Role of parental age in newborn telomere length prolongation

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Abstract: Telomere length, a marker of biological aging, can be altered by parental telomere genetics. In this study, we aimed to find an association between parental age and newborn telomere length (TL) and deterioration patterns in parents and newborns. This was a cross-sectional study on 204 parent–newborn pairs from September 2021 to July 2022. Quantitative polymerase chain reaction (qPCR) was used to measure the telomere length (T/S ratio). A correlation and linear regression were used for the association between newborn TL and parental age. There was a positive correlation ($r = 0.185$, $p = 0.007$) between the fathers’ age and newborn TL. However, regression analysis highlighted an association between the mother’s as well as the father’s age and newborn TL ($B = 0.032, 0.04$; $p = 0.09, 0.009$). The old-age mothers (35.1–40 years old) had newborn girls with longer TL; however, old-age fathers (35.1–45 years old) had boys with longer TL ($1.94 \pm 0.72, 2.48 \pm 1.22$) ($p = 0.23$). Therefore, longer telomere length was seen in newborns of older parents. Moreover, parental age, especially the father’s age, showed an association with newborns’ telomere genetics.

Keywords: telomere; telomerase; telomere length; newborn; aging

1. Introduction

Telomere shortening is a well-known hallmark of biological aging. The genomic instability of chromosomes is very much dependent on the telomeres, a ribonucleoprotein complex structure at the end of chromosomes [1]. They protect chromosomes from catastrophic events of degradation or interchromosomal fusion with another telomere or with a broken DNA end. Telomeres protect the genome from degradation like plastic caps protect shoelaces [1]. Human telomeres are less than 1% [150 million base pairs (bp)] of the total genome and are called the mitotic clock of a cell. During every
cell division, telomeres shorten (30 to 200 bp) due to the failure of DNA polymerase to complete the synthesis of lagging strand; this is termed “end replication problem” [2,3]. Such problems are seen in somatic cells but not in germ cells, stem cells, or cancerous cells due to the presence of the telomerase enzyme. In humans, the average telomere length (TL) is from 10000 to 15000 bp [4]. At birth, telomeres are the longest, with a size of approximately 6000–15000 bp [5,6], reducing in adults to 2000–7000 bps and further reducing to less than 2000–3000 bp in old age [7]. Overall, telomere repeats vary per chromosome, from 20 bp to many kilobp among different individuals [2].

As telomere length decreases during cellular division, a progressive deterioration takes place, which is known as senescence and also referred to as aging. When telomeres become extremely short, which is known as the Hayflick limit, this is recognized by p53 causing apoptosis. Such changes increase the replicative senescence of cells along with cellular apoptosis, telomeropathies, and life span [8].

Although it is well established that TL shortens with age in somatic cells in most proliferating tissues like lymphocytes, intestinal mucous cells, and thymus, germ cells are an exception due to the presence of the telomerase enzyme. Older men have sperm with longer telomeres [9]; as it has been found that offspring inherit half of their chromosomes from sperm, offspring of older fathers tend to have longer telomeres [10]. In contrast, ova have different TL with age, because ova are established in utero. That is why many studies highlighted associations between maternal age and TL in offspring and their role in reprogrammed TL [11,12]. Due to scarce data on paternal age and its association with newborn TL, there is a need to study delayed paternal age of reproduction in humans and its association with longer telomeres across generations.

As telomeres are an exciting and emerging research field, they have secured researchers’ attention and interest in their potential impact on health and aging, especially regarding the role of parental age in newborn telomere prolongation. Therefore, in this study, we aimed to find an association between parental age and newborn TL and TL deterioration patterns in parent–newborn pairs.

2. Methods

In this study, 204 parent–newborn pairs were recruited from Ziauddin Hospitals. After receiving approval from the Ziauddin University Ethics Review Committee (Ref no. 3950721SFBC), the samples were collected between September 2021 and July 2022. Females and males between the ages of 15–40 and 15–45, respectively, were asked for consent for blood sampling. Females above 36 weeks of gestational age were included. Fourteen fathers did not give consent for blood sampling. Then, 5 mL of parents’ venous blood and 5 mL of the umbilical cord’s venous blood was drawn into ethylenediaminetetraacetic acid (EDTA) tubes. The blood was immediately stored at 4°C until further processing. The DNA Blood Mini Kit (Qiagen, catalog number: 51306, Germany) was used to extract DNA, which was then stored at −80°C. Quantitative polymerase chain reaction (qPCR) was used to measure the telomere length of leukocytes, as previously done [13]. To create a standard curve for all qPCR runs, reference DNA (standard) from four healthy males and females was pooled in an EDTA tube. Syber green (Maxima) was used for parents–newborn DNA quantification in nanograms of both telomere (T) and beta-globin gene (S). Then, TL was calculated by the T/S ratio. All samples were run in triplicate [13]. Statistical Package for Social Sciences (version 24) was used for data analysis. All quantitative variables of the study were calculated as mean and standard deviation (SD), and frequency and percentages were used for qualitative variables. The graphs of the study were prepared by GraphPad Prism Software. A correlation analysis was used to find a correlation between parents and
newborn TL. An ANOVA was used to determine the mean difference between the parents’ age range and TL. A linear regression was used to study the association between newborn TL and the parents’ age. A p-value < 0.05 was considered statistically significant for all the study data.

3. Results

In this study, 204 parent–newborn pairs were included with a 27 ± 2.12 mean age for mothers and 34 ± 1.36 for fathers (mean ± SD). The comparison between mother and newborn TL among different age groups showed significant results (p = 0.034) in newborns with longer TL than their mothers (Table 1). Longer TL (1.96 ± 1.22) was seen in 15–20-year-old mothers compared with older mothers with ages greater than 35 (1.23 ± 1.75). In father–newborn pairs, longer TL (1.99 ± 1.16) was seen in fathers with an age range of 25.5–30; however, their newborns had shorter TL (2.18 ± 1.71) compared with newborns of older fathers. Among all groups, newborn TL was found to be longer (2.65 ± 1.51) in newborns of the oldest fathers (>35 years) (2.65 ± 1.51) (p = 0.102).

Table 1. Comparison between parents’ and newborn’s telomere length (T/S ratio) among different age groups.

<table>
<thead>
<tr>
<th>Mothers Age (years)</th>
<th>N = 204 TL (mean ± SD)</th>
<th>Newborn TL (mean ± SD)</th>
<th>Fathers Age (years)</th>
<th>N = 190 TL (mean ± SD)</th>
<th>Newborn TL (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–20</td>
<td>21 1.96 ± 1.22</td>
<td>1.98 ± 1.47</td>
<td>15–20</td>
<td>4 1.92 ± 0.5</td>
<td>1.95 ± 0.66</td>
</tr>
<tr>
<td>20.5–25</td>
<td>45 1.94 ± 1.2</td>
<td>1.99 ± 1.33</td>
<td>20.5–25</td>
<td>14 1.77 ± 1.08</td>
<td>1.98 ± 1.36</td>
</tr>
<tr>
<td>25.5–30</td>
<td>74 1.73 ± 1.36</td>
<td>2.32 ± 1.54</td>
<td>25.5–30</td>
<td>39 1.99 ± 1.16</td>
<td>2.18 ± 1.71</td>
</tr>
<tr>
<td>30.5–35</td>
<td>59 1.71 ± 1.22</td>
<td>2.37 ± 1.42</td>
<td>30.5–35</td>
<td>59 1.42 ± 1.13</td>
<td>2.26 ± 1.2</td>
</tr>
<tr>
<td>35.1–40</td>
<td>4 1.23 ± 1.75</td>
<td>2.56 ± 1.63</td>
<td>35.1–45</td>
<td>72 1.35 ± 0.86</td>
<td>2.65 ± 1.51</td>
</tr>
<tr>
<td>p-value</td>
<td>0.24</td>
<td>0.034</td>
<td></td>
<td>0.184</td>
<td>0.102</td>
</tr>
</tbody>
</table>

There was a negative correlation (r = −0.20) between the father’s age and the father’s TL (Figure 1b) with significant results (p = 0.007); in the mother, no correlation was observed (p = 0.416) (Figure 1a). When mothers’ and fathers’ TLs were compared, it was found that mothers had longer TLs in all ages except in the oldest age group (35.1–45) (Figure 1c). Further regression analysis highlighted that for every 1-year increase in the mother’s and father’s age, there was a 0.032 and 0.04 unit increase in the newborn TL (T/S ratio) (B = 0.032, 0.04; p = 0.09, 0.009) (data not shown).
Figure 1. Correlation analysis between parents’ age and their telomere length.

Overall comparison between TLs of newborn girls and boys showed longer TL in girls (1.98 ± 1.9) than boys (1.54 ± 1.87) (Figure 2). Further, in Table 2, it was found that when mother age groups were observed, all girls had longer TL than boys, except those of females with age greater than 35 (TL = 2.67, p = 0.32) (Figure 3a). On the other hand, when the father’s age was observed, all girls had longer TL (1.99 ± 0.87, 2.14 ± 1.56, 2.25 ± 1.17), except in 15–20 and ≥35.1 age groups (Figure 3b). Longer TL (p = 2.48 ± 1.22) was seen in boys of older fathers, but the results were not statistically significant (p = 0.23).

Table 2. Comparison between parents age and newborn boys and girl’s telomere length (TL) (T/S ratio).

<table>
<thead>
<tr>
<th>Mothers’ age (years)</th>
<th>N = 115</th>
<th>Girl TL (mean ± SD)</th>
<th>p-value</th>
<th>N = 89</th>
<th>Boy TL (mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–20</td>
<td>13</td>
<td>1.64 ± 1.33</td>
<td>0.18</td>
<td>8</td>
<td>1.54 ± 1.60</td>
<td>0.32</td>
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<tr>
<td>20.5–25</td>
<td>23</td>
<td>1.73 ± 1.44</td>
<td></td>
<td>22</td>
<td>1.64 ± 1.22</td>
<td></td>
</tr>
<tr>
<td>25.5–30</td>
<td>42</td>
<td>2.04 ± 1.45</td>
<td></td>
<td>32</td>
<td>1.68 ± 1.60</td>
<td></td>
</tr>
<tr>
<td>30.5–35</td>
<td>35</td>
<td>2.36 ± 1.49</td>
<td></td>
<td>23</td>
<td>2.22 ± 1.33</td>
<td></td>
</tr>
<tr>
<td>35.1–40</td>
<td>2</td>
<td>2.55 ± 1.70</td>
<td></td>
<td>1</td>
<td>2.67</td>
<td></td>
</tr>
<tr>
<td>Fathers’ age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–20</td>
<td>1</td>
<td>0.94</td>
<td>0.29</td>
<td>3</td>
<td>1.94 ± 0.72</td>
<td>0.23</td>
</tr>
<tr>
<td>20.5–25</td>
<td>7</td>
<td>1.99 ± 0.87</td>
<td></td>
<td>8</td>
<td>1.98 ± 1.01</td>
<td></td>
</tr>
<tr>
<td>25.5–30</td>
<td>24</td>
<td>2.14 ± 1.56</td>
<td></td>
<td>19</td>
<td>2.04 ± 1.04</td>
<td></td>
</tr>
<tr>
<td>30.5–35</td>
<td>36</td>
<td>2.25 ± 1.17</td>
<td></td>
<td>27</td>
<td>2.19 ± 1.92</td>
<td></td>
</tr>
<tr>
<td>35.1–45</td>
<td>47</td>
<td>2.25 ± 1.64</td>
<td></td>
<td>29</td>
<td>2.48 ± 1.22</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2. Telomere length of newborns of both genders.

Figure 3. Comparison between parents’ age and newborns’ TL.

Correlation analysis between parents’ age and newborn TL showed a positive correlation ($r = 0.185$, $p = 0.007$) between the fathers’ age and newborn TL (Figure 4a) but not of mothers’ age ($r = 0.118$, $p = 0.092$) (Figure 4b). When gestational age and newborn TL correlation was studied, no correlation was found in both girls and boys ($p > 0.05$) (Figure 4c and d).

Figure 4. Correlation analysis between parents’ age and newborns’ telomere length (a and b) and between gestational age and newborns’ TL (c and d).
4. Discussion

Telomere length is a heritable trait that is dynamic and can be altered by genetic and environmental factors. Telomere shortening is a key sign of physiological stress and biological aging [14] and, as a result, may differ amongst people of the same age. This variance is also present in neonates, pointing to possible parental and intrauterine influences on the developing fetus’ TL.

The present study showed that newborn TL and its association with the parents’ age had significant results with maternal age (18–35 years) \( (B = 0.032, p = 0.09) \) and paternal age (18–45 years) \( (B = 0.04, p = 0.009) \) and highlighted that an increase in newborn TL was associated with each 1-year increase in the mother’s and father’s age. Comparably, Chen et al. reported a longer maternal TL \( (β = 0.14, P = 1.99E–05) \) and higher paternal age \( (β = 0.10, P = 3.73E–03) \) positive association with the newborn TL [15]. The study highlighted the effects of parental TLs on newborns and concluded that the mother’s TL is interlinked with her metabolic health and nutritional state, which may have a transgenerational effect on the offspring’s TL. Mothers who exhibited higher anxiety levels, higher blood glucose levels, and lower plasma levels of vitamin B12, as well as insulin-like growth factor binding proteins and active smoking status during pregnancy had a higher likelihood of having children with shorter TL irrespective of their gender [15]. The above study also provided evidence that female newborn TL variance was influenced by maternal TL, mental health, and plasma vitamin B12 levels, whereas male newborn TL variation was best explained by paternal age, maternal education, and metabolic health [15].

The telomeres within oocytes are affected by age because oocytes in older females have undergone more DNA replication during fetal oogenesis compared to younger women. Therefore, with age, exposure to multiple risk factors like epigenetic factors and reactive oxygen species may cause the deterioration of mother’s TL [16]. There are enough studies to suggest that a mother’s age significantly impacts the offspring’s TL [17,18]. Newborn telomere genetics is the outcome variable of this study; it was found that girls had longer TL compared to boys \( (p = 0.017) \), which is similar to many other studies \( (0.181 \text{ kb}, 6.83\%, 50–100 \text{ bp}) \) [17–19]. Therefore, longer TL in girls is due to the protective impact of hormones that may shield TL from different stress factors and reactive oxygen species [20,21].

The disparities in telomere length and dynamics between males and females might potentially be elucidated by biological factors, namely the influence of gender-associated hormones that are present throughout prenatal development and persist throughout one’s life. It has been observed that estrogen possesses the ability to stimulate telomerase activity and exhibit antioxidant qualities [22]. Additionally, both TL and attrition exhibit heritable characteristics, with heritability estimates around 70% for TL and 28% for attrition [23]. This study does not support prior research indicating a correlation between newborns and mothers’ TL [13]. Furthermore, it suggests the presence of a heritable element in the establishment of initial TL and the dynamic characteristics during early life [24].

In particular, the current study observed that older fathers had offspring with longer TL and highlighted a positive association \( (r = 0.185, p = 0.007) \) compared to mothers. Sperm cells exhibit a unique trait, with increased telomerase activity in the testes and the male stem cells compared with oocytes. Therefore, it can be inferred that the fathers’ age has a more dominating effect on newborns. Studies of twins also suggest that older men may have more sperm with longer telomeres than younger men [23]. Consequently, the offspring inherit the longer telomeres from their father’s sperm according to the normal rules of genetics, since half of a child’s genetic material comes from the father’s sperm [25–27]. Moreover, it was also observed that there is selective loss of spermatogonia of shorter TL but proliferation of spermatogonia with longer telomeres, due to high testicular
telomerase activity [28–30]. A substantial number of studies indicate that paternal age significantly affects neonatal health parameters [31,32]. On the other hand, Sends et al. reported no association between paternal age and TL in newborns [33].

Nevertheless, based on our findings and the available literature, it may be predicted that longer TL in elderly parents may contribute to an increased likelihood of cancer in their progeny [11,34]. Telomere length is a key factor that influences the balance between cell proliferation and senescence. Long telomeres allow more cell divisions and somatic repair but also increase the risk of cancer due to the accumulation of mutations in the cell population. Short telomeres limit cell proliferation and cancer risk but also impair tissue maintenance and lead to degenerative diseases. This notion can be further potentiated by increased telomerase activity resulting in longer telomeres, which increases the proliferative potential of germ cells and may lead to the accumulation of de novo mutations and enhanced cancer susceptibility. A large, population-based record-linkage study reported advancing parental age was associated with higher pediatric cancer risk [35,36]. Another factor that may contribute to this is the alteration of expression of genes involved in telomere biology due to parental aging having epigenetic effects on the offspring. This needs to be validated in large-scale cohort studies.

The strength of this study highlighted that maternal and paternal age is a crucial determining factor of TL, which could impact newborn health. Hence, monitoring the age of parents can prevent telomere attrition and boost cellular longevity. Moreover, a limited sample size of mothers with an age greater than 35 years was due to convenient sampling, whereas in fathers, an age group greater than 45 years could have been further monitored for old-age TL patterns. Another limitation was the use of only qPCR for TL analysis, which may be validated by other techniques like flow fish and Southern blotting for confirmation of the result outcomes.

Further studies should have larger sample sizes and follow up children with longer or critically short TL for disease incidence. Such research can be a step forward in interpreting the telomere role and regulatory mechanism in the emergence of diseases.

5. Conclusions

It was found that longer telomere length was seen in newborns to older parents. Longer parental TL was positively associated with newborn TL. Therefore, parental age, especially fathers’ age, and its effect on TL at the birth of an offspring is an important contributing factor for newborn health outcomes.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

All authors declare no conflicts of interest in this paper.

References


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