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Leading article

Lifestyle, telomeres and aging – what is the connection?

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Abstract

Telomere shortening is the mayor contributor of cellular aging and telomere length is reliable biomarker of aging process, both at individual as well as at the population level. Short telomeres are also connected with aging related diseases like cancer, cardiovascular diseases and diabetes which are the leading causes of death in the world today. Recently, it has been demonstrated, for the first time, that comprehensive lifestyle changes can slow aging process at molecular level. Such changes include food rich in fiber, fruits and vegetables as well as low fat and low refined carbohydrates diet. If this diet is combined with moderate exercise and stress management techniques, it can result in increased telomerase activity in peripheral mononuclear blood cells during three months period only, which subsequently slow down telomere loss in humans.

INTRODUCTION

Cancer, cardiovascular and neurodegenerative diseases are by waste the leading causes of death in the world today and every year huge amount of money is spent on medical care treating these diseases *(4, 20)*. While medication and medical treatments are expensive and aggressive toward the patient, it has been proven that adequate changes in feeding habit and lifestyle are effective in disease prevention and healing *(25)*. Even more, lifestyle changes are cost saving and causes great difference in risk, progression and final outcome of the disease. Telomere dynamics is most reliable molecular marker in following these changes as well as normal aging at individual and population level *(15,19)*. Numerous reports support telomere shortening as a prognostic marker of disease risk and progression *(5,13)*. Short telomeres are clearly associated with aging and most frequent aging related diseases like diabetes, cancer, cardiovascular and neurodegenerative diseases *(22, 29)*.

TELOMERES AND TELOMERASE

Telomeres are specialized structures at the ends of linear chromosomes *(6)*. They are composed of short tandem repeat sequences essential for genome stability *(21)*. Their lariat structure prevents degradation, illegitimate fusion and aberrant recombination of chromosome termini and facilitate proper chromosome end replication *(6)*. Due to inherent property of the mechanism of DNA replication, in normal somatic cells telomeres progressively shorten with each cell division *(15)*. Normally, when telomere shortening reaches a critical

limit, cells are susceptible to chromosomal aberrations such as end-to-end fusion and aneuploidy *(9,10, 28)*. To avoid such scenario, when at least one telomere is critically shortened, the cells cease to divide and enter replicative senescence *(2)*. In various somatic cells, telomere length can serve as a biomarker of their replicative history and predictive factor for their future division capacity *(3)*. In order to prevent senescence, telomeres are normally elongated by the activation of enzyme telomerase in germ and stem cells *(9)*. While wast majority of somatic cells do not express telomerase activity, peripheral-blood mononuclear cells (PBMCs), limphocytes and granulocytes have active telomerase *(34)*. Since telomerase activity as well as telomere length in these cells are affected by age, diseases, stress and various other factors, their telomere length is used as a reliable biomarker to follow these processes *(7, 11)*.

INFLUENCE OF LIFESTYLE CHANGES ON TELOMERASE ACTIVITY AND TELOMERE LENGTH

For the last five years a longitudinal study on human subjects has been conducted in order to closely examine the influence of lifestyle changes on telomerase activity and telomere length *(22)*.

Pilot study. The study started with a pilot experiment during three months period in which they examined whether the improvements in nutrition and lifestyle can influence telomerase activity in PBMC *(24)*. 24 men with biopsy-diagnosed low risk prostate cancer which chose active surveillance rather than conventional treatments were asked to take 3 month comprehensive lifestyle changes which included specific diet accompanied with stress management, moderate aerobic exercise and group support session. Dietary requirements were based on food low on fat and refined carbohydrates, with plenty of fruits, vegetables, unrefined grains and legumes supplements with soy, fish oil, vitamins E, C and selenium. Moderate exercise presumes walking 30 minutes a day, 6 days a week. Stress management included gentle yoga based stretching, breathing, meditation and relaxation techniques for 1 hour a day, 6 days a week accompanied with 1 hour group support sessions, once per week. Precooked meals were provided to participants as well as professional support and counseling.

Telomerase activity was measured in PMBC samples at baseline and after three months. Collected data were compared to assess changes in telomerase activity. Psychological stress was measured using Impact of Event Scale as well as lifestyle index which represents overall adherence to intervention guidelines. Results showed that patients were following lifestyle recommendations with great success which resulted in improvements of risk factors for cardiovascular diseases like decreased body mass index, blood pressure, lipid as well as reduction of waist circumference, triglycerides and C reactive protein (CRP) value. Participants also reported decrease in psychological distress. But most important result is

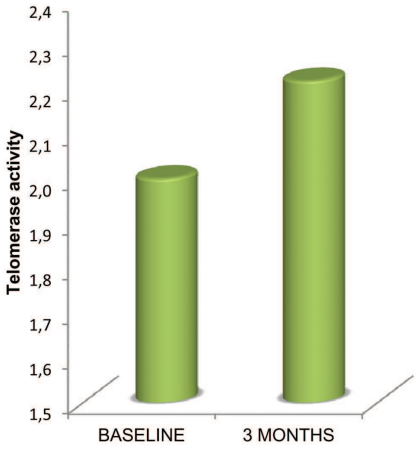

Figure 1. *Increase in telomerase activity induced by comprehensive lifestyle changes is visible after only three months period. Adapted from (24).*

that only three months of changed lifestyle was sufficient to increase telomerase activity in PMBC of these subjects on average by 29,84 % (Figure 1).

This was the first time that someone directly demonstrated that lifestyle changes are significantly linked to telomerase activity in human cells. Decrease in LDL cholesterol levels and psychological distress were associated with increased telomerase activity with statistical significance. It is important to mention that there was no clinical evidence of disease progression in these men during the study period.

5 year follow up study. Although important, because of relatively small group of subjects and absence of usual control these results were presumed preliminary. Also, the changes in telomere length were not measured because three month period is too short to observe some differences in relative telomere length. Namely, the rate of telomere shortening in humans is around 30–60 bp per year *(32)*. On the other hand changes in telomerase activity may occur much sooner *(23)*. Nevertheless, at that point subjects undergoing lifestyle changes should decrease their telomere loss, lower their aging rate and prolong their healthspan. In order to answer those open questions Ornish and colleagues conducted five year follow-up study in order to determine whether the long term lifestyle changes affect telomere length and telomerase activity, and also whether the degree of adherence to these changes would have a significant effect on obtained results *(23)*. After five years period, telomere length, telomerase activity and life style index score were measured in intervention and control group of participants. The both groups shared similar characteristics like age, weight, BMI and blood pressure at a beginning of the study. 11 of 24 patients in intervention group and 25 of 34 participants in control group had enough of blood samples at baseline and after five years for telomere length and telomerase activity analysis. Relative telomere length was measured by quantitative real time PCR and expressed as a telomere to single copy gene ratio (T/S).

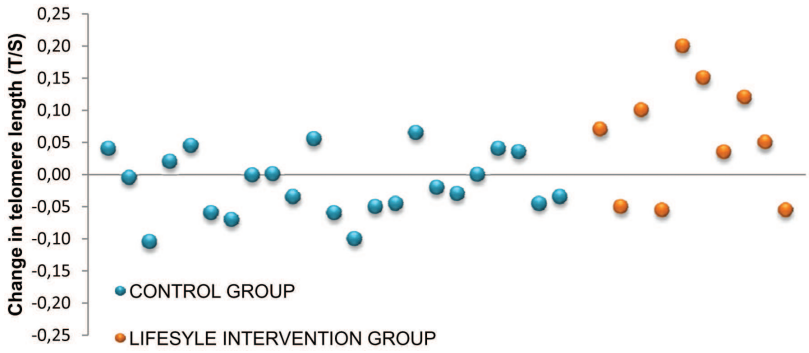

Figure 2. *Five years follow-up study demonstrated significantly lower rate of telomere loss in intervention group compared to controls (see explanation in text). Adapted from (23).*

Results were stunning. In lifestyle intervention group telomere length increased by a median of 0.06 T/S units (–0.05 to 0.11) and in control group decreased by –0,03 T/S (–0.05 to 0.3) comparing to measurement undertaken 5 years ago. Translated to percentages, relative telomere length decreased in only ~30 % of subjects in lifestyle intervention group compared to 64 % of subjects in the control group (Figure 2).

OXIDATIVE STRESS AND TELOMERES

Explanation for these extraordinary results could be found in protective effects of implemented changes in food consumption and regular exercise through diminished influence of free radicals and inflammation on cell structures, including telomeres.

Generally, free radicals are normal products of cell metabolism generated in mitochondria *(18)*. It has been found that free radicals have a significant impact on human cell senescence *(36)*. Telomeres are G rich repetitive sequences, very sensitive to DNA damage induced by ROS. Accumulation of these damages can accelerate telomere shortening and induce replicative senescence *(27)*. Further, it has been shown that senescence of normal human fibroblasts is related to dysfunctional mitochondria and shorter telomeres, indicating that ROS generation could be an important factor of the cell senescence signalling pathway *(16, 26, 31)*.

ROS can have either harmful or beneficial effect on living systems *(33)*. Beneficial effects of ROS occur at low concentrations and involve physiological roles in cellular responses to anoxia or in defence against infectious agents by induction of a mitogenic response *(12)*. Overproduction of ROS results in oxidative stress, harmful process involved in a number of human diseases as well as in the ageing process. It is shown that increased oxidative stress induces premature senescence in many human cell types *(8)*. Link between oxidative stress and telomere length has been shown *in vivo* as well *(1)*.

Harmful effects of free radicals in the cell can be neutralized by antioxidants *(30)*. Ascorbic acid derivative (ascorbate-2-O-phosphate) could slow down age-dependent telomere shortening in human vascular endothelial cells, *in vitro (14)*. Human embryonic cells treated with ascorbic acid phosphoric ester magnesium salt (*APM*) have decreased level of oxidative stress which prevents telomere attrition and extend replicative life span in these cells. The same effect of *APM* was also demonstrated in normal human adult cells and Werner syndrome (*WS*) cells *(17)*.

Beside *in vitro* experiments with antioxidants, *in vivo* experiments are considered more important because there are many other biological factors that may play a role in telomere shortening. While usage of multivitamin supplements has been associated with longer telomeres in women, when analyzed for individual vitamin intake, only antioxidant vitamins C and E were associated with effects on telomere length *(35)*.

CONCLUSION

Described results demonstrate that it is possible to preserve our telomeres, reduce aging rate and prolong healthspan. Therefore, it is advised to eat less and include more antioxidants and high fibre food in our diet. Also, one should balance body weight, implement anti – stress behaviour and moderate exercise on a daily bases.

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