	2019	337522 subjects	Longer telomere length increases blood pressure and pulmonary function traits among middle-aged U.K. Biobank participants (p<0.05).
3	Nettleton JA et al.(31)	2008	840 subjects	After adjustment for demographic factors, age, lifestyle factors, other food or beverage consumption; the intake of processed meat was negatively influenced by telomere length (p<0.05)
4	Ornish D et al.(32)	2008	30 males	Higher telomerase activity was significantly associated with decline in LDL cholesterol (r=-0.36, p=0.041) and reduced psychological distress (r=-0.35, p=0.047).
5	Nordfjäll K et al.(33)	2008	989 individuals	Borderline or significant relation was found between telomere length and obesity parameters (BMI, weight, waist circumference and hip circumference) in women after adjusting for age and center. Whereas, a positive association to HDL was observed in males (p<0.05).
6	Cassidy A et al.(34)	2010	2284 females	Waist circumference was negatively influenced by telomere length (p<0.05)
7	Broer L et al.(35)	2014	11,448 participants	Raised leptin levels are associated with short relative telomere length (p<0.05).
8	Njajou OT et al.(36)	2012	2721 elderly subjects	Shorter telomere length is significantly correlated with increased adiposity (p<0.05)
9	Révész D et al.(27)	2014	2848 participants	The shorter baseline telomere length was associated with HDL, waist circumference, triglycerides, and fasting glucose, as well as the presence of metabolic syndrome and the total number of components (p<0.05). Though baseline differences gradually decreased over time, at the two-or six-year follow-up, shorter baseline telomere length was significantly associated with poorer scores of majority of metabolic syndrome components.

10	Zhang WG et al.[38]	2015	139 healthy subjects	Telomere restriction fragment length is associated with kidney function ($p<0.05$) and may serve as a marker of aging ($r=-0.314$, $P<0.001$)
11	Eunkyong K et al.(42)	2017	130 surgically resected paraffin-embedded hepatocellular carcinoma tumor tissue samples	H_2O_2 contributes to telomere elongation in advanced hepatocellular carcinoma through protein kinase B (AKT) activation
No association of metabolic syndrome with telomere length				
12	Khalangot MD et al.(37)	2019	115 adults	A high risk of shorter telomeres, which remained important after adjustment for gender, age and 2hPG rates, was associated with metabolic syndrome. Other components of metabolic syndrome and fasting plasma glucose levels did not influence the magnitude of the correlation, and the independent effect of these factors was not disclosed ($p>0.05$).
Controversial results				
13	Bhupatiraju C et al. (29)	2012	194 subjects; 96 hypertensive and 98 normal subjects	A significant negative correlation was found in both the hypertensive and normal individuals ($p<0.05$) between age and telomere length. Although insignificant ($p>0.05$), the diastolic and systolic blood pressure were negatively correlated with relative telomere length.
14	Verhulst S et al.(41)	2016	684 participants	Baseline insulin resistance during the follow-up period was not related with age-dependent changes in leucocyte telomere length (attrition), whereas baseline leucocyte telomere length was linked with increases in insulin resistance during this time.
15	Kim NW et al.[43]	2015	101 biopsies	Telomerase become less active in somatic cells however their activity appears to be increased in cancer cells which help them in growing exponentially and make them immortal.

Conclusion

This review concluded that there are two ways to decrease the important role of telomeric length as the well-known event in age. One reflects the impact of various chronic diseases such as insulin resistance and diabetes by attrition of telomeres, an effect most likely due to mitochondrial dysfunction

and pro- inflammatory state. Second, shortening the telomere causes damage to DNA, cellular senescence and apoptosis, and triggers associated metabolic syndrome-related ageing disorders. In contrast, telomer length maintenance or elongation is associated with cell immortality and ultimately tumor growth. Future Directions

There is still an unresolved and puzzling relationship between obesity and telomere morphology. Interesting work on this relationship is therefore needed in order to cure life and prolong survival. Future well- designed multi-faceted intervention studies must take this bidirectional relationship into account and examine whether targeting obesity can minimize, interrupt, or even reverse telomere attrition to avoid further deterioration to cardiovascular and aging- related complications.

References

1. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation. 2005;112(20):3066-72.

2. Katzmarzyk PT, Leon AS, Wilmore JH, Skinner JS, Rao DC, Rankinen T, et al. Targeting the metabolic syndrome with exercise: evidence from the HERITAGE Family Study. Medicine and science in sports and exercise. 2003;35(10):1703-9.

3. Fauci AS, Braunwald E, Kasper DL, Hauser S, Longo D, Jameson J. Harrison's principles of internal medicine: McGraw-Hill. Medical Publishing Division; 2008.

4. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112(17):2735-52.

5. Borch-Johnsen K, Wareham N. The rise and fall of the metabolic syndrome. Diabetologia. 2010;53(4):597-9.

6. Guize L, Thomas F, Pannier B, Bean K, Jego B, Benetos A. All-cause mortality associated with specific combinations of the metabolic syndrome according to recent definitions. Diabetes care. 2007;30(9):2381-7.

7. Zambon S, Zanoni S, Romanato G, Corti MC, Noale M, Sartori L, et al. Metabolic syndrome and all-cause and cardiovascular mortality in an Italian elderly population: the Progetto Veneto Anziani (Pro.V.A.) Study. Diabetes care. 2009;32(1):153-9.

8. Haffner S, Taegtmeyer H. Epidemic obesity and the metabolic syndrome. Circulation. 2003;108(13):1541-5.

9. Vasudevan AR, Ballantyne CM. Cardiometabolic risk assessment: an approach to the prevention of cardiovascular disease and diabetes mellitus. Clinical cornerstone. 2005;7(2-3):7-16.

10. Iqbal AZ, Basharat S, Basharat A, Basharat S. Prevalence of the metabolic syndrome and its component abnormalities among school age Pakistani children. Journal of Ayub Medical College Abbottabad. 2014;26(2):194-9.

11. Knopp RH, Paramsothy P. Oxidized LDL and abdominal obesity: a key to understanding the metabolic syndrome. The American journal of clinical nutrition. 2006;83(1):1-2.

12. Saez GT, Tormos C, Giner V, Chaves J, Lozano JV, Iradi A, et al. Factors related to the impact of antihypertensive treatment in antioxidant activities and oxidative stress by- products in human hypertension. American journal of hypertension. 2004;17(9):809-16.

13. Palmieri VO, Grattagliano I, Portincasa P, Palasciano G. Systemic oxidative alterations are associated with visceral adiposity and liver steatosis in patients with metabolic syndrome. The Journal of nutrition. 2006;136(12):3022-6.

14. Couillard C, Ruel G, Archer WR, Pomerleau S, Bergeron J, Couture P, et al. Circulating levels of oxidative stress markers and endothelial adhesion molecules in men with abdominal obesity. The Journal of clinical endocrinology and metabolism. 2005;90(12):6454-9.

15. Pak JW, Herbst A, Bua E, Gokey N, McKenzie D, Aiken JM. Mitochondrial DNA mutations as a fundamental mechanism in physiological declines associated with aging. Aging Cell. 2003;2(1):1-7.

16. Judge S, Leeuwenburgh C. Cardiac mitochondrial bioenergetics, oxidative stress, and aging. American journal of physiology Cell physiology. 2007;292(6):C1983-92.

17. Paradies G, Petrosillo G, Paradies V, Ruggiero FM. Oxidative stress, mitochondrial bioenergetics, and cardiolipin in aging. Free radical biology & medicine. 2010;48(10):1286-95.

18. Nettleton JA, Diez-Roux A, Jenny NS, Fitzpatrick AL, Jacobs DR, Jr. Dietary patterns, food groups, and telomere length in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2008;88(5):1405-12.

19. Morley JE. The Metabolic Syndrome and Aging. The Journals of Gerontology: Series A. 2004;59(2):M139-M42.

20. Bonomini F, Rodella LF, Rezzani R. Metabolic syndrome, aging and involvement of oxidative stress. Aging and disease. 2015;6(2):109-20.

21. Veronica G, Esther RR. Aging, metabolic syndrome and the heart. Aging and disease. 2012;3(3):269-79.

22. Guarner V et al 2005.Aging of the cardiovascular system. In: Benhagen EF, editor. Hypertension: New Research. USA: Nova Biomedical Books Publishers,47–68. .

23. Passos JF, Saretzki G, Ahmed S, Nelson G, Richter T, Peters H, et al. Mitochondrial dysfunction accounts for the stochastic heterogeneity in telomere-dependent senescence. PLoS biology. 2007;5(5):e110.

24. Kong CM, Lee XW, Wang X. Telomere shortening in human diseases. The FEBS journal. 2013;280(14):3180-93.

25. Salpea KD, Talmud PJ, Cooper JA, Maubaret CG, Stephens JW, Abelak K, et al. Association of telomere length with type 2 diabetes, oxidative stress and UCP2 gene variation. Atherosclerosis. 2010;209(1):42- 50.

26. Valdes AM, Andrew T, Gardner JP, Kimura M, Oelsner E, Cherkas LF, et al. Obesity, cigarette smoking, and telomere length in women. Lancet (London, England). 2005;366(9486):662-4.

27. Revesz D, Milaneschi Y, Verhoeven JE, Penninx BW. Telomere length as a marker of cellular aging is associated with prevalence and progression of metabolic syndrome. The Journal of clinical endocrinology and metabolism. 2014;99(12):4607-15.