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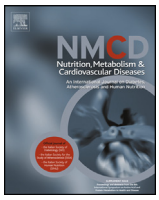

REVIEW

Telomeres and atherosclerosis

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Abstract The pathogenesis of atherosclerosis, an age-related disorder, may be due to a premature biological ageing. Cellular senescence, the finite replicative lifespan of cells, plays a critical role in the pathogenesis of atherosclerosis. The biological mechanism that triggers the onset of cellular senescence is thought to be telomere shortening. The two major mechanisms responsible for telomere shortening are the end-replication problem, oxidative DNA damage as well as inflammation induced by environmental risk factors. Repair of the endothelium depends on the presence of endothelial progenitor cells which depends on the hematopoietic stem cells (HSC) reserves. In numerous past studies, short LTL has been associated with atherosclerosis. Here we review the literature on telomere biology and coronary artery disease (CAD).

Introduction

Atherosclerosis, an age-related disorder [1] may recognize as a determinant factor a premature biological ageing. In fact cellular senescence, defined as the finite replicative lifespan of cells, plays a critical role in its pathogenesis [2–4]. An important feature of atherosclerosis is vascular endothelial cell dysfunction. Studies on atherosclerotic plaques have demonstrated that endothelial and vascular smooth muscle cells in atherosclerotic lesions display changes of senescence [5,6]. In stable atherosclerotic plaques there are few senescent cells, whereas in advanced, complicated plaques, senescent cells accumulate because of high cell turnover [7]. The biological mechanism that triggers the onset of cellular senescence is thought to be telomere shortening. Telomeres are structures composed of DNA repeats that protect the end of chromosomes, but shorten at each cell division. Recently their role in the onset, development and prognosis of cardiovascular disease has generated considerable interest leading to a number of studies investigating telomeres length and cardiovascular disease. In this regard telomere shortening has been reported to be associated also with the classical risk factors for atherosclerosis such as insulin resistance [8,9] diabetes [10–13], obesity [14], hypertension [8] and smoking [14,15].

Overall this would suggest that cellular senescence may represent the ultimate event responsible for the pathological changes characteristic of atherosclerosis. Such a view would theoretically have several implications. Firstly understanding the relation between telomere biology and

Abbreviations: HSC, hematopoietic stem cells; CAD, coronary arteries disease; LTL, leukocyte telomere length,; MI, myocardial infarction; T2D, type 2 diabetes.

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cardiovascular disease may help elucidate ways to measure cardiovascular aging based not only on physiological changes but also by the use of biomarkers such as leukocyte telomere length (LTL). Secondly, it may help to better define the need and the type of interventions on the risk factors for atherosclerosis. Thirdly the understanding of cardiovascular aging and telomere biology may help to identify new strategies of interventions such as stem cell therapy or agents that could retard this aging process beyond conventional risk factors.

The telomere complex

Telomeres consist of repetitive DNA sequences (TTAGGG) associated with a specialized protein complex named shelterin and are located at the ends of linear chromosomes. They function as a cap to stabilize and protect chromosomes from erosion and from being mistaken for double-strand DNA breaks [16]. During each cell division, telomeres shorten due to the "end-replication problem" that is the DNA polymerase's inability to fully replicate the 3′ end of chromosomes. In order to limit telomere attrition, germline and some somatic cells express telomerase, a reverse transcriptase that maintains telomere length by synthesizing new DNA sequences and adding them to the end of the chromosome [17]. Telomerase is an enzymatic protein complex including the telomerase reverse transcriptase (TERT) and the telomerase RNA component (TERC) used as a template to synthesize telomere DNA. When telomeres are too short, they signal the arrest of cell proliferation resulting in cell senescence or apoptosis. If protective mechanisms, such as the p53 tumor-suppressor gene, are inactive, thus allowing continued proliferation, telomeres become extremely short and dysfunctional; they may cause chromosomes end-to-end fusions and ultimately chromosomal instability. Conversely, cells transfected with the telomerase gene can proliferate indefinitely [18]. Despite telomerase activity, telomere shortening is inevitable, thereby limiting the proliferative lifespan of human cells. As expected, for a given organ, telomere length decreases with the age of the subjects. There are also iatrogenic causes of telomere shortening: for example after bone marrow transplantation when hematopoietic stem cells and progenitor cells are highly proliferative in order to reconstitute hematopoiesis. In addition, telomere attrition may be genetically determined as a result of telomerase complex's genes mutations leading to an inherited inability to elongate telomeres [19]. Variability in telomere length is influenced by heredity, race and gender. It is known that telomere length is shorter in healthy offspring of patients with coronary artery disease (CAD) [20,21]. This finding offers some explanation for the increased familial risk of CAD and also implies that shorter telomeres are likely a primary abnormality in the pathogenesis of the disease [22]. It is also known African-Americans have longer telomeres than Caucasians and Indians [23–25] and females have longer telomeres than their males counterparts [26].

Telomere and endothelial cells

The atherosclerotic process is characterized by endothelial cell dysfunction therefore is dependent on the balance between injury and repair of the endothelium—injury from oxidative stress and inflammation, and repair by hematopoietic stem cell reserves (HSC).

An important mechanism responsible for telomere shortening is the oxidative DNA damage induced by environmental risk factors (Fig. 1). Telomere shortening induced by oxidative stress is proportional to telomere length, as longer telomeres are larger targets for free radicals [27,28]. Telomeres are exposed to reactive oxygen species, which have a predilection for the single stranded, G-rich telomere overhang. This site specificity for guanine is because guanine is the most easily oxidized DNA base as its oxidation potential is lower compared to the other three bases. This is an important variable associated with aging and with accelerating the telomere attrition [29]. An important consequence of oxidative stress is the initiation of an inflammatory response (Fig. 1). Chronic systemic inflammation is responsible for an increase in peripheral white blood cell turnover, which in turn leads to an exaggerated telomere attrition rate [30]. The increased white cell consumption induces hematopoietic stem cells to divide, thereby shortening their telomere length as well. Moreover exposure to TNF-α also reduces telomere length by negative regulation of telomerase activity [31]. In several studies it has been shown that short telomeres are associated with the classical risk factor for atherosclerosis: hypertension [8] diabetes [32,33], coronary artery disease, carotid atherosclerosis [34,35] and stroke [14,36,37]. This could be due to chronic inflammation that associates with these clinical conditions and/or to the influence of a less healthy life style, including smoking habit and alcohol consumption [14].

Repair of the endothelium depends on the presence of endothelial progenitor cells on the sites of vascular injury to initiate repair. Endothelial progenitor cells are produced by HSC, which, due to their higher telomerase activity, have a greater proliferative capacity. Exhaustion of the progenitor cell is an important factor in endothelial cell dysfunction and shortened telomere length in HSC is indicative of diminished reparative capacity [22,23].

Telomere length quantification is generally determined on DNA sourced from circulating white blood cells. The problem is whether telomere length determination in peripheral blood cells really reflects the tissue cell telomere length. Some studies have shown that the correlation between LTL and telomere length in vascular tissue really exists. The study by Wilson et al. demonstrated that telomere attrition in circulating blood leucocytes reflects similar changes in the vasculature and is an acceptable surrogate for vascular ageing in population studies [37]. In concordance with this, there is evidence that the relation between LTL and telomere length in various human tissues is strong [38]. In another study LTL was related to the presence of carotid atherosclerotic plaque but not with the plaque telomere length; plaque telomere length was

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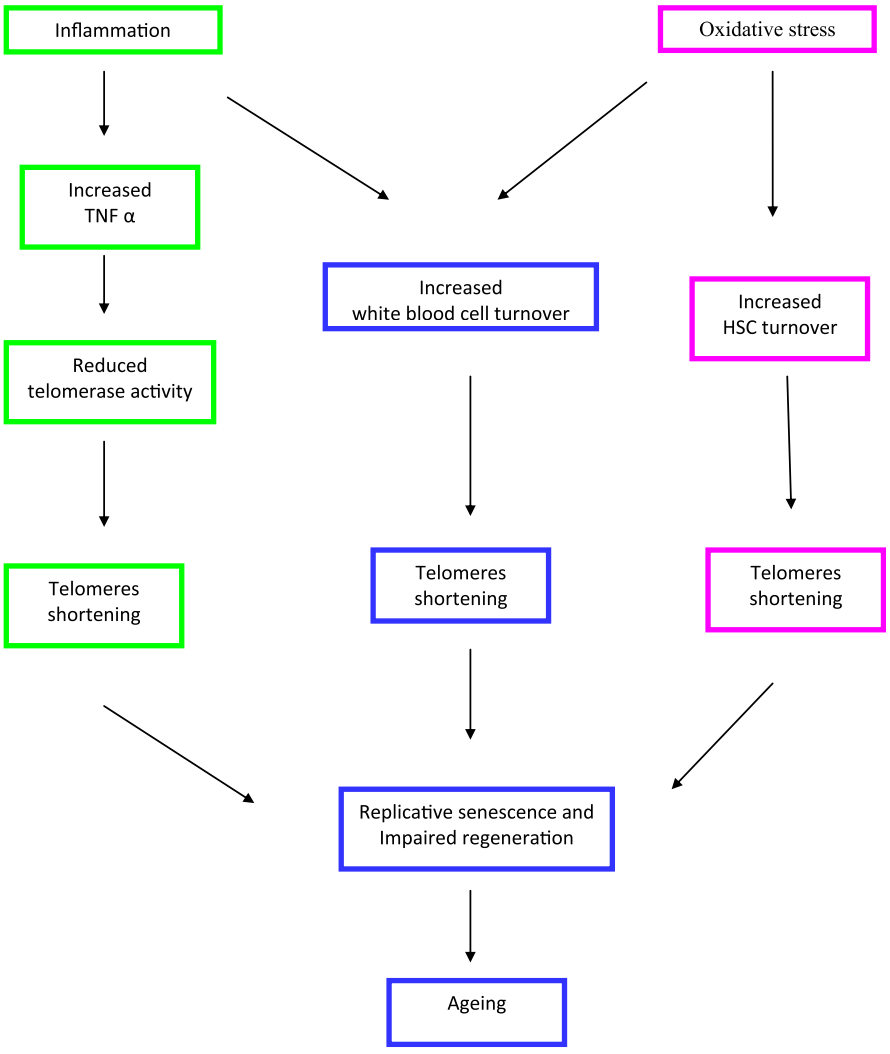

Figure 1 Telomere shortening induced by inflammation and oxidative stress. Systemic inflammation through an increase in peripheral white blood cell turnover and increased TNF-α also plasma levels, that reduces telomerase activity, leads to telomeres attrition as well as does oxidative stress increasing HSC turnover.

related to the plaque characteristics and development of restenosis after endarterectomy in a group of patients undergoing angiography and intervention [39].

Telomeres and classical atherosclerosis risk factors

It has been recently stressed the association of short telomeres with the classical risk factor for atherosclerosis (Fig. 2).

Insulin resistance and diabetes

The pro-atherogenic mechanism of insulin resistance includes its systemic effects leading to dyslipidaemia, hypertension and a pro-inflammatory state as well as direct effects on vascular endothelial cells, smooth muscle cells and macrophages [40].

In early atherosclerosis, insulin resistance causes decreased nitric oxide production and an increase in VCAM-1, which are responsible for impaired vasodilation and inflammation.

In advanced plaques, insulin resistance triggers apoptosis of cells via the Akt pathway [41–44].

Apoptosis of smooth muscle cells causing fibrous cap thinning and apoptosis of macrophages leading to plaque necrosis are the pathological processes that precipitate acute coronary syndromes.

In type 2 diabetes, hyperglycaemia “per se”, induces oxidative stress [45–48] and ultimately leads to cellular senescence. Cellular senescence and apoptosis occur not only in vascular endothelial and smooth muscle cells but in multiple cell lines, including endothelial progenitor [49,50].

Therefore type 2 diabetes can be considered a premature-ageing syndrome and several clinical studies have shown an association between shorter telomere length and type 2 diabetes (T2D) [10–13]. The extent of telomere shortening seems to be gradual and reflecting the severity of the disease and the presence of complications [51].

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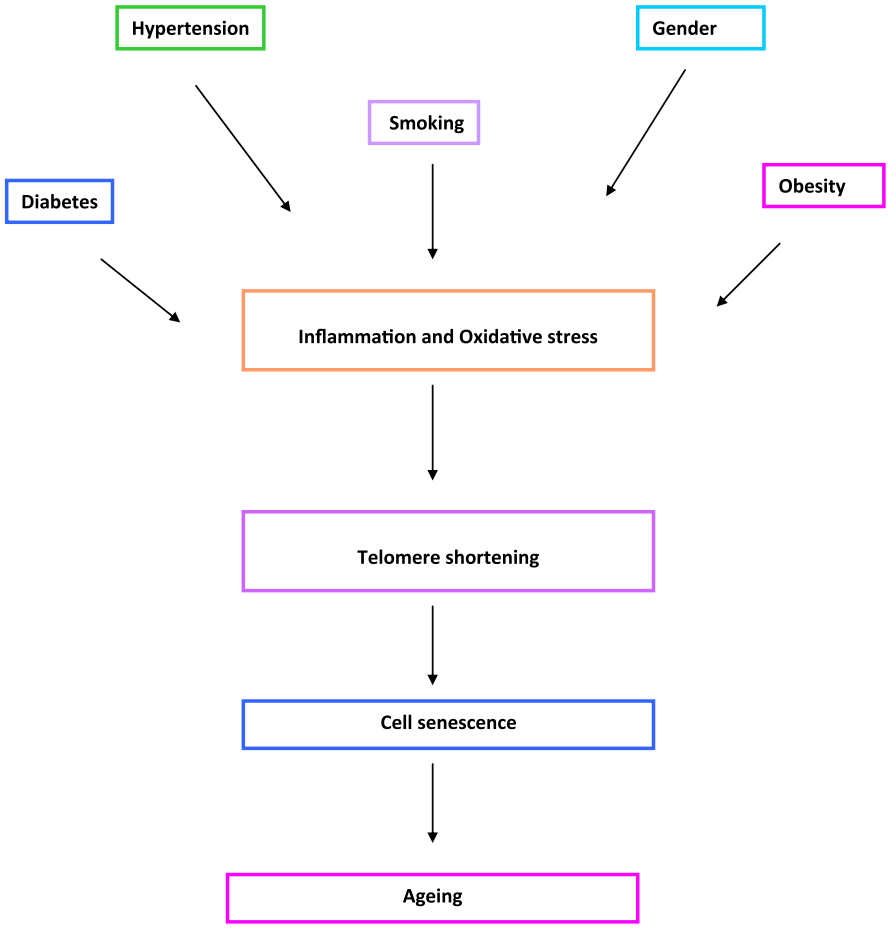

Figure 2 Telomeres and classical atherosclerosis risk factors. The association between short telomeres and the classical risk factors for atherosclerosis might be mediated by systemic inflammation and oxidative stress and/or the influence of a less healthy life style (smoking habit, alcohol consumption, physical inactivity) that usually associates with these conditions.

Also the metabolic syndrome seems to have an influence on telomere length, in a study by Satoh et al. it has been shown that CAD patients with the metabolic syndrome had shorter telomeres than CAD patients without the metabolic syndrome [52]. Moreover among diabetic patients, those with atherosclerotic plaques have greater shortening of telomere length compared to those without plaques [53].

Finally diabetic patients with myocardial infarction have shorter telomeres than diabetic subjects without myocardial infarction [13,54].

Based on these observations, it has been postulated that critically shortened telomeres, due to a combination of inherited short telomeres, oxidative stress and inflammation induced telomere attrition, caused by the common risk factors, lead to cellular ageing in vascular endothelial, and may be a useful biomarker of tissue ageing and disease progression.

Obesity

Adipose tissue is not only a source of ROS and pro-inflammatory cytokines but also secretes of bioactive peptides named “adipokines” that impact on multiple functions including insulin sensitivity, angiogenesis and blood pressure, lipid metabolism and hemostasis, all of which influence the function and structural integrity of the cardiovascular system [55,56].

Indeed obesity promotes the clustering of risk factors such as dyslipidaemia, hypertension, diabetes and the metabolic syndrome and obese subjects experience elevated morbidity and mortality from all forms of cardiovascular disease [57,58].

It is interesting to point out that the relation between weight gain (BMI) and telomere shortening rate is accounted for by increased insulin resistance rather than body weight per se.

In the Bogalusa Heart study it was observed that the relative changes in telomere length were correlated with the homeostasis model assessment of insulin resistance and changes in the body mass index [9].

In a study conducted on 1122 healthy adult female twins it was observed that the telomere length in obese women were 240 base pairs shorter compared to the lean sibling and the difference in telomere length accounted for 8.8 years of ageing.

The study also suggested that the mechanism by which obesity affects telomere length is through increased leptin levels rather than BMI per se [14,59].

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Hypertension

Systolic blood pressure rises with age and might be considered as a phenotype of biological ageing. In a study conducted on 49 twin pairs from the Danish Twin Register, it was observed a significant inverse correlation between pulse pressure and telomere length [60] and this correlation was highly familial.

In a study on 163 treated hypertensive males, Benetos et al. observed that telomere length was shorter in hypertensive men with carotid plaques compared to hypertensive men without plaque. The findings from this study suggest that in the presence of hypertension, which is a major risk factor for carotid arteries atherosclerosis, short telomere act as an important additional risk factor [61].

Smoking

Smoking appears to result in an elevation of biomarkers od oxidant stress, some in a dose-related fashion. There is also evidence that endothelial dysfunction in smokers may be attributable to oxidative stress [62].

Several epidemiological studies, have shown an association between telomere shortening and smoking habit.

In the Flemish study on environment, genes and health outcomes, shorter telomeres were observed in smokers compared to non-smokers [26]. In another study women who had never smoked had longer telomeres than former smokers, and both had longer telomeres than current smokers, moreover it was observed that the effect of smoking habit on telomere length was dose-dependent; each pack-year smoked was equivalent to the loss of an additional five base pairs (18%) of telomere length compared to the rate in the overall cohort [14].

The dose dependent effect was subsequently replicated in another study conducted on a cohort of male smokers with and without chronic obstructive pulmonary disease; the study confirmed that the smoking exposure enhances telomere shortening and demonstrated a dose effect relationship independently from the presence chronic pulmonary obstruction [15].

Telomere length and atherosclerosis

It has been shown that in atherosclerotic regions of coronary arteries, endothelial cells present characteristic features of senescence and inhibiting telomere function induced senescence, whereas introducing telomerase suppressed senescence and extended the lifespan of endothelial cells [3]. It is known that telomeres of coronary endothelial cells are shorter in patients with CAD compared to age-matched subjects without CAD and that in the CAD patients, telomere length is shorter in endothelial cells at atherosclerotic sites compared to non-atherosclerotic sites [63]. Studies have also shown that endothelial cells in regions of the vascular tree that are subjected to greater hemodynamic stress have more pronounced telomere attrition than endothelial cells from areas with less stress [64], this is because that areas of the vasculature that undergo greater shear wall stress have higher cellular turnover rates and consequently shorter telomere length [65]. This variable telomere attrition rate indicates the significant impact of environmental stress on telomere length. In numerous past studies, short LTL has been associated with CAD [23,34,66]. In the pioneering study by Samani et al., it was observed that in patients with early onset CAD with premature myocardial infarction (MI) had a shorter mean telomere length compared with age and gender matched healthy subjects. Furthermore, although both groups experienced telomere attrition with aging, there was a residual difference that served as a marker of increased cardiovascular risk in those patients with early CAD [67]. In another study patients with premature MI had significantly shorter mean telomere lengths compared to healthy subjects, with a consequent calculated reduction in biological age of 11.3 years [68]; the same results were observed in a study that associated shorter LTL with an increase in prospective risk of MI [69]. A study on 143 normal blood donors over the age of 60 years, showed that subjects with shorter telomeres had poorer survival, with a 3.18-fold higher mortality rate from heart disease [70]. In a sub-study of the West of Scotland Primary Prevention Study (WOSCOPS) comparing telomere lengths at recruitment in individuals who went on to develop coronary heart disease events with those from age-matched controls who remained free of CAD, it was shown that subjects with shorter telomere length at the time of recruitment had a significantly higher risk of developing subsequent coronary heart disease [71]. It has been also observed that LTL is shorter in patients with carotid plaques compared with those without, however, further studies are needed to compare peripheral measurements with those in central tissue to determine whether there is a close correlation between measurements as indicated previously [31]. Finally, in the prospective population-based Bruneck study, baseline telomere length was a significant risk predictor for subsequent myocardial infarction and stroke, independent of standard risk factors. Of note in this study telomere length was strongly associated with advanced pathology and acute vascular syndromes but not early atherosclerosis [7].

Conclusion

Understanding the relation between telomere biology and atherosclerosis may be important because of the high incidence of both premature CAD in the general population.

Short telomere in the early life may indicate a genetic predisposition and therefore help identifying susceptible individuals who may be appropriate targets for future molecular therapies and candidates for educational and surveillance programs.

In addition, in adult life telomere length might be a measure of cumulative DNA damage from multiple environmental risk factors, therefore it might be a better predictor of CAD than the currently available risk markers, which are single, point measurements in time.

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Studies with a large number of patients affected by short telomere are needed to evaluate the real rate of association of clinical or subclinical CAD and the prevalence of telomeres shortening. Finally, novel therapies aimed at delaying cellular senescence by manipulation of the telomere/telomerase complex may be of benefit.

Conflict of interest

Authors declare no conflict of interest.

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