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Review Article

Aging and Age-Induced Cardiovascular Disease: Molecular Mechanism and Biomarkers for its Early Prognosis

Hemshankar Laugi[1]* and Hom Nath Chalise[2,3]

[1]*Bal Kalyan Vidya Mandir, Biratnagar, Nepal*

[2]*Faculty Member, Department of Public Health, Nobel College Affiliated to Pokhara University, Sinamangal, Kathmandu, Nepal*

[3]*Vice President, Population Association of Nepal, Kathmandu Nepal*

***Corresponding Author:** Hemshankar Laugi, Bal Kalyan Vidya Mandir, Biratnagar, Nepal.

Received: July 05, 2021; **Published:** July 31, 2021

Abstract

The world is witnessing a rapid demographic shift towards an aging population. Biologically, aging is gradual decline in the ability of a cell to perform its own function followed by cellular senescence. Aging-induced diseases are the leading causes of deaths which have plagued humankind. The purpose of this article is to discuss how molecular mechanism using biomarkers may be useful for the controlling of Cardiovascular diseases (CVD).

With age, imbalance in energy demand and supply occurs. This decreases cellular ability to repair and replace damaged cells. Telomere shortening, increase in oxidative stress, klotho deficiency, and epigenetic factors trigger cellular senescence with age. These factors disturb the original state of the body and hence, body becomes susceptible to a number of human diseases including CVD, cancer, diabetes, and Alzheimer's disease. A number of functional and structural changes occurring in the heart with age induce reduction in stress tolerance causing decreased cardiac function.

The use of accurate, reliable, cheaper, and sensitive biomarkers greatly helps in the early prognosis of CVD, which prevents further complications and reduces death rate due to CVD.

Keywords: *Cellular Aging; Apoptosis; Cardiovascular Disease; CVD Biomarkers; Senescence*

Abbreviations

TERT: Telomerase Reverse Transcriptase; ROS: Reactive Oxygen Species; DNMT: DNA Methyltransferases; CVD: Cardiovascular Disease; RONS: Reactive Oxygen and Nitrogen Species; LTL: Leukocyte Telomere Length; CNP: Cardiac Natriuretic Peptides; NT-proBNP: N-Terminal Pro-B-Type Natriuretic Peptide; CKD: Chronic Kidney Disease; CRP: C-Reactive Protein; CAV: Cardiac Allograft Vasculopathy

Introduction and Background

Aging is a lifelong process of growing up and growing old. It begins at conception and ends with death. Today, people are living longer than ever before due to advances in education, technology, medicine, food distribution, and sanitary conditions [1]. In almost every country, the proportion of people aged over 60 years is growing faster than any other age group, as a result of both longer life expectancy and

declining fertility rates. The size of older population 60 years and above is expected to grow to two billion by 2050 [2]. Therefore, there is much urgency in understanding the societal, molecular, and cellular hallmarks of aging and their co-relation with the onset of various human diseases.

Rapid population aging is a global phenomenon, regardless of a nation's level of development [1]. Today, people are living longer than ever before due to advances in education, technology, medicine, food distribution, and public health [3]. With increase in age, objectively measured health and functional status decline, physical and cognitive capacities decrease, and the number of chronic diseases and the extent of disability in performing daily activities increases [4]. Aging is linked to the gradual loss of physiological integrity and the increased rate of disease emergence such as cardiovascular disease (CVD), cancer, diabetes, hypertension, sight loss, memory loss, etc. Damage to cells, tissues, and organs increases with aging and leads to increased risk of mortality. A large number of factors could be involved in aging [5-7] and the molecular information on the aging hallmark has just begun to be unveiled.

Biologically, aging is a spontaneous phenomenon that occurs automatically after reproductive maturity in all living organisms followed by decrease in the cellular ability to perform its functions. During this process, normal molecular mechanisms going inside the cell get disturbed which further affects repair capacities of cells. With age, accumulation of damaged cellular macromolecules and processes increase triggering pathogenesis of human diseases [8]. Aging changes occur in all of the body's cells, tissues, and organs. These changes affect the functioning of all body systems. Living tissue is made up of cells. Cells are the basic, structural, and functional unit of tissues. Aging causes changes in every types of cells in different parts of human body. This disturbs the normal functionality of all human body systems resulting in abnormal functions. The affected cells become larger and are less able to divide and multiply. Among other changes, deposition of fatty substances inside the cell also increases. Many cells even begin to function abnormally [1]. So, aging is considered as one of the major risk factors for many human diseases such as cardiovascular diseases, cancer, arthritis, cataracts, type-2 diabetes, osteoporosis, hypertension and Alzheimer's diseases [9]. With the growing elderly population, patients with the afore-mentioned aging-induced diseases are also growing which have plagued humankind.

The purpose of this article is to discuss molecular mechanism of cellular aging and major biomarkers which can be used in the early prognosis of CVD.

Biomarker

In 1988, the National Institute of Health Biomarkers Definition working Groups defined biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological, pathogenic, or pharmacologic responses to a therapeutic intervention [10]. An effective biomarker must be accurate, reliable, and should have therapeutic impact with early intervention [37]. An ideal cardiac biomarker has high sensitivity, specificity, and ensures rapid clearance from the blood and body fluids [11]. Biomarkers can detect the progression of CVD which helps in the early prognosis of the disease. This greatly reduces complications in the disease and hence, controls death rate due to the disease.

However, the current understanding of the use of biomarkers in the prognosis of CVD and their relation with the process of aging is still unclear, though several attempts have been made to solve this. Moreover, the current knowledge on whether cystatin C is a direct marker of CHD or just a marker of renal dysfunction is still insufficient enough to use it in the control of CVD. The better understanding of the process of aging and CVD provides novel insights into the reduction of deaths due to CVD. This paper tries to discuss the cellular changes with age leading to progression of CVD and using biomarkers for its early prognosis.

Molecular mechanism of cellular aging

Cellular aging starts with the loss in the ability to repair damage due to cellular senescence. Here, cellular damage means decrease in the level of telomerase, alteration in gene expression, increase in oxidative stress, etc. According to Kirkwood, the main cause of cellular

aging is DNA damage over time [13]. DNA is responsible to carry out every physiological activities in human body and hence its damage leads to the cellular defects and tissue dysfunction resulting in age-related diseases. Our cells can recognize the damage to DNA, RNA, and proteins to repair them [58-60]. However, this requires huge energy demand, which cannot be fulfilled in the elderly population. Hence, all molecular components including DNA, proteins, lipids and organelles are susceptible to damage [12]. In the late 1990s, it was found that a number of cellular processes are involved in triggering cellular senescence rather than a single set of molecular event [14]. Hence, the better understanding of the relation between all these mechanisms leads to the effective control of aging-induced diseases. In the subsequent section, we will discuss some of these molecular and cellular events owing to the aging process.

Telomerase and telomere shortening

Short telomeres are found to be responsible for causing cellular senescence. This further triggers the secretion of inflammatory factors that promote aging. So far, telomere length has been detected as a biomarker of oxidative stress and cellular senescence in human [55]. In simple sense, telomeres are the specialized repetitive DNA sequences present at the terminals of the linear chromosomes. These DNA sequences are responsible for maintaining the chromosomal integrity. Tandem repeats of the TTAGGG sequence and telomere-DNA binding factors present in the telomere safeguards chromosomal ends from being recognized as a broken DNA end [20]. The telomere length is regulated by a ribonucleoprotein DNA polymerase complex called Telomerase [18]. This enzyme is made up of TERC and telomerase RNA [19]. Aging causes decrease in the level of telomerase, thereby reduction in the length of telomeres. Scientists have successfully reported that telomere length decreases with age at a rate of 24.8 - 27.7 base pairs per year in human. Hence, this has been recognized as a natural phenomenon occurring with age that is associated with the emergence of age-related diseases and thus, decreased lifespan in humans [21].

Oxidative stress

According to the free radical theory proposed by Harman, reactive oxygen species (ROS) such as Superoxide radicals ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and singlet oxygen ($^1O_2$) produced during normal aerobic metabolism accumulates with age in the body cells. The excess accumulation of these species damages genomic DNA, proteins and other cellular components [22,24]. It has been found that the imbalance between production and accumulation of ROS commonly occurs in the elderly population which leads to oxidative stress. Moreover, overproduction of ROS affect the delicate balance between the members of Bcl2 family protein. This further leads to the release of cytochrome C, and other apoptogenic factors [23].

ROS are the major agents responsible for increasing oxidative stress in the body cells thereby triggering DNA damage. Nuclear DNA damage increases apoptosis or cellular dysfunction [15]. Therefore, any factors or molecular mechanisms that increase the accumulation of ROS are responsible for causing cellular senescence [20]. With regard to the emergence of age-induced cardiovascular diseases due to excess accumulation of ROS, it has been found that overproduction of ROS decreases the availability of nitric oxide in the cells and also causes vasoconstriction. This invites the increase in the blood pressure and hence, arterial hypertension [56]. So far, scientists have successful discovered several biomarkers of oxidative stress. However, the better understanding of the diversity in oxidative stress and its relation with different diseases is still lacking.

Klotho

Klotho has also been recognized as one of the important biomarkers of aging. It plays vital role in regulation of energy and mineral metabolism and maintenance of anti-inflammatory and anti-oxidative effects associated with vascular health [27,57]. Hence, imbalance in klotho level is also responsible for the emergence of heart diseases. Successful experiments in murine models have revealed greater probability in the occurrence of atherosclerosis, vascular calcifications, defects in angiogenesis, and endothelial dysfunction in the absence of klotho in their body, which ultimately triggers CVD [57].

The enzyme klotho is encoded by KL-gene [22]. It is an anti-aging protein, essential for maintaining the well-functionality of many organs [26]. In 1997, transgenic mice was accidentally created by insertion of a transgene unknowingly. The mice later showed several age-induced disorders. Successful experiments in Klotho-deficient mice have revealed the close resemblance between the inherited phenotypes of aging in mice and human. On the contrary, lifespan was extended in a model with Klotho overexpression [26] whereas defective Klotho results in rapid aging and early death [27]. Hence, decrease in the expression of Klotho leads to increase in aging process thereby triggering age-induced disorders.

Epigenetic factors

Epigenetic factors are also found to be associated with several molecular mechanisms causing aging. Epigenetic regulatory mechanisms including DNA, RNA, and hydroxyl methylation, histone modification, and regulation by small and long non-coding RNAs affect gene expression without altering DNA/RNA/protein sequences [28]. DNA methylation regulates gene expression in a number of organisms [29]. In this process, there is a covalent transfer of a methyl group to the C-5 position of the cytosine ring of DNA by an enzyme called DNA methyltransferases (DNMTs) [30]. These changes detect the progression of several age-induced diseases such as cancer, osteoarthritis, and neurodegeneration. Methylomic changes are even directly responsible for causing a hereditary form of sensory neuropathy accompanied by dementia [29].

Cellular Aging	Genomic Instability
	Telomere attrition
	Epigenetic alteration
	Loss of proteostasis
	Deregulated nutrient sensing
	Mitochondrial dysfunction
	Cellular Senescence
	Stem cell exhaustion
	Altered intercellular communication

Table 1: *Indicators of cellular aging as proposed by Carlos Lopez-otin., et al [60].*

Besides these, Carlos Lopez-otin., *et al*. proposed nine hallmarks of aging, as mentioned in table 1, which can be important biomarkers of aging. Apart from these, sun exposure, smoking, excessive alcohol consumption, diet, stress, etc. also trigger early aging [64]. The use of accurate, reliable, and sensitive biomarkers helps to identify these risk factors inducing aging and age-related diseases in their early stage.

Cardiovascular disease

Cardiovascular disease (CVD) is a series of diseases that involve cellular damages in the heart or blood vessels. CVD includes heart failure, coronary artery disease, stroke, rheumatic heart disease, and peripheral artery disease [61]. Age has been found to be one of the most important determinants of cardiovascular health [31]. It has been estimated that the world's population of age 65 and older will reach to about 20% of the total population by 2030. With the increase in elderly population, age-induced cardiovascular disease will be one of the leading causes of death resulting in about 40% of total deaths [31]. According to the Center for Disease Control and Prevention, CVD results in the death of a person every 36 second [62]. Hence, it is of utmost importance to discuss the interaction between aging and CVD. The better understanding of the relation provides better hope in reducing CVDs.

Interaction of aging and CVD

Aging results in several functional and morphological changes in the cardiac cells [33]. Morphological changes include increase in the thickness of ventricular walls and vascular stiffening which lead to diastolic dysfunction. Moreover, aging triggers functional changes like increase in the heart beat rate, systolic and diastolic volume, prolonged diastolic relaxation and systolic contraction [34]. These abnormal changes in the cardiomyocytes cause reduction in the heart function, stress tolerance and lead to the progression of the disease. The total number of cardiomyocytes also decreases due to necrosis and apoptosis, changes in myocyte activation, and reduction in the ability to repair or replace damaged cells to address morphological and functional changes [33].

CVD is predetermined by a progressive decline in stroke volume, cardiac output and oxygen consumption. These changes increase the susceptibility of the cardiac cells to inflammation and oxidative stress [32]. Therefore, with the increase in oxidative stress due to the increase in reactive oxygen species (ROS), cardiomyocytes senescence increases. This can be detected by the use of senescence markers and reduction in telomere length [31]. Leukocyte telomere length (LTL) is found to be associated with aortic valve stenosis and a number of CV risk factors including hypertension, obesity, diabetes mellitus, and atherothrombotic events. Recently, researchers have found that individuals with shorter LTL are more prone to ischemic and hemorrhagic stroke as compared with the individuals having longer telomere length [35].

Biomarker of cardiovascular disease

In medicine, biomarker is a measurable indicator of the progression of any disease. Genetically, it is considered as a DNA that either causes the disease or is linked with the susceptibility to the disease [17]. Biomarkers are increasingly used in empirical studies to understand changes in physiological processes occurring with age. They can even identify the aging process [16]. Hence, their use is significant in controlling physiological process, anatomic and functional changes involved in cellular senescence. Biomarkers play key roles in risk identification, prognosis and diagnosis of CVD and its monitoring. Nowadays, they are increasingly employed in the identification of therapeutic targets in CVD [36].

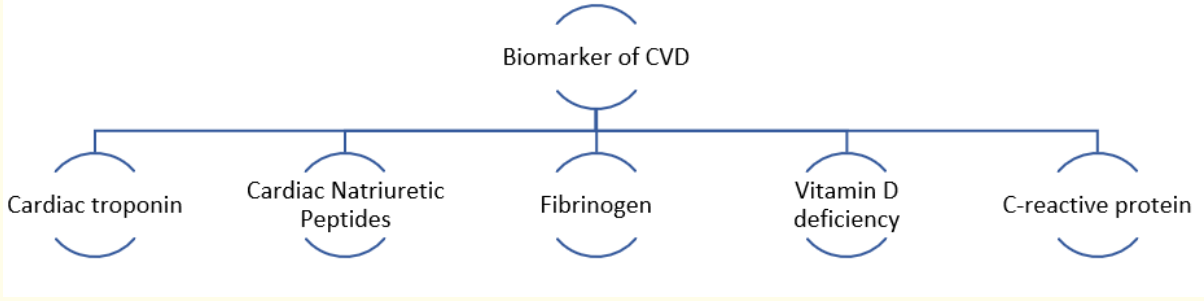

Figure 1: *Important biomarkers of CVD [37,40,42,48].*

Biomarker research in cardiology is significantly targeted to circulating and imaging biomarkers. Lipoprotein, apolipoprotein, haemoglobin A1C, Natriuretic peptide, and urinary albumin are circulating biomarkers whereas echocardiogram falls under imaging biomarker [37]. Some of the important biomarkers involved in predicting risk for CVD, as shown in figure 1 [37,51], are discussed below.

Cardiac troponin

Troponin has been used as a biomarker for the detection of damages or injuries in the cardiac cells [42]. In many cardiovascular diseases especially coronary heart disease, circulating cardiac troponin (cTn) concentration is used as an important biomarker for the non-invasive detection of myocardial injury. An increase in cTn levels is considered as a sign of myocyte necrosis. Patients with heart diseases like heart failure (HF) generally show increased level of circulating cTn. Hence, the detection of cTn can be useful in the early prognosis of the disease. However, our current understanding of underlying mechanisms of elevated cTn released in acute and chronic HF is still insufficient [41].

Cardiac natriuretic peptides

The natriuretic peptide (NP) family plays pivotal role in maintaining homeostatic balance of volume, osmosis, and pressure regulation of the circulatory system. So far, scientists have discovered five cardiovascular peptides ANP, BNP, CNP, DNP and VNP and a renal NP called urodilatin [44]. Cardiac Natriuretic Peptides (CNP) help in the early prognosis of standard risk factors for cardiovascular morbidity and mortality in patients with chronic heart failure, hypertension, acute coronary syndromes, myocardial infarction, coronary artery disease, or high coronary risk [43]. Circulating B-type natriuretic peptide and its more stable by-product N-terminal pro-B-type natriuretic peptide (NT-proBNP) is strongly recommended for early diagnosis and management of patients with cardiac diseases including heart failure [45]. Increased NT-proBNP levels indicate excessive prevalence of cardiovascular mortality [46].

Fibrinogen

Fibrinogen, an acute phase protein, is the most abundant coagulation factor found in the blood. Several studies have revealed its significance in the initial and progressive phase of atherosclerosis [40]. Fibrinogen is regarded as one of the strongest biomarkers for predicting stroke and cardiovascular disease in populations without pre-existing CVD. It is even associated with hemostasis and blood viscosity [38]. Several researches based on it have revealed that people with relatively high fibrinogen exhibit a greater chance of suffering from coronary heart disease [39]. However, according to fibrinogen genetic studies, polymorphism related to fibrinogen level is reported not to be linked with an increased cardiovascular risk [40].

Vitamin D deficiency

Sunlight exposure as well as intake of Vitamin D from the diet usually contributes to the maintenance of adequate vitamin D concentrations in serum [48]. Several studies have reported that vitamin D deficiency results in an increased risk of CVD, including heart failure, hypertension, and ischemic heart disease. Douglas., *et al*. have successfully demonstrated higher mortality rates from coronary heart disease especially in the winter, when vitamin D levels are the lowest. Although several hypotheses have been proposed, the actual mechanism for how vitamin D may protect individuals from CVD has not been fully elucidated [47].

C-reactive protein (CRP)

Inflammation is a key pathogenetic mechanism found to be associated with the development and progression of atherosclerosis and clinical atherothrombotic CVD. C-reactive protein (CRP) is reported to be a useful biomarker of vascular inflammation. It plays a direct role in promoting vascular inflammation and vessel damage [52]. Several pro-inflammatory cytokines obtained from monocytes/macrophages or adipose tissue in liver help in the production of CRP [50]. Hence, any cellular mechanisms such as tissue damage or infection that lead to the release of cytokines results in the high level of CRP. As a biomarker, it has an important role in the usual pathway to atherosclerosis and hence, is the most frequently studied inflammatory marker in cardiovascular disease [51].

Moreover, plasma cystatin C is said to be an important biomarker of CKD, a disease said to be associated with an increased risk for cardiovascular disease. However, it is unclear whether cystatin C is a direct marker of CHD or merely a marker for renal dysfunction because

of the association between renal dysfunction and cardiovascular diseases [49]. Furthermore, changes in the DNA sequence and epigenetic changes result in the alteration in gene expressions and phenotypes have also been linked with CVD traits and disease risk [54].

Challenges of using biomarker of cardiovascular disease

Heart transplantation has become a common and effective approach to reduce mortality rates from end stage heart failure. However, its success is limited by several complications seen in the heart transplantation, such as antibody-mediated rejection, acute cellular rejection, and cardiac allograft vasculopathy (CAV). Development of effective, efficient and cheap biomarkers for early diagnosis of these serious complication is still lacking [53]. This development can give a better hope in controlling these complications. Furthermore, the current understanding of using several biomarkers is insufficient enough to be used in controlling CVD. Several studies are to be made to understand the relation between cTn concentration and heart failure. Also, the mechanism of how vitamin D deficiency increases risk of CVD is to be explored.

Conclusion

Telomere shortening, defective klotho, alteration in gene expression, and oxidative stress due to excessive accumulation of RONS species lead to aging. This eventually induces a number of dreadful diseases including cardiovascular diseases which have plagued humankind since decades. CVD is said to be one of the leading causes of deaths in the world. The use of effective biomarkers such as cardiac troponin, cardiac natriuretic peptides, fibrinogen, CPR, and plasma cystatin C play very important role in the early prognosis of CVD thereby reducing further complications and deaths due to CVD. However, the current understanding of the use of biomarkers in the prognosis of CVD and their relationship with the process of aging is still unclear, though several attempts have been made to solve this. Early diagnosis of CVD could be instrumental in controlling their effect and developmental biomarkers could be pivotal toward this direction. However, the current understanding on the safety, efficiency, and cost effectiveness of the biomarkers in the diagnosis of CVD is still lacking. Moreover, the current knowledge on whether cystatin C is a direct marker of CHD or just a marker of renal dysfunction is still insufficient enough to use it in the control of CVD. The better understanding of the process of aging and CVD provides novel insights into the reduction in death rates due to CVD.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data generated and analyzed during the study are obtained from databases such as Google scholar, Pubmed, Medline, and Scopus.

Competing Interests

The authors declare to have no competing interests.

Funding Support

No funding was received from any source during the study and preparation of manuscript.

Author's Contributions

The authors jointly analyzed the information, prepared a study design, read, and approved the final manuscript.

Appendix 1: Definition of the medical terms used.

Definitions of Medical Terms Used

- Apoptosis: A form of programmed cell death that occurs in multicellular organism.
- Tandem Repeat: A sequence of two or more nucleotides that is repeated in such a way that the repeats lie adjacent to each other on the chromosome.
- Bcl2 family protein: A member of proteins that either promote or inhibit apoptosis
- Cytochrome C: It is heme protein that is localized in the compartment between the inner and outer mitochondrial membrane and favors mitochondrial electron transport and intrinsic apoptosis.
- Atherothrombotic event: An event characterized by a sudden atherosclerotic plaque disruption and thrombus (blood clot) formation.
- Hemostasis: A process to prevent and stop bleeding within a damaged blood vessel.
- Infarction: A tissue death (necrosis) due to inadequate blood supply to the affected area.
- Cardiac allograft vasculopathy: A major factor limiting long-term survival after heart transplantation. It is a common complication of heart transplantation affecting to half of people undergoing transplantation within 10 years.

Bibliography

1. Chalise HN. "Aging: Basic Concept". *American Journal of Biomedical Science and Research* 1.1 (2019).
2. World Health Organization". Aging. (2020).
3. Chalise HN and Rosenberg E. "Social and Health Status of Community-Dwelling Older Adults in Nepal". *Advances in Aging Research* 8.4 (2019): 63-74.
4. Chalise HN., *et al*. "Functional disability in activities of daily living and instrumental activities of daily living among Nepalese Newar elderly". *Public Health* 122.4 (2008): 394-396.
5. García-Velázquez L and Arias C. "The emerging role of Wnt signaling dysregulation in the understanding and modification of age-associated diseases". *Ageing Research Reviews* 37 (2017): 135-145.
6. Ferrucci L., *et al*. "Measuring biological aging in humans: A quest". *Aging Cell* 19.2 (2020): e13080.
7. Bhadra M., *et al*. "Alternative splicing in aging and longevity". *Human Genetics* 139.3 (2020): 357-369.
8. Leonard Hayflick, Aging: The Reality: "Anti-Aging" Is an Oxymoron, The Journals of Gerontology: Series A 59.6 (2004): B573-B578.
9. Belikov Aleksey V. "Age-related diseases as vicious cycles". *Ageing Research Reviews* 49 (2019): 11-26.
10. Strimbu Kyle and Jorge A Tavel. "What are biomarkers?" *Current opinion in HIV and AIDS* 5.6 (2010): 463-466.

11. Mythili Sabesan and Narasimhan Malathi. "Diagnostic markers of acute myocardial infarction". *Biomedical Reports* 3.6 (2015): 743-748.

12. Mc Auley MT., *et al*. "Modelling the molecular mechanisms of aging". *Bioscience Reports* 37.1 (2017): BSR20160177.

13. Kirkwood TB. "Understanding the odd science of aging". *Cell* 120.4 (2005): 437-447.

14. Kowald A and Kirkwood TB. "A network theory of ageing: the interactions of defective mitochondria, aberrant proteins, free radicals and scavengers in the ageing process". *Mutation Research* 316.5-6 (1996): 209-236.

15. Freitas AA and De Magalhães JP. "A review and appraisal of the DNA damage theory of ageing". *Mutation Research* 728.1-2 (2011): 12-22.

16. Crimmins E., *et al*. "Biomarkers related to aging in human populations". *Advances in Clinical Chemistry* 46 (2008): 161-216.

17. Wikipedia contributors. "Biomarker". Wikipedia, The Free Encyclopedia. Wikipedia, The Free Encyclopedia (2020).

18. Hornsby PJ. "Telomerase and the aging process". *Experimental Gerontology* 42.7 (2007): 575-581.

19. Dey A and Chakrabarti K. "Current Perspectives of Telomerase Structure and Function in Eukaryotes with Emerging Views on Telomerase in Human Parasites". *International Journal of Molecular Sciences* 19.2 (2018): 333.

20. Jian-Hua Chen., *et al*. "DNA damage, cellular senescence and organismal ageing: causal or correlative?" *Nucleic Acids Research* 35.22 (2007): 7417-7428.

21. Shammas MA. "Telomeres, lifestyle, cancer, and aging". *Current Opinion in Clinical Nutrition and Metabolic Care* 14.1 (2011): 28-34.

22. Pizzino G., *et al*. "Oxidative Stress: Harms and Benefits for Human Health". *Oxidative Medicine and Cellular Longevity* (2017): 8416763.

23. Salehi F., *et al*. "Oxidative DNA damage induced by ROS-modulating agents with the ability to target DNA: A comparison of the biological characteristics of citrus pectin and apple pectin". *Scientific Reports* 8 (2018): 13902.

24. Giovanni G Camici., *et al*. "Molecular mechanism of endothelial and vascular aging: implications for cardiovascular disease". *European Heart Journal* 36.48 (2015): 3392-3403.

25. Matsumura Y., *et al*. "Identification of the human klotho gene and its two transcripts encoding membrane and secreted klotho protein". *Biochemical and Biophysical Research Communications* 242.3 (1998): 626-630.

26. Olejnik A., *et al*. "The Biological Role of Klotho Protein in the Development of Cardiovascular Diseases". *BioMed Research International* (2018): 5171945.

27. Dërmaku-Sopjani M., *et al*. "Significance of the anti-aging protein Klotho". *Molecular Membrane Biology* 30.8 (2013): 369-385.

28. Sierra MI., *et al*. "Epigenetics of Aging". *Current Genomics* 16.6 (2015): 435-440.

29. Johnson AA., *et al*. "The role of DNA methylation in aging, rejuvenation, and age-related disease". *Rejuvenation Research* 15.5 (2012): 483-494.

30. Jin B., *et al*. "DNA methylation: superior or subordinate in the epigenetic hierarchy?" *Genes Cancer* 2.6 (2011): 607-617.

31. North BJ and Sinclair DA. "The intersection between aging and cardiovascular disease". *Circulation Research* 110.8 (2012): 1097-1108.

32. Kwak HB. "Effects of aging and exercise training on apoptosis in the heart". *Journal of Exercise Rehabilitation* 9.2 (2013): 212-219.

33. Sheydina A., *et al*. "Molecular mechanisms of cardiomyocyte aging". *Clinical Science* 121.8 (2011): 315-329.

34. Strait JB and Lakatta EG. "Aging-associated cardiovascular changes and their relationship to heart failure". *Heart Failure Clinics* 8.1 (2012): 143-164.

35. Paneni F., *et al*. "The Aging Cardiovascular System: Understanding It at the Cellular and Clinical Levels". *Journal of the American College of Cardiology* 69.15 (2017): 1952-1967.

36. Arthur Mark Richards. "Future biomarkers in cardiology: my favourites". *European Heart Journal* 20.1 (2018): G37-G44.

37. Ge Y and Wang TJ. "Identifying novel biomarkers for cardiovascular disease risk prediction". *Journal of Internal Medicine* 272.5 (2012): 430-439.

38. Van Holten TC., *et al*. "Circulating biomarkers for predicting cardiovascular disease risk; a systematic review and comprehensive overview of meta-analyses". *PLoS One* 8.4 (2013): e62080.

39. M Woodward., *et al*. "Fibrinogen as a risk factor for coronary heart disease and mortality in middle-aged men and women: The Scottish Heart Health Study". *European Heart Journal* 19.1 (1998): 55-62.

40. Zhang Y., *et al*. "Higher fibrinogen level is independently linked with the presence and severity of new-onset coronary atherosclerosis among Han Chinese population". *PLoS One* 9.11 (2014): e113460.

41. Ni L and Wehrens XHT. "Cardiac troponin I-more than a biomarker for myocardial ischemia?" *The Annals of Translational Medicine's* 6.1 (2018): S17.

42. Babuin L and Jaffe AS. "Troponin: the biomarker of choice for the detection of cardiac injury". *Canadian Medical Association Journal* 173.10 (2005): 1191-1202.

43. Ventura HO and Silver MA. "Natriuretic peptides as markers of cardiovascular risk: the story continues". *Mayo Clinic Proceedings* 86.12 (2011): 1143-1145.

44. Januzzi JL Jr. "Natriuretic peptides as biomarkers in heart failure". *Journal of Investigative Medicine* 61.6 (2013): 950-955.

45. Natriuretic Peptides Studies Collaboration., *et al*. "Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis". *The lancet. Diabetes and Endocrinology* 4.10 (2016): 840-849.

46. Rudolf H., *et al*. "NT-proBNP for risk prediction of cardiovascular events and all-cause mortality: The getABI-study". *The International Journal of Cardiology* 29 (2020): 100553.

47. Judd SE and Tangpricha V. "Vitamin D deficiency and risk for cardiovascular disease". *The American Journal of the Medical Sciences* 338.1 (2009): 40-44.

48. Nitsa A., *et al*. "Vitamin D in Cardiovascular Disease". *In Vivo* 32.5 (2018): 977-981.

49. Rui Zhao., *et al*. "Serum Cystatin C and the Risk of Coronary Heart Disease in Ethnic Chinese Patients With Normal Renal Function". *Laboratory Medicine* 47.1 (2016): 13-19.

50. Lopes Cardoso Inês and Teresa, Paulos. "C Reactive Protein and Cardiovascular Disease". *International Archives of Cardiovascular Diseases* 1 (2017).

51. Bell SP., *et al*. "Cardiovascular biomarkers and their utility in the older adult". *Current Cardiovascular Risk Reports* 6.5 (2012): 397-403.

52. Cozlea DL., *et al*. "The impact of C reactive protein on global cardiovascular risk on patients with coronary artery disease". *Current Health Sciences Journal* 39.4 (2013): 225-231.

53. Frangogiannis NG. "Biomarkers: hopes and challenges in the path from discovery to clinical practice". *Translational Research* 159.4 (2012): 197-204.

54. Dhingra R and Vasan RS. "Biomarkers in cardiovascular disease: Statistical assessment and section on key novel heart failure biomarkers". *Trends in Cardiovascular Medicine* 27.2 (2017): 123-133.

55. Sanders Jason L and Anne B Newman. "Telomere length in epidemiology: a biomarker of aging, age-related disease, both, or neither?" *Epidemiologic Reviews* 35.1 (2013): 112-131.

56. Senoner Thomas and Wolfgang Dichtl. "Oxidative Stress in Cardiovascular Diseases: Still a Therapeutic Target?" *Nutrients* 11.9 (2019): 2090.

57. Donate-Correa Javier., *et al*. "Klotho in cardiovascular disease: Current and future perspectives". *World Journal of Biological Chemistry* 6.4 (2015): 351-357.

58. Li Z., *et al*. "Battle against RNA oxidation: molecular mechanisms for reducing oxidized RNA to protect cells". *Wiley Interdisciplinary Reviews: RNA* 5.3 (2014): 335-346.

59. Malla S and Li Z. "Functions of Conserved Domains of Human Polynucleotide Phosphorylase on RNA Oxidation". *Insights of Biomedical Research* 3.1 (2019): 62-67.

60. Malla Sulochan. "Unraveling the Molecular Mechanism of Human Polynucleotide Phosphorylase (hPNPase) in Controlling Oxidized RNA. Diss. Florida Atlantic University (2019).

61. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015". *Lancet* 388.10053 (2016):1459-1544.

62. Center for Disease Control and Prevention, CDC (2020).

63. López-Otín Carlos., *et al*. "The hallmarks of aging". *Cell* 153.6 (2013): 1194-1217.

64. Antell DE and Taczanowski EM. "How environment and lifestyle choices influence the aging process". *Annals of Plastic Surgery* 43.6 (1999): 585-588.

Volume 8 Issue 8 August 2021