Is Telomere Length a Biomarker of Adaptive Response in Space? Curious Findings from NASA and Residents of High Background Radiation Areas

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ABSTRACT

Telomere length and stability is a biomarker of aging, stress, and cancer. Shortening of telomeres and high level of DNA damages are known to be associated with aging. Telomere shortening normally occurs during cell division in most cells and when telomeres reach a critically short length, DNA damage signaling and cellular senescence can be triggered. The induction of an adaptive response by space radiation was first documented in 2003. Telomere length alterations are among the most fascinating observations in astronauts and residents of high background radiation areas. While study of the chronic exposure to high levels of background ionizing radiation in Kerala, India failed to show a significant influence on telomere length, limited data about the NASA astronaut Scott Kelly show that exposure to space radiation can induce telomeres to regain length. Interestingly, his telomeres shortened again only a couple of days after returning to Earth. The difference between these situations may be due to the differences in radiation dose, dose-rate, and/or type of radiation. Moreover, Scott Kelly's spacewalks (EVA) could have significantly increased his cumulative radiation dose. It is worth noting that the spacewalks not only confer a higher dose activity but are also characterized by a different radiation spectrum than inside the space craft since the primary particles would not interact with the vehicle shell to generate secondary radiation. Generally, these differences can possibly indicate the necessity of a minimum dose/dose-rate for induction of adaptive response (the so called Window effect).

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Keywords

Telomere Length, Adaptive Response, Astronauts, Background Radiation, Natural Radiation

Introduction

As defined by the National Institutes of Health (NIH) Biomarkers Definitions Working Group a biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[1]. Telomere length is a biomarker of aging, stress, and cancer [2]. Despite the complexity of aging, it seems that a wide variety of factors ranging from oxidative stress to shortening of telomeres are involved in this phenomenon. Short telomere length can stop cell replication and cause cell death. Telomere plays a key role in preventing triggering a DNA damage response from the blunt end of DNA [3]. Shortening of telomeres and high level of DNA damages are shown to be associated with aging. Telomere shortening occurs during cell division and when telomeres reach a critically short length, DNA damage signaling and cellular senescence can be triggered. The telomere length alteration is among the most fascinating issues in astronauts and the residents of high background radiation areas.

Space Environment

The space radiation environment is complex and includes contributions from galactic cosmic radiation (GCR) and solar particle events (SPEs). The complexity of this radiation environment is summarized in Table 1 and includes electrons, protons, light ions, heavy ions, charged target fragments, and neutrons [4,5]. These radiation types have a wide range of energies and interact with the spacecraft shell to produce a wealth of secondary radiation types including pions, muons, photons, and electromagnetic and hadronic cascade radiation [6-9].

The shielding of a variety of radiation types with a wide range of associated energies is a difficult problem. Shielding the space radiation environment with limited space using a single material is also problematic. Neutrons shielding illustrates this difficulty. As noted in Table 1, there is a also range of energies for these radiation types that requires evaluation.

Table 1: Comparison of adaptive response in the residents of high background radiation areas of Kerala and Ramsar with astronauts (currently the only available data are Scott's telomere findings)

	Adaptive Response Observed as		References
	Telomere Elongation	Other Endpoints (e.g. cytogenetic or CBMN)	
High Background Radiation Areas (Kerala)	No@	Yes#	@Das et al. 2009 [2] #Ramachandran et al. 2018 [10]
High Background Radiation Areas (Ramsar)	NA	Yes#	#Mortazavi et al. 2002 [11] #Masoomi et al. 2006 [12] #Mohammadi et al. 2006 [13]
International Space Station (ISS)	Yes@	NA	@NASA 2018 [14]

Low energy neutrons (< 5-10 MeV) are effectively shielded using hydrogenous compounds because the 1H (n,n) and 1H (n, γ) reaction cross sections effectively attenuate the neutron in this energy range [6-9]. However, higher energy neutrons are not effectively attenuated by these reactions. They can be effectively attenuated using thick shielding of a single material if space is not a concern. The classic example is accelerator shielding using concrete or earth shielding that is accomplished because space is not an issue. The primary accelerator radiation types of biological significance are neutrons, muons, and photons. However, if space is limited, a second material typically iron or lead is used to degrade the energy spectrum using the inelastic scattering reactions (e.g., Fe(n,n') or Pb(n,n')) to reduce the neutron energy to the 5-10 MeV range where the 1H(n,n) and 1H(n, γ) reactions effectively attenuate the resulting neutrons [4-7]. Since space is limited in a spacecraft, a single material will not be an optimum choice for radiation shielding. The issue is more difficult when the various radiation types of Table 1 are considered.

The Importance of Biological Protection in Deep Space Missions

Substantial evidence shows that a pre-exposure to a low level stressor (e.g. low dose radiation) can induce an adaptive response by stimulating the defense mechanisms such as increasing antioxidant levels, reducing the endogenous DNA damage, increasing DNA repair capacity, and increasing apoptosis of damaged cells [15]. A NASA report published in 2016 refers to reports about the importance of radioadaptation in deep space missions including our 2003 report and states that it would be realistic to expect that astronauts' cells will be exposed to multiple hits of protons before being traversed by an HZE particle "There have been several studies performed that indicate an adaptive response to low-dose ionizing radiation can provide a level of protection against future exposures (Bhattacharjee and Ito 2001; [16] Mortazavi et al. 2003; [17] Elmore et al. 2008; [18] Rithidech et al. 2012 [19]). This may be particularly important for understanding risks in the space environment because the GCR environment is comprised predominantly of protons, and it is realistic to expect that cells will be exposed to multiple hits of protons prior to being traversed by an HZE particle" [14]. Moreover, other reports also indicate the role of biological protection as an effective radiation risk reduction strategy for astronauts participating in space missions [20]. During the mission, chronic exposure to elevated levels of galactic cosmic radiation (GCR) can considerably decrease radiation susceptibility and better protect astronauts against the unpredictable exposure to sudden and dramatic increase in flux due to solar particle events (SPE) [21]. Given this consideration, elongation of telomeres can also be considered as a biological protective effect (the well-known phenomenon of adaptive response) to high-radiation environment in space.

The Role of Telomere Length in Aging

Oxidative stress, western and high fat diet (HFD), depression, consumption of alcohol, genetic abnormalities and pollution are among the processes at cellular level which are involved in aging phenomenon [22]. Studies conducted on rodents suggest that telomere attrition (shortening of telomeres during cell division), increases the speed of development of ageing-related lung emphysema [23]. Some studies show that not only males have a higher rate of telomere attrition but they have shorter telomeres [24]. The progressive shortening of telomeres is among the known mechanisms of aging [25]. Some evidence also shows that long non-coding RNAs (lncRNAs) play a role in aging [26]. Some vitamins (Vitamin C, D, E, folate or folic acid, and β-carotene) and minerals such as zinc and magnesium are reported to enhance protection against oxidative stress and inflammation which in turn are positively associated with telomere length and leads to protection of telomeres and in humans [27]. Shortening of telomeres along with other factors such as decreased efficiency of DNA repair, and loss of heterochromatin are believed to be involved in the loss of genomic integrity in premature ageing and ageing-associated diseases (AADs) [23].

Alterations in telomere length (shortening of telomere) is reported to be the main pathway by which oxidative stress increases the speed of biological aging and age-related diseases [28]. It is worth noting that since physical activity decreases chronic inflammation and oxidative stress, it can reduce the shortening of telomeres observed with aging process [29]. Telomerase plays an important role in increasing the cell lifetime.

Some reports show that the activity of this enzyme decreases in peripheral blood lymphocyte of patients with Schizophrenia (SZ) or other severe mental disorders [28]. Although there is a link between the telomere length and telomerase activity, the level of this enzyme does not reliably correlate with the length telomere. A study performed on 124 healthy individuals showed low but stable telomerase expression despite continued telomere shortening in 65% of individuals aged 40 years or older [30].

Telomere Length in People Chronically Exposed to Elevated Levels of Natural Radiation

Some evidence shows that in short and long term cultures exposure to low and high LET radiation can lead to elongation of telomere length [31]. Moreover, the relationship between telomere stability and human longevity has been has been reported in some in vitro experiments [32].The huge natural laboratory of high background radiation areas (HBRAs) can be considered as a great source of knowledge about the health effects of chronic exposure to elevated levels of natural radiation. In 2009 Das et al. isolated genomic DNA from the peripheral blood mononuclear cells of 233 residents of HBRAs of Kerala, India and 77 individuals from a normal background radiation area. Using real time q-PCR, they determined the telomere length of the participants. Their study failed to show any significant dose response relationship between telomere length and annual radiation doses groups (≤1.50, 1.51-3.00, 3.01-5.00 and >5.00 mGy/y) [2]. Three years later, Das et al. conducted another study on 128 newborns from HBRAs (3 dose groups: 1.51-3.00, 3.01-5.00, and >5.00 mGy/y) and 43 newborns from NBRAs (<1.50 mGy/year). The mean telomere length in these 4 groups did not show a statistically significant difference and the researchers concluded that elevated levels of background radiation in Kerala coast caused no significant effect on telomere length of newborns [33].

Telomere Length in Astronauts

Mark and Scott Kelly are identical twins and both are NASA astronauts and the only known siblings to have both participated in space journeys. Scott Kelly started a mission spending about one year (a 340-day mission) in space on the International Space Station (ISS). Scott Kelly and his Russian counterpart, Mikhail Kornienko returned to Earth on March 1, 2016. Scott Kelly is the first American astronaut to spend a year in space. NASA believes that Scott Kelly's one-year mission aboard the ISS has helped scientists advance deep manned space missions such as a journey to Mars. NASA Administrator Charles Bolden states "Scott Kelly's one-year mission aboard the International Space Station has helped to advance deep space exploration and America's Journey to Mars" and "Scott has become the first American astronaut to spend a year in space, and in so doing, helped us take one giant leap toward putting boots on Mars." [34].

As Scott and Mark Kelly are identical twins, they were studied during and after mission to find biological differences caused by space environment compared to a baseline on Earth.

NASA states that while there was no basic changes in Scott's DNA, gene expression changes were observed. Interestingly, these changes in gene expression were reported to lie within the range for human exposures to stress (e.g. conditions such as mountain climbing or SCUBA diving). A promising key finding in NASA's twin study is Scott's telomere elongation in space.

In this regard, NASA reports that "Scott's telomeres (endcaps of chromosomes that shorten as one ages) actually became significantly longer in space. While this finding was presented in 2017, the team verified this unexpected change with multiple assays and genomics testing. Additionally, a new finding is that the majority of those telomeres shortened within two days of Scott's return to Earth." [35]. Figure 1 shows the elongation of telomeres in space as an adaptive response to higher levels of space radiation.

HBRAs versus Astronauts

Given the above mentioned consideration, an important question is why the adaptive response observed as elongation of telomeres was found after exposure to space radiation (and other stressors in space), while chronic exposures of the residents of high background radiation areas failed to show such an adap-

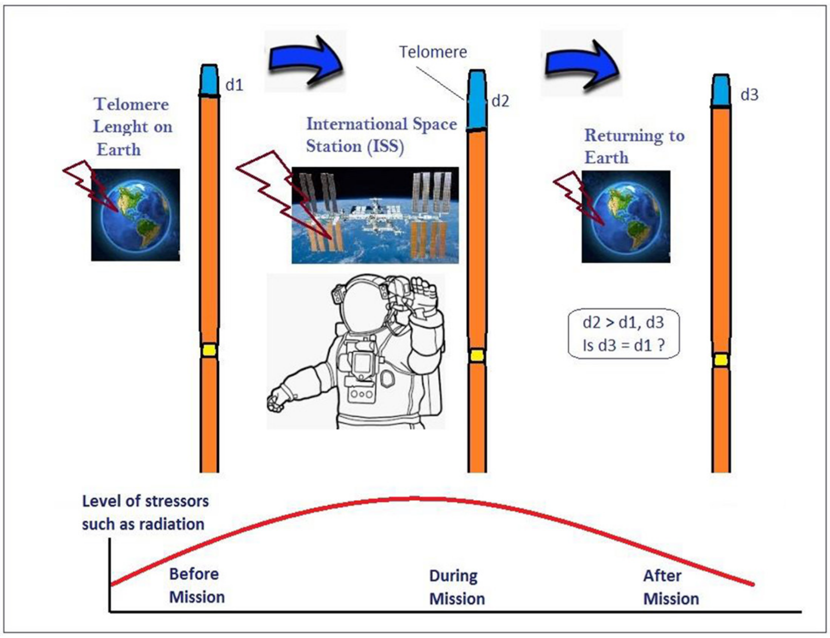


Figure 1: Elongation of telomeres in space that can be considered as an adaptive response to higher levels of space radiation. http://spaceflight.nasa.gov/gallery/images/shuttle/sts-132/hires/s132e012208.jpg

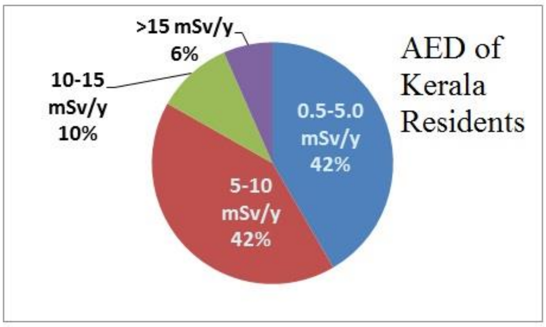
tive response. Despite, answering this question is not easy, the significant differences between the dose levels seems to be involved in this variation. A study conducted in Kerala in 2004 showed that the residents of 41.6% of the dwelling surveyed received effective doses ranging between 0.5-5 mSv/y, 41.6% between 5 and 10 mSv/y, 10.2% between 10 and 15 mSv/y and only 6.6% greater than 15 mSv/y (Figure 2.a) [36], while the average effective dose for 6 month ISS missions is about 80 mSv (Figure 2.b) [37]. Moreover, reports show that Scott Kelly participated in 3 spacewalks (EVA). The EVA would be a higher dose activity and would be characterized by a different spectrum than the space craft since the particles would not interact with the vehicle shell. His total EVA time was 18 hours and 20 minutes. Therefore, lack of spacecraft shielding in these EVAs could significantly increase the Scott Kelly's dose. Altogether these findings confirm the necessity of a minimum dose/dose rate for induction of adaptive response (Window effect).

Conclusion

It is still early to claim that elongation of telomeres is a well-established biological adaptive response to high-radiation environments in space. Moreover, as NASA states that the telomeres again shortened upon return to Earth, a key question is do they return to the original length - or do they remain slightly longer than otherwise (a hormetic response to previous exposures)? Moreover, the difference between HBRAs and space environment can be due to the dose. The average effective dose for 6 month ISS missions is much higher than the annual dose in HBRAs of Kerala. Generally, these differences confirm the necessity of a minimum dose/dose rate for induction of adaptive response (the so called Window effect).

Conflict of Interest

None



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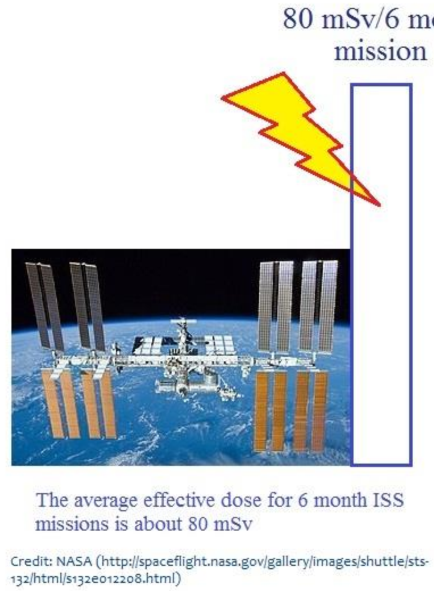

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Figure 2: Comparison of annual effective dose in HBRAs of Kerala and a 6-month ISS mission. a) Annual effective doses in residents of HBRAs of Kerala, India. b) the average effective dose for 6 month ISS missions. http://spaceflight.nasa.gov/gallery/images/shuttle/sts-132/hires/s132e012208.jpg

References

1. Biomarkers Definitions Working G. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;**69**:89-95. doi: 10.1067/mcp.2001.113989. PubMed PMID: 11240971.
2. Das B, Saini D, Seshadri M. Telomere length in human adults and high level natural background radiation. *PLoS One*. 2009;**4**:e8440. doi: 10.1371/journal.pone.0008440. PubMed PMID: 20037654; PubMed Central PMCID: PMC2793520.
3. Keefe DL. Telomeres, Reproductive Aging, and Genomic Instability During Early Development. *Reprod Sci.* 2016;**23**:1612-5. doi: 10.1177/1933719116676397. PubMed PMID: 27821557.
4. NCRP. Operational Radiation Safety Program For Astronauts In Low-Earth Orbit: A Basic Framework. Bethesda: NCRP Report No. 142; 2002.
5. Bevelacqua JJ. Radiation protection consequences of the emerging space tourism industry. *JJ Earth Science*. 2017;**1**:1-11.
6. Bevelacqua JJ. Health physics in the 21st century: John Wiley & Sons; 2008.
7. Bevelacqua JJ. Contemporary health physics: problems and solutions: John Wiley & Sons; 2009.
8. Bevelacqua JJ. Contemporary Health Physics: Problems and Solutions. *Medical Physics-New York-Institute of Physics.* 1995;**22**:2123.doi: 10.1118/1.597656.
9. Bevelacqua JJ. Health physics: radiation-generating devices, characteristics, and hazards: John Wiley & Sons; 2016.
10. Ramachandran EN, Karuppasamy CV, Kumar VA, Soren DC, Kumar PR, Koya PK, et al. Radio-adaptive response in peripheral blood lymphocytes of individuals residing in high-level natural radiation areas of Kerala in the southwest coast of India. *Mutagenesis.* 2017;**32**:267-73. doi: 10.1093/mutage/gew057. PubMed PMID: 27831478.
11. Ghiassi-nejad M, Mortazavi SM, Cameron JR, Niroomand-rad A, Karam PA. Very high background radiation areas of Ramsar, Iran: preliminary biological studies. *Health Phys*. 2002;**82**:87-93.doi: 10.1097/00004032-200201000-00011.PubMed PMID: 11769138.

12. Masoomi JR, Mohammadi S, Amini M, Ghiassi-Nejad M. High background radiation areas of Ramsar in Iran: evaluation of DNA damage by alkaline single cell gel electrophoresis (SCGE). *J Environ Radioact.* 2006;**86**:176-86. doi: 10.1016/j.jenvrad.2005.08.005. PubMed PMID: 16376699.
13. Mohammadi S, Taghavi-Dehaghani M, Gharaati MR, Masoomi R, Ghiassi-Nejad M. Adaptive response of blood lymphocytes of inhabitants residing in high background radiation areas of ramsar-micronuclei, apoptosis and comet assays. *J Radiat Res.* 2006;**47**:279-85.doi: 10.1269/jrr.0575. PubMed PMID: 16988494.
14. Huff J, Carnell L, Blattnig S, Chappell L, Kerry G, Lumpkins S, et al. Evidence report: risk of radiation carcinogenesis. 2016.
15. Feinendegen LE. Evidence for beneficial low level radiation effects and radiation hormesis. *Br J Radiol.* 2005;**78**:3-7. doi: 10.1259/bjr/63353075. PubMed PMID: 15673519.
16. Bhattacharjee D, Ito A. Deceleration of carcinogenic potential by adaptation with low dose gamma irradiation. *In Vivo.* 2001;**15**:87-92. PubMed PMID: 11286136.
17. Mortazavi S, Cameron J, Niroomand-Rad A, editors. Is the adaptive response an efficient protection against the detrimental effects of space radiation. International cosmic ray conference; 2003.
18. Elmore E, Lao XY, Kapadia R, Swete M, Redpath JL. Neoplastic transformation in vitro by mixed beams of high-energy iron ions and protons. *Radiat Res*. 2011;**176**:291-302. doi: 10.1667/rr2646.1.PubMed PMID: 21732791.
19. Rithidech KN, Lai X, Honikel L, Reungpatthanaphong P, Witzmann FA. Identification of proteins secreted into the medium by human lymphocytes irradiated in vitro with or without adaptive environments. *Health Phys*. 2012;**102**:39-53. doi: 10.1097/HP.0b013e31822833af. PubMed PMID: 22134077; PubMed Central PMCID: PMC3744879.
20. Cortese F, Klokov D, Osipov A, Stefaniak J, Moskalev A, Schastnaya J, et al. Vive la radioresistance!: converging research in radiobiology and biogerontology to enhance human radioresistance for deep space exploration and colonization. *Oncotarget.* 2018;**9**:14692-722. doi: 10.18632/oncotarget.24461. PubMed PMID: 29581875; PubMed Central PMCID: PMC5865701.
21. Mortazavi SM, Cameron JR, Niroomand-rad A. Adaptive response studies may help choose astronauts for long-term space travel. *Adv Space Res.* 2003;**31**:1543-51.doi: 10.1016/s0273-1177(03)00089-9.PubMed PMID: 12971409.
22. Iqbal G, Ahmed T. Co-exposure of metals and high fat diet causes aging like neuropathological changes in non-aged mice brain. *Brain Res Bull.* 2019;**147**:148-58. doi: 10.1016/j.brainresbull.2019.02.013. PubMed PMID: 30807793.
23. Kubben N, Misteli T. Shared molecular and cellular mechanisms of premature ageing and ageing-associated diseases. *Nat Rev Mol Cell Biol.* 2017;**18**:595-609. doi: 10.1038/nrm.2017.68. PubMed PMID: 28792007; PubMed Central PMCID: PMC6290461.
24. Marquez-Ruiz AB, Gonzalez-Herrera L, Valenzuela A. Usefulness of telomere length in DNA from human teeth for age estimation. *Int J Legal Med.* 2018;**132**:353-9. doi: 10.1007/s00414-017-1595-5. PubMed PMID: 28439695.
25. Labat-Robert J, Robert L. Longevity and aging. Mechanisms and perspectives. *Pathol Biol (Paris)*. 2015;**63**:272-6. doi: 10.1016/j.patbio.2015.08.001. PubMed PMID: 26416405.
26. Moskalev AA, Aliper AM, Smit-McBride Z, Buzdin A, Zhavoronkov A. Genetics and epigenetics of aging and longevity. *Cell Cycle.* 2014;**13**:1063-77. doi: 10.4161/cc.28433. PubMed PMID: 24603410; PubMed Central PMCID: PMC4013158.
27. Vidacek NS, Nanic L, Ravlic S, Sopta M, Geric M, Gajski G, et al. Telomeres, Nutrition, and Longevity: Can We Really Navigate Our Aging? *J Gerontol A Biol Sci Med Sci.* 2017;**73**:39-47. doi: 10.1093/gerona/glx082. PubMed PMID: 28510637.
28. Czepielewski LS, Massuda R, Panizzutti B, da Rosa ED, de Lucena D, Macedo D, et al. Telomere length in subjects with schizophrenia, their unaffected siblings and healthy controls: Evidence of accelerated aging. *Schizophr Res*. 2016;**174**:39-42. doi: 10.1016/j.schres.2016.04.004. PubMed PMID: 27131910.
29. Arsenis NC, You T, Ogawa EF, Tinsley GM, Zuo L. Physical activity and telomere length: Impact of aging and potential mechanisms of action. *Oncotarget.* 2017;**8**:45008-19. doi: 10.18632/oncotarget.16726. PubMed PMID: 28410238; PubMed Central PMCID: PMC5546536.
30. Chilton W, O'Brien B, Charchar F. Telomeres, Aging and Exercise: Guilty by Association? *Int J Mol Sci.* 2017;18. doi: 10.3390/ijms18122573. PubMed PMID: 29186077; PubMed Central PMCID: PMC5751176.
31. Sgura A, Antoccia A, Berardinelli F, Cherubini R, Gerardi S, Zilio C, et al. Telomere length in mammalian cells exposed to low- and high-LET radiations. *Radiat Prot Dosimetry*. 2006;**122**:176-9. doi: 10.1093/rpd/ncl478. PubMed PMID: 17223635.

32. Sharma GG, Hall EJ, Dhar S, Gupta A, Rao PH, Pandita TK. Telomere stability correlates with longevity of human beings exposed to ionizing radiations. *Oncol Rep*. 2003;**10**:1733-6.doi:10.3892/or.10.6.1733.PubMed PMID: 14534687.
33. Das B, Saini D, Seshadri M. No evidence of telomere length attrition in newborns from high level natural background radiation areas in Kerala coast, south west India. *Int J Radiat Biol.* 2012;**88**:642-7. doi: 10.3109/09553002.2012.699135. PubMed PMID: 22668000.
34. Administration NASA. NASA Astronaut Scott Kelly Returns Safely to Earth after One-Year Mission. Washington: NASA; 2016.
35. Edwards M, Abadie L. NASA Twin Study Confirms Preliminary Findings. National Aeronautics and Space Administration https://www.nasa.gov/feature/nasa-twins-study-confirms-preliminary-findings. 2018.
36. Chougaonkar M, Eappen K, Ramachandran T, Shetty P, Mayya Y, Sadasivan S, et al. Profiles of doses to the population living in the high background radiation areas in Kerala, India. *J Environ Radioact*. 2004;**71**:275-97.doi: 10.1016/s0265-931x(03)00174-7.
37. Cucinotta FA, Kim MH, Willingham V, George KA. Physical and biological organ dosimetry analysis for international space station astronauts. *Radiat Res*. 2008;**170**:127-38. doi: 10.1667/RR1330.1. PubMed PMID: 18582161.