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MODERN BIOMARKERS - PREDICTORS OF EARLYCARDIOVASCULAR AGEING (LITERATURE REVIEW)

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Annotation

An analysis of the current state of the problem of studying biomarkers of human cardiovascular ageing was carried out based on an analysis of international experience. Ageing is an inevitable, constantly progressive systemic process, which is a significant risk factor for the development of most common chronic human diseases, including cardiovascular diseases. Therefore, studying markers of early cardiovascular ageing is a logical goal for developing measures to prevent the development of cardiovascular disease and to improve the quality of life and prolong active longevity. The intensive care unit. The application of a multidisciplinary approach to diagnose and treat a life-threatening complication as tracheal rupture in a short time allowed us to stabilize the patient's condition and avoid the development of further complications.

Жүрек-қантамырлардың ерте қартаюын болжаушы заманауи биомаркелер (әдебиет шолу)

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Түйінді сөздер:

қартаю биомаркерлері, жүрек-қантамырлары қартаюының болжаушылары, қартаю теориялары, қартаю дыреттеу, ұзақ өмір сүру.

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Түіндеме

Халықаралық тәжірибеге сүйене отырып, адамның жүрек-қантамырлары қартаюының биомаркерлерін зерттеудің қазіргі жағдайымен мәселелеріне талдау жасалды. Қартаю-бұладамның созылмалы ауруларының, соның ішінде жүрек-қантамырлары ауруларының дамуында маңыздықа үйфактор болып табылатын, еріксіз, үнемі үдемелі жүретін жүйелі процесс. Жүрек-қантамырларының ерте қартаюының

маркерлерін зерттеу - жүрек-қантамырлары ауруларының дамуының алдыналу, өмір сүру сапасын жақсарту және белсенді ұзақ өмір сүруді ұзарту бойынша шараларды әзірлеу дің маңызды мақсаттарының бірі болыпта былады.

Современные биомаркеры – предикторы раннего сердечно-сосудистого старения (обзор литературы)

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Аннотация

На основе международного опыта, был проведён анализ современного состояния и проблем изучения биомаркеров сердечно-сосудистого старения человека. Старение — неизбежный, постоянно прогрессирующий системный процесс, являющийся значимым фактором риска развития большинства распространённых хронических заболеваний человека, в том числе сердечно-сосудистых заболеваний. Изучение маркеров раннего сердечно-сосудистого старения является одним из значимых целей для разработки мер профилактики развития сердечно-сосудистых заболеваний, улучшения качества жизни и продления активного долголетия.

Ключевые слова:

биомаркеры старения, предикторы сердечно-сосудистого старения, теории старения, регуляция старения, долголетие

Introduction

According to World Health Organization (WHO) data from October 1, 2022, the number of people aged 60 years and older surpassed the number of children under 5 years of age in 2020. This trend highlights the urgent need to identify and determine the most significant biomarkers of ageing, which will hold immense value in assessing the health status of older and senescent individuals. Over the past few centuries, the global population has experienced a progressive shift towards ageing. In 2017, the number of individuals aged 60 years and older reached 962 million worldwide, more than doubling the number from 1980. By 2050, the elderly population is projected to double again, reaching approximately 2 billion.¹

Old age is recognized as the most significant risk factor for chronic age-re-

lated diseases. According to *Zhendong D. Zhang et al.*, over 90% of individuals over 65 years of age have at least one chronic disease, such as cardiovascular disease, cancer, dementia, diabetes, osteoarthritis, or osteoporosis, and more than 70% have at least two of these conditions. These data highlight the substantial socioeconomic burden that will be placed on healthcare systems. Therefore, studying the ageing process, maintaining health in older individuals, and developing methods for preventing and treating age-related diseases is crucial for extending the period of healthy ageing.¹

Ageing is a systemic process that affects various levels of biological organization. It is characterized by gradually inhibiting fundamental bodily functions, including regenerative and reproductive capabilities, leading to decreased adaptability to environmental conditions.² This

decline in adaptability makes individuals less resilient to stress, diseases, and injuries, which ultimately makes death inevitable. Ageing is an inherently emerging, naturally developing, and destructive process that limits the body's adaptive capabilities, increases the likelihood of death, reduces life expectancy, and contributes to the development of age-related pathologies.

Currently, there are over 130 theories of ageing, among which the most studied are autointoxication, telomeric, free radical, genetic, and epigenetic theories.³ Particular attention is focused on ageing and longevity's genetic and epigenetic mechanisms.⁴

In recent years, there has been a growing surge in scientific meetings, articles, and books dedicated to anti-ageing methods, reflecting the widespread interest in this topic among the general public. Consequently, the search for biomarkers of ageing continues unabated, as such biomarkers would offer several advantages:

1. Predicting Ageing Rate: Biomarkers would provide a precise indication of an individual's position within their lifespan, allowing for accurate predictions regarding their ageing trajectory.

2. Monitoring Ageing Processes: Biomarkers would enable monitoring of the underlying mechanisms driving the ageing process rather than simply assessing the effects of age-related diseases.

Ageing and risk of cardiovascular diseases

Ageing is a significant risk factor for most chronic diseases and functional impairments, and age-related diseases are the leading cause of death. Approximately 60% of all deaths are attributed to cardiovascular diseases, followed by oncological diseases, which account for 14% of all deaths.²

Over the last four decades, medicine has shifted from treating diseases as "patient care" to further identifying and preventing risk factors before they manifest as diseases, a concept referred to as "health care". For instance, high cholesterol and high blood pressure are not diseases themselves but increase the risk of heart attacks and strokes. Similarly, ageing is not a disease but a significant risk factor for various diseases,

including heart attacks, strokes, certain cancers, macular degeneration, osteoarthritis, neurodegeneration, and many more. The risk of cardiovascular disease doubles every 10 years after age 40, even after adjusting for other risk factors - similar to adding a new significant risk factor (smoking, hypertension, etc.) every decade.⁴ Decades of cardiovascular research have shown that treating risk factors, even in patients without symptoms, prevents harm. Identifying biomarkers of ageing and associated health consequences will allow early detection of individuals at high age-related risk throughout their lifespan and in different clinical settings.⁵

Even within the same age group, individuals exhibit varying disease risks and functional decline, highlighting the need for reliable biomarkers to track ageing processes and stages. The diversity of biological factors, lifestyles, and treatments further challenges biomarker identification. Therefore, no single biomarker can definitively assess healthy ageing.⁶

Cardiovascular diseases are the leading cause of death and disability worldwide (as per the WHO), including Kazakhstan. The ability to reach the current maximum lifespan (≥ 110 years) in low-mortality countries is attributed to protection from cardiovascular disease, as this system is particularly susceptible to oxidative stress and inflammation and plays a crucial role in maintaining oxygen and metabolite delivery to vital organs.⁷ These findings emphasize the need for specific cardiac markers that predict premature ageing and prevent adverse outcomes during ageing.

Centenarians (≥ 90 years) extend the human lifespan by evading or surviving major illnesses. Identifying specific biomarkers associated with exceptional longevity may provide insights into combating ageing-related diseases.⁸

According study published in "Nature Communications" by Japanese researchers *Hirata A. et al., 2020*, examined the association of cardiovascular biomarkers and plasma albumin with exceptional survival to the highest ages.⁷ They selected nine circulating biomarkers representing distinct cardioprotective and pathogenic pathways:

1. N-terminal pro-B-type natriuretic peptide (NT-proBNP)
2. Erythropoietin
3. Adiponectin
4. Extracellular superoxide dismutase (EC-SOD or SOD3)
5. Interleukin-6
6. Tumor necrosis factor-alpha (TNF-alpha)
7. Angiotensin-like protein 2 (Angptl2)
8. Cystatin C
9. Cholinesterase

We comprehensively analyzed relevant scientific literature to understand better and assess healthy and pathological ageing indicators to identify risk markers for early involutinal changes in the cardiovascular system and the development of age-associated cardiovascular diseases. We focused our literature search on peer-reviewed articles published in PubMed, Scopus, and Google Scholar, excluding non-peer-reviewed publications. We prioritized meta-analyses, systematic reviews, cohort studies, and cross-sectional studies, as these provide the most robust evidence. Our review summarizes current data on potential ageing biomarkers that are early predictors of cardiovascular ageing.^{9,10} These include:

1. Biochemical markers: NT-proBNP
2. Oxidative stress
3. Cystatin C
4. Cholinesterase
5. Inflammatory and Immunological markers

B-type natriuretic peptide

A biologically active analogue of NT-proBNP, causes natriuresis and diuresis, dilation of arteries and antagonism of the renin-angiotensin-aldosterone system, thereby counteracting hemodynamic disturbances in heart failure. The underlying mechanisms responsible for the association between low circulating NT-proBNP levels and exceptional survival are currently unclear, but a potential explanation can be considered. In the present review, centenarians and (semi-)supercentenarians showed a low prevalence of clinical and subclinical cardiovascular disease detected by ECG and low cardiometabolic risk profiles, except for a relatively high prevalence of chronic kidney disease. However, median NT-proBNP levels in-

creased consistently with age regardless of cardiovascular status, reaching 1530 pg/mL in individuals aged ≥ 110 years. In addition, 42.9% of centenarians had NT-proBNP levels ≥ 1800 pg/ml, which is the threshold value for diagnosing heart failure in people over 75 years of age.^{11,12}

The study found that NT-proBNP, interleukin-6, cystatin C, and cholinesterase were significantly associated with increased survival to super centenary age, while adiponectin and erythropoietin were not significantly associated.^{7,9,8,10}

Furthermore, combined data from three prospective cohort studies: the Tokyo Centenarian Study (TCS), the Japanese Semi-supercentenarian Study (JSS), and the Tokyo Oldest Study of General Health (TOOTH). The analytic cohort included a cohort of 1427 older adults of 36 centenarians (≥ 110 years), 572 semi-centenarians (105–109 years), 288 centenarians (100–104 years) and 531 very old people (85–99 years).¹³ The concordance index (C-index) was calculated using Cox proportional hazards models to assess each biomarker's prognostic performance.

The finding suggested that adding each predictive biomarker (NT-proBNP, interleukin-6, cystatin C, and cholinesterase) to the baseline model significantly improved risk prediction with minimal optimism in the entire cohort. When stratified by age, the predictive power of the models decreased significantly, suggesting that age itself is the primary predictor.¹¹

Thus, the base model weakly predicted mortality over age 105 (C-index 0.617 95% CI [0.577; 0.656], optimism-adjusted C-index = 0.588). However, NT-proBNP increase, and to a lesser extent, cholinesterase, significantly improved prognosis at older ages, NT-proBNP: C-index, 0.653 95% CI [0.615; 0.691], P = 0.001, C-index adjusted for optimism = 0.625; cholinesterase: C-index = 0.636 95% CI [0.596; 0.676], P = 0.019, Optimism-adjusted C-index = 0.609, respectively.¹⁴

Oxidative Stress

Oxidative stress is when the body produces excess free radicals, which can damage cells.¹² This process involves the pathogenesis of various diseases, including chronic heart failure (CHF).^{15,16} Studies have shown that peo-

ple with CHF have lower levels of an enzyme that helps protect cells from free radicals.¹⁷

CHF is a significant health problem due to its high prevalence and mortality rates among working-age adults. Free radicals, produced in large quantities during oxidative stress in CHF patients, primarily damage the vascular endothelium and cardiomyocytes. They can also promote the activation of cytokines, which contributes to disease progression and often determines the prognosis in CHF patients.^{15,16}

According study by Russian scientists *Polunina et al., 2018*, investigated 280 CHF patients and 60 healthy controls.¹⁷ The patients were divided into groups depending on their left ventricular ejection fraction and the stage of their disease. The researchers found that the activity of superoxide dismutase (SOD), an antioxidant enzyme, was significantly lower in CHF patients compared to healthy individuals.¹⁷ This suggests that oxidative stress plays a significant role in CHF pathogenesis.

Cystatin C

Accurate and early detection of nephropathy is crucial for timely intervention with nephroprotective and cardioprotective therapies, thereby reducing the risk of cardiovascular diseases and mortality.⁶ Cystatin C, a novel biomarker, holds promise as a more sensitive indicator of reduced glomerular filtration rate (GFR) compared to traditional methods like serum creatinine.

Cholinesterase

As the prevalence of heart failure (HF) among older adults rises, it is increasingly important to consider not only the pathophysiology of HF but also the overall decline in health associated with ageing.^{18,19} Nutritional status plays a crucial role in the prognosis of HF mortality, necessitating proper assessment and intervention.^{8,10} In this regard, serum cholinesterase (ChE) levels have emerged as a potential new biomarker for nutritional status. ChE is a protein produced in the liver and is associated with prognosis in patients with HF.

Serum ChE levels as a potential biomarker for myocardial ischemia in stable coronary artery disease (CAD). A study involving 559 consecutive patients

with suspected stable CAD and no prior cardiovascular history, investigated the relationship between myocardial ischemia and serum cholinesterase (ChE) levels.^{20,21} The findings revealed that:

1. Myocardial ischemia incidence significantly increased as serum ChE levels increased ($p < 0.001$).

2. Higher ChE levels were associated with higher body mass index (BMI) ($p < 0.001$), dyslipidaemia ($p < 0.001$), including elevated low-density lipoprotein cholesterol (LDL-C) ($p < 0.001$), triglycerides (TG) ($p < 0.001$), and serum albumin ($p < 0.001$), as well as younger age ($p < 0.001$).

3. At a ChE level of 286 IU/L, the specificity and sensitivity for myocardial ischemia were 0.599 and 0.658, respectively.

4. Elevated serum ChE levels (OR = 1.66, $p < 0.001$) were an independent risk factor for myocardial ischemia in patients with suspected stable CAD.

These findings suggest that serum ChE levels may be a valuable diagnostic biomarker for myocardial ischemia in patients with suspected stable CAD.^{20,21}

Other Inflammatory and immunological biomarkers

In a prospective cohort study known as the Study of Ageing and Longevity in the Sirente Geographical Area, researchers investigated whether interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF- α) protein levels could predict all-cause mortality in older adults.²² The study included 362 participants aged 80 years or older living in a mountain community in Italy. Participants were categorized based on the mean of three inflammatory markers: IL-6 (2.08 pg/mL), TNF- α (1.43 pg/mL), and CRP (3.08 mg/L). Additionally, a summary inflammation score was calculated. The primary outcome was the risk of death after four years of follow-up. During the four-year follow-up period, 150 deaths occurred.²³

Unadjusted analyses revealed that elevated levels of each of the three markers were associated with increased mortality. After adjusting for potential risk factors, high levels of IL-6 hazard ratio (HR) = 2.18, 95% CI [1.29; 3.69] and CRP, HR = 2.58, 95% CI [1.52; 4.40] remained significantly associated with a higher risk of death. However, the association between TNF- α

protein levels and mortality was no longer significant, HR = 1.26, 95% CI [0.74; 2.15]. Thus, a composite summary score of inflammation demonstrated a strong association with mortality, with the highest risk estimated for those with all three inflammatory markers above the median. This study suggests that lower levels of inflammatory markers are linked to improved survival in older adults, independent of age and other clinical and functional variables.^{22,23}

Older adults exhibit a higher level of lymphoproliferation, characterized by increased CD10+, CD25+ T-lymphocytes, and CD16+ natural killer (NK) cells compared to middle-aged individuals.²⁴ In the peripheral blood of elderly individuals, up to 95% of NK cells express high levels of CD16 but low levels of CD56. These NK cells exhibit high cytolytic activity but impaired secretion of TNF- α , IFN- γ , IL-5, IL-8, and colony-stimulating factors. Consequently, the reduced NK cell concentration in the peripheral blood of elderly individuals may diminish their ability to combat intracellular infections effectively.²⁵

Recent studies have highlighted the role of immune inflammation in atherosclerosis development. Cytokines, critical mediators of immune inflammation, can be produced by altered endothelial cells and modulate vascular wall functions. TNF- α activates leukocytes involved in inflammatory reactions and induces the expression of adhesion molecules on endothelial cells, facilitating the adhesion of neutrophils, monocytes, and lymphocytes, leading to inflammatory infiltration of the vascular wall. IL-6, acting downstream of TNF- α , contributes to endothelial dysfunction and may trigger acute coronary events. Elevated IL-6 levels in arterial walls correlate with markers of endothelial dysfunction and signs of insulin resistance, which are associated with an increased risk of vascular damage and atherosclerosis progression.²⁶

C-reactive protein (CRP) is another marker of cardiovascular risk. Inflammation, as reflected by increased CRP levels, contributes to the development of vascular atherosclerosis. Additionally, under experimental conditions, CRP has been shown to upregulate the expression of type II AG receptors on

vascular smooth muscle cells.^{7,16,20,24,25, [8,17,22,25-27]}

A study by *Niki Murtziet al.*, discovered that a genetic predisposition to downregulating IL-6 signaling, weighted by CRP levels, was associated with a lower risk of frailty.²⁷ IL-6, a pro-inflammatory cytokine implicated in various age-related ailments, including frailty, plays a significant role in this finding. Frailty is a syndrome characterized by physical weakness, fatigue, slowness, and unintentional weight loss, increasing the risk of hospitalization, institutionalization, and death. This finding supports a potential causal link between IL-6 signaling and frailty, suggesting that reducing IL-6 levels may lower frailty risk.²⁷

Conclusion

A review of the available literature suggests that survival to the current highest age in low-mortality countries is supported by protection from cardiovascular disease, given the inherent susceptibility of this system to oxidative stress and inflammation and its central role in maintaining oxygen and metabolite delivery to major organ systems. These findings underscore the need to identify specific cardiac markers that can effectively predict premature ageing and prevent adverse outcomes during ageing.²⁷

Median NT-proBNP levels increase consistently with age, regardless of cardiovascular status. Serum ChE levels may be a valuable diagnostic biomarker in patients with suspected stable CAD.

In the context of inflammatory markers, centenarians exhibited fewer signs of inflammation. Inflammatory peptides were either absent or present in lower abundance than in younger cohorts, while levels of anti-inflammatory cytokines such as IL-10 and transforming growth factor β were elevated in centenarians.

Currently, the primary objectives in the review of ageing predictors are as follows:

1. To determine the characteristics of healthy and pathological (early) ageing, identifying risk factors (clinical, immunological, lifestyle-related, and functional state of the cardiovascular system, among others).

2. To assess the state of T-cell immunity in different types of ageing (healthy and previously pathological) and to investigate the population profile of lymphocytes, expression of activation markers, and functional state of immune cells (based on the expression of cytokines, primarily IL-6 and TNF, as the most significant markers of ageing) in different subtypes of ageing.

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