EXPLORING THE RELATIONSHIP BETWEEN TELOMERE LENGTH AND ALZHEIMER'S Disease: THE ROLE OF SPECIFIC BIOMARKERS AND CONTRIBUTING FACTORS

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ABSTRACT

Aiming to provide a better understanding of the interconnection between telomere length and Alzheimer's Disease, this paper also tries to consider the role of certain biomarkers in mediating this relation. Chromosomes are structures that contain DNA and hence, other genetic materials; every chromosome has a protective cap known as telomeres that reduce the risk of misread DNA during replication, and these telomeres constantly and relatively shortening with each subsequent cell division especially with increasing age and stress. Shortened telomeres have been linked to different age-related Diseases and conditions including; Alzheimer's Disease- a Disease that is neurodegenerative in nature and is characterized by slowness in the overall cognitive function as well as memory. The present synthesis provides current literature about the telomere biology, more specifically, telomere shortening and its potential role in the development and course of Alzheimer's Disease. We pinpoint biomarkers which may account for the associations described above, including inflammatory indexes, measures of OS, and polymorphisms. These biomarkers have not only contributed to the elucidation of the Alzheimer's mechanism but also provided early markers and also therapeutic targets. As well as assessing biomarkers (telomere length, neuroplasticity potential, cognitive reserve) this paper discusses potential factors influencing biomarkers and their implications on the development and progress of Alzheimer's Disease. Some of the causes include; The use of certain foods and drinks, age, level of physical activity, stress, exposure to certain chemicals among others. For instance, dietary intake of antioxidant and vigorous exercise have been found to lessen the extent of telomere shorting, whereas cluttered stress and unhealthy living patterns have been linked to heightened progression towards shortening of telomeres. This also seeks to synthesise information from various studies examine this interaction by encompassing results from cross-sectional and longitudinal, multinational, interventional and observational studies to amalgamate knowledge on the complex relationship between telomere length, Alzheimer's Disease and its determinants. This integrative strategy not only refines our understanding of the underlying pathophysiological processes but also creates opportunities for the creation of individualized methods for the prevention and management of Alzheimer's Disease.

Keywords:*Telomere Length, Alzheimer's Disease, Biomarkers, Aging Diet, Lifestyle Factors, Neurodegeneration, Cellular Aging, Genetic Predispositions, Environmental Influences.*
DOI Number: 10.48047/nq.2024.22.4.nq24002 **NeuroQuantology 2024; 22(4):7-30**

I. INTRODUCTION

A. Background

Alzheimer's Disease (AD) is a type of dementia that is chronic and demonstrates progression in severity[1] that mostly affects the population of the elderly due to reduction in the abilities to reason, remember and adapt to appropriate behavioural changes as result of the Disease. The global prevalence of Alzheimer's is estimated at 27 million, and is presently the primary cause of progressive dementia[2].It poses a considerable cost on healthcare and social services and impacts millions of families. Although it has been the subject of many investigations, the exact morpho physiologic alterations[3] that cause Alzheimer's Disease have not been fully identified, and, correspondingly, therapeutic approaches are somewhat limited. Telomeres [4], which are the main nucleotide sequences within chromosomes' extremities, are responsible for genome stabilization. These protect any genetic information that is present within a cell and also ensure that chromosomes do not break, become intertwined or fuse together during cell division [5]. However, with each cell division, the telomeres get progressively abbreviated, and, when reached a certain length, cells can become senescent or undergo apoptosis. This decrease in the length of the telomere is a normal event or process that occurs when an organism grows older [6], but it also happens at a faster clip if certain conditions, causes such as elevation in oxidative stress, increase in inflammation, and engagement in vices such as smoking, poor diet, or alcohol intake exist [7]. Thus, telomere length has become a focus for more accurate explanations of the aging process and producers of age-related Diseases [8]. The last-mentioned geographical factor interdependence of Telomerase activity and Alzheimer's Disease, and shortening of the telomeres [9]. Such a reduction could also be helpful in growth and development of neurodegenerativediseases due to factors like enhanced cell cycle arrest, inflammation, and poor capability in DNA repair. Elucidating this relationship could significantly help in unravelling the mechanisms of Alzheimer's Disease and could lead to identification of novel biomarkers and novel potential therapeutic strategies.

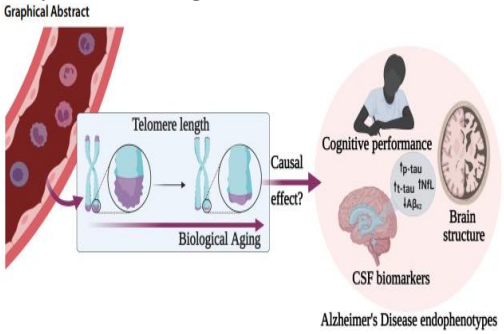

Fig1.Alzheimer's Disease endophenotypes [10]

B. Objectives of the

They are to focus on exploring the associations between telomere length and Alzheimer's Disease [11], and to identify several biomarkers [12]. Biomarkers are biological characteristic that can be measured and can serve as an index for estimating biological state or response to a particular treatment. In the Alzheimer's Disease context,biomarkers [12] in the form of inflammatory messengers, markers of oxidative stress, and certain genetic signatures – may help us understand the processes through which telomere shortening leads to neurodegeneration. Further, this also paves way for understanding various factors which can potentially affect any aspect of telomeres with emphasis on how telomere shortening influences Alzheimer's Disease [13]. The following are some interfering parameters age [14], diet [14], physical activity [15], stress [15], and the environment [15]. Through such considerations, it is hoped this review will give a holistic perspective on how predisposition and modifiability of lifestyle and environmental factors could potentially influence the risk and severity of Alzheimer's Disease via the dynamics of telomere shortening. In this way, it will systematically review the current literature of basic research, present specific biomarkers, and elucidate how those contributing factors influence

telomere length and Alzheimer's Disease. We hope that such an approach will provide some information regarding preventive and curative actions that could reduce the influence of the shortening of telomeres and slow down the development of Alzheimer's Disease. The current systematic review and meta-analysis is designed to expand upon existing knowledge regarding the complex relationships between telomere biology, biomarkers, and neurodegeneration with regards to its prognosis for the creation of a personalized medicine model for Alzheimer's Disease.

II. Telomere Biology and Function

A. Structure and Function of Telomeres

Telomers are unique structures containing nucleotide sequences in direct repetition series and protein molecules localized at the ends of the linear chromosomes. Telomeres have less DNA content and are composed of tandem repeats of the hexanucleotide sequence TTAGGG in humans.

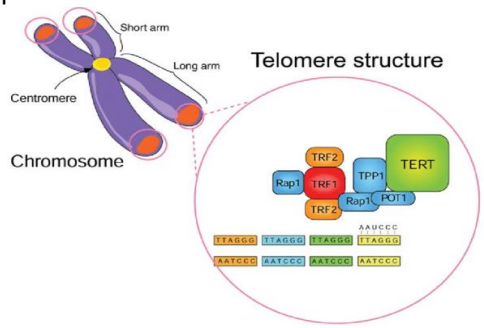

Fig2. Telomere Structure [16]

This cyclic repetition coupled with theprotein complex shelter in, helps avoid the non-homologous end joining pathways on the ends of the chromosomes, which if activated may cause aberrant DNA repair that leads to chromosomal instability, end to end fusions and other genomic rearrangements. In summary, the primary purpose of telomeres appears to be to protect the genetic continuity and integrity when cell division occurs. Each time cell divides, DNA polymerase can replicate only the immediately adjacent few nucleotide bases in linear DNA because of 'end replication problem However, these ends have non-coding telomere sequences [17], which provide such tolerance by shortening in every cell division. At a certain point when telomeres get shortened, they signal cells to stop further division or commit suicide in a process known as apoptosis and therefore can be thought of as a mitotic counter that controls the potential of cells to divide and avert cancerous division.

B. Telomere Maintenance and Cellular Aging

Much at the same time, preserving telomeres is imperative when it comes to the overall well-being and longevity of the cells. Telomerase is a task-specific enzyme highly conserved in RNA protein complexes, which are responsible for the synthesis of telomeric repeats to ensure the stability of chromosomes. Telomerase is composed of two main components namely the TElomerase Reverse Transcriptase (TERT) [18] and the TElomerase RNA Component (TERC) [19] which provides the template for the addition of telomeric repeats. In many somatic cells, telomerase function is low or non-existent, and even though the DNA replication process involves copying both strands of telomere DNA, the length of telomeres decreases over time with each cellular division. Therefore, it was discovered that in some cells like germ cells, stem cells, as well as any immune cells at its fully activated state, telomerase whichever is ever active to ensure the telomeres are not shortened to the point of compromise of the cell's functionality and longevity.

It is noteworthy that the exhaustion of telomeres are a characteristic feature of the process of aging of cells. Ideally, as telomeres shorten, they get to a length that produces signals of DNA damage leading to either cellular senescence or apoptosis. Cellular senescence is defined by the ability to enter a state of irreversible cell cycle arrest and to process alterations in gene expression, to phenotype of a cell that secretes inflammatory markers called the Senescence Associated Secretory Phenotype (SASP) [20]. Though senescence is beneficial as a cancer protective mechanism that ceased the divide and proliferative potential of damaged cells, the presence and survival of these senescent cells contribute to the tissue dysfunction and inflammation or reactive interventions,

inflammation being one of the characteristics of aging and aged related Diseases involving the neurodegenerative disorders like Alzheimer's Disease.

C. Telomere Shortening Mechanisms

It now appears that telomere shortening is potentially regulated by various endogenous and exogenous factors of proximal and distal gradients that either potentiate or attenuate the overall rate of telomere erosion. The most important mechanism of telomere shortening is the end replication problem and comes as a result of replication of DNA. It is meaning that every cycle of cell division were loss of 50200 base pairs of the telomeric DNA and thereby leading to telomere shortening. Thus, there are more than one issues that can be associated with the premature telomere shorting, among them is oxidative stress as well. Metabolic byproducts including ROS are capable of inducing oxidative damage to the telomeric DNA, which is sandwiched with guanine. If telomeric DNA is oxidized, then it becomes fragmented and this may lead to single strand breaks which make it difficult for the telomerase enzymes to accomplish their work of replication and lengthening of telomeres.

Another determinant of telomere shortening is inflammation; a condition that occurs when there is swollen or irritated tissue. Chronic inflammation is associated with production of such factors as proinflammatory cytokines and ROS [21], which could directly harm chromosomes, particularly their telomeric regions, and cause replicative stress. It is also important to note that inflammatory conditions can also increase the amount of matrix metalloproteinase and other enzymes that break down existent materials in the extracellular matrix which also encourages tissue remodelling and cell turnover and consequently individuals with inflammatory Diseases are likely to have telomeres that are significantly shorter than others without. Further, factors that include diet, exercise, stress, and pollutants affect telomere behaviour at some point in life. Subjects who adopted negative lifestyles such as having an unhealthy diet, a sedentary lifestyle, chronic psychological stress, and exposure to environmental toxins, have been noted to exhibit shortened telomeres, On the other hand, a healthy diet, exercise, stress management practices have been seen to buffer or even lengthen telomeres. Knowledge of telomeres' organization and implementing their roles, protection, and shortening strategies helps in deciphering the cellular aging process and age-associated pathologies. This is knowledge critical in understanding the link between telomere length and Alzheimer's Disease and to uncover the biomarkers as well as targets for cure that slow telomere shortening and its effects.

III. ALZHEIMER'S DiseaseOVERVIEW

Alzheimer's Disease: Understanding the Development of the Disease

Alzheimer's Disease (AD) may be considered as a chronic cerebral Disease that results in a progressive dementia of cognitive and memory faculties of the human brain, that culminates in the patient being unable to perform activities that are part of human daily life. Alzheimer Disease has extensive pathophysiology and the major mechanisms that lead to neuronal dysfunction and cell death are multiple and integrated networks.

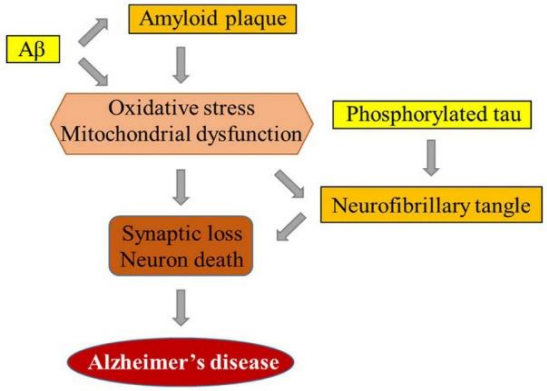

Fig3. Alzheimer's Disease Associations [22]

1.Amyloid Plaques: Another characteristic neuropathologic finding of Alzheimer's Disease biology is amyloid-beta (Aβ) protein deposit or plaque formation. Amyloid beta is a peptide generated through saccade of Amyloid Pressure Protein (APP) [23] by the wizard enzymes, beta secretase and gamma secretase. Alzheimer's Disease is characterized by a loss of homeostatic regulation in amyloid beta production and degradation, forming

insoluble plaques. These plaques interfere with cell-to-cell signalling, initiate inflammation and produces neuronal toxicity.

2. Neurofibrillary Tangles: Another pathological hall mark of Alzheimer's Disease [24] is the formation of neuro fibrillary tangles which is a form of tau protein that has been hyper phosphorylated. Tau protein is identified as a microtubule-associated protein that binds to microtubules in neurons to stabilize them. In Alzheimer's Disease, tau protein is overly phosphorylated, and this leads to its dissociation from the microtubules and the formation of insoluble tangles. This negates the integrity of microtubules, affects the axonal transportation and, in effect, triggers neuronal degeneration and death.

3. Synaptic Dysfunction: DWS are the some of the first pathological findings in AD and are closely associated with cognitive impairment data [25]. Amyloid beta oligomers are soluble species of amyloid beta and rank high in terms of sync toy to the synapses. They inhibit synaptic transmission, decrease rather than enhance the activity of synapses, and promote the loss of dendritic spines.

4. Inflammation: Neuroinflammation is proposed to be a continuous process in Alzheimer's Disease [26] and is considered to be essential component maladaptive mechanisms present in this dementia subtype. This happens with microglia which are the immune cells resident in the central nervous system and they become activated due to presence of amyloid beta plaques and tau tangles. Despite its function to safeguard the neurons, constant stimulation of microglia transforms it into a destructive element that produces inflammatory mediators such as cytokines, chemokines, and reactive oxygen species, which further contributes to neuronal pathology and Disease course.

5. Mitochondrial Dysfunction and Oxidative Stress: Mitochondrial dysfunction and increased oxidative stress are also implicated in Alzheimer's Disease [27]. Impaired mitochondrial function results in decreased energy production and increased production of reactive oxygen species, which can damage cellular components, including DNA, proteins, and lipids. Oxidative damage further accelerates the pathological processes in Alzheimer's Disease.

B. Genetic and Environmental Risk Factors

These are subsequent to genetic and environmental risk factors that have an impact on the development of the Disease.

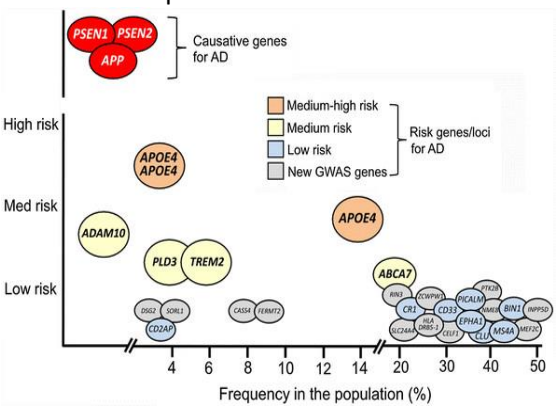

Fig4. Risk vs Frequency of Population [28]

1. Genetic Risk Factors:
   - APOE Gene: The other well-documented genetic susceptibility factor for developing IAD suggest that possession of the; APOlipoprotein E (APOE) ε4 type [29]. Genotype 1 and 2 were associated with early onset of Alzheimer's Disease and with higher risk of getting Alzheimer's Disease compared to the genotype 3 and 4 people who do not have APOE ε4 allele at all or those who have one copy of the APOE ε4 allele. The APOE is associated with lipid metabolism and amyloid beta transport and hence version ε4 is known to have comparatively less efficiency in transporting amyloid beta, leading to its aggregation
   - Familial Alzheimer's Disease: Onset before the age of 65 is rather uncommon, and the disorder is attributed to genetic factors with APP, presenilin 1 (PSEN1) [29] and presenilin 2 (PSEN2) mainly implicated in the development of the Disease. These mutations result in the enhanced synthesis or changed metabolic course of amyloid beta that engenders plaque formation.
2. Environmental Risk Factors:

- Age: The top characteristics associated with the possibility of Alzheimer's Disease include age, with the elderly being at a higher risk of developing the Disease. The likelihood of individuals contracting Alzheimer's Disease approximately doubles itself every five years after the age of 65.
- Lifestyle Factors: Lifestyle factors that include food choice, physical activity, and level of cognitive stimulation should be considered. Sedentary lifestyle coupled with diet enriched in saturated fats and sugars and lack of mentally challenging activities promote MS risk while Mediterranean diet, physical activity and mental stimulation discourage it.
- Cardiovascular Health: Several Diseases that are able to affect the blood vessels, including high blood pressure, diabetes, obesity and high cholesterol also increase the risks of developing Alzheimer's Disease. These conditions for instance may cause vascular damage, decreased perfusion of the brain as well as accumulation of amyloid beta.
- Education and Socioeconomic Status: There is growing evidence to show that education, income, occupation, and lifestyle factors influence the risks of developing Alzheimer's Disease which may be mediated through cognitive reserve.

Understanding the pathophysiology of Alzheimer's Disease and the genetic and environmental risk factors involved is essential for developing strategies to prevent, diagnose, and treat this debilitating condition. This knowledge forms the foundation for exploring the relationship between telomere length, biomarkers, and the multifactorial nature of Alzheimer's Disease.

IV. RELATIONSHIP BETWEEN TELOMERE LENGTH AND ALZHEIMER'S Disease

A. Evidence Linking Telomere Length to Alzheimer's

Numerous studies have investigated the relationship between telomere length and Alzheimer's Disease, providing evidence that telomere shortening may be associated with the onset and progression of the Disease.

Table1: Various Studies exploring relation between Telomere length and Alzheimer's Disease

Study Type	Key Findings	Example Study
Observational Studies	Individuals with Alzheimer's Disease tend to have shorter telomeres compared to age-matched healthy controls.	Found significantly shorter telomeres in the leukocytes of Alzheimer's patients [30].
Longitudinal Studies	Shorter telomere length is associated with an increased risk of developing Alzheimer's Disease over time.	Showed that individuals with shorter telomeres were more likely to develop dementia, including Alzheimer's, over a follow-up period [31].
Meta-Analyses	Significant association between shorter telomeres and the risk of Alzheimer's Disease, suggesting that telomere attrition may play a role in the Disease's development.	Concluded a significant association between shorter telomeres and the risk of Alzheimer's Disease [32].
Post-Mortem Analyses	Shorter telomeres observed in neurons and glial cells of Alzheimer's patients compared to non-demented controls, indicating telomere shortening may contribute to neuronal dysfunction and loss.	Post-mortem studies: Found shorter telomeres in brain tissue from Alzheimer's patients [33].

B. Mechanisms of Telomere Shortening in Alzheimer's

The mechanisms underlying telomere shortening in Alzheimer's Disease are multifaceted, involving both genetic and environmental factors that exacerbate the natural aging process.

Table2: Mechanisms of Telomere Shortening in Alzheimer's

Factor	Description	Key Points
Oxidative Stress [34]	Several studies have linked oxidative stress with telomere shortening and as mentioned earlier, the brains cells are being attacked by oxidative stress since the brain is metabolically active and its environment is lipid rich. Reactive oxygen and nitrogen species produced during metabolism affect telomeric DNA negatively, thus its fast degradation. It intensifies the formation of these aggregates in Alzheimer's through increased oxidative stress.	High susceptibility of the brain to oxidative damage, ROS damages telomeric DNA, Amyloid beta accumulation and mitochondrial dysfunction increase oxidative stress
Inflammation [35]	The evidence based on animal and human studies points to the fact that longer-spanning neuroinflammation, driven by microglial and astrocyte activation, generates ROS and pro-inflammatory cytokines and leads to telomeric DNA damage and reduction in telomerase regeneration capacity. Chronic inflammation has now been found to cause shortening of telomeres which in turn leads to neurodegeneration and dementia.	Proinflammatory cytokines and ROS damage telomeres, Persistent inflammation in Alzheimer's, Contributes to neurodegeneration
Amyloid-Beta Toxicity [36]	Amyloid-beta plaques are toxic to the neurons and the plaques contribute to telomere shortening by directly attacking the DNA resulting in structural damage including telomeres and by activation of cellular stress pathways which leads to neuronal senescence. The existing toxic effects exerted by amyloid beta on both neurons and glial cells exacerbate telomere shortening, thereby enhancing the degradation of Alzheimer's ailment.	Direct DNA damage by amyloid beta, Activation of stress response pathways, accelerates neuronal and glial telomere shortening
Tau Pathology [37]	Post translationally modified tau protein, in particular the hyperphosphorylated species that aggregates into NFs, has deleterious effects on telomeres by inducing oxidative stress and perturbing cellular	Increased oxidative stress, Disruption of cellular homeostasis, Impairment of telomere maintenance

	stability. Under the influence of Tau, the negative effects are mitigated on the neuronal cells; therefore, telomere maintenance is compromised and enhanced attrition witnessed.	
Lifestyle Factors [38]	There is clear evidence that aspects of people's daily lives, including diet, inactivity, and stress, alter telomere length. Unhealthy eating habits raise the levels of oxidants and inflammation that meditate the shrinkage of telomeres. On the other hand, regular dieting and exercising prevent telomeres from shortening and thus decrease Alzheimer's Disease chance.	Poor diet, inactivity, and stress increase telomere shortening, Healthy choices mitigate telomere attrition
Genetic Factors [39]	Pathologic mutations associated with Alzheimer's Disease or alterations in enzymes regulating telomerase activity or oxidative stress and inflammation have been shown to determine telomere shorten age rates directly. These genetic factors may lead to the deterioration of the protective caps and worsening the Alzheimer's risk in the affected individuals.	Alzheimer's associated gene mutations, Variants reducing telomerase activity, Increased susceptibility to oxidative stress and inflammation

It is therefore important to review the research on telomere length and Alzheimer's Disease, as wells as the mechanisms of telomere shortening with a view of understanding the biomarkers that may be generated out of the investigators' research. When it comes to understanding the pathophysiological mechanisms that underpin the telomere shortening, these cellular aging markers could definitely need interventions that prevents Alzheimer's Disease progression and enhances the quality of life of patients with this illness.

V. SPECIFIC BIOMARKERS

A. Inflammatory Markers

Alzheimer's Disease is also characterized by inflammation, and multiple inflammation parameters correlate with both conditions; shortened telomeres.

Table3. Inflammatory Markers

Inflammatory Marker	Description	Key Points
C-Reactive Protein (CRP) [40]	CRP is an acute phase protein with orchestrating function that is synthesized and released to the circulation predominantly from the liver upon tissue inflammation. Thus, high levels of CRP in Alzheimer's patients suggest increased requirement for defence and are linked to short telomeres. We have provided evidence that raised levels of CRP are associated with declining	Produced by liver in response to inflammation, Elevated levels in Alzheimer's patients, indicates systemic inflammation, Associated with shorter telomeres and increased Alzheimer's risk

	intelligence and greater propensity for Alzheimer's.	
Interleukin-6 (IL-6) [41]	IL-6 is a pro-inflammatory cytokine associated with Alzheimer's Disease since it has been detected in brains and plasma of AD patients. Evidence indicates that increased IL-6 levels are associated with shortening of TEL which further results in neuro-inflammation and neuronal degeneration. IL-6 induces the synthesis of other cytokines that cause inflammation, which phenomena is observed in Alzheimer's Disease.	Elevated in Alzheimer's brains and plasma, correlates with shorter telomeres, contributes to neuroinflammation, Promotes expression of inflammatory mediators in Alzheimer's
Tumour Necrosis Factor-Alpha (TNF-α) [42]	It is known that TNF-α is involved in inflammation process and has been identified in Alzheimer's Disease. TNF-α is pro-inflammatory and influences the gain of membrane protein or loss of synaptic proteins, reduction in the length of telomeres, neuronal cell death, and activation of microglia cells. TNF-α is centrally implicated to participate in the inflammatory sequence that is characteristic of Alzheimer's Disease.	Implicated in Alzheimer's pathology, associated with shorter telomeres, contributes to synaptic dysfunction and neuronal apoptosis, Activates microglia in Alzheimer's inflammatory response
Interleukin-1 Beta (IL-1β) [43]	IL-1β is an inflammatory cytokine related to Alzheimer's Disease, which has a higher concentration in the brain of the AD patient. It is associated with shortened telomeres and can cause amyloid-beta formation and tau proteins to become abnormally phosphorylated and directed at Alzheimer's Disease development. Thus, central and pivotal place in the above-mentioned inflammatory processes in Alzheimer's Disease belongs to IL-1β.	Found at elevated levels in Alzheimer's brains, linked to shorter telomeres, inducesamyloid beta and tau pathology, Contributes to Alzheimer's inflammatory processes

B. Oxidative Stress Indicators

Alzheimer's Disease, a progressive neurodegenerative disease is associated with oxidative stress, which is known to have causal influence on telomere shortening. Biomarkers of oxidative stress are valuable for understanding the issue at the cellular and molecular levels as well as the progression in aging.

Table4: **Oxidative Stress Marker**

Oxidative Stress Marker	Description	Key Points
Malondialdehyde (MDA) [44]	MDA constitutes as a product of lipid peroxidation, which indicates oxidative injury to cells and membranes. Analysis of plasma and brain samples from Alzheimer's patients revealed that increased MDA levels are accompanied by shorter telomeres. It means that MDA value reflects the state of oxidative stress and the damage done to cells' structures.	Byproduct of lipid peroxidation, elevated in Alzheimer's plasma and brains, associated with shorter telomeres, Reflects oxidative damage to cellular membranes
8-Hydroxy-2'-deoxyguanosine (8-OHdG) [45]	8-OHdG which is an oxidative DNA damage marker was observed to be up regulated in the Alzheimer's Disease brain. The species with increased 8-OHdG levels demonstrate a shortened telomeres lifespan that signifies that oxidative modification of DNA influences TE and neuronal degeneration in Alzheimer'sDisease.	Marker of oxidative DNA damage, elevated in Alzheimer's brains, correlates with shorter telomeres, Indicates DNA damage impact on telomere attrition
F2-Isoprostanes [46]	F2-isoprostanes are isomers generated from arachidonic acid during lipid peroxidation and are useful biological markers for oxidative stress. Higher amounts of the molecule in the CSF and plasma of Alzheimer's patients correspond to shorter telomere length. They suggest lipid peroxidation in the Alzheimer brains affecting neuronal structures and their functions.	Stable markers of lipid peroxidation, elevated in Alzheimer's CSF and plasma, associated with shorter telomeres, Impacts neuronal integrity and function
Superoxide Dismutase (SOD) [47]	SOD is an antioxidant enzyme which catalyses and dismutase's superoxide radicals. Patients diagnosed with Alzheimer's Disease showed lower SOD activity levels along with significantly smaller telomeres, potentially suggesting compromised antioxidant protection and enhanced oxidization. This they say leads to cellular damages, as well as increases the process of telomere shortening in the Disease.	Antioxidant enzyme, Reduced activity in Alzheimer's, Associated with shorter telomeres, Impaired antioxidant defences in Disease

C. Genetic Variants

I agree with the above facts that telomere maintenance and Alzheimer's Disease risk involve genetics. It is also important to note that there are multiple genetic variants associated with these changes.

Table5: Genetic Factors

Genetic Factor	Description	Key Points

APOE ε4 [48]	The research also revealed that the APOE ε4 allele is significantly associated with a person's susceptibility to Alzheimer's Disease. People with the APOE ε4 gene are sick earlier and have shorter telomeres. APOE ε4 has deleterious effects such as altering amyloid-beta formation, lipid homeostasis, and inflammation level, which leads to both telomere shortening and neuronal loss.	Genetic risk factor for Alzheimer's, Shorter telomeres in carriers, Influences amyloid beta deposition and inflammation, Increased Disease risk
TERT and TERC Variants [49]	Rare genetic components attributed with regards to telomere and ageing are present in the TERT and TERC genes. Reduced telomerase activity leads to the accelerated shortening of telomeres as a result of point mutations. It means these variants can influence the progression of Alzheimer's since the Disease could alter cellular aging patterns and telomere modalities.	Influence telomere length and aging, Mutations reduce telomerase activity, Impact susceptibility to Alzheimer's through cellular aging
Presenilin (PSEN1 and PSEN2) Mutations [50]	Mutations in PSEN1 and PSEN2 genes are linked to early-onset familial Alzheimer's Disease. They alter amyloid precursor protein processing, leading to increased amyloid-beta production. PSEN1 and PSEN2 mutations also affect cellular stress responses and may influence telomere maintenance mechanisms.	Linked to early onset familial Alzheimer's, Increase amyloid beta production, Impact cellular stress responses and telomere maintenance
ATM and ATR Variants [51]	ATM and ATR genes are involved in DNA damage response and telomere maintenance. Variants impair DNA repair mechanisms, accelerating telomere shortening. Dysfunctional ATM and ATR pathways are implicated in neurodegenerative Diseases, including Alzheimer's.	Involved in DNA damage response and telomere maintenance, Variants impair DNA repair mechanisms, Implicated in neurodegenerative Diseases

D. Other Relevant Biomarkers

In addition to inflammatory markers, oxidative stress indicators, and genetic variants, other biomarkers provide insights into the relationship between telomere length and Alzheimer's Disease.

Table6: Biochemical Factors

Biochemical Factor	Description	Key Points
Homocysteine[52]	Elevated levels of homocysteine are associated with increased Alzheimer's Disease risk and shorter telomeres. Homocysteine promotes oxidative stress, inflammation, and endothelial dysfunction, contributing to telomere attrition and	Associated with increased Alzheimer's risk, promotes oxidative stress and inflammation, Contributes to telomere attrition and neurodegeneration

	neurodegeneration.	
Brain-Derived Neurotrophic Factor (BDNF)[53]	BDNF is critical for neuronal survival, plasticity, and cognitive function. Reduced BDNF levels in Alzheimer's patients correlate with shorter telomeres. BDNF deficiency contributes to synaptic loss and cognitive decline in Alzheimer's Disease.	Essential for neuronal survival and plasticity, Reduced levels in Alzheimer's patients, Correlates with shorter telomeres
Nerve Growth Factor (NGF) [54]	It also promotes the survival and development of neurons relevant in the transmission of cholinergic signals. Currently NGF levels are down in Alzheimer's patients and this phenomenon was seen to be linked to increased telomere shortening. Neuronal growth factor, through a deficiency process will cause neuronal functions and degeneration leading to Alzheimer's Disease.	Important for cholinergic neuron maintenance, Decreased levels in Alzheimer's patients, Correlates with shorter telomeres
Insulin-Like Growth Factor 1 (IGF-1) [55]	It is involved in many different activities of the body which include growth, development and neuroprotection as will be described in the following sub-paragraphs. IGF-1 has been associated with a reduced risk of Alzheimer's Disease and longer telomeres, suggesting that low IGF-1 levels are the major risk underlying both conditions. Thus, IGF-1 deficiency affects the neurons developing the Disease and participating in Alzheimer's progression.	Regulates growth, development, and neuroprotection, linked to Alzheimer's Disease and shorter telomeres, Deficiency impairs neuronal survival and cognitive function

This allows researchers to better understand the signals that connect telomere length to Alzheimer's and, therefore, to develop better strategies for prevention and treatment of this severe condition. It can also aid in the creation of specific diagnostic methods and treatment to address the aggregation of telomere shortening and Alzheimer's Disease.

VI. CONTRIBUTING FACTORS

Table7: Contributing Factors

Factor	Influences on Telomere Length	Impact on Alzheimer's Disease
Age	Cellular aging causes progressive telomere shortening	Increased risk of Alzheimer's due to neurodegeneration and oxidative stress [56]
	Increased oxidative stress and inflammation accelerate telomere attrition	
	Shortened telomeres trigger cellular senescence or apoptosis	
Diet and Nutrition	Antioxidants protect telomeres from oxidative damage	Diets rich in antioxidants, omega3 fatty acids, and Mediterranean diet linked to lower Alzheimer's risk [57]

	Omega3 fatty acids reduce inflammation and support brain health	Caloric restriction and intermittent fasting enhance DNA repair and reduce metabolic stress [58]
	Mediterranean diet provides balanced nutrients supporting cellular health	
Physical Activity	Regular exercise linked to longer telomeres due to reduced oxidative stress and inflammation	Physical activity supports cognitive function, brain health, and reduces Alzheimer's risk [59]
	Exercise enhances neurogenesis, synaptic plasticity, and cerebral blood flow	
Stress and Psychological Factors	Chronic stress accelerates telomere shortening through elevated cortisol levels and oxidative stress	Chronic stress and mental health disorders increase risk of cognitive decline and Alzheimer's Disease [60]
	Effective stress management mitigates negative effects on telomeres	Stress management practices improve psychological resilience and overall wellbeing [61]
Environmental Exposures	Air pollution and heavy metals shorten telomeres and induce oxidative stress and inflammation	Pollutants and toxins linked to increased risk of neurodegenerative Diseases [62]
	Lifestyle factors like smoking, excessive alcohol, and poor sleep quality accelerate telomere shortening	Poor lifestyle choices increase risk of Alzheimer's through metabolic dysfunction and neurotoxicity [63]

VII. IMPACT OF CONTRIBUTING FACTORS ON TELOMERE LENGTH AND ALZHEIMER'S

Table8: Contributing Factors on Telomere Length and Alzheimer's

Factor	Influences on Telomere Dynamics	Impact on Alzheimer's Disease
A. Age and Telomere Dynamics [64]		
1. Telomere Attrition with Aging	Telomeres shorten progressively with each cell division; accelerated with age	Leads to neuronal loss, reduced regenerative capacity, and tissue degeneration in the brain
2. Oxidative Stress and Inflammation	Increased oxidative stress and chronic inflammation accelerate telomere shortening	Promotes cellular aging and increases susceptibility to neurodegenerative Diseases like Alzheimer's
3. Mitochondrial Dysfunction	Age related mitochondrial dysfunction increases ROS production, damaging telomeric DNA	Contributes significantly to telomere shortening and neurodegenerative processes in Alzheimer's
4. Genetic and Epigenetic Changes	Genetic and epigenetic alterations impair telomere maintenance mechanisms	Accelerated telomere shortening due to impaired telomerase function and increased Alzheimer's risk
B. Diet and Nutrition [65]		
1. Antioxidant-Rich Diets	Protect telomeres from oxidative damage by neutralizing ROS	Associated with longer telomeres and a lower risk of Alzheimer's
2. Mediterranean Diet	Provides balanced antioxidants, anti-inflammatory nutrients, and	Linked to longer telomeres and reduced risk of Alzheimer's

	healthy fats	
3. Omega-3 Fatty Acids	Anti-inflammatory properties beneficial for telomere length and brain health	Associated with longer telomeres and reduced risk of cognitive decline and Alzheimer's
4. Caloric Restriction and Fasting	Reduces metabolic stress, oxidative damage, and enhances DNA repair mechanisms	Contributes to longer telomeres and improved brain health
C. Physical Activity [66]		
1. Impact on Telomere Length	Regular physical activity linked to longer telomeres through reduced oxidative stress and inflammation	Supports cognitive function and reduces Alzheimer's risk
2. Cognitive Benefits	Promotes neurogenesis, synaptic plasticity, and cerebral blood flow	Enhances brain derived neurotrophic factor (BDNF) crucial for neuronal survival and synaptic plasticity
3. Reduction of Alzheimer's Risk	Improves cardiovascular health, reduces risk of diabetes and obesity, enhancing brain function	Associated with a lower risk of cognitive decline and Alzheimer's Disease
D. Stress Management [67]		
1. Psychological Stress and Telomere Shortening	Chronic stress accelerates telomere shortening via elevated cortisol, oxidative stress, and inflammation	Increases risk of cognitive decline and Alzheimer's
2. Mental Health and Telomere Length	Depression, anxiety, and mental health disorders linked to shorter telomeres	Contribute to proinflammatory state, oxidative damage, and neurodegeneration
3. Effective Stress Management	Techniques like mindfulness meditation, yoga, and CBT reduce cortisol levels and enhance resilience	Mitigates negative effects on telomeres and brain health, promoting overall wellbeing
E. Environmental Influences [68]		
1. Air Pollution	Exposure to fine particulate matter (PM2.5) associated with shorter telomeres and oxidative stress	Increases risk of neurodegenerative Diseases and cognitive decline
2. Heavy Metals	Lead, mercury, and cadmium exposure linked to telomere shortening and neurotoxicity	Generates ROS, disrupts cellular processes, and increases Alzheimer's risk
3. Lifestyle Factors	Smoking, excessive alcohol consumption, and poor sleep quality accelerate telomere shortening	Contributes to oxidative stress, inflammation, metabolic dysfunction, and increased Alzheimer's risk

VIII. DIAGNOSTIC &THERAPEUTIC IMPLICATIONS

A. Biomarker-Based Diagnostics for Alzheimer's

The identification and utilization of biomarkers related to telomere length and Alzheimer's Disease offer promising avenues for early diagnosis and improved Disease monitoring.

Table9: Biomarkers and Relevance to Alzheimer's and Telomere Length

Biomarker	Description	Relevance to Alzheimer's and Telomere Length
Telomere Length [69]	One of the peripheral tissues that have been linked with Alzheimer's Disease risk, severity and duration is terminal profiling specifically on telomere length. based on current research, it is believed that short telomeres are an indication of the potential for Diseases. Various structural and functional measurements include quantitative PCR, fluorescent in situ hybridization, and Southern blotting; these help in studying biological aging and pathological Disease states.	Biomarker for Alzheimer's risk, shorter telomeres linked to Disease severity, Reflects biological aging
Inflammatory Markers [70]	C-reactive protein, IL-6, and TNF-α, the inflammatory biomarkers described earlier, enhance tau protein phosphorylation and, at the same time, promote telomere shortening – factors which are accountable for Alzheimer's Disease. High levels are useful in diagnosing the Disease early and even in the monitoring of the Disease.	Systemic inflammation links to telomere shortening and Alzheimer's, CRP, IL6, TNFα markers of inflammation
Oxidative Stress Indicators [71]	We are referring to the markers as: MDA, 8-OHdG and F2-isoprostanes which are indicators of oxidative damage which contributes to the shortening of telomeres and also to the pathogenesis of Alzheimer's Disease. High levels are involved in the initiation of further cell destruction and its overall aging.	Indicate oxidative damage and aging, Associated with telomere attrition and Alzheimer's Disease progression
Genetic Biomarkers [72]	Genetic variants such as APOE ε4, TERT, and TERC mutations influence Alzheimer's risk and affect telomere maintenance. These biomarkers identify individuals at high risk for targeted preventive strategies.	APOE ε4 increases Alzheimer's risk and affects telomere length, TERT and TERC mutations impact telomere maintenance, Genetic predisposition for targeted interventions

B. Potential Therapeutic Interventions Targeting Telomeres and Related Pathways

Targeting telomere biology and associated pathways presents a novel approach to developing therapeutic interventions for Alzheimer's Disease.

Table10: Impact on Telomere Biology and Alzheimer's Disease Risk

Intervention	Description	Impact on Telomere Biology and Alzheimer's Disease Risk

Telomerase Activation	Compounds like TA-65 enhance telomerase activity [73], potentially slowing telomere shortening. Preclinical studies suggest increased telomerase activity and longer telomeres may delay Alzheimer's onset and progression.	Enhances telomerase activity and telomere length, May delay Alzheimer's onset and progression.
Antioxidant Therapy	Antioxidants such as vitamins C and E, coenzyme Q10, and polyphenols reduce oxidative stress, protecting telomeres from damage [74]. This can potentially preserve telomere length and mitigate Alzheimer's risk.	Reduces oxidative stress and protects telomeres, preserves telomere length and potentially lowers Alzheimer's risk [74]
Anti-inflammatory Agents	Anti-inflammatory drugs like NSAIDs and cytokine inhibitors (e.g., IL-6 inhibitors) reduce chronic inflammation, which helps maintain telomere integrity and prevent neurodegeneration [75]. Lowering inflammatory markers can protect against telomere shortening.	Reduces chronic inflammation and inflammatory markers, maintains telomere integrity and potentially prevents neurodegeneration.
Lifestyle Interventions	Lifestyle modifications including balanced diet, regular physical activity, stress management, and avoidance of environmental toxins positively influence telomere biology [76]. These interventions enhance cellular health and cognitive function, potentially reducing Alzheimer's risk.	Improves telomere biology through healthy lifestyle choices, Reduces Alzheimer's risk by enhancing cellular health and cognitive function.

C. Personalized Medicine Approaches

Personalized medicine involves tailoring preventive and therapeutic strategies to an individual's genetic, biomarker, and lifestyle profile.

Table11: Application to Alzheimer's Disease

Approach	Description	Application to Alzheimer's Disease
Genetic Profiling [77]	Before, diagnostic tests involve genetics, where possible APOE ε4 carriers may wish to know if they are at increased risk of getting Alzheimer's Disease, and diagnostic tests for TERT and TERC mutations that have been associated with the Disease. Such actions as making lifestyle changes and early use of therapies are estimated to be part of prevention programs customized depending on one's genetic risks.	Identifies individuals at higher risk for Alzheimer's, Guides personalized prevention strategies
Biomarker Monitoring [78]	The measurement of length, activity, inflammatory, and oxidative measurements for telomere, both in cross-sectional and longitudinal research can inform individualized Disease course and therapeutic response. By following this system, therapeutic solutions can be changed depending on the analyses of biomarkers.	Tracks Disease progression and treatment response, Allows for personalized adjustments in therapeutic strategies
Tailored Interventions [79]	This kind of approaches focuses on unique mechanisms such as cellular aging, oxidative damage, inflammation depending on the	Targets underlying mechanisms of Alzheimer's pathology, optimizes

	biochemical markers. For instance, antioxidant treatment for scenarios with high oxidative stress or anti-inflammatory drugs for long-term inflammation.	treatment efficacy based on individual biological profiles
Patient-Centred Care [80]	Incorporates patient preferences and lifestyle factors into treatment plans to enhance adherence and efficacy. Engages patients in decision-making and provides tailored recommendations aligned with their unique profiles.	Improves treatment adherence and quality of life, Considers individual preferences and lifestyle factors in treatment planning

Through the advancements in biomarker-based analysis and diagnostics as well as individualized medicine and targeted therapies, the early diagnosis and management of Alzheimer's Disease can be improved. The delineated plan below cascades to address shorter telomeres and resultant consequences that affect healthy mind, body and aging.

IX. CONCLUSION

A. Summary of Key Findings

Hence, this research will aim at identifying an empirical relationship between telomere length and Alzheimer's Disease and other biomarkers associated with the ailments as well as other factors such as age, diet, physical activity or inactivity, stress levels, and the environment among patients suffering from the condition.

- ✓ Telomere Biology and Function: It has a role in protecting the terminal ends of the chromosome and guiding the telomerase and other associated proteins with the chromosome. Furthermore, telomers shorten naturally with aging; one can identify the fact that telomere shortening is connected with cellular aging and senescence, which are also the factors that provoke Alzheimer's Disease.
- ✓ Alzheimer's Disease Pathophysiology: Alzheimer's Disease is clinical detected by evaluating the presence of amyloid-beta plaques in the brain tissues, tau tangles and inflammatory elements. It has considerable genetic and environmental predispositions: this research pointed out that age and lifestyle are determinants for its formation.
- ✓ Relationship Between Telomere Length and Alzheimer's Disease: Shorter telomerases are associated with the likelihood of Alzheimer's, with telomere erosion inclusive of those with less telomeres. The elements which have been seen to contribute towards the shortening of the telomeres and neurodegeneration include oxidative stress, inflammation, and damage the of mitochondria.
- ✓ Specific Biomarkers: From these results, it is deduced that inflammatory markers, oxidative stress markers, genetic variations, and other biomarkers play a crucial role in relating telomere length and Alzheimer's Disease. These products can also be used as diagnostic indicators to diagnose Diseases in the early stages and assess Disease progression.
- ✓ Contributing Factors: Lifestyle changes including diet, exercise, stress, and exposure to certain agents have an effect on telomere shortening and the onset of Alzheimer's Disease. Knowledge of such factors can enable one to design appropriate therapeutic approaches that can prevent or slow down the process of losing telomeres and, in consequence, the emergence of Alzheimer's Disease.
- ✓ Diagnostic and Therapeutic Implications: Diagnostic tests using biomarkers and possible treatments seemingly linking to telomeres and pathways associated with Alzheimer's are other early detection and intervention tools. Additionally, the results of this research also show that

incorporation of personalized medicine in implementing these interventions can even improve its outcomes because the chance of relapses and deaths will be focused based on the risk level of each participant.

B. Future Research Directions

Directions for future research on Alzheimer's Disease and telomere length will be aimed at the following perspectives, where several important aspects should be accentuated to enhance the number of outcomes obtained and the possibilities of prevention and treatment. First of all, longitudinal research is essential in assessing fluctuations in telomere length in the concerned patients with the prospective of developing Alzheimer's Disease. Thus, the specified approach will be helpful for obtaining important information on the correlation of changes in the telomere length and the occurrence of Alzheimer's Disease during different periods of time. Secondly, fewer mechanistic investigations that aim to understand the molecular processes involved in the decline of telomeres as well as its contribution to Alzheimer's Disease are required. It would be possible to find new targets for therapy in general given how little is known about how oxidative stress, inflammation, and other factors affect telomere shortening and neurodegeneration. Thirdly, the justification of using telomere length and biomarkers associated with it has to be proven a suitable approach to diagnose Alzheimer's Diseases. Large-scale investigations should further define the biomarkers of fertility and their variability, which could be used for routine diagnostic examinations.

However, the belief or certainty about these facts has not translated into proper clinical trials, particularly, randomized controlled trials to test interventions relevant for telomere maintenance including telomerase activators, antioxidant and anti-inflammatory agents. Such trials should seek to establish effectiveness of these interventions through the degree of change in telomere length as well as cognitive performance and stager of Alzheimer's Disease. Moreover, it is critical to continue to develop strategies that will adjust, at the individual level, diagnosis, prevention, and treatment based on genetic and biomarker and lifestyle characteristics. Research should further direct its efforts towards investigating response heterogeneity to intervention efforts in the hope of enhancing the intervention approaches, and consequently the patients' wellbeing.

Finally, the study of the impact of inclusive LMCs, which accommodate dieting, exercising, stress control, and other environmental changes, on the length of telomeres and Alzheimer's risk can help in giving healthier guidelines to decrease the Disease occurrence.

In this context, these research directions will help the reviews progress telomere biology research, progress diagnostic tools and therapeutic strategies for AD, and improve the prevention and treatment of the Disease.

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