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Markers of Cardiovascular Toxicity in CKD Patients-where we are now?

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Abstract

Numerous diseases such as heart failure, ischemic heart disease and sudden cardiac death are one of the most common reasons of increased morbidity and mortality in CKD through all stages. In view of such devastating epidemiology prediction of CV morbidity and mortality in the population especially those with creatinine clearance (e GFR) below 60 ml/min/1.73m^2, is becoming more and more important. Old, biomarkers such as troponin and braine natriuretic peptides and novel superfamilies of membrane receptors and their ligands, among which we single out Soluble ST2 (sST2) and Growth differentiation factor-15 (GDF-15) as markers that were examined in groups of patients with CKD. The body's defense against increased oxidative stress passes through several lines of defense, and in the first line are enzymes and enzyme systems than "collectors" of pro-oxidants *de novo* enzymes who are responsible for repairing and eliminating the damage caused by free oxygen radicals. Considering the importance of inflammation as a risk factor for atherosclerosis, a large number of studies examined a different biomarkers that were shown to be indicators of inflammation including adiponectin, leptin, interleukin-1, interleukin-6, interleukin-18, C-reactive protein and tumor necrosis factor. There is an increasing number of investigated biomarkers of acute kidney injury, which have even been examined in terms of predicting the progression of CKD and the occurrence of CV events. A lot of research studies have examined the impact of a large number of different miRNAs on the increase in CV morbidity and mortality in the population of CKD patients. Despite the great possibilities and far more modern applied diagnostic and therapeutic procedures, there is still a very high general and CV morbidity and mortality in the population of CKD patients, which is partly a consequence of the lack of application of newer CV biomarkers for prognosis and early prediction of events. Insufficiently defined newer cut of values regarding the application of classic, old biomarkers need attention.

Keywords: Cardiovascular morbidity, cardiovascular mortality, old and novel biomarkers

Cardiovascular morbidity and mortality in CKD patients

Chronic kidney disease (CKD) contributes to an increase in overall morbidity and mortality in the group of non-communicable diseases, and is also recognized as a strong and independent risk factor that contributes to the development of cardiovascular diseases (CVD) [1,2]. A whole series of diseases such as heart failure, ischemic heart disease and sudden cardiac death are one of the most common reasons of increased morbidity and mortality in CKD, and severe cardiovascular (CV) events account for almost 50% of all deaths in the kidney patient population [3,4]. The risk of developing CVD in patients with CKD surpasses the risk of reaching end-stage chronic kidney disease, and therefore, CKD is considered as one of the strongest risk factors for the development, progression and complications of CVD [5]. Although the application of numerous diagnostic and therapeutic procedures is enabled for the treatment of CKD, patients with CKD still have a dramatically reduced life expectancy, with a loss of 25 years of life at advanced stages compared with individuals in general population without kidney disease [6,7]. CV mortality accounts for 40% to 50% of all deaths in patients with advanced CKD (stage 4) as well as end-stage kidney disease (stage 5), compared with 26% in controls group with normal kidney function [8,9]. In more than 70 studies in nondialyzed patients with diagnosis of CKD, correction for CV risk factors, such as arterial hypertension, diabetes mellitus, and dyslipidemia, did not neutralize the impact of CKD on cardiovascular risk [10]. Large number of diverse cardiovascular risk factors can be classified into the group of traditional (arterial hypertension, hyperlipidemia, diabetes mellitus, age, smoking) and non-traditional factors risks (inflammation, oxidative stress, malnutrition,

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anemia, mineral metabolism disorder, proteinuria, hypervolemia) [11-13].
In view of such devastating epidemiology data the investigation of biomarkers for the prediction of CV morbidity and mortality in the population of patients with CKD, especially those with creatinine clearance (estemited glomerular filtration rate; GFR) below 60 ml/min/1.73m^2, is becoming more and more important.

Old and novel cardiospecific biomarkers

Increasingly, combinations of old, traditional biomarkers such as troponin and braine natriuretic peptides (BNP), and newer ones, are used more often in the prediction of CV morbidity and mortality in CKD patients. There are groups of novel superfamilies of membrane receptors and their ligands, among which we single out Soluble ST2 (sST2) and Growth differentiation factor-15 (GDF-15) as markers that were examined in groups of patients with CKD.
Troponin, as a well-known biomarker of acute myocardial infarction, can also be seen in other conditions and diseases such as myocarditis, cardiac decompensation, pulmonary embolism. Also, it proved to be more of a predictive biomarker than a diagnostic one in the group of CKD patients, especially those on chronic dialysis [14]. In addition, there are a number of different doubts regarding its use in patients with CKD, given the fact that its values increase with a decrease in GFR due to a probable decrease in its clearance and even "leakage" of troponin through the cell membrane of cardiomyocytes due to uremic cardiomyopathy. Therefore, true cut-off values of this biomarker in patients with CKD arises and some centers accept the limit of normal values that is up to ten times higher than in non-CKD patients [15]. The same story applies to BNP as a marker of cardiac decompensation, either new-onset, acute, or exacerbation of existing chronic heart failure. Its elevated values have been observed in various variants of cardiomyophaties, chronic constrictive pericarditis and acute coronary syndrome, as well as in pulmonary diseases. Different authors and hospital centers have different ranges of normal values of BNP biomarkers in patients diagnosed with CKD, considering its altered metabolism and clearance, so its cut off values are also subject to discussion [15].
Legitimate question arises as to how sensitive and specific the standard diagnostic biomarkers in the general population are for the diagnosis and prediction of new CV events in CKD patients. There are more and more investigations about newer biomarkers in order to obtain the most useful tool in risk stratification, diagnosis and prediction of CV events, especially decompensated heart failure and acute myocardial infarction [16].
sST2 is a relatively new biomarker of CV events that belongs to the IL-1 receptor superfamily, and the natural ligand of the said receptor family is IL-33 [17]. It is believed that sST2 by neutralizing the effect of IL-33, acts as a promoter of hypertrophy and fibrosis of the heart and inflammation itself with the progression of atherosclerosis [18]. Association of sST2 with heart failure as well as with other major CV events has been confirmed, but its association with the progression of renal failure is less well known. It is considered that the alteration in the examined values is a consequence of the parallel process of the progression of heart failure and CKD or simply occurs to changes in the cardiorenal syndrome [19,20]. Its potential as a cardiobiomarker in the group of predialysis patients was also confirmed in the CRIC study mentioned below.
GDF-15 belongs to the TGF-beta cytokine family, also known as macrophage inhibitor of cytokine 1, whose elevated values are observed in damage, repair and stress of a large number of tissues, including cardiovascular system [21,22]. In a study by Ho *et al*. that examined 85 CV markers for CV risk assessment in 3523 subjects with a median follow-up of 14.3 years, only GDF-15 was associated with all possible outcomes (overall and CV mortality, heart failure, atherosclerotic CVD) [23]. The study by Pareek *et al.* also indicated the superior capabilities of GDF-15 for predicting composite adverse CV outcomes, independently of certain older cardiac biomarkers [24]. It was observed that the mentioned biomarker has the ability to predict the progression of CKD and further reduction of GFR independent of the effect of a wide range of different risk factors [25]. A slightly smaller number of studies, but with a large number of subjects, investigated the association of GDF-15 with CV events and the progression of renal failure. CANVAS study came out with the conclusion that patients with DM type 2 and with a initial high CV risk had high values GDF-15 levels which were associated with onset of heart failure and progression of renal failure. In this study, patients with GFR over 30 ml/min were included, and therefore, the group of hemodialysis patients was not examined, which is also the case for the CRIC study [26].
A large, multicenter, prospective study (CRIC) including 3939 patients with a calculated GFR between 20 and 70 ml/min was aimed to examine the association of CV events with combination of old and new cardiac biomarkers including high-sensitivity cardiac troponin T, N-terminal pro-B-type natriuretic peptide, GDF-15, and sST2. The results of the aforementioned study support the fact that elevated baseline values of all four investigated biomarkers were associated with increased total and cardiac mortality in CKD patients [27].

Biomarkers of oxidative stress

The body's defense against increased oxidative stress passes through several lines of defense, and in the first line are enzymes and enzyme systems (superoxide dismutase, catalase and glutathione peroxidase). In the

second line are the elements that act as "collectors" of pro-oxidants; by binding them they become less harmful or are completely neutralized (ubiquinol, ascorbic acid, alpha tocopherol, glutathione). In the third line of defense, *de novo* enzymes are responsible for repairing and eliminating the damage caused by free oxygen radicals (enzymes for repairing damaged DNA molecules). In the last, fourth line of defense, we classify adaptation mechanisms that enable a faster and more efficient fight against free oxygen radicals. It is possible to conclude that examination of those enzymes (as potential biomarkers of oxidative stres), among other markers, could predict CV events [28].

Superoxide-dismutase (SOD) is the most effective intracellular enzyme in the first line of defense against free oxygen radicals [29]. In some studies, the association of SOD with certain cardiovascular diseases such as coronary artery disease (CAD) was observed, and of all isoenzymes, the SOD 2 variant proved to be the most promising biomarker for predicting the occurrence CAD [30,31].

Ischemia-modified albumin (IMA) is considered a newer biomarker that can be an indirect indicator of increased inflammation, ischemia, tissue hypoxia and, at the same time, increased oxidative stress [32]. Changes in IMA values were observed in patients with ischemic heart disease as well as in patients with acute myocardial infarction, after performed percutaneous coronary interventions, which actually reflects the ischemia-reperfusion model with increased oxidative stress [33,34]. Many authors find IMA a more sensitive indicator of acute coronary syndrom than troponin, myoglobin, and creatin kinase-MB. Evaluation of serum IMA is recommended not only for early detection of myocardial ischemia but also as a prognostic indicator of disease severity. People with higher IMA showed longer hospitalization days and had more readmissions as compared to patients with high troponin [35]. IMA has been shown to be a predictor of mortality in end-stage CKD patients in some studies [36]. By some authors IMA may serve as a useful biomarker in determining oxidative stress, and it should be kept in mind that the changes in anemia and albumin values are likely to have an impact on IMA [37].

Biomarkers of inflammation

Considering the importance of inflammation as a risk factor for atherosclerosis, a large number of studies examined a different biomarkers that were shown to be indicators of inflammation. The most frequently investigated biomarkers were adiponectin, leptin, interleukin-1, interleukin-6, interleukin-18, C-reactive protein and tumor necrosis factor [38-40].

Visceral adipose tissue is considered an important for the regulation of inflammation as well for the production of a large number of different adipocytokines [40]. For example, adiponectin (ADP) is an extremely important polypeptide that has a strong anti-inflammatory and anti-atherogenic effect, while enhancing the action of insulin at the level of insulin-dependent peripheral tissues [41]. It exerts its effect by suppressing the production of inflammatory cytokines Il-6 and tumor necrosis factor alpha [42]. ADP values are significantly increased in the population of patients with CKD, most likely due to reduced clearance or increased catabolism, while reduced values were registered in patients with metabolic syndrome, obesity, ischemic heart disease and other CV diseases [43,44]. A large number of observational studies confirmed the association of the lowest ADP values with the occurrence of adverse CV events in the population of patients with CKD [40,45,46]. The confirmation of ADP as a CV biomarker requires additional research and monitoring, given that its values depend on many other parameters in CKD patients (nutritional status, catabolism, inflammation of any other reason).

Leptin, is a neurotransmitter that is exclusively produced within adipocytes, and has a role in the regulation of metabolism, appetite and calorie consumption [40]. It is interesting that leptin is also a pro-inflammatory cytokine and elevated value of leptin was observed in patients with metabolic syndrome, which represents a state of inflammation and CV risk factor [40]. Elevated leptin values were observed in patients with CKD, which is a consequence of multiple factors such as reduced clearance, metabolic acidosis and the effect of uremic toxins [47,48]. Leptin has a proatherogenic effect, leads to strong stimulation of the sympathetic nervous system and is considered one of the early markers of atherosclerosis [49,50]. Hence, the value of leptin as a marker of risk remains unclear in CKD, although there are studies that have confirmed reduced leptin values in CKD patients with adverse CV events [51].

Interleukin 18 (IL-18) as a biomarker of inflammation has been considered as a potential biomarker of a large number of diseases including peripheral vascular disease, cerebrovascular and ischemic heart disease [52]. In high concentrations, it is registered in unstable atherosclerotic plaques and can lead to plaque destabilization and occurrence of an arterial ischemic event [53]. Based on previous studies, increased IL-18 serum concentration values are an important indicator of CV mortality in patients with CKD [54].

Biomarkers of acute kidney injury

There is an increasing number of investigated biomarkers of acute kidney injury, which have even been examined in terms of predicting the progression of CKD and the occurrence of CV events. Among others we single out Fatty acid-binding protein liver, the previously mentioned IL-18, which is also a marker of inflammation, and finally perhaps the most studied Neutrophil

Gelatinase Associated Lipocalin (NGAL) and Kidney Injury Molecule-1 (KIM-1).

NGAL is a small protein that is released from kidney tubulocytes under the action of various harmful agents and conditions, most often in conditions of hypoperfusion, ischemia and the action of nephrotoxins. Although investigated as an early indicator of acute kidney injury, the latest studies talk about its role in the progression of CKD. In the CRIC cohort study of 3386 patients suffering from CKD 2-4 stages, NGAL was an independent predictor of worsening of CKD [55,56]. With an increase in the value of NGAL in the urine, there is an increase in the incidence of ischemic atherosclerotic events in patients with CKD, independently of GFR, albuminuria and other comorbidities [57]. It is often compared to BNP in terms of prognosis and prediction in patients with the onset of heart failure where proved to be a more potent marker [58]. It has also been described that an elevated value of NGAL in the plasma of patients with CKD can be an independent predictor of future CV events [59]. Finally, there is a limited number of results that would confirm the possibility of applying NGAL markers in the prediction of CV events in daily clinical work.

Likewise, KIM-1 is released during the ischemic and nephrotoxic action of agents on the proximal tubules of the kidney, initially presented as a urinary biomarker of acute kidney injury, but its association with the progression of CKD has been proven [60]. It is also a marker of reparation and proliferation of proximal tubulocytes. Recent studies indicate that elevated values of urinary KIM-1 may be associated with a higher risk of ischemic heart disease, heart failure and overall mortality in patients with CKD [61]. Like with NGAL, there is a limited number of results that would confirm the possibility of applying KIM-1 markers in the prediction of CV events in daily clinical work.

Micro RNA family

The micro RNA (MiRNA) family represents a wide and heterogeneous group of newer biomarkers that actually represent short segment non-coding RNA molecules, and participate in the regulation of protein translation in a direct or indirect way, and over 2000 different miRNAs have been described so far [62]. The studies done so far have not yet clarified the participation of this group of biomarkers in the development and progression of CKD, although animal models confirm this [63]. A lot of research studies have examined the impact of a large number of different miRNAs on the increase in CV morbidity and mortality in the population of CKD patients, so some studies state, for example, that miRNA-223 and miRNA-126 did not prove to be prognostic markers, markers of all-cause mortality, cardiovascular events or renal events, but on the other hand, Fourdinier *et al.* for the previous two molecules, they state that there is a connection in the change of their expresion with mortality, CV events that are most probably GFR dependent [63,64]. This is the case with almost the largest number of miRNAs, whose values and results differ from author to author, as well as from study design, and require a lot of additional research.

Despite the insufficient results, a large number of researchers believe that biomarkers of miRNA origin, which are measured in hundreds, are the future in terms of their use as prognostic, diagnostic and markers for monitoring the effectiveness of therapeutic procedures, which is of particular importance for the population of kidney patients.

Despite the great possibilities and far more modern applied diagnostic and therapeutic procedures, there is still a very high general and CV morbidity and mortality in the population of CKD patients, which is partly a consequence of the lack of application of newer CV biomarkers for prognosis and early prediction of events. Insufficiently defined newer cut of values regarding the application of classic, old biomarkers need attention. In meantime, it is crucial to follow up the parameters and indicators of common risk factors (malnutrition, anemia, left ventricular hypertrophy), while it is necessary to continue further investigations of novel biomarkers during a longer period of follow-up on a larger number of patients, and especially vulnerable patient groups whose GFR is below 60 ml/min [15].

Conflict of interest statement. None declared.

Reference

1. Bikbov B, Purcell CA, Levey AS, *et al*. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020; 395: 709-733.
2. Go AS, Chertow GM, Fan D, *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351: 1296-1305.
3. Di Lullo L, Gorini A, Russo D, *et al*. Left Ventricular Hypertrophy in Chronic Kidney Disease Patients: From Pathophysiology to Treatment. *Cardiorenal Med* 2015; 5: 254-266.
4. Heywood JT, Fonarow GC, Costanzo MR, *et al*. ADHERE Scientific Advisory Committee and Investigators High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail* 2007; 13: 422-430.
5. Tonelli M, Wiebe N, Culleton B, *et al*. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006; 17: 2034-2047.
6. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. *Adv Chronic Kidney Dis* 2016; 23: 19-28.
7. Mallappallil M, Friedman EA, Delano BG, *et al*. Chronic kidney disease in the elderly: evaluation and management. *Clin Pract (Lond)* 2014; 11: 525-535.

8. Thompson S, James M, Wiebe N, *et al*. Cause of death in patients with reduced kidney function. *J Am Soc Nephrol* 2015; 26: 2504-2511.
9. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet* 2017; 389: 1238-1252.
10. Vanholder R, Argiles A, Baurmeister U, *et al*. Uremic toxicity: present state of the art. *Int J Artif Organs* 2001; 24: 695-725.
11. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32(5 Suppl 3): 112-119.
12. Johnson DW, Craven AM, Isbel NM. Modification of cardiovascular risk in hemodialysis patients: An evidence-based review. *Hemodial Int* 2007; 11: 1-14.
13. Segall L, Nistor I, Covic A. Heart Failure in Patients with Chronic Kidney Disease: A Systematic Integrative Review. *Biomed Res Int* 2014; 2014:937398.
14. Matsushita K, Ballew SH, Coresh J. Cardiovascular risk pre-diction in people with chronic kidney disease. *Curr OpinNephrol Hypertens* 2016; 25(6): 518-523.
15. Stopic B, Medic-Brkic B, Vujovic K, *et al*. Biomarkers and Predictors of Adverse Cardiovascular Events in Different Stages of Chronic Kidney Disease. *Dose-Response* 2022; 20; 155932582211275.
16. Aleksova A, Paldino A, Beltrami AP, *et al*. Cardiac Biomarkers in the Emergency Department: The Role of Soluble ST2 (sST2) in Acute Heart Failure and Acute Coronary Syndrome-There is Meat on the Bone. *J Clin Med* 2019; 8(2): 270.
17. Iwahana H, Yanagisawa K, Ito-Kosaka A, *et al*. Different promoter usage and multiple transcription initiation sites of the interleukin-1 receptor-related human ST2 gene in UT-7 and TM12 cells. *Eur J Biochem* 1999; 264: 397-406.
18. Weinberg EO, Shimpo M, Hurwitz S. Identification of serum soluble ST2 receptor as a novel heart failure biomarker. *Circulation* 2003; 107: 721-726.
19. Lupu S, Agoston-Coldea L.Soluble ST2 in Ventricular Dysfunction. *Adv Clin Chem*. 2015;69:139-59.
20. Alam ML, Katz R, Bellovich KA, *et al*. Soluble ST2 and Galectin-3 and Progression of CKD. *Kidney Int Rep* 2018; 4(1): 103-111.
21. Unsicker K, Spittau B, Krieglstein K. The multiple facets of the TGF-beta family cytokine growth/differentiation factor-15/macrophage inhibitory cytokine-1. *Cytokine Growth Factor Rev* 2013; 24: 373-384.
22. Su AI, Wiltshire T, Batalov S, *et al*. A gene atlas of the mouse and human protein-encoding transcriptomes. *Proc Natl Acad Sci U S A* 2004; 101: 6062-6067.
23. Ho JE, Lyass A, Courchesne P, *et al*. Protein biomarkers of cardiovascular disease and mortality in the community. *J Am Heart Assoc* 2018; 7: e008108.
24. Pareek M, Bhatt DL, Vaduganathan M, *et al*. Single and multiple cardiovascular biomarkers in subjects without a previous cardiovascular event. *Eur J Prev Cardiol* 2017; 24: 1648-1659.
25. Bao X, Xu B, Borne Y, *et al*. Growth differentiation factor-15 and incident chronic kidney disease: a population-based cohort study. *BMC Nephrol* 2021; 22: 351.
26. Sen TLiJ, Neuen BL, Arnott C, *et al*. Association Between Circulating GDF-15 and Cardio-Renal Outcomes and Effect of Canagliflozin: Results From the CANVAS Trial. *J Am Heart Assoc* 2021; 10(23): e021661.
27. Wang K, Zelnick LR, Anderson A, *et al*. Cardiac Biomarkers and Risk of Mortality in CKD (the CRIC Study). *Kidney International Reports* 2020; 5(11): 2002-2012.
28. Locatelli F, Bommer J, London GM, *et al*. Cardiovascular disease determinants in chronic renal failure: clinical approach and treatment. *Nephrol Dial Transplant* 2001; 16(3): 459-468.
29. Ighodaro OM, Akinloye OA. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. *Alexandria J Med* 2018; 54(4): 287-293.
30. Jimenez-Rosales A, Amaya-Chavez A, Dominguez García MV, *et al*. Association of Inflammatory and Oxidative Stress Biomarkers in Subjects With Cardiovascular Risk. *Am J Ther* 2013; 20(4): 422-431.
31. Peng JR, Lu TT, Chang HT, *et al.* Elevated Levels of Plasma Superoxide Dismutases 1 and 2 in Patients with Coronary Artery Disease. *Biomed Res Int* 2016; 2016: 3708905.
32. Nepal M, Jaisawal S, Guragain M, *et al*. Ischemic Modified Albumin (IMA) As a Novel Marker for Ischemic Heart Disease and Surrogate Marker for Other High Oxidative - Ischemic Conditions. *J Cardiovascular Disease Res* 2017; 8(4): 112-116.
33. Bar-Or D, Winkler J, VanBenthuysen K, *et al*. Reduced cobalt binding of human albumin with transient myocardial ischemia following elective percutaneous transluminal coronary angioplasty compared to CK-MB, myoglobin and troponin I. *Am Heart J* 2001; 141: 985-991.
34. Shevtsova A, Gordiienko I, Tkachenko V, Ushakova G. Ischemia-Modified Albumin: Origins and Clinical Implications. *Dis Markers* 2021; 2021: 9945424.
35. Sharma R, Gaze D, Pellerin D, *et al.* Ischemia-Modified Albumin Predicts Mortality in ESRD. *Am J Kidney Dis* 2006; 47(3): 493-502.
36. Ozkurt S, Ozcan O, Dogan I. Assessment of Ischemia Modified Albumin as a Marker of Oxidative Stress in Chronic Kidney Disease. *Saudi Journal of Kidney Diseases and Transplantation* 2021; 32(4): 1006-1012.
37. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA* 2001; 285(19): 2481-2485.
38. Sattar N, Murray HM, Welsh P, *et al*. Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) Study Group. Are markers of inflammation more strongly associated with risk for fatal than for nonfatal vascular events? *PLoS Med* 2009; 6(6): e1000099.
39. D'Marco L, Bellasi A, Raggi P. Cardiovascular biomarkers in chronic kidney disease: state of current research and clinical applicability. *Dis Markers* 2015; 2015: 586569.
40. Bouskila M, Pajvani UB, Scherer PE. Adiponectin: a relevant player in PPARγ-agonist-mediated improvements in hepatic insulin sensitivity? *International Journal of Obesity* 2005; 29(suppl 1): S17–S23.
41. Wulster-Radcliffe MC, Ajuwon KM, Wang J, *et al*. Adiponectin differentially regulates cytokines in porcine macrophages. *Biochemical and Biophysical Research Communications* 2004; 316(3): 924-929.
42. Komura N, Kihara S, Sonoda M, *et al*. Increment and impairment of adiponectin in renal failure. *Cardiovascular Research* 2010; 86(3): 471-477.
43. Kumada M, Kihara S, Sumitsuji S, *et al*. Association of hypoadiponectinemia with coronary artery disease in men. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2003; 23(1): 85-89.
44. Kollerits B, Fliser D, Heid IM, *et al*. Gender-specific association of adiponectin as a predictor of progression of

chronic kidney disease: the Mild to Moderate Kidney Disease study. *Kidney International* 2007; 71(12): 1279-1286.
45. Zoccali C, Mallamaci F. Adiponectin and leptin in chronic kidney disease: causal factors or mere risk markers? *Journal of Renal Nutrition* 2011; 21(1): 87-91.
46. Diez JJ, Iglesias P, Fernandez-Reyes MJ, *et al*. Serum concentrations of leptin, adiponectin and resistin, and their relationship with cardiovascular disease in patients with end-stage renal disease. *Clinical Endocrinology* 2005; 62(2): 242-249.
47. Teta D, Bevington A, Brown J, *et al*. Acidosis downregulates leptin production from cultured adipocytes through a glucose transport-dependent post-transcriptional mechanism. *Journal of the American Society of Nephrology* 2003; 14(9): 2248-2254.
48. Scholze A, Tepel M. Role of leptin in reverse epidemiology in chronic kidney disease. *Seminars in Dialysis* 2007; 20(6): 534-538.
49. Ciccone M, Vettor R, Pannacciulli N, *et al*. Plasma leptin is independently associated with the intima-media thickness of the common carotid artery. *International Journal of Obesity* 2001; 25(6): 805-810.
50. Scholze A, Rattensperger D, Zidek W, Tepel M. Low serum leptin predicts mortality in patients with chronic kidney disease stage 5. *Obesity* 2007; 15(6): 1617-1622.
51. Chang CH, Fan PC, Lin CY, *et al*. Elevation of Interleukin-18 Correlates With Cardiovascular, Cerebrovascular, and Peripheral Vascular Events: A Cohort Study of Hemodialysis Patients. *Medicine* 2015; 94(42): e1836.
52. Mallat Z, Corbaz A, Scoazec A, *et al*. Expression of Interleukin-18 in Human Atherosclerotic Plaques and Relation to Plaque Instability. *Circulation* 2001; 104(14): 1598-1603.
53. Formanowicz D, Wanic-Kossowska M, Pawliczak E, *et al*. Usefulness of serum interleukin-18 in predicting cardiovascularmortality in patients with chronic kidney disease-systems and clinical approach. *Sci Rep* 2015; 5: 18332.
54. Smith ER, Lee D, Cai MM, *et al*. Urinary neutrophil gelatinase-associated lipocalin may aid prediction of renal decline in patients with non-proteinuric Stages 3 and 4 chronic kidney disease (CKD). *Nephrol Dial Transplant* 2013; 28: 1569-1579.
55. Liu KD, Yang W, Anderson AH, *et al*. Urine neutrophil gelatinase-associated lipocalin levels do not improve risk prediction of progressive chronic kidney disease. *Kidney International* 2013; 83(5): 909-914.
56. Liu KD, Yang W, Go AS, *et al*. Urine Neutrophil Gelatinase-Associated Lipocalin and Risk of Cardiovascular Disease and Death in CKD: Results From the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis* 2015; 65(2): 267-274.
57. Maisel AS, Mueller C, Fitzgerald R, *et al*. Prognostic utility of plasma neutrophil gelatinase-associated lipocalin in patients with acute heart failure: the NGAL EvaLuation Along with B-type NaTriuretic Peptide in acutely decompensated heart failure (GALLANT) trial. *European Journal of Heart Failure* 2011; 13(8): 846-851.
58. Hasegawa M, Ishii J, Kitagawa F, *et al*. Plasma Neutrophil Gelatinase-Associated Lipocalin as a Predictor of Cardiovascular Events in Patients with Chronic Kidney Disease. *Biomed Res Int* 2016; 2016: 8761475.
59. Alderson HV, Ritchie JP, Pagano S, *et al*. The Associations of Blood Kidney Injury Molecule-1 and Neutrophil Gelatinase-Associated Lipocalin with Progression from CKD to ESRD. *Clin J Am Soc Nephrol* 2016; 11(12): 2141-2149.
60. Park M, Hsu CY, Go AS, *et al*. Urine Kidney Injury Biomarkers and Risks of Cardiovascular Disease Events and All-Cause Death: The CRIC Study. *Clin J Am Soc Nephrol* 2017; 12(5): 761-771.
61. Rong D, Sun H, Li Z, *et al*. An emerging function of circRNA-miRNAs-mRNA axis in human diseases. *Oncotarget* 2017; 8: 73271-73281.
62. Ho J, Ng KH, Rosen S, *et al*. Podocyte-specific loss of functional microRNAs leads to rapid glomerular and tubular injury. *J Am Soc Nephrol* 2008; 19: 2069-2075.
63. Metzinger L. microRNAs as promising biomarkers of chronic kidney disease. The case of miR-223. *Int J Ren Dis Ther* 2020; 2: 107.
64. Fourdinier O, Schepers E, Metzinger-Le Meuth V, *et al*. Serum levels of miR-126 and miR-223 and outcomes in chronic kidney disease patients. *Sci Rep* 2019; 9: 4477.