



Telomeres and endocrine dysfunctions of the adrenal axis and GH/IGF-1 system

Journal:	<i>Clinical Endocrinology</i>
Manuscript ID:	CEN-2013-000314.R2
Manuscript Type:	5 Unsolicited Review
Date Submitted by the Author:	n/a
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Key Words:	Cushing syndrome < Conditions: < Adrenal, Cortisol < Hormones/related: < Adrenal, insulin-like growth factor type 1, Growth hormone < Hormones/related: < Pituitary, telomere

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Telomeres and endocrine dysfunctions of the adrenal axis and GH/IGF-1 system

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Summary

Telomeres, located at the end of lineal chromosomes, are essential to maintain genomic stability. Telomere biology has recently emerged as an important player in the fields of ageing and disease. In order to maintain telomere length (TL) and reduce its degradation after mitosis, the telomerase enzyme complex is produced. Genetic, epigenetic, hormonal and environmental factors can regulate telomerase function. These include stress hormones such as cortisol and growth factors.

The hypothalamic-pituitary-adrenal (HPA) axis has been evaluated in psychiatric diseases where hypercortisolism and oxidative stress are often present. Some researches have linked TL shortening to increases in stress-related cortisol, but others have not. The effects of cortisol on the telomere system are complex and may depend on the intensity and duration of exposure.

On the other hand, low levels of IGF-1 are associated with inflammation and aging-related diseases (ischemic heart disease, congestive heart failure). Both, IGF-1 and TL diminish with age and are positively and strongly correlated with each other. It is not clear whether this positive relation reflects a single association or a cause-effect relationship. Further research will ideally investigate longitudinal changes in telomeres and both these hormonal axes.

To our knowledge TL dysfunctions have not been described in either endogenous hypercortisolism (Cushing's syndrome) or in acromegaly where excessive amounts of GH and consequently IGF-1 are produced.

This review focuses on the possible relations between telomere dysfunctions and the hypothalamic-pituitary-adrenal (HPA) axis and GH-IGF-1 system.

Keywords: Cushing's syndrome, cortisol, growth hormone, telomere, insulin-like growth factor type 1

Introduction

Telomeres are non-coding repetitive DNA sequences, composed of multiple repetitions of a guanine-rich sequence (TTAGGG), located at the end of lineal chromosomes, and protecting them from erosion and end-to-end chromosome fusions. These sequences are covered by a protein complex called Shelterin, which stabilize and protect them. Without telomeres, genetic material could be lost after every cell division; thus, when telomeres are critically short, cell division stops and senescence and apoptosis are induced¹. Telomere biology has recently emerged as an important player in the fields of ageing and disease.

In order to avoid telomere attrition and to maintain telomere length, germ-line cells and a few somatic ones produce telomerase. Telomerase is a specific enzymatic complex involved in telomere repair and elongation. It catalyses telomeric DNA synthesis to reduce chromosomal end degradation after terminal DNA replication and thus to maintain telomere length (TL)². Telomerase consists of several components, the catalytic component (hTERT) with telomerase reverse transcriptase activity, the telomerase RNA component (TERC) which is used by hTERT as a template to synthesize telomere DNA, dyskerin complex and several proteins which stabilize the whole telomerase machinery³.

Telomere length typically decreases with ageing, but the shortening rate is not uniform for all kind of tissues and cells; for example, brain cells and cardiomyocytes show few attritions^{4,5}. Undifferentiated stem cells have longer TL, while in more differentiated cells, TL are shorter⁶. Even in “non-dividing” cells, telomeres can be shortened by oxidative stress, which preferentially damages guanine rich sequences as telomeres, to a greater extent than nontelomeric DNA^{7,8}. Stem cell dysfunction provoked by telomere shortening may be one of the mechanisms responsible for ageing⁹. Moreover, TL is considerably heterogeneous, even in the same cell and for individuals of similar age. Recent studies revealed that TL changes could be dependent on the baseline TL (newborns). In early life, inheritance seems to be an important point, being one of the main determinants of TL. However, the inherited impact decreases with increasing age, due to the impact of environmental factors on TL^{10,11}.

Genetic, epigenetic and enviromental factors can regulate telomerase function. These include socio-economic status, lifestyle, autoimmunity, histone methylation and

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3 acetylation, stress level, hormones (stress hormones such as cortisol, catecholamines
4 and sex hormones), growth factors, personal habits (smoking, diet, physical exercise)
5 and drugs (such as angiotensin-converting enzyme inhibitors, resveratrol...,) which can
6 influence and modulate telomerase dynamics and activity¹. ***Processes known to***
7 ***modulate telomerase dynamics and to affect telomere length either by shortening or***
8 ***lengthening are summarized in Figure 1.*** Some behavioural and psychological
9 interventions such as long-term exercise or cognitive behavioural stress management
10 have been shown to increase telomerase activity^{12,13}. However, one limitation to most
11 behavioural interventions is poor long-term maintenance of behavioural changes, since
12 these biochemical changes mentioned may last only as long as there exist maintenance
13 of the behavioural and psychological changes.

14 Measuring TL may contribute to the understanding of their clinical and biological
15 significance, since it can be used as an indicator of chromosome stability, telomerase
16 activity, proliferative capacity and cellular ageing. Different methods are available to
17 determine TL, each with specific features^{2,14}. However, up to now they have mostly
18 been in experimental research rather than in clinical diagnosis and prognosis, for which
19 improvements in cost-effectiveness, sensitivity and availability of large amounts of
20 patients would be necessary.

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23 Therefore, telomere biology can be involved in the pathophysiology of several clinical
24 entities such as cancer¹⁵, pre-malignant lesions, aplastic anemia¹⁶, fibrosis of the lungs
25 and liver, dyskeratosis congenita, as a risk factor for cardiovascular diseases¹⁷ (poor
26 lipid profile, high systolic blood pressure, fasting glucose, smoking, greater abdominal
27 adiposity), ageing, etc.^{5,6} Whether a common molecular mechanism is causally involved
28 in the development of these human diseases requires further research with prospective,
29 longitudinal and interventional studies.

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32 Some endocrine diseases like adrenal and GH dysfunctions are associated to aging-like
33 processes and increased cardiovascular risk; but the underlying mechanisms are
34 complex and not always clear. Given the role of telomeres in some of these
35 mechanisms, we decided to review what evidence there was to associate the telomere
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system with endocrine dysfunctions of the hypothalamic-pituitary-adrenal (HPA) axis and the GH-IGF-1 system.

Hypothalamic-pituitary-adrenal axis and the telomere system

To our knowledge, telomere dysfunctions have not been described in endogenous hypercortisolism, due to Cushing’s disease or adrenal adenomas, nor in the most common situation of exogenous hypercortisolism after glucocorticoid (GC) therapy¹⁸.

In contrast, this has been evaluated in different psychiatric diseases like acute and chronic stress and posttraumatic stress disorder, where hypercortisolism is often present, representing another model of endogenous hypercortisolism. However, these neuropsychiatric conditions are not the best model of hypercortisolism in which to base conclusions about telomere dynamics, due to their complexity with concurrent changes in stress hormones, neurotransmitters, autonomic activity, cytokines, inflammation and oxidative factors.

There is substantial evidence supporting an association between psychiatric disorders and abnormalities in stress-related biological systems, such as the HPA axis and inflammatory responses^{19,20}. These abnormalities could provide a basis for investigating a relationship between telomere shortening and accelerated ageing^{21,22}.

Chronological aging impairs the organism’s ability to sustain efficient allostasis when responding to different stressors. This is well-demonstrated by examining physiological regulation of HPA axis responses. The cortisol response to stressors can be exaggerated in the elderly, with a slow negative feedback, so that cortisol stays elevated longer²³. The actual significance of hypercortisolemia remains unknown, and it is still debatable whether “hypercortisolemia” results in net hypercortisolism at the cellular level, or rather in net hypocortisolism due to a downregulation of the GC receptor. Furthermore, in some situations hypercortisolemia could represent a homeostatic attempt to overcome GC-receptor resistance²². Thus, cortisol levels in blood do not necessarily reflect cortisol signalling at the cellular and genomic levels²⁴. In fact, the research linking chronic stress, telomere system and HPA function is sometimes contradictory, some studies reporting increased activations of telomerase activity while others the opposite²⁵.

Psychological and oxidative stress related with increased HPA activity and the telomere system:

Recently, a meta-analysis of GCs as modulators of oxidative stress showed that GCs increased oxidative stress with duration of treatment. In addition, GCs cause different levels of oxidative stress among tissues, with brain being the target most susceptible to damage²⁶. It seems that chronic psychological stress is perceived by the cortex of the brain, inducing secretion of hypothalamic corticotropin-releasing hormone (CRH), leading to increases in ACTH and cortisol levels, which could be used as an index of stress reactivity. Chronic stress is believed to favor disease by activating the HPA axis^{21,27}. This stress-related dysregulation of the HPA axis leads to cortisol-induced changes such as reduced availability of intracellular glucose energy stores, neurotoxic effects in certain brain areas (prefrontal cortex and hippocampus), excitotoxicity (increasing glutamate secretion), neuroinflammation (immune alterations) and accelerated cell ageing, via effects on the telomere/telomerase maintenance system. In fact, in patients with major depression, hippocampal atrophy is often reported^{28,29}. These lesions are similar to those observed in patients with Cushing's syndrome, and both share as a main link hypercortisolemia, suggesting a possible "pro-ageing" effect of GCs in certain cells of the body^{18, 30-32}.

Furthermore, altered HPA axis activity together with stress can increase oxidative damage and decrease antioxidant mechanisms. Oxidative stress damage occurs when the production of oxygen free-radicals exceeds the capacity of the body's antioxidants to neutralize them. Elevated plasma and/or urine oxidative stress markers, have been reported in patients with depression or individuals with chronic psychological stress³³. As we mentioned before, the guanine-rich strand of telomeres is more sensitive to oxidative damage compared to other genome sequences⁸. In fact, oxidative stress is inversely correlated with telomerase activity as well as TL³⁴⁻³⁶. Therefore, accelerated telomere shortening may reflect stress-related oxidative damage to cells and accelerated aging.

Some studies have linked accelerated leukocyte telomere shortening to several psychosocial stress situations, such as mood disorders and caregivers, like mothers of chronically ill children or partners of patients with Alzheimer's disease. Mothers who look after a chronically ill child have shorter telomeres in peripheral blood mononuclear

cells (PBMCs), relating more years of caregiving to lower telomerase activity, higher levels of perceived stress and of oxidative stress index (isoprostanes per milligram of creatinine/vitamin E) compared to controls (non-caregiving mothers)³⁷. These findings provide a potential mechanism for stress-associated TL attrition. Studies examining the relationship between TL and HPA axis are summarized in table 1.

Supporting the chronic stress model of accelerated ageing, preliminary evidence shows that certain mood disorders are associated with accelerated ageing, and could be a novel mechanism for mood disorder-associated morbidity and mortality³⁸. Shorter leukocyte telomeres in 44 patients with depressive mood or bipolar disorders were observed when compared to 44 gender and sex-matched control subjects, corresponding to 10 years of accelerated cell-ageing³⁸.

This telomere shortening, at least in part, could be related to increases in stress-related cortisol and catecholamine output. Average leukocyte telomere length was evaluated in 647 women who had a sister with breast cancer, in relation to perceived stress and urinary catecholamines and cortisol. They observed accelerated telomere shortening in the groups with higher perceived stress and with higher levels of urinary catecholamines. A trend towards telomere shortening in those with higher levels of urinary free cortisol was also observed without reaching statistical significance³⁹. These results suggest that the effect of stress on TL may vary depending on neuroendocrine responsiveness and external stressors as well as on age.

In the same line, shorter buccal-cell TL in children was observed in six-year-old children exposed to laboratory stressors, with higher levels of salivary cortisol and higher autonomic reactivity. These authors suggest that buccal cell TL may be a useful marker of early biological aging⁴⁰.

Some preliminary data suggest that telomere shortening depends on the duration of the exposure to depression or a stressor³³. In 18 patients with major depressive disorders and 17 sex and age-matched controls, average leukocyte telomere length was significantly inversely correlated with lifetime depression exposure, even after controlling for age³³. This suggests that telomere shortening may progress in proportion to lifetime depression exposure, and after a larger exposure of hypercortisolemia could lead to a greater decrease in telomere length.

Greater cortisol responses and dysregulated patterns of daily cortisol secretion were associated with shorter telomeres in PBMCs in 14 post-menopausal women caring for a partner with dementia, compared to age- and BMI-matched non-caregivers⁴¹. Specifically, higher overnight urinary free cortisol levels, higher salivary cortisol response to acute stress and flatter daytime cortisol slopes were associated with shorter TL. However, when they evaluated TL in whole blood (mostly of short-life granulocytes), they found no relation between TL and HPA axis dysregulations. This may be explained by the fact that these cells are not exposed to blood cortisol as much as the more long-lived circulating PBMCs, which play an active role in the early acute stress response. Future studies examining different leukocyte cell types and their relationship to TL in specific subpopulations of leukocytes may contribute to clarify these phenomena further.

Another group observed similar findings when 22 high stress dementia caregivers were exposed to a brief laboratory psychological stressor compared to 22 matched low stress controls. At baseline caregivers had lower telomerase activity, but during acute stress telomerase activity increased similarly in both groups independently of leukocyte cell type and associated with greater salivary cortisol increases in response to stressors. These findings suggest novel relationships of dynamic telomerase activity with exposure to an acute stressor⁴².

In the same line, leukocyte telomere length was evaluated in a group of pre- and postmenopausal women with self-reported dietary restraints (defined as chronic worry with weight and attempts at restricting food intake) which are often linked to greater perceived stress as well as to physiological factors known to be related to long-term stress, such as elevated salivary and urinary cortisol⁴³. Dietary restraint, independently of body mass index, was a risk factor for premature telomere shortening, in which HPA dysfunctions could be implied⁴⁴.

Moreover, chronic stress is related with a low health index, with an increase of cardiovascular risks factors and alterations in immunological systems, similar to what is observed in patients with Cushing's syndrome. However, the exact mechanisms involved are still unknown. Chronic stress can lead to a state of metabolic stress (overeating, co-elevations of cortisol and insulin levels and suppression of certain

anabolic hormones such as androgens or GH), which in turn promotes abdominal adiposity. Both metabolic stress and abdominal adiposity can facilitate systemic inflammation and oxidative stress, which appear to mediate several cell aging mechanisms such as leukocyte telomere length shortening and cell senescence⁴⁵. Hence, HPA dysregulations could provide a common biological link, inducing changes in the telomere system, impairing the health status and increasing cellular damage both in Cushing's syndrome and chronic psychosocial stress. Hypercortisolemia probably contributes to premature ageing by inducing accelerated telomere shortening, which could be implied in the persistent morbidity and clinical consequences associated to Cushing's disease, even years after being biochemically cured of hypercortisolism^{18,46}. Consistent with these observations, one study in vitro observed that the exposure to high hydrocortisone levels comparable to those that might be reached in vivo during stress, are related to a significant reduction of telomerase activity of T lymphocytes, by as much as 50% three days later⁴⁷. This effect is observed in both CD4 and CD8 T lymphocytes, and is associated with reduced transcription of hTERT, the telomerase catalytic component. This could be one of the mechanisms in which hyperstimulation of the HPA could alter the immunological system, inducing immunosenescence and conferring higher infection susceptibility, as observed in patients with higher levels of stress or with Cushing's syndrome. These data suggest that immunosenescence may be closely related to both psychological distress and stress hormones (cortisol), and partially to telomere dysfunctions⁴⁸. Based on the hypothesis that glucocorticoids are a well-known immunosenescence inducers, Ichiyoshi et al, investigated the changes in thymocytes after dexamethasone administration in mice. They observed that dexamethasone-treated thymocytes exhibited rapid and dynamic loss of telomeric sequences and up-regulation of telomerase RNA as an early event in the apoptotic process. The loss of thymocytes coincided with the appearance of small dense cells with characteristic features of apoptosis (condensed chromatin, internucleosomal DNA cleavage and hypodiploid peak on flow cytometry)⁴⁹. Some mechanisms such as the regulation of shelterins and dyskerin expression or the regulation of genes implied in the mechanism of alternative lengthening of telomeres (such as ATRX or DAXX) could be affected by glucocorticoids. Moreover, the methylation pattern of the subtelomeric regions either directly or indirectly by some miRNA families, could also be regulated

by cortisol levels. However, to our knowledge, the effect of cortisol in these possible mechanisms which could modify telomere length, has not been evaluated and is unclear. Recent research has observed that embryonic exposure to corticosteroids in domestic chickens resulted in higher levels of reactive oxygen metabolites and shorter telomeres compared with the control birds⁵⁰. Similarly, findings in humans in vivo have been found in 62 healthy women that lower levels of leukocyte telomerase activity were associated with exaggerated autonomic reactivity to acute mental stress and with increased excretion of stress hormones (catecholamines and cortisol). They also observed that low telomerase activity was associated with major risk factors for cardiovascular disease (smoking, poor lipid profile, high systolic blood pressure, high fasting glucose, greater abdominal adiposity). However PBMCs TL was not correlated with cardiovascular disease risk factors, suggesting that telomerase activity may be an earlier marker of cell aging than TL⁵¹.

Recently, the first study to show a longitudinal association between co-occurring changes in cortisol and telomerase activity in unstimulated PBMCs has been published⁵². The authors examined whether participation in a mindfulness-based intervention and improvements in psychological distress, eating behavior and metabolic factors (weight, serum cortisol, fasting glucose and insulin, and insulin resistance) were associated with increases in telomerase activity in PBMCs. They observed that changes in chronic stress, anxiety, dietary restraint, cortisol and glucose were negatively correlated with changes in telomerase activity. These results support the model that changes in stress-related cortisol might be one of the signals regulating telomerase levels in humans⁵².

Psychological and oxidative stress related with decreased HPA activity and the telomere system:

Although stress has traditionally been associated with increased cortisol secretion and HPA axis over activity, recently some literature describes low cortisol levels in some stress-related disorders, suggesting that chronic stress could lead to an exhaustion of the HPA axis²⁵. Hypocortisolemia or low CRH, has been related with atypical depression, states of chronic fatigue and post-traumatic stress syndrome, contributing functionally

to symptoms of inflammation and fatigue^{53,54}. A recent paper reports that leukocyte shorter telomeres were associated with depression and hypocortisolism⁵⁵. To our knowledge, telomere dysfunctions have not been described in Addison's disease, the ideal model of primary endogenous hypocortisolism due to adrenal insufficiency, nor in hypopituitarism, where often secondary adrenal insufficiency is present.

Dexamethasone cortisol suppression (the percentage change of cortisol between pre- and post-dexamethasone cortisol) was higher in a group of depressive patients compared with the control group. Furthermore, subjects exhibiting a high level of suppression (lower post-dexamethasone cortisol levels) had significantly shorter leukocyte TL⁵⁵. Decreased activity of the HPA axis has been shown to develop from a long term chronic stress exposure, where an initial stage of a hyperactive HPA axis eventually evolves into a hypoactive HPA axis. A highly sensitive negative feedback of the HPA axis (low post-dexamethasone cortisol, high degree of cortisol suppression) is probably the most common finding in subjects exhibiting hypocortisolism. The observation of shorter TL and hypocortisolism could be the result of independent pathways of chronic stress exposure or due to higher degrees of inflammatory processes, which would lead to increased proliferation of leukocytes and higher levels of oxidative stress, both contributing to accelerated TL shortening³. It is difficult to know clearly which is the responsible condition for accelerated telomere shortening, when a hypocortisolemic status is often preceded by a hypercortisolemic phase. The observation of shorter leukocyte TL in these situations, suggests leukocyte TL could be a good measure of cumulative stress.

To summarize, it should be noted that the effects of cortisol on the telomere system are complex and may depend on the intensity and duration of exposure.

Shorter exposure and shorter duration appear stimulatory to the telomerase system rather than suppressive. Although acute spikes in cortisol could be associated with a short-term increase in telomerase, they are also associated with a longer term measure of shorter leukocyte telomere length, suggesting that over time, stress and cortisol reactivity could promote telomere shortening.

We should considered some important limitations of the available studies that could provide explanations for the differences observed between studies. Different methods to

measure cortisol exposure has been used (questionnaires, circadian rhythm disruption, urinary free cortisol, salivary cortisol, response to dexamethasone, hydrocortisone administration in vitro...). Moreover, different methods to measure telomere length has been reported, mostly conventional techniques (Southern Blot, PCR), while none of the presented studies use novel technologies such as STELA which seems to show a better relationship with aging and disease.

Future research will ideally enable further investigations on longitudinal changes in telomeres.

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Growth hormone (GH) and Insulin-like Growth Factor type 1 (IGF-1) axis and the telomere system

It is well known that leukocyte TL reduces with increasing age. The shortening of telomeres may act as a mitotic clock regulating the number of divisions a cell can undergo, being a biomarker of aging^{4, 56}. However, in elderly men, TL may not decrease further reaching a plateau, possibly due to a selection of mortality, meaning that mortality may increase in men with shorter telomeres and the disappearance of men with shorter telomeres would result in an increase in the mean value in the remaining men. Alternatively, telomerase seems to be more active to prolong leukocyte TL in men with critically short leukocyte TL⁵⁷.

IGF-1 is an important regulator of cell growth and proliferation. Its serum concentration is reduced with increasing age. Also, serum IGF-1 concentration, with increasing age, is positively associated with parameters reflecting general health such as lean mass, physical activity and nutritional intake. Relatively low circulating levels of IGF-1 in humans are associated with aging-related diseases and decrease in longevity. Diminished longevity has been observed in pathological situations which display low levels of IGF-1 such as hypopituitarism due to multifactorial explanations compared to age- and sex-matched controls⁵⁸. In GH resistance syndromes or untreated patients with isolated childhood-onset GH deficiency reduced longevity has also been observed⁵⁹.

Despite these links between GH/IGF-1 and good metabolic health in humans, IGF-1 has been linked to shorter lifespan in lower species and some mammalian models⁶⁰. Therefore, probably the link between IGF-1 and longevity in humans, does not fit neatly into a simple paradigm; for these reasons some groups have examined the association of leukocyte TL with circulating levels of IGF-1. Not only low levels of IGF-1, but also short leukocyte TL are associated with aging-related diseases mainly atherosclerosis and diminished longevity. Barbieri et al. examined this possible association in healthy individuals free of any major aging-related diseases. Both variables, leukocyte TL and IGF-1, diminished with age and presented positive and strong correlations between each other⁶¹. Therefore, short leukocyte TL can be a reflection of the poor general health of these men.

On the other hand, IGF-1 may reduce inflammation which could have a protective role against telomere attrition. IGF-1 acts as an anti-inflammatory molecule inhibiting IL-6 expression and increasing its clearance. Both higher IL-6 and lower IGF-1 levels confer increased risk of having metabolic syndrome⁶². IGF-1 seems to up-regulate nitric oxide synthase in the vascular endothelium, which would cause vasorelaxation, a beneficial phenomenon to the aging vasculature, which also would decrease oxidative stress/inflammation⁶³. This systemic effect of IGF-1 might ultimately explain the link between IGF-1 and TL in humans. Additionally, low serum IGF-1 concentration has been found to be a risk factor for ischemic heart disease, congestive heart failure and even for increased mortality⁶⁴. It is not clear whether the positive relation between IGF-1 concentration and TL reflects a single association or a cause and effect relationship.

The possible interaction between circulating IGF-1 and TL has been studied in a few series. Table 2 summarizes studies examining the relationship between telomere system and the GH/IGF-1 axis.

IGF-1 affects cell replication and is involved in growth proliferation and transformation of many cell types. It plays a critical role in the G1 and S phase of the cell cycle. On its own, it cannot stimulate entry into the G1 phase, but it is supposed to be necessary for maintaining G1 and entry into the S phase in many cell types, including mitogen-stimulated human leukocytes. Therefore, IGF-1 could be a tangible candidate involved in telomerase activation in cell growth and proliferation. Up-regulation of telomerase activity by IGF-1 has been observed in several cancer cell lines⁶⁵. For the first time, Tu et al. in 1999 studied in vitro the effect of IGF-1 on telomerase activity and on telomerase component's complex in human cord blood mononuclear cells. Interestingly, IGF-1 alone did not increase the telomerase activity of cord blood mononuclear cells but could enhance the phytohaemagglutinin-induced (T-cell stimulating agent) increase in telomerase activity. The results suggested that IGF-1 may modulate telomerase activity supporting its potential role in increasing replicative potential of cord blood lymphoid cells or haematopoietic stem cells. Nevertheless, little is known whether these two systems interact in vivo⁶⁶. The mechanisms of telomerase activation in cancer cells by IGF-1 and the potential effects of IGF-1 on telomerase in normal somatic cells need to be further elucidated.

In a recent study, the relation between leukocyte TL and IGF-1 in 551 adults older than 65 years was evaluated. No correlation between TL and plasma IGF-1 concentration was observed in a univariate regression analysis. However, in a multivariate regression analysis, a positive association between plasma IGF-1 and TL was observed after adjustment for multiple confounding factors, such as age, sex, race, smoking status, body mass index, hypertension, diabetes and serum lipids⁶⁷. The results of this study suggest that higher IGF-1 values may be an independent predictor of longer leukocyte TL, consistent with prior evidence suggesting the role of IGF-1 in mechanisms related to telomere maintenance in immune cells⁶⁷. They also observed that this association was stronger in men than in women, possibly due to gender differences in the regulation of leukocyte TL.

Another large population-based cross-sectional study with 2744 elderly men (mean age 75.5 years), observed that leukocyte telomere length was positively associated with serum IGF-1 and negatively associated with age⁶⁸. In contrast with other studies, in this last series, leukocyte TL was independently associated with serum C-reactive protein concentrations, where IGF-1 seems to reduce inflammation⁶².

Mechanisms underlying the association between TL, IGF-1 and senescence remain to be determined. It is not fully clear whether measurements of TL in leukocytes are representative of the processes that occur in other somatic cells, since TL may differ by cell type. Nevertheless, there are correlations between TL in different tissues, which suggests that TL in leukocytes could serve as a surrogate for relative TL in other tissues. We must also take into account that telomere shortening and IGF-1 axis are not the only mechanisms that affect cell senescence; environmental stress-mediated accumulations of DNA mutations (reactive oxygen species, ultraviolet irradiation, chemical mutagens or endocrine signals such as IGF-1/insulin signaling) and the intrinsically encoded biological clock that dictates lifespan events of any particular cell type can also affect cell senescence. Some genes implied in the regulation of the mechanism of alternative lengthening of telomeres such as ATRX (ATP dependent helicase) or DAXX (death domain-associated protein) participate in chromatin remodelling of telomeres and other genomic sites. In ATRX-null embryonic mice, which exhibit telomere dysfunction, reduced growth and shortened lifespan, DNA damage and tissue attrition are found in the anterior pituitary cells, resulting in low circulating levels of IGF-1⁶⁹. On the other

hand, a type III protein deacetylase (SIRT1), is considered a novel anti-aging protein involved in regulation of cellular senescence/aging and inflammation, being a positive regulator of telomere length in vivo. SIRT1 has been shown to modulate the activity of FoxO, a transcription factor that is downstream of the IGF signalling system. The loss of SIRT1 in mice results in increased expression of the IGF Binding protein type 1 (IGFBP1) a modulator of IGF-1 function. Whether these alterations are also present in humans and any potential effects on telomere system, are unclear⁷⁰.

These mechanisms are directly tied to the change of nuclear function and structure and they affect both somatic and mainly stem cells which are responsible for proper tissue rejuvenation⁷¹.

To our knowledge, the telomere system has not been evaluated in patients with acromegaly, where excessive amounts of GH and consequently IGF1 are produced.

Further investigations are necessary to examine how the interplay between the GH/IGF1 system and telomere regulation affect immune aging and risk of age-associated diseases.

To summarize, telomeres are essential to maintain genomic stability. When telomeres are critically short, cell division stops and senescence and apoptosis are induced. Telomere length can be influenced and modified by genetic, epigenetic, environmental and hormonal factors. The review focuses on the possible relations between telomere dysfunctions and the HPA axis on the one hand and the GH-IGF-1 system on the other.

Most of the evidence linking the telomere system and HPA function has been evaluated in psychiatric diseases (mainly in chronic stress, posttraumatic stress disorders and major depressive disorder), where hypercortisolism is often present. It is sometimes contradictory, some studies reporting increased activations on telomerase activity while a few others conclude the opposite. The possible mechanisms by which cortisol could modify telomere length have not been systematically evaluated and are presently unclear.

Both IGF-1 and TL diminish with age and are positively and strongly correlated. Low levels of IGF-1 are associated with inflammation and aging-related diseases, processes in which TL has been found to be shorter. However, mechanisms

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underlying the association between TL, IGF-1 and senescence remain to be determined.

TL dysfunctions have not yet been evaluated in either endogenous hypercortisolism due to Cushing’s syndrome or in acromegaly where excessive amounts of cortisol or IGF-1, are present, respectively.

Acknowledgments

AA is supported by a grant from Spanish Ministry of Health, ISCIII, PI 11/00001.

For Peer Review

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Table 1: Studies examining the relationship between telomere system and the HPA axis.

Diagnosis or type of stress	References	Total n	Findings
Perceived stress (Breast cancer's sisters)	36	647	Accelerated telomere shortening with higher levels of urinary catecholamines and urinary free cortisol.
Laboratory stressors	37	78	Shorter buccal-cell TL in children with higher levels of salivary cortisol and higher autonomic reactivity
High caregiver stress (dementia caregiver)	38	14	Shorter telomeres in PBMCs were associated with greater cortisol responses and dysregulated patterns of daily cortisol secretion
	39	22	Telomerase activity increases during acute stress associated with greater salivary cortisol increases in response to stressor
Acute mental stress	48	62	Lower leucocyte telomerase activity was associated with exaggerated autonomic reactivity and with increased excretion of stress hormones (catecholamines and cortisol) to acute mental stress.
Dietary restraint	40	56	Premature telomere shortening is observed in women with dietary restraints linked to greater perceived stress and elevated salivary and urinary cortisol
High hydrocortisone levels in vitro	45		50% reduction of telomerase activity of T lymphocytes is observed with the exposure to high hydrocortisone levels in vitro
Embryonic exposure to corticoesterone	47	60 (eggs)	Shorter telomeres were observed with exposure to exogenous corticoesterone during embryonic development (domestic chickens)
Mindfulness-based intervention for stress eating	49	47	Changes in telomerase activity were negatively associated with changes in serum morning cortisol levels (after intervention)
Dexamethasone administration in mice thymocytes	49		Rapid and dynamic loss of telomeric sequences in dexamethasone-treated thymocytes
Major Depressive Disorder and hypocortisolism	52	91	Shorter TL is associated with depression and hypocortisolemic state (low post-DST cortisol and high percentage of cortisol reduction after the DST)

Abbreviations: DST: dexamethasone; PBMCs: peripheral blood mononuclear cells

Table 2: Studies examining the relationship between TL and the GH/IGF1 axis.

Study population	References	Total n	Findings
Healthy subjects	58	476	Longer leukocyte TL are associated with higher circulating levels of IGF1
In vitro: cord blood MNC stimulated by PHA	62		IGF1 increases telomerase activity in PHA stimulated cells.
Participants among the cardiovascular health study (adult men)	63	551	Higher IGF1 values may be an independent predictor of longer leukocyte TL.
Elderly men	64	2744	TL is positively associated with serum IGF1 and negatively associated with age.

Abbreviations: TL: telomere length; MNC: mononuclear cells; PHA: phytohaemagglutinin; IGF1: insulin growth factor 1;

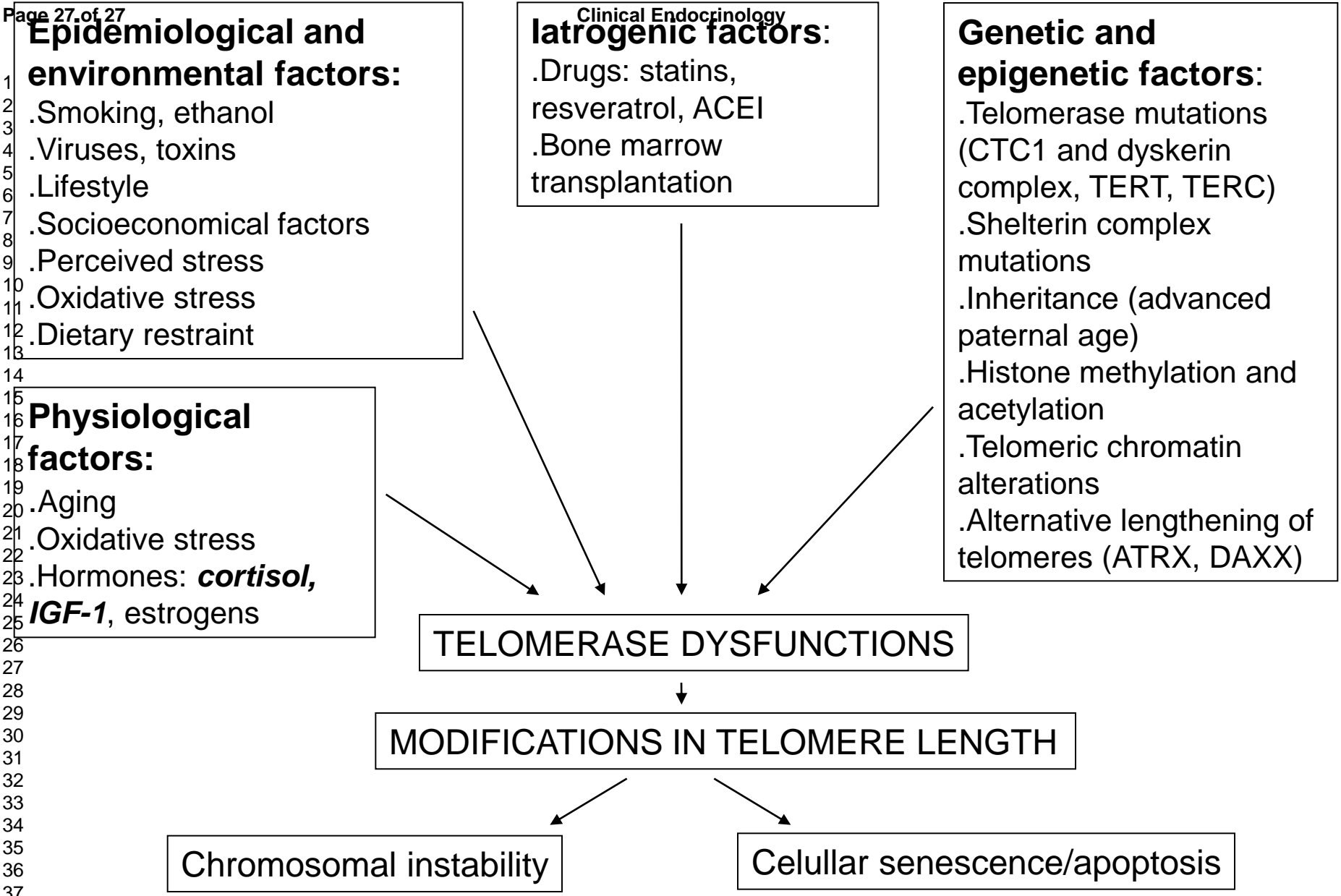


Fig 1: Processes known to affect telomere length either by shortening or lengthening (CTC1: conserved telomere maintenance complex component 1; IGF-1: insulin-like growth factor type 1; TERT: Telomerase reverse transcriptase; TERC: Telomerase RNA component; ATRX: ATP-dependent helicase; DAXX: death associated protein 6; ACEI: angiotensin-converting enzyme inhibitors)