DOI: 10.20514/2226-6704-2023-13-4-253-262
УДК 616.1:616.6
EDN: FJYEEH

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БИОМАРКЕРЫ РАЗВИТИЯ НЕЖЕЛАТЕЛЬНЫХ СЕРДЕЧНО-СОСУДИСТЫХ СОБЫТИЙ ПРИ ЗАБОЛЕВАНИЯХ ПОЧЕК

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Biomarkers of Adverse Cardiovascular Events in Kidney Disease

Резюме

В обзоре представлена информация по анализу научно-исследовательских сведений в отечественных и международных источниках литературы о факторах риска и биомаркерах развития неблагоприятных сердечно-сосудистых событий у пациентов с хронической болезнью почек и острым повреждением почек. Исследования биомаркеров имеют важное значение, особенно на ранних стадиях хронической болезни почек, когда профилактические и лечебные мероприятия работают более эффективно. В обзоре рассматриваются такие предикторы сердечно-сосудистых событий при хронической болезни почек как биомаркеры: окислительного стресса (малоновый диальдегид, ишемически-модифицированный альбумин; супероксид дисмутаза), воспаления (интерлейкин-6, интерлейкин-18), острого повреждения почек (молекула повреждения почек 1; нейтрофильный желатиназа-ассоциированный липокалин), кардиоспецифические биомаркеры (высокочувствительный тропонин) и циркулирующие микрорибонуклеиновые кислоты: 133a и 21, а также обсуждаются перспективы дальнейшего изучения биомаркеров. Отдельный акцент сделан на необходимости установления пороговых значений для различных биомаркеров при хронической болезни почек в зависимости от степени снижения функции почек, что позволит эффективно использовать эти показатели в клинической практике сердечно-сосудистых заболеваний, поскольку обычные референсные значения, используемые в общей популяции, будут выше при заболеваниях почек. В настоящее время известны референсные значения для тропонина и натрийуретических пептидов, которые в популяции с хронической болезни почек не достаточно изучены, по сравнению с общей популяцией.

Ключевые слова: *хроническая болезнь почек, острое повреждение почек, предикторы, сердечно-сосудистая система, биомаркеры*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 02.02.2023 г.
Принята к публикации 03.07.2023 г.

Для цитирования: Камышникова Л.А., Горбачевская К.С., Ефремова О.А. и др. БИОМАРКЕРЫ РАЗВИТИЯ НЕЖЕЛАТЕЛЬНЫХ СЕРДЕЧНО-СОСУДИСТЫХ СОБЫТИЙ ПРИ ЗАБОЛЕВАНИЯХ ПОЧЕК. Архивъ внутренней медицины. 2023; 13(4): 253-262. DOI: 10.20514/2226-6704-2023-13-4-253-262. EDN: FJYEEH

Abstract

Based on domestic and international literature the review refers to the analysis of the research data on risk factors and biomarkers for the development of adverse cardiovascular events in patients with chronic kidney disease and acute kidney injury. Biomarker studies are important, especially in the early stages of chronic kidney disease, that is, in patients with creatinine clearance above 60 ml/min/1.73 m2, when preventive and therapeutic measures work more effectively. Among the potential predictors of adverse cardiovascular events, the biomarkers related to the following pathological processes

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(conditions) should be noted: oxidative stress (malondialdehyde, ischemic-modified albumin; superoxide dismutase), inflammation (interleukin-6, interleukin-18), acute kidney injury (kidney injury molecule 1; neutrophil gelatinase-associated lipocalin), cardiospecific biomarkers (highly sensitive troponin) and circulating microribonucleic acids (specific miRNA-133a, miRNA-21), as well as the prospects for further study of some biomarkers in cardionephrology are discussed. A separate emphasis is placed on the need to establish threshold values for various molecules in chronic kidney disease, depending on the degree of decline in kidney function, which will allow these indicators to be effectively used in clinical practice as diagnostic and prognostic biomarkers for cardiovascular diseases, since their usual reference values are used in the general population, will be higher in kidney disease. Currently, only for troponin and natriuretic peptides, certain reference values are established, which are less clear-cut in the population with chronic kidney disease than in the general population, and for all other biomarkers, cut-off values are not yet known.

Key words: *chronic kidney disease, acute kidney injury, predictors, cardiovascular system, biomarkers*

Conflict of interests
The authors declare no conflict of interests

Sources of funding
The authors declare no funding for this study

Article received on 02.02.2023
Accepted for publication on 03.07.2023

For citation: Kamyshnikova L.A., Gorbachevskaya K.S., Efremova O.A. et al. Biomarkers of Adverse Cardiovascular Events in Kidney Disease. The Russian Archives of Internal Medicine. 2023; 13(4): 253-262. DOI: 10.20514/2226-6704-2023-13-4-253-262. EDN: FJYEEH

AVP — arginine-vasopressin, hsTnT — highly sensitive troponin T, LVH — left ventricular hypertrophy, CAD — coronary artery disease, IL — interleukin, KIM-1 — kidney injury molecule 1, MMP — matrix metalloproteinase, microRNA — microribonucleic acid, MPO — myeloperoxidase, NUP — natriuretic peptides, AMI — acute myocardial infarction, AKI — acute kidney injury, GFR — glomerular filtration rate, HF — heart failure, SOD — superoxide dismutase, CRP — C-reactive protein, CVD — cardiovascular diseases, CVE — cardiovascular events, CKD — chronic kidney disease, Gal 3 — galectin 3, NGAL — neutrophil gelatinase-associated lipocalin

Introduction

Chronic kidney disease (CKD) is an independent risk factor of cardiovascular diseases (CVD) affecting the overall and cardiovascular mortality [1, 2]. CVD are one of the main causes of morbidity and mortality in patients with CKD [3]. In patients on chronic dialysis the level of cardiovascular mortality is 10-20-fold higher than in the general population [4, 5].

Timely CVD diagnosis and treatment will improve CKD outcomes and the patient's quality of life, leading to decreased number of hospitalizations and consumption of medical resources. Overall, this will result in general direct and indirect treatment cost reduction [6]. Lately more and more cardionephrology investigators actively study various biomarkers of cardiovascular lesions both as CVD risk factors in patients with CKD and as a target for early detection and prevention of life-threatening conditions [4, 7, 8].

Cardiovascular risk factors

The causes of significant increase in the number of cardiovascular events (CVE) in CKD progression are still analyzed; however, it is considered that they are related to the complex mode of action of traditional and non-traditional CVD risk factors.

Traditional risk factors are well-known and widely presented both in the general population and the CKD population. They have been studied and identified in a well-known Framingham study, including the age, male sex, hypertension, diabetes mellitus, hyperlipidemia, family history, and smoking [7]. In later studies the following CVD factors and mechanisms typical for CKD have been added: inflammation, oxidative stress, impaired metabolism in uremic cells, malnutrition, hyperhomocystinemia, hyperuricemia, increased leptin levels, carnitine deficiency, vascular calcification, hypertriglyceridemia, anemia, endothelial dysfunction, quick changes of the circulatory volume and electrolytes on dialysis, impaired blood coagulation, immunosuppressive treatment after renal transplant, sympathetic hyperactivity, cardiac microvascular diseases, high levels of final glycolysis products, impaired nitrogen oxide balance, left ventricular hypertrophy (LVH) [4, 7–9].

Tawfik A.M. et al. (2022) describe not only traditional risk factors associated with CKD progression, but also divide them into several categories: inflammation, oxidative stress, anemia, uremia, endothelial dysfunction, impaired calcium-phosphorus metabolism and secondary hyperparathyroidism, etc. [7]; specific molecules participating in the pathogenesis of CVD in CKD may be analyzed as biomarkers in each of those categories.

Biomarkers of cardiovascular diseases in chronic kidney disease

It is well-known that approximately 10 % of adults in the general population suffer from some form of CKD, and up to 50 % of them die from CVD not reaching final CKD stage, the necessity of detecting CVD biomarkers in CKD is quite understandable [3, 4] (Table 1). The complexity of biomarker tests lies in their reference values,

Table 1. *Some biomarkers of cardiovascular disease in kidney disease*

Группа маркеров/ Markers group	Биомаркеры/ Biomarkers
Oxidative stress biomarkers	Superoxide dismutase Myeloperoxidase Ischemic modified albumin Malondialdehyde Asymmetric dimethylarginine Glycolysis end products
Biomarkers of acute kidney injury	KIM-1 (Kidney injury molecule-1) NGAL (Neutrophil gelatinase–associated lipocalin)
Cardiospecific biomarkers	High-sensitive troponin
Neurohormones	Natriuretic peptides Endothelin Arginine-Vasopressin
Inflammation biomarkers	C-reactive protein Interleukin-1 (IL-1) Interleukin-6 (IL-6) Interleukin-18 (IL-18)
Biomarkers of mineral metabolism disorders	Osteoprotegerin Fetuin-A Fibroblast growth factor-23 Vitamin D Parathyroid hormone
Biomarkers associated with the matrix	Galectin 3
Microribonucleic acids (microRNA)	MicroRNA-133a MicroRNA-21
Biomarkers of endothelial dysfunction	Matrix metalloproteinase (MMP-2, MMP-9)
Biomarkers of hypoxia	Hypoxia-inducible factor 1 (HIF-1α) Endogenous erythropoietin (EPO)

accounting for the fact that the concentration depends on the excretory and metabolic renal function. Higher target levels are used currently — these have a diagnostic and prognostic value for the CKD population [7, 8].

Below are the data on CVD biomarkers in CKD divided into groups based on the pathogenesis.

Oxidative stress biomarkers

Due to the fact that oxidative stress plays one of the dominating roles in the pathogenesis of atherosclerosis, it is important to analyze biomarkers which could become CVE predictors in patients with CKD. The following biomarkers are the ones studied most extensively: myeloperoxidase, malondialdehyde, asymmetric dimethylarginine, as well as other molecules of lipid or protein peroxidation [10].

Myeloperoxidase (MPO) is the main source of oxidative stress. Uncontrollable MPO hyperexpression is related to negative cardiovascular outcomes and increased cardiovascular mortality risks [10, 11].

Protection from increased oxidative stress has several barrier lines, the first of which being superoxide dismutase (SOD). SOD is the most effective intracellular enzyme available for analysis as a biomarker [12]. Some data have been discovered about the potential role of SOD in the development of vascular calcification, which is deleterious to the cardiovascular system and promotes CKD progression [13]. However, separate studies aimed at analyzing SOD levels as a biomarker were not arranged in patients with CVD and CKD. The ischemia-modified albumin (IMA) is also one of the newer CVE biomarkers associated with ischemic conditions and enhanced oxidative stress. The biomarker is very well-studied in CVD [14]; its levels have been analyzed in single studies in CKD [15]. CKD enhances the oxidative stress; besides, hemodialysis additionally promotes its increase. Authors demonstrate IMA levels increasing as the glomerular filtration rate (GFR) drops and conclude that this biomarker is suitable to determine oxidative stress in CKD [15].

Acute kidney injury biomarkers

Studies of acute kidney injury (AKI) biomarkers in CVD are currently studied extensively. The neutrophil gelatinase-associated lipocalin (NGAL) and the kidney injury molecule 1 (KIM-1) are one of the most analyzed AKI biomarkers which can potentially participate in the pathogenesis of CKD and prediction of cardiovascular events (CVE).

It is known that NGAL values are increased in atherosclerotic plaques, while its expression increases in ischemic, hypoxic conditions, and in myocardial infarction. The NGAL level is regulated by the vascular inflammation response to ischemia [16]. The association between NGAL and coronary artery diseases has been studied lately. The article of Freitas I.A. et al. (2020) analyzes 8 new prediction biomarkers in patients with atherosclerotic coronary artery disease. The main results confirmed that increased NGAL levels were associated with the better prognosis after cardiac arrest and concomitant kidney damage [17]. Some data demonstrate that NGAL may be a new biomarker that can help to stratify the risk in patients with coronary artery disease [18]. It should be noted that this biomarker monitoring may be significantly important for early disease diagnosis and course not only in CKD patients, but also in those with the cardiorenal syndrome, heart failure, cardiopulmonary bypass, and cardiothoracic surgeries [19].

In CKD patients, increased plasma NGAL levels may also be an independent predictor of future CVE [20]. It should be noted that elevated urine NGAL levels increase the rate of ischemic atherosclerotic events in patients with CKD and does not depend on GFR, albuminuria, and concomitant diseases [21].

KIM-1 is released with ischemic and toxic effects of causative agents on proximal kidney tubules. The studies show that elevated KIM-1 urine levels may be associated with increased risks of the coronary artery disease (CAD), heart failure (HF), and all-cause mortality in CKD patients. New data are expected regarding the use of this molecule as a potential biomarker of cardiovascular events [22]. Feldreich T. et al. (2019) analyzed the group of patients with terminal renal failure and detected that plasma KIM-1 was a biomarker of coronary calcification, increasing the CVD mortality risk [23].

Cardiospecific biomarkers

The highly sensitive troponin T (hsTnT) has turned out to be the best biomarker for cardiovascular outcome prediction and acute CVE biomarker in the group of patients with CKD [24]. The authors of the meta-analysis (2022) concluded that increased troponin levels were associated with severe diffuse CAD in dialysis and pre-dialysis patients [25]. In their study Ledwoch J. et al. (2022) detected weak negative correlation between the estimated glomerular filtration rate (eGFR) and hsTnT (Pearson r = -0.16; p<0.001), with eGFR being the only variable to be independently associated with hsTnT [24]. Authors defined the threshold hsTnT value of 40 ng/L for acute HF in patients with eGFR ≥45 mL/min/1.73 m^2 (sensitivity 73 %, specificity 71 %) and 55 ng/L with eGFR <45 mL/min/1.73 m^2 (sensitivity 63 %, specificity 62 %). The prognostic hsTnT accuracy in patients hospitalized with acute HF was lower in patients with the decreased renal function regarding the 30-day mortality [24]. Thus, threshold hsTnT values used to predict acute HF in patients with decreased eGFR require further studies in real clinical practice.

Some data demonstrate various threshold troponin levels in acute myocardial infarction (AMI) among patients with CKD versus the general population. According to Russian clinical cardiology guidelines [26], a 10-fold troponin increase with its increasing trend are used for AIM diagnosis in Russian medical institutions. The recent meta-analysis of Kampmann et al. (2022) discusses threshold troponin levels in patients with AIM and impaired renal function, proposing the following values for AIM diagnosis in CKD — 42 ng/L for troponin I, 48 ng/L for troponin T. For patients on dialysis, the troponin T threshold is significantly higher (over 239 ng/L). Specific troponin I levels for dialysis patients have not been established yet due to missing study results [27].

Neurohormones

B-type brain natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are well-known indicators of decompensated HF, which may also be used in CVD diagnosis and prediction in patients with CKD. However, their common standard reference values used in the general population increase in CKD [16]. This is related to decreased clearance of natriuretic peptides in CKD, which should be accounted for in patients with creatinine clearance below 60 mL/min/1.73 m^2. Studies among dialysis patients have confirmed the prognostic NT-proBNP value regarding the lower survival and increased cardiovascular mortality risks [28].

Arginine-vasopressin (AVP) is an antidiuretic and vasoconstrictive peptide hormone released in response to hyperosmolality and hypovolemia. Key AVP functions include water reabsorption in kidney tubules, increased peripheral vascular resistance, and subsequent blood pressure increase [29]. Due to poor stability and short AVP half-elimination for diagnostic purposes, copeptin (C-terminal provasopressin fragment, CT-proAVP) has been introduced into clinical practice as a robust AVP equivalent [30]. The literature contains evidence of AVP increase in patients with HF [29]. Among patients with HF with preserved ejection fraction (HFpEF), AVP was independently associated with left ventricular hypertrophy (LVH) and higher mortality risk or recurrent HF-related hospitalizations. Copeptin has also been confirmed to be a significant predictor of poor prognosis in the HF population [30].

Circulating plasma levels of endothelin-1 and related peptides formed during endothelin-1 synthesis have

been studied widely as potential CVE risk biomarkers. Jankowich M. (2020) describes the association of endothelin-1 with aging and CKD, as well as the association between endothelin-1 levels and cardiac remodeling signs, including increased left atrial diameter and increased left ventricular mass [31]. Some data confirm increased endothelin-1 levels as eGFR decreases in CKD stages 1–4 [32].

Inflammatory biomarkers

Accounting for the importance of inflammation as a factor affecting the development of atherosclerosis, individual inflammatory biomarkers for CVE prediction have been studied in CKD patients in a large number of studies.

C-reactive protein (CRP) is the most well-known and widely used biomarker of acute-phase systemic inflammation in the general population and CKD patients. Tawfik A.M. et al. (2022) [7] discovered inverse correlation between creatinine clearance and highly sensitive CRP (p = 0.0174). Increased highly sensitive CRP levels were detected not only in patients on hemodialysis, but also in elderly patients with CKD [7].

Interleukin 6 (IL-6) is a protein/inflammation biomarker produced in the liver; it is a potential predictor of all-cause or CVD mortality in the population of CKD patients with various renal injury stages [33]. The STABILITY study included 14,611 patients with known baseline IL-6 levels. During the follow-up, CVE developed in 1,459 people (10.0 %). Higher IL-6 levels were independently associated with the CVE risk (p<0.001) in CKD. Elevated IL-6 levels (≥2.0 vs. <2.0 ng/L) was associated with increased CVE risk both with preserved renal function and in CKD of various stages: 2.9 % events/year with preserved renal function (GFR ≥90 mL/min/1.73 m^2) [risk ratio (RR), 1.35; 95 % confidence interval (CI), 1.02–1.78], 3.3 % with mild CKD (GFR 60–90 mL/min/1.73 m^2) [RR, 1.57; 95 % CI, 1.35–1.83], 5.0 % with moderate or severe CKD (GFR <60 mL/min/1.73 m^2) [RR, 1.60; 95 % CI, 1.28–1.99]). In patients with chronic coronary syndrome, higher IL-6 levels were associated with the CVE risk in all CKD groups. The authors concluded that IL-6 and CKD stage could be the predictors for the administration of anti-inflammatory treatment in patients with the chronic coronary syndrome [33]. Russian investigators also detected inverse correlation between IL-6 and eGFR (r = -0.42, p = 0.0001) in patients with CHF and CKD [34].

Experimental data confirm the role of IL-1 in the development of kidney diseases and essential hypertension. IL-1 studies as a cardiovascular risk biomarker have demonstrated promising results in patients on hemodialysis and those after renal transplant. The study of Schunk et al. (2021) demonstrated that IL-1α was a central regulator of leukocyte-endothelial adhesion in myocardial infarction and CKD; thus, IL-1α inhibition may serve a new strategy of anti-inflammatory treatment in this population [35].

Interleukin 18 (IL-18) is an increasingly mentioned and tested inflammation biomarker for CVE prediction in CKD patients. IL-18 initiates the cascade of other pro-inflammatory cytokines which activate the lymphocytic response of T-helpers (1 or 2). This lymphocytic activation triggers the immune response and accelerates the atherosclerotic process. Elevated serum IL-18 levels are an important indicator of cardiovascular mortality in CKD patients [36].

Biomarkers of mineral metabolism disorders

Serum phosphorus, calcium, and magnesium imbalance, elevated levels of vascular calcification inducers (alkaline phosphatase, osteocalcin, osteonectin, bone morphogenic protein, fibroblast growth factor 23), decreased levels of vascular calficication inhibitors (fetuin A, osteopontin, Gla and α-Klotho matrix protein) are among common mineral metabolism disorders in CKD patients [37]. Thus, KDIGO (Kidney Disease Improving Global Outcome) guidelines recommend those biomarkers in the CKD patient population [38]. Target parathyroid hormone (PTH) levels change as CKD progresses, reaching 9-fold values compared to reference values in the general population [38].

Serum phosphorus, calcium, and magnesium imbalance are associated with increased HF risk, development of vascular calcification and subsequent complications, while hyperphosphatemia is widely prevalent at the terminal CKD stage [39]. Elevated serum phosphate and calcium levels promote the increased cardiovascular morbidity and mortality due to vascular calcification and endothelial dysfunction [40]. As vascular calficiation promotes significantly increased cardiovascular morbidity and mortality in CKD, it is important to study the calcification, related biomarkers, and approaches to its correction [38].

Fibroblast growth factor 23 (FGF-23) is a biomarker stimulating the vascular calcification. Elevated biomarker levels are associated with the progression of CKD, atherosclerotic CVD, and increased cardiovascular mortality [41, 42].

The group of endogenous vascular calcification inhibitors includes specific molecules which have also been tested as biomarkers of resistance to cardiovascular diseases in CKD [43]. Fetuin A, osteopontin, osteoprotegerin, Gla and α-Klotho matrix protein are only several inhibitors analyzed among CKD patients [8]. The association between serum osteoprotegerin and cardiovascular risk factors has been confirmed in CKD [44].

Biomarkers of the extracellular matrix condition

Galectin 3 (Gal-3) is a protein from the family of galectins (b-galactoside-binding lectins) which has important functions in many biological processes, including cardiac and renal fibrosis, HF development [45]. Initially Gal-3 was studied as a cardiac injury biomarker, though its role as a kidney injury biomarker was evaluated in several latest studies [46, 47]. Plasma Gal-3 levels after cardiac surgeries were analyzed for AKI prediction among 1,498 patients — the highest Gal-3 tertile was associated with severe AKI (odds ratio (OR) 2.95; p<0.001) [48].

In the long-term study of 1,320 patients with type 2 diabetes mellitus and eGFR ≥30 mL/min/1.73 m^2, Tan et al. (2018) demonstrated that Gal-3 was independently associated with 2-fold serum creatinine levels (RR 1.19, CI 95 % [1.14; 1.24], p<0.001) even after adjusting for baseline eGFR and albuminuria status [49]. Some data show that plasma Gal-3 levels on admission of patients with various CVD to the intensive care unit was robustly associated with AKI regardless of other known AKI predictors (OR 1.12, CI 95 % [1.04, 1.2]). Elevated plasma Gal-3 levels correlated with AKI severity: 16.6 (12.7–34.2) ng/mL without AKI, from 23.6 (18.2–34.2) ng/mL for AKI Stage 1 to 38 (24.5–57.1) ng/mL for Stage 3 [50]. These studies presume potential plasma and urine Gal-3 use as a biomarker of AKI severity in the heterogenous population, regardless of renal dysfunction origin. Besides, it has been reported that Gal-3 plays a key role in the renal interstitial fibrosis and CKD progression [51]. Gal-3 is a robust biomarker of unfavorable cardiovacular prognosis in AKI patients [52]. These results underline the role of Gal-3 in the cardiorenal syndrome. Some non-clinical studies have started to identify Gal-3 as a significant prognostic factor in Type 3 cardiorenal syndrome (acute renocardial syndrome) [53].

Endothelial dysfunction biomarkers

An interaction between matrix metalloproteinase 2 (MMP-2) and subclinical atherosclerosis was summarized in CKD patients in a meta-analysis (2016) including 16 studies [54]. MMP-2 and tissue metalloproteinase 1 inhibitor were most commonly analyzed in those studies, as well as their interaction with the subclinical atherosclerosis parameter (carotid intima media thickess (IMT)). Only MMP-2 demonstrated stable positive association with IMT. Authors concluded that MMP-2 imbalance was involved in the pathogenesis of atherosclerosis, its clinical signs, and cardiovascular prognosis in CKD patients [54]. Some data indicate that increased MMP-2 and MMP-9 activity in kidney tubules may lead to structural changes in the basal tubular membrane, which triggers the epithelial-mesenchymal transition, which leads to decreased cellular adhesion, while epithelial cells gain the mesenchymal phenotype, expressing and producing α-smooth cell actin and extracellular matrix protein [55]. All these mechanisms subsequently trigger tubular atrophy and renal fibrosis. MMP-2 and MMP-9 can release the latent transforming growth factor beta, which mediates crossover interactions between endothelial cells and vascular smooth muscle cells [55]. MMP imbalance and changes in endothelial cells are factors for the abnormal expansion of extracellular matrix, vascular calcification, atherogenesis; they also promote high pulse pressure, which leads to CVD and CKD progression [55]. The literature data report limited use of endothelial dysfunction biomarkers, including MMP-7 and MMP-9, in clinical conditions [1]. Zhang J. (2022) defines the following limitations: endothelial CVD biomarkers in humans are usually non-specific and have limited sensitivity; small sample sizes in clinical trials may be a serious obstacle for the development of robust biomarkers [1]. Thus, multicenter large-scale clinical trials are important for MMP evaluation. One should account for the fact that biomarkers of endothelial origin are usually related to other biomarkers, and without corresponding interactions the isolated use of endothelial biomarkers limits their application.

Microribonucleic acids

Microribonucleic acids (microRNA) are endogenous small non-coding RNA consisting of 21–24 nucleotides which control the post-transcription gene expression, inducing microRNA target destabilization or inhibiting protein translation [16].

Being the main pathogenetic CVD process, atherosclerosis is regulated with several microRNA molecules. Several molecules have been identified that participate in endothelial dysfunction (microRNA-31, 126) [56], development of atherosclerotic plaques (21, 155, 221), cholesterol homeostasis (122, 33a/b), neoangiogenesis (155, 210, 221, 222), and even plaque instability and rupture (100, 127, 145) [57].

A large number of microRNA was tested as potential diagnostic and prognostic biomarkers of various cardiovascular diseases. Changes in expression have been reported in patients with LVH, CAD, chronic heart failure, peripheral artery disease, and stroke [58, 59].

A small number of studies analyzed the microRNA-133a association with the development of CVE in the CKD patient population, as well as its association with CVD risk factors and other complications in CKD [58, 60]. Plasma microRNA-133a levels were analyzed using the PCR method in 30 patients with terminal renal failure

on hemodialysis [60]. Significant decrease in microRNA-133a levels was confirmed in the group of patients on hemodialysis with LVH versus patients without LVH and the control group. Elmadbouly A.A. et al. (2017) concluded that plasma microRNA-133a levels may be used as a new biomarker for LVH and left ventricular dysfunction prediction in CKD on hemodialysis [60].

Wang Y. et al. (2020) studied cicrulating microRNA-21 levels as a diagnostic biomarker in older patients with Type 2 cardiorenal syndrome (i.e. chronic renal dysfunction developed due to chronic cardiac pathology) [16]. Authors demonstrate that in the population of older patients circulating microRNA-21 has a small diagnostic value in Type 2 cardiorenal syndrome (sensitivity 55.9 %, specificity 84.9 %), unlike the combination of microRNA-21 and Cystatin C (sensitivity 88.1 %, specificity 83.6 %) [16].

Hypoxia biomarkers

It is well-known that anemia prevalence increases with CKD and chronic HF progression. Pharmacological mechanisms of anemia, such as decreased endogenous erythropoietin (EPO) and oxygen transport, lead to tissue hypoxia [61]. Thus, hypoxia biomarkers (hypoxia-induced factor 1α (HIF-1α) and EPO) are considered potentially useful in patients with chronic HF and CKD. Efremova E.V. et al. (2022) [34] analyzed various biomarkers in patients with chronic HF and CKD and reported EPO superiority over other markers. Based on the author's opinion, this defines the leading role of hypoxia and not only myocardial stress or inflammation in the prognosis of these patients. Low EPO levels define the favorable prognosis within a 1-year long follow-up of elderly patients in chronic cardiorenal syndrome [34]. The same study did not detect the association between HIF-1α and eGFR ($r = -0.05$, $p = 0.64$), and EPR ($r = 0.16$, $p = 0.15$) [34]. Thus, accounting for the high prognostic potential of these biomarkers and ambiguity of the results obtained, their studies should be continued.

Further potential studies of CVD biomarkers in renal diseases (CKD, AKI)

MicroRNA use for CVD prediction is promising, though currently it has not been sufficiently tested for routine use among CKD patients, which requires its further analysis, especially determining threshold values in specific clinical conditions.

Gal-3 studies as a diagnostic biomarker in CVD patients with CKD and as a prognostic biomarker in this patient cohort are also quite promising.

Despite the fact that MMP demonstrates high potential as subclinical atherosclerosis and CAD biomarkers, they are not sufficiently studied in CKD. Larger studies are required for several MMP with more uniform approaches for CVD detection in CKD.

Determining reference values for various biomarkers in CKD is an important clinical task. Reference values are determined only for troponin and natriuretic peptides that are less analyzed in the CKD population than for CVD in the general population. Threshold values are not sufficiently analyzed for all other biomarkers. Besides, it is well-known that the biomarker level may change as the GFR decreases, which requires the analysis of change range depending on the CKD stage for the possibility of use in the clinical practice as a diagnostic or prognostic biomarker.

EPO and HIF-1α demonstrate a high prognostic potential in the cardiorenal syndrome, however they have not been sufficiently studied in large-scale studies, and their threshold values for various CKD stages have not been determined.

Conclusion

Despite multiple achievements in cardionephrology, CKD patient mortality from CVD remains high, which requires constant searches of newer and robust biomarkers and predictors of cardiovascular morbidity and mortality in CKD patients. Currently the majority of analyzed cardiovascular outcome predictors in CKD patients can evaluate the prognosis in significant clinical signs [7, 38]. Besides, one should not just detect biomarkers, but also determine their threshold values in patients with various CKD stages.

Biomarker studies have an important value specifically in early CKD stages (in patients with creatinine clearance ≥60 mL/min/1.73 m^2), when the prophylactic and therapeutic measures are the most efficient. Many molecules participating in oxidative stress, inflammation, AKI, and other pathological studies are currently actively studied as CVD biomarkers in CKD patients, including in early stages.

Thus, new studies are required for the biomarkers that can timely and efficiently prevent cardiovascular diseases in CKD patients, improving their survival.

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Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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