RESEARCH ARTICLE

The effect of aerobic exercise on relative leukocyte telomere length in male Sprague-Dawley rats given a high fat-diet

[version 1; peer review: 2 approved with reservations]

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Abstract

Background: There is an increasing number of studies showing that physical activity and aerobic exercise have a positive effect on telomere length. Some studies also show that dynamics of telomere length is influenced by various environmental factors such as lifestyle and diet. However, the association between exercise and diet with telomere length is still questionable. The aim of this study was to examine the effects of aerobic physical exercise on relative telomere length changes in high fat-diet condition in rat animal models.

Methods: This study was an *in vivo* experimental study using twelve Sprague-Dawley male white rats (12-month-old). Subjects were evenly and randomly divided into two groups (n=6): (1) high fat-diet fed control group; (2) high fat-diet fed and aerobic exercise treatment group. Aerobic exercise was conducted using animal treadmill with intensity of 20 m/min, 5 days/week. At weeks 4 and 8, relative telomere length was compared with week 0 control group, using q-RT-PCR.

Results: Lengthening of relative telomere length was observed in both control and treatment groups at weeks 4 and 8, when compared to week 0 control group. The lengthening in the control group was much greater than the treatment group.

Conclusions: Excessive increase of relative telomere length was seen in high fat-diet conditions. Aerobic exercise for 8 weeks suppresses excessive increase of relative telomere length in high fat-diet conditions.

Keywords

aerobic exercise, telomere length, high fat-diet

Open Peer Review

Approval Status ? ?

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Universitas Padjadjaran, Bandung, Indonesia
Hanna Goenawan, Universitas Padjadjaran, Bandung, Indonesia
- Andrew T. Ludlow** , University of Michigan, Ann Arbor, USA

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: **Santoso DIS:** Conceptualization, Data Curation, Funding Acquisition, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Paramita N:** Conceptualization, Data Curation, Funding Acquisition, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Prijanti AR:** Conceptualization, Data Curation, Formal Analysis, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Hendrawan T:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Visualization, Writing – Original Draft Preparation; **Wicaksono S:** Conceptualization, Funding Acquisition, Investigation, Resources, Software

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Table 1. Characteristics of the animals.

	Control Group	Treatment Group
Age (months)	12-13	12-13
Body weight (g)	370.5 ± 51.32	352.5 ± 30.95
Body Mass Index (Lee Index)	307.34 ± 8.66	318.71 ± 10.34
Telomere length at baseline (week 0)	0.993 (0.302 – 3.026)	0.971 (0.493 – 5.059)

There was no significant difference in age, body weight, Lee index and telomere length between control and treatment groups.

There was an increase in relative telomere length at weeks 4 and 8 compared to week 0 in both groups. At week 4, the relative telomere length of the control group (2.231) did not differ much with the treatment group (1.802) when compared to week 0 of control group. At week 8, there was a progressive increase of relative telomere length in both groups compared to week 0 and week 4. Relative telomere length increase in week 8 of the control group was much higher (178.62) compared to week 8 treatment group (74.86) (Figure 1; Table 2).

Dataset 1. Raw data including the relative telomere length for control and treatment groups at week 0, 4 and 8, and 2^{ΔΔCt} calculations

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Discussion

One important structures located at the ends of the linear chromosomes is the telomere. In human cells, they are composed of TTAGGG repeats and a number of proteins. Their function is to protect the integrity and stability of the DNA¹⁴.

Many studies showed that telomere length is influenced by a number of factors^{9,12,15}. Sedentary lifestyle, high blood glucose levels, and increased percentage of body fat have a negative influence on telomere length. The underlying mechanism have been suggested as being mediated through oxidative stress and inflammation¹⁶.

Exercise as a lifestyle intervention has been associated with longer leukocytes telomere length¹⁵. A study by Cherkas on 2401 subject showed that telomere length has a direct relation with increased level of physical activity¹⁷. An observation of physical activity and telomere length by Du *et al.* on 7813 adult women concluded that moderate and vigorous intensity activity increased telomere length compared with least active women¹⁸. Ludlow *et al.* studied the effect of physical activity on telomere length in three different groups: sedentary, moderate and overtraining. The result showed a positive effect on telomere length in the moderate group¹⁹.

To date, to our knowledge, very few studies have investigated the relative effect of a specific diet on telomere length. Cassidy *et al.* found that total fat intake was only inversely

associated with leukocytes telomere length and higher polyunsaturated fatty acids (PUFA) intake, specifically linoleic acid intake, was inversely associated with leukocytes telomere length¹¹. Li *et al.* found that there was no difference in telomere length between consumption of fish oil-rich diet and soy oil-rich diet²⁰. Kiecolt-Glaser *et al.* compared telomere length between subjects with n-6 PUFA and n-3 PUFA supplementation. They found that telomere length is longer in subject with omega 3 or n-3 PUFA supplementation (high in fish oil) compared to n-6 PUFA supplementation²¹.

Results from our current study showed a lengthening of relative telomere length in both groups in week 4 and week 8. This was in contrast with studies showing telomeres usually shortened with age⁹, but there are also studies which indicate that *in vivo*, telomere may shorten or elongate, and leukocyte telomere length may fluctuates within months^{22,23}.

In general, preserved telomere length and lengthening of telomere are considered as something good because it is thought to play an important role in extending the biological age of cells^{12,21,24}.

Nevertheless, studies have also shown that telomere lengthening can be an initial response that arises after exposure to low doses of various carcinogenic chemicals *in vitro* and in experimental animals²³. Zhang *et al.* concluded from their study that subject with longer telomere length had a higher risk of getting lung cancer, and this was especially true for men²⁵.

The positive associations between high fat-diet conditions and telomere length is difficult to explain because a high fat-diet is associated with increased risk of various diseases. Telomeres generally shorten with age, thus, the discovery of telomere elongation in the provision of high-fat diet can be regarded as something that deviates from normal condition. Therefore, the positive associations between high fat-diet conditions and telomere length observed in this study are notable.

Telomere will shorten at each cell division. Telomeres that elongate excessively in both groups in this study may indicate a prolonged period before apoptosis, and this could indicates a change from normal cell function. Currently, the implications of excessive telomere lengthening are still unknown. Our result shows that aerobic exercise can act as a barrier to progressive changes that occur in the relative telomere length caused by a high-fat diet condition. Modulation of oxidative stress in the

Figure 1. Comparison of relative telomere length in leukocytes of rats fed a high fat-diet at weeks 0, 4 and 8 between control group (no aerobic exercise) and treatment group (aerobic exercise).

Table 2. Comparison of relative telomere length in leukocytes of rats fed with high-fat diet at week 0, 4 and 8 between control group (no aerobic exercise) and treatment group (aerobic exercise). Median (minimum-maximum).

	Control Group	Treatment Group	Kruskal-Wallis test (p-value)
Week 0	0.993 (0.302-3.026)	0.971 (0.493-5.059)	0.749
Week 4	2.321 (0.633-9.344)	1.802 (0.912-9.721)	0.873
Week 8	178.621 (95.158-812.49)	74.864 (36.218-295.895)	0.055

body is one possible mechanism that may explain how aerobic exercise resist relative telomere changes. Aerobic exercise upregulate genes that encode various antioxidant enzymes. Several studies shows that regular physical exercise increase the body's endogenous antioxidant activity and thus increase body's resistance to oxidation events^{15,26}.

Conclusions

Our study showed that exposure to a high fat-diet plays an important role to the emergence of altered telomere length, and aerobic exercise could reduce the progression of the alteration in length. Our results support the hypothesis that leukocyte telomere length is associated with daily dietary intake and physical activities. Further investigation is still needed to explore the mechanism and implications of telomere length changes found in this study.

Data availability

Dataset 1: Raw data including the relative telomere length for control and treatment groups at week 0, 4 and 8, and $2\Delta\Delta C_t$ calculations. DOI, [10.5256/f1000research.15127.d211681](https://doi.org/10.5256/f1000research.15127.d211681)²⁷.

Competing interests

No competing interests were disclosed.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Current Peer Review Status: ? ?

Version 1

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Andrew T. Ludlow

University of Michigan, Ann Arbor, MI, USA

Santoso et al. explore the relationship between a high fat diet, aerobic exercise and telomere length. In this small-scale animal research study, the authors make the unexpected observation that after 8 weeks of high fat diet, telomeres are elongated in circulating blood cells (leukocytes). They observed in aerobically trained animals that the apparent telomere elongation was significantly attenuated compared to a sedentary control. These interesting findings observations call into question the strict dogmatic view that telomere shortening is the rule in pathology. Human epidemiological studies have reported similar discrepancies, where telomere shortening is not always observed in pathological scenarios but rather telomere elongation can also be apparent in disease situations. While these observations are provocative, I have several concerns with the sample size, the model organism, the method used to measure telomere length, and the interpretation of the data.

This study is very positive in terms that it points out the need to perform longitudinal analysis of telomere biology in both human and model organism studies. Repeat sampling will be critical to moving the field of telomere biology and environmental/lifestyle impacts forward. For instance, what happens to telomere biology or cell biology after 12 weeks on a high fat diet following the apparent rapid and massive telomere elongation event at 8 weeks?

The negatives of this study are the model organism of choice, the measurement biochemistry, the data analysis, and the lack of mechanistic insights provided by the authors.

1. Sample size, model organism, and statistical treatment of the data.

While the effect observed in this study is large, the sample size is small. Further the authors utilize a repeated-measures design and do not analyze the data as such. Each rat's telomere length was measured three times. Thus, change in telomere length per individual rat should be reported between each time point and analyzed via a repeated measures analysis. Further, with the assay of choice, 6 animals would be borderline powered enough to detect a meaningful change. What were the authors expectations in terms of a priori predictions on the magnitude of change in

telomere length?

Are the rats inbred or outbred? This needs to be reported in the document.

Translatability of findings to humans. Rats use a different life history/ life course strategy to promote survival of the species. These animals grow quickly, have a small body size, do not suppress telomerase, reproduce young, and are cancer susceptible while humans grow slowly, have a large body size, suppress telomerase, reproduce late in life, and are cancer resistant. Thus, could this extreme lengthening be due to evolutionary differences between humans and the chosen model organism? That is, humans might not have a similar response compared to rodents.

2. Assay choice.

The Cawthon method or T/S ratio to determine relative telomere length is a valid assay when performed by certain labs, but it can have issues. A critical validation step in the assay that I did not see in the online data is the reference DNA sample. Did the authors have a reference sample of known telomere length that was run on each plate to ensure their assay was performing as expected? This should have been done on each plate and the inter and intra plate coefficient of variation should be reported for the assay in general. This is critical to be sure the findings are not erroneous. The authors could purchase a cell line with a known telomere length, isolate DNA and repeat the T/S ratio on all samples (both known and unknowns/experimental) to ensure the measurement is correct.

I would have expected higher T values across the board. Rats have 25-40 kb telomeres and a single copy of 36B4. Thus, the ratio of telomere copy to 36B4 copy should have been more like 2 or 3, not 1.

3. Interpretation concerns.

What is known about rapid telomere elongation to my knowledge is as follows:

E. Blackburn's group showed that yeast mutants for telomerase RNA result in ultra-elongated telomeres rapidly and impair cellular survival. Further, some mutants acted as a 'time-bomb' and killed cells later in life (slow on set of telomere elongation ¹). In human cancer cells telomere elongation induces cell differentiation and less aggressive tumors ². Another line of evidence from the L. Harrington lab is that telomere elongation reduced cell survival after radiation treatment ³. From epidemiological evidence, telomere trajectory in CVD can be maintained, shorten or elongated in follow up ⁴. Whether or not these changes correlate to health outcomes or are correlated with secondary CVD events is unknown.

Thus, it appears that ultra-long telomere lengths (greater than 15 kb in human) could be equally as 'bad' as short telomeres for cell fate decisions. The major cellular and molecular issues of long telomeres are stalled replication forks at telomeres and double strand breaks in the telomeres that are refractory to repair. Do the authors suspect that the immune cells with ultra-long telomeres will die soon after the 8-week period? Is there a major shift in immune cell distribution after 8 weeks on a high fat diet that would indicate a lasting impact of this observation? Are the cells with long telomeres dying?

The concept that telomere length must be maintained at the correct telomere length and that telomere structure and sensing by the cell may be more important than absolute length is an

emerging concept in the field. The results from the current study lend to the hypothesis that absolute length is not critical but rather tight regulation and sensing of telomere length is critical to cellular health and in turn gene expression regulation and cellular physiology. This idea needs and deserves more investigation as much of our evidence to date comes from cells grown in culture which may be very different than cells *in vivo* when it comes to telomere biology.

4. Short duration and extreme impact.

My hypothesis would have been no or very subtle changes in telomere length for this duration of intervention. What are the speculative mechanisms the authors see occurring? Are the leukocytes entering a stress mode whereby they activate telomerase and elongate telomeres dramatically to try to survive? Could this be the beginning of alternative lengthening of telomeres in these cells? Can the author speculate a bit about what they think might be happening in terms of mechanisms?

Issue of timing – in terms of physiology – after 8 weeks on a high fat diet what else is changed in the immune system of these animals? Can the authors provide about how long 8 weeks in a rats' life would be equivalent to how long on a high fat 'western' diet for humans would be?

What other physiological changes occur? Fatty liver? Higher cholesterol? Higher fasting blood glucose? Hormone levels (epi, nor-epi, insulin, IGF-1, glucagon, cortisol, growth hormone, TNF alpha, IL-6, IL-10, etc.). All of these measures could identify correlates to the change in telomere length.

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 13 August 2018

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Study is interesting, however there are some points need to be added:

1. Training protocol should followed and compared with the protocol of the aerobic exercise in previous report, please cross check and add reference (lesmana et al, 2017¹).
2. Please present the change in level of profil lipid
3. Discuss more about factor change and induce telomere characteristic
4. Reasons the using high fat diet connected to the change telomere.

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Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

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If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

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