Telomeres and human disease

Predrag Slijepčević

Telomeres are specialized structures at chromosome ends required for chromosome stability maintenance. They consist of a specific repetitive DNA sequence and a set of associated proteins that form a protective structure at chromosome ends. The enzyme telomerase, which is active in stem cells but not in normal somatic cells, synthesizes telomeric DNA sequence. This enzyme is important for cell proliferative potential and most cancer cells have active telomerase. Telomeres are shorter in older individuals than in younger individuals and they may be viewed as a "biological clock". The evidence is accumulating that telomere maintenance plays a significant role in the pathology associated with some human diseases. There are several human genetic diseases that show accelerated shortening of telomeric DNA sequences including Dyskeratosis congenita, Fanconi anemia, ataxia telangiectasia, Nijmegen breakage syndrome, Werner syndrome, Bloom syndrome, pulmonary fibrosis and ataxia telangiectasia like disease. A common feature of these diseases is accelerated telomere shortening due to increased cell turnover that eventually leads to signs of premature ageing. Common diseases lacking an apparent genetic component such as atherosclerosis, heart failure, liver cirrhosis and ulcerative colitis, also show accelerated telomere shortening in affected tissues, that eventually causes tissue specific pathology. Factors that increase cell turnover may be detected by measuring telomere length in the human population and so far several such factors have been identified including: smoking, obesity and exposure to psychological stress. It is likely that future research will reveal an even more extensive role of defective telomere maintenance in human disease and conditions that elevate disease risk.

Key words: Genetic diseases, Telomeres, DNA sequences, Premature ageing.
Introduction

Telomeres are specialized nucleo-protein complexes at the ends of chromosomes identified ~ 70 years ago by Herman Joseph Muller and Barbara McClintock (1, 2). Their pioneering experiments on drosophila and plant cells respectively unravelled the protective properties of natural chromosomal ends, later termed telomeres by Muller using the Greek words telos (end) and meros (part). These simple cytological experiments revealed resistance of telomeres to fusion with either broken chromosomal fragments or other telomeres. The protective property of telomeres is now known as the “capping” function i.e. telomeres provide a protective “cap” for chromosomal DNA against various molecular insults, including nucleolitic degradation, oxidative stress, interaction with other DNA sequences etc.

The molecular dissection of telomeres started in 1970’s by identifying the DNA sequence of telomeres in a single cell organism called *Tetrahymena thermophila* (3). This was followed by identification of telomeric DNA sequences in other species including humans and the discovery of telomerase, the enzyme that synthesizes telomeric DNA (4, 5). Subsequent experimental work led to the discovery of an apparent link between the mechanisms that maintain telomeres in our cells and two processes of great importance to human health: ageing and carcinogenesis. It is now clear that telomeric DNA is gradually lost with consecutive cell divisions leading to proposals that telomeres act as a “biological clock” that regulates cell and organismal ageing (6). It is also interesting that telomerase is inactive in human somatic cells but highly active in cancer cells which, owing to telomerase, can proliferate indefinitely, suggesting that telomerase activity is a key requirement for a cell to become cancerous (7).

The above observations were certainly exciting and in the last 20 years numerous studies addressing different aspects of these observations have been published. It has also become apparent that there are several human genetic diseases characterized by premature ageing and predisposition to cancer that show abnormalities in telomere maintenance (see below) thus indicating the medical relevance of telomere biology. This is further substantiated by more recent observations, pointing to a clinically relevant scenario that individuals with susceptibility to cardiovascular diseases may have abnormal telomere metabolism, or that exposure to psychological stress may lead to pathological telomere shortening (see below). Factors such as obesity and smoking are now known to contribute to pathological telomere shortening (see below).

The purpose of this article is to provide a brief overview of the molecular biology of telomere maintenance and address the role of telomeres in human genetic diseases. Furthermore, some common human diseases without an identified genetic component that show defects in telomere maintenance will be discussed. It is also becoming increasingly clear that measurement of telomere length has important prognostic and diagnostic values and some examples will be given to illustrate this point.

Molecular organization of telomeres

As stated earlier, telomeres are specialized structures at chromosomal ends consisting of a specific DNA sequence and a set of associated proteins that bind the sequence. The telomeric DNA sequence in all vertebrates, including humans, is a hexanucleotide, TTAGGG, repeated many times (Fig 1). In human cells the size of telomeric repeat DNA sequences is, on average, between 10 and 15 kb (kilo bases) (4). The size of telomeric DNA sequences varies between individuals and is thought to be genetically regulated. Telomeric DNA is arranged in the form of
a loop known as the T (telomeric) – loop (8) (see also Fig 2). In this configuration the protruding 3’ telomeric single strand, the size of which is approximately 100 or more b.p. (base pairs), folds back to form the loop. A set of proteins called sheltretin regulates the arrangement and folding of the T-loop (9). This set consists of six proteins, some of which have affinity for telomeric double stranded DNA sequence (TRF1 and TRF2) and some for telomeric single stranded DNA sequence (Pot1). The purpose of the T-loop is to provide stability for the chromosome. Without this configuration the chromosomal end would be recognized as a DNA double strand break (DSB) by cellular mechanisms that detect and repair DNA damage. The presence of proteins that participate in DSB repair at telomeres, through interaction with shelterin, signifies the importance of interactions between telomeres and DSB repair mechanisms (9). The list of proteins that form shelterin and proteins involved in DSB repair and other types of DNA repair present at telomeres is shown in Table 1.

An important feature of the telomeric DNA sequence is its constant loss with each cell division cycle. It is estimated that this loss is on average ~ 100 b.p. / cell cycle (6). The loss is caused by two mechanisms: the end-replication problem and exonucleolytic degradation. Conventional DNA polymerases that replicate DNA cannot replicate the end of the chromosome properly and this is known as the end-replication problem. The problem was first identified by Olovnikov (10). He proposed that the loss of telomeric DNA may act as a “biological clock”, a counting mechanism which may signal cells how many times to divide. When the loss eventually causes a near complete exhaustion of telomeric DNA, this will signal the cell cycle stop. The affected cell will no longer be able to divide and it will be replaced by a younger cell with longer telomeres. Experiments have confirmed the view of telomeres

![Figure 1](image1.png) A human cell showing 46 chromosomes (blue) after fluorescence in situ hybridization with the telomeric TTAGGG probe (red).

![Figure 2](image2.png) Molecular structure of telomeres. A. Linear telomeric DNA with a 3’ single stranded overhang, the size of which is ~ 100 base pairs. B. This single strand overhang folds back, invades the DNA double strand to form a local DNA triplex (three strands) known as D-loop (Displacement loop). The whole loop structure is called T-loop (Telomeric loop). The protein named TRF2 enables formation of a local DNA triplex.
as the “biological clock”. For example, telomeres in older individuals are shorter than telomeres in younger individuals (6). However, the end-replication problem is not the only source of telomeric DNA loss. The enzymes with exonucleolytic activity must prepare the T-loop substrate (protruding single stranded telomeric sequence) after each DNA replication cycle and the consequence of the activity of these enzymes is the loss of telomeric DNA (11). Therefore, the end replication problem and exonucleolytic activity will eventually cause degradation of telomeric DNA, after multiple cell divisions, to the extent that the affected cell will no longer be able to divide.

Telomere shortening is an important tumour suppressor mechanism which strictly regulates tissue homeostasis. Cells forming tumours differ from normal somatic cells (with the exception of stem cells) in their growth properties. Normal somatic cells can divide up to a maximum of ~ 50 times, after which they exit the cell cycle. In contrast, tumour cells can divide indefinitely. What is the mechanism that confers this indefinite cell division potential of tumour cells? After many years of research, scientists discovered that tumour cells acquire the capacity to prevent telomere loss and subsequent telomere shortening. This capacity is provided by a specialized enzyme termed telomerase, which synthesizes telomeric DNA and by doing so stops telomeric DNA loss (6). Telomerase is a complex enzyme consisting of its own RNA component known as TERC, the catalytic protein component known as TERT and a protein called Dyskerin. Experiments have shown that up to 85% tumours have active telomerase, whereas normal somatic cells lack telomerase activity (6). (The only normal somatic cells that have relatively high levels of telomerase are stem cells. This is understandable given that stem cells must have high growth potential in order to maintain tissue homeostasis.) Those remaining 15% of tumours that lack telomerase use another mechanism to stop telomere loss, known as ALT (Alternative Lengthening of Telomers) (6). Inhibiting telomerase or ALT mecha-
nisms in cancer cells constitutes a promising avenue for cancer therapy.

The medical relevance of telomere biology

As indicated above, there are two clear areas of telomere biology relevant to medicine. These include mechanisms of human ageing and mechanisms of carcinogenesis. The area of telomere biology related directly to cancer is beyond the scope of this review.

Although the current understanding of mechanisms that regulate human ageing is limited, it is clear that telomere biology represents a significant contributing mechanism. This is recognized by the fact that one of the theories proposed to explain mechanisms of ageing, known as “Telomere theory of aging”, directly implicates telomere shortening as a cause of ageing or senescence in human cells (6). It is not yet completely clear whether the accelerated process of cell senescence will cause accelerated ageing of an organism but the evidence is accumulating that this may be true.

According to the “Telomere theory of ageing”, most somatic cells in the human body must have a limited capacity to divide, known as the Hayflick limit (6). In 1960s Leonard Hayflick concluded, after his experiments with human somatic cells, that they cannot divide more than ~ 50 times in vitro. He argued that this mechanism regulates tissue homeostasis, but he did not have an explanation as to how this mechanism may work. The explanation was provided after the discovery of telomerase and improved understanding of telomere maintenance mechanisms. As discussed above, telomeric DNA is progressively lost after each cell division cycle, until the loss signals the end of cell division potential. Experiments have shown a good correlation between the Hayflick limit and telomere shortening, thus implicating the latter as a key regulator of the “biological clock”. The key evidence supporting the essential role of telomeres in the “biological clock” came from experiments in which forced activation of telomerase in otherwise normal human somatic cells resulted in the acquired capacity of these cells to divide indefinitely (6). This means that when physiological telomere shortening is stopped, human cells in effect become “immortalized” and the key tumour suppressing mechanism that regulates tissue homeostasis is lost. Further evidence in support of the “Telomere theory of ageing” was provided by observations that human diseases characterized by premature ageing symptoms show abnormal telomere metabolism (see below). Some of these diseases will be described in more detailed below and evidence that links premature ageing symptoms and defective telomere maintenance will be highlighted.

Human genetic diseases with dysfunctional telomere maintenance

The common features of diseases described in this section include: a) symptoms associated with premature ageing and b) some form of abnormality in telomere maintenance that may manifest either as accelerated telomere shortening, or loss of telomere capping function. Research has shown that defects in telomere maintenance associated with these diseases contribute significantly to disease pathology (see below).

Dyskeratosis congenita (DC)

DC is an inherited bone marrow (BM) failure syndrome with clinical features becoming apparent in childhood (12). BM failure can be defined as the inability of bone marrow to provide a sufficient number of circulating blood cells. This suggests that hematopoietic stem cells that reside in the BM, function abnormally in DC. Other symptoms of DC, including abnormal skin pigmentation, nail dystrophy
and leucoplakia are consistent with stem cell failure in organs such as the skin.

Molecular and cell biology research has provided a reasonable explanation as to how failure in HSCs leads to symptoms of DC. It is now clear that DC is caused by mutations in genes encoding components of telomerase and this ultimately leads to abnormally short telomeres in DC patients (12). Abnormally short telomeres are ultimately responsible for diminished growth potential of the stem cells that maintain highly proliferative tissues, such as BM and skin. This also strongly indicates that telomerase activity is an essential requirement for normal proliferation of stem cells.

Genetic research has identified three forms of DC (12). The first known form of DC was the so-called X-linked dominant DC because the gene responsible was located on the X chromosome. The gene called DKC1 was eventually identified as responsible for this form of DC. It encodes a protein called dyskerin. Initially, it was thought that this protein is the key to the biogenesis of ribosomes, until the link with telomerase was discovered. Dyskerin is now known to be a component of telomerase. Given that some DC patients did not show mutations in DKC1 it became obvious that other genes may be involved in this disease. Through the so-called linkage analysis, a family with many members affected by DC was identified. Genetic research revealed that a gene in the region of chromosome 3q, the same region where the TERC gene resides, was responsible for this form of DC. Further investigation revealed TERC mutations in the family, thus leading to the conclusion that a new form of DC, now known as autosomal dominant DC, is due to mutations in TERC. Subsequent studies revealed that abnormally short telomeres are one of the key molecular features of DC, suggesting that this disease is a disease of abnormal telomere maintenance (12). During the course of these studies another form of DC was discovered, now known as autosomal recessive DC. However, the gene or genes responsible for autosomal recessive DC have not been identified yet. It is likely that these genes will be involved in telomere maintenance. Finally, a group of DC patients, with mutations in the TERT component of telomerase, has recently been described, adding further support to the view of abnormal telomere maintenance as the key molecular cause of DC (12). Patients with TERT mutations are classified as the autosomal dominant variant of DC.

**Fanconi anemia (FA)**

Similarly to DC, FA is an inherited BM failure syndrome (13). Patients are typically diagnosed in the first decade of life and many will die as young adults as a result of BM complications. In addition, FA patients show extreme predisposition to cancer and many will die as a result. The disease is inherited mainly in an autosomal recessive fashion. Apart from BM failure, many patients show somatic abnormalities, including skin, skeletal, neurological, cardiovascular and other abnormalities.

Cells from FA patients show high sensitivity to the chemicals that cause DNA cross-links, such as mitomycin C (MMC) and diepoxybutane (DEB), which manifest by the presence of high level of chromosomal abnormalities in the patients’ cells relative to control cells. This is the key diagnostic test for FA. Genetically, FA is a very complex disease, with at least 12 different genes involved, known as FANCA to FANCM (13). All genes are involved in DNA damage response, in particular the pathway that regulates response to DNA crosslinking agents.

FA patients have significantly shorter telomeres than corresponding control patients (14, 15). In addition, FA cells show increased incidence of end-to-end chromosome fusions as a result of accelerated...
telomere shortening. It can be argued, as in the case of DC, that telomere shortening observed in FA patients causes the inability of HSCs to replenish BM, thus leading to symptoms of BM failure.

**Ataxia telangiectasia (AT) and Nijmegen breakage syndrome (NBS)**

AT and NBS are genetic diseases characterized by increased sensitivity of patients to ionizing radiation, high incidence of cancer and chromosomal instability (16). In contrast to DC and FA, only one gene is responsible for AT and NBS respectively. The genes are known as ATM (AT mutated) and NBS1. Both genes are involved in DNA damage response mechanisms. ATM is a key signalling molecule, activated by the presence of DNA damage in affected cells, whereas NBS1 is part of a protein complex called MRN consisting of NBS1 and two more proteins, MRE11 and Rad50 (16). Both diseases are inherited in an autosomal recessive fashion.

There are clear abnormalities in telomere maintenance in cells from AT and NBS patients (16). Telomere shortening is evident in both cases. However, in the case of AT cells, telomere shortening is accompanied by increased incidence of end-to-end chromosome fusions and the presence of extra-chromosomal telomeric fragments, whereas these are absent in NBS cells. Both proteins, ATM and NBS1, physically interact with the components of shelterin, thus indicating close cooperation between DNA damage response mechanisms and telomere maintenance. Genetically deficient mice, defective in ATM, also show alterations in telomere maintenance. It is important to stress that all diseases mentioned so far, DC, FA, AT and NBS are considered premature ageing syndromes as patients show many features of premature ageing. This provides a formal link between accelerated telomere shortening and ageing at the clinical level.

**Werner syndrome (WS) and Bloom syndrome (BS)**

WS is a premature ageing syndrome characterized by signs of ageing at an early age, usually in the second decade of life, that include grey hair, alopecia, skin ageing, cataracts, ischemic heart disease etc. (17). Affected individuals also show high levels of inflammatory diseases such as atherosclerosis and type 2 diabetes, as well as a high incidence of cancer. The gene responsible for WS is called WRN. It encodes a protein with helicase domain involved in DNA metabolism including replication, recombination and repair. Fibroblasts isolated from WS individuals show premature senescence in vitro that can be rescued by ectopic expression of telomerase (17). This implicates dysfunctional telomere maintenance as a cause of WS associated pathology. Consistent with this possibility, biochemical experiments revealed direct interaction between WRN and telomeric proteins such as TRF1 and TRF2. It is therefore likely that abnormal WRN will affect the so called telomere capping function and lead to increased telomeric fusions and subsequent chromosomal instability.

BS shows some similarity to WS. The protein affected in BS, known as BLM, is a helicase like WRN and BS patients show limited signs of premature ageing, such as early menopause and elevated rates of cancer. It is interesting that BLM also interacts with telomeric proteins, such as TRF1 and TRF2 (18). Published studies that directly examined the state of telomere maintenance in BS patients are not yet available. However, mice defective in BLM and TERC show pathology associated with telomere loss that is directly attributed to dysfunctional BLM (18). It is therefore possible that BS patients may show some form of telomere dysfunction. Another interesting feature of BLM is its involvement in the ALT pathway of telomere maintenance (19).
AT-like disorder (ATLD), pulmonary fibrosis (PF) and aplastic anemia (AA)

The evidence is accumulating that telomere defects may exist in the above three disease. A subset of AA patients shows mutations in \textit{TERT} and \textit{TERC} genes (20). These mutations cause accelerated telomere shortening and could cause the premature death of AA patients. Mutations in \textit{TERT} and \textit{TERC} genes have been identified in patients with PF (20). PF is characterized by lung scarring, which eventually leads to respiratory failure and the disease could be lethal. ATLD patients show mutations in the gene encoding the Mre11 protein. The protein is part of the MRN complex (see above) known to be involved in DNA damage response. One of the features of ATLD is accelerated telomere shortening (20). All diseases described in this section are summarized in Table 2.

Common human diseases with defective telomere maintenance

Research in the last decade revealed several common human diseases that show alterations in telomere maintenance. Common diseases are defined as diseases occurring in the human population with a relatively high frequency, but lacking an apparent inheritance pattern. This does not mean that common diseases completely lack the genetic component. It is likely that common diseases are caused by multiple genes, the individual effect of which is small, and as a result the inheritance pattern is not obvious, as in the case of classical genetic diseases.

One of the first common diseases in which alterations in telomere maintenance were observed was atherosclerosis. Atherosclerosis is now believed to be the result of systemic chronic inflammation. Given that chronic inflammation requires increased cell turnover, it has been argued that patients with atherosclerosis may have abnormally short telomeres in some or all tissues. Consistent with this possibility it was shown that atherosclerosis patients have significantly shorter telomeres in their leukocytes relative to control individuals (21).

Similarly, investigation of heart muscle cells, known as myocytes, from patients with heart failure, revealed a 25% reduction in telomere length relative to their control counterparts (22). Furthermore, myocytes in affected patients showed a higher level of apoptosis, programmed cell death, as well as alterations in expression of the telomeric protein TRF2 relative to cells from control individuals (22). Given that heart failure is caused by myocyte deficiency, which even-

<table>
<thead>
<tr>
<th>Disease name</th>
<th>Disease main characteristics</th>
<th>Protein affected</th>
<th>Effect on telomere maintenance</th>
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<tbody>
<tr>
<td>Dyskeratosis congenita</td>
<td>Bone marrow failure</td>
<td>TERC, TERT, Dyskerin</td>
<td>Accelerated telomere shortening</td>
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<tr>
<td>Fanconi anemia</td>
<td>Bone marrow failure</td>
<td>At least 12 FANC proteins</td>
<td>Accelerated telomere shortening, chromosome fusions</td>
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<tr>
<td>Ataxia telangiectasia</td>
<td>Radiation sensitivity syndrome</td>
<td>ATM</td>
<td>Accelerated telomere shortening, chromosome fusions</td>
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<tr>
<td>Nijmegen breakage syndrome</td>
<td>Radiation sensitivity syndrome</td>
<td>NBS1</td>
<td>Accelerated telomere shortening</td>
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<tr>
<td>Werner syndrome</td>
<td>Premature ageing syndrome</td>
<td>WRN</td>
<td>Accelerated telomere shortening</td>
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<td>Bloom syndrome</td>
<td>Defective DNA damage response</td>
<td>BLM</td>
<td>Effect on ALT</td>
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<td>Ataxia telangiectasia like disease</td>
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<td>MRE11</td>
<td>Accelerated telomere shortening</td>
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<td>Pulmonary fibrosis</td>
<td>Respiratory disease</td>
<td>TERC, TERT</td>
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ultimately leads to failure in the heart pumping function, the results of the above study established a formal link between telomere maintenance and heart diseases. Furthermore, more recent studies indicate that telomere length is a good predictor of the risk for cardiovascular diseases. The highest risk of cardiovascular diseases is associated with the shortest telomeres in affected patients (23).

Another common disease, in which telomeres are affected, is liver cirrhosis. Irrespective whether cirrhosis is caused by viral hepatitis, increased consumption of alcohol, autoimmunity or cholestasis, telomeres were always significantly shorter in hepatocytes from affected patients than in hepatocytes from control individuals (24). In contrast, telomere length in leukocytes from cirrhosis patients was normal (24). The study therefore supports the view that chronic hepatocyte damage and induced hepatocyte regeneration accelerate telomere shortening in hepatocytes. The study also implies that restoration of telomere length in hepatocytes from patients affected by cirrhosis could constitute a potential therapy for this disease.

Ulcerative colitis is the last example of a common human disease in which telomere maintenance is affected (25). This is a chronic inflammatory disease of the colon, associated with a high risk of colon cancer. Accelerated telomere shortening and associated chromosomal abnormalities, such as end-to-end chromosome fusions, are apparent in non-dysplastic mucosal cells taken from individuals affected by the disease (25).

In summary, all the above common diseases are associated with accelerated telomere loss. It is likely that the accelerated telomere loss is caused by increased cell turnover which eventually reduces the regenerative capacity of affected tissues, most likely through the failure of stem cells to maintain tissue homeostasis (see Fig. 2).

Telomere length as a prognostic marker

In view of the fact that human diseases, characterized by an increased cell turnover in highly proliferative tissues, show accelerated telomere shortening (see above) telomere length can serve as a marker capable of detecting any factor that stimulates cell turnover. It is likely that such factors will cause damage to cells and as a result stimulate tissue processes which eventually replace damaged cells by healthy cells through increased proliferative activity of stem cells. Although stem cells have a higher proliferative potential than differentiated cells, this potential is not unlimited and increased cell turnover constitutes a risk factor that accelerates ageing and may cause early mortality. In line with this prediction, telomere length was reported to be a good predictor of mortality rate among people aged 60 or more (26). This study has important implications, as the factors that lead to increased cell turnover, and thus accelerated telomere shortening, can be identified. Once such factors are identified, lifestyles can be changed accordingly, to avoid exposure to identified risk factors.

Factors that cause accelerated telomere shortening include obesity, smoking and exposure to psychological stress. Analysis of telomere length in leukocytes from a large group of women revealed an inverse association between the number of cigarettes smoked and telomere length (telomeres were shorter in smokers) (27). A similar inverse correlation was observed between the body mass index (BMI) and telomere length i.e. the higher the BMI, the shorter the telomeres (27). In a separate study, telomere length was measured in a group of care-giving mothers whose children were chronically ill. The chronicity of care-giving was considered to be a significant stress factor. There was an inverse correlation between chronic-
ity of care-giving and telomere length i.e. the higher the number of care-giving years, the shorter the telomeres (28). In addition, telomerase levels were lower in women exposed to stress longer.

It is interesting to note that there are numerous causes of psychological stress. The question is whether each one of these causes is capable of causing accelerated telomere loss. The answer to this question may be positive according to a recent study, which revealed shorter telomeres in people with lower socio-economic status than in their counterparts with higher socio-economic status (29). The argument here is that low socio-economic status is associated with a high level of psychological stress. However, this study received some criticism and its conclusions were questioned (30, 31). In addition, another study was designed to detect whether telomeres and telomerase are affected by psychological stress arousal and risk of cardiovascular disease. The study revealed that low telomerase activity in leukocytes was associated with major risk factors for cardiovascular diseases, including poor lipid profile, hypertension and abdominal adiposity (32).

**Conclusion**

Only 20 years ago the structure and function of telomeres were relatively poorly understood and there was no indication that telomere metabolism may play a significant role in understanding the mechanisms of human diseases. As explained above there are now a growing number of human genetic and common diseases that show alterations in telomere maintenance and these alterations contribute significantly to disease pathology. A common feature of diseases with affected telomere maintenance is premature ageing. Signs of premature ageing in these diseases can be explained by increased cell turnover, which leads to the increased proliferative capacity of stem cells and accelerated telomere shortening in differentiated somatic cells. Factors that increase cell turnover can be detected by measuring telomere length in the human population and so far several such factors have been identified, including smoking, obesity and exposure to psychological stress. Taken together, these observations suggest that telomere maintenance plays a significant mechanistic role in human disease pathology.

**References**


