CARDIOVASCULAR-KIDNEY-METABOLIC SYNDROME (literature review)

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ABSTRACT

Background. In recent years, the importance of the concept of cardiovascular-kidney-metabolic health has been increasingly emphasized, reflecting the close pathogenetic and clinical relationship between cardiovascular disease, renal dysfunction, and metabolic health in general. Cardiovascular and renal diseases, type 2 diabetes mellitus are key causes of high disability and mortality worldwide, and therefore impose a heavy economic burden on the health systems of all countries. The search for additional opportunities to provide more complete cardio- and nephroprotection in patients with diabetes mellitus and chronic kidney disease is a pressing issue at present.

Aim. Demonstration of the scientific and pathophysiological rationale for expanding the concept of metabolic syndrome to cardiovascular-renal-metabolic syndrome, as proposed by the American Heart Association (AHA).

Materials and Methods. This study is an analytical review of clinical and epidemiological studies from electronic databases, including PubMed and Google Scholar, mostly in the last five years, as well as official guidelines from the American Heart Association. Extensive population-based studies, including NHANES (National Health and Nutrition Examination Survey) III, were analyzed, and the pathophysiology, clinical manifestations, and treatment approaches for cardiovascular-renal-metabolic syndrome were examined. This study was conducted on the authors' own initiative and without additional funding.

Research Ethics. This work is a review of published scientific evidence and clinical guidelines and does not involve the implementation of interventions involving patients or the use of personal data, so local ethical committee approval was not required.

Results. In October 2023, the AHA for the first time officially defined what is called cardiovascular-kidney-metabolic syndrome, which is defined as a systemic disease characterized by pathophysiological interactions between metabolic risk factors, chronic kidney disease, and the cardiovascular system, leading to multiple organ dysfunction and a high level of unfavorable cardiovascular outcomes.

Conclusions. This review describes approaches to the definition, principles of staging, strategies for prevention, as well as algorithms for the treatment of cardiovascular- kidney-metabolic syndrome, presents the key provisions for the management of cardiovascular-kidney-metabolic syndrome, proposed in the indicated clinical recommendations.

Keywords: *therapy, cardiovascular diseases, chronic kidney disease, type 2 diabetes mellitus, obesity.*

Abbreviations

AASLD – American Association for the Study of Liver Diseases
ACE – Angiotensin-Converting Enzyme
AF – Atrial Fibrillation
AH – Arterial Hypertension
AHA – American Heart Association
ARBs – Angiotensin Receptor Blockers
ASCVD – Atherosclerotic CVD
BMI – Body Mass Index
BP – Blood Pressure
CaReMe – CardioREnal and MEtabolic
CHF – Chronic Heart Failure
CKD – Chronic Kidney Disease
CKM syndrome – Cardiovascular-Kidney-Metabolic Syndrome
CKMH – Cardiovascular-Kidney-Metabolic Health
CVD – CardioVascular Disease
CVM – CardioVascular Mortality
CVS – CardioVascular System

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DM – Diabetes Mellitus
DOACs – Direct Oral Anticoagulants
EASL – European Association for the Study of the Liver
GFR – Glomerular Filtration Rate
GLP-1 – Glucagon-Like Peptide 1
GLP-1Ra – Glucagon-Like Peptide 1 Receptor Agonist
HbA1c – Glycosylated Hemoglobin
HF – Heart Failure
IGT – Impaired Glucose Tolerance
KDIGO – Kidney Disease: Improving Global Outcomes
MASLD – Metabolic Dysfunction-Associated Steatotic Liver Disease
MAU – Microalbuminuria
MS – Metabolic Syndrome
NHANES – National Health and Nutrition Examination Survey
NT-proBNP – N-terminal Pro-Brain Natriuretic Peptide
RF – Risk Factors
SGLT2 – Sodium-Glucose Cotransporter 2
TG – triglyceride
T2DM – Type 2 Diabetes Mellitus

Introduction

Chronic Heart Failure (CHF), as the inevitable outcome of almost all cardiovascular diseases, occupies a leading position in the structure of total mortality and persistent disability of the population, including those of working age. Despite the impressive achievements of modern pharmacology and cardiac surgery, the prognosis of CHF remains unfavorable. Based on a number of studies, a number of comorbid conditions have been identified, which significantly influence the course and prognosis of CHF.

Until recently, the relationship between the «heart-kidney» axis and metabolic syndrome has not been discussed in detail. Cardiorenal, cardiometabolic and metabolic syndromes stood separately from each other. However, the high incidence of morbidity and mortality, in particular from cardiovascular causes, raises many questions, the answers to which have not yet been completely found. Cardiovascular-Kidney-Metabolic Health (CKMH) is a relatively new interdisciplinary concept reflecting the relationship of metabolic risk factors, CKD and the CVS, which have a serious impact on morbidity and mortality of the population [1].

According to data from the Third National Health and Nutrition Examination Survey (NHANES III, conducted from 1988 to 1994, published in 2002) [2], the combination of any two cardiovascular risk factors leads to an increase in the likelihood of developing CKD with a decrease in the glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 by 3.7 times, and with an increase in BP within 130–139/85–89 mm Hg, the likelihood of developing MAU increases by 2.13 times compared to patients with normal BP values [3].

At the same time, one of the most important risk factors determining the high incidence of both CVD and CKD is T2DM. Insufficient control of each component of the cardio-kidney-metabolic continuum leads to multisystem consequences, the most significant of which are CVD and CVM. Finding additional opportunities to provide more complete cardio- and nephroprotection in patients with DM and CKD is a pressing problem nowadays.

In view of the suboptimal CKMH, especially among individuals with unfavorable social determinants (living conditions), international professional communities emphasize the need for a clear definition of the concept of CKM syndrome, principles of staging, prediction of outcomes and a holistic approach to the treatment of patients with CKM syndrome. The introduction of unified management strategies for this syndrome will improve the effectiveness of currently used treatment methods for comorbid patients. It is also critical to address social determinants of health in care delivery models and reduce separation of care through simplified approaches to a patient-centered interdisciplinary model.

The **aim** of this review was to demonstrate how, as a result of extensive discussion and scientific evidence, citing the strong pathophysiological interactions between heart disease, kidney disease, type 2 diabetes, and obesity, the American Heart Association has for the first time formally recommended expanding the concept of metabolic syndrome to cardiovascular-kidney-metabolic syndrome and to show the principles of staging, prevention strategies, as well as treatment algorithms for this syndrome.

Materials and Methods

This study is an analytical review of contemporary clinical and epidemiological studies from the past five years, using electronic databases, including PubMed and Google Scholar, as well as official guidelines from the AHA. The data from large population-based studies, including the NHANES III registry, examining the relationship between cardiovascular risk factors, chronic kidney disease, and metabolic disorders were analy-

zed. A descriptive and comparative analysis of the pathophysiological mechanisms, clinical manifestations, and treatment approaches for cardiovascular-renal-metabolic syndrome was used.

Research Ethics

This work is a review of published scientific evidence and clinical guidelines and does not involve the implementation of interventions involving patients or the use of personal data, so local ethical committee approval was not required.

Results

Today, a bidirectional relationship between dysfunction of the cardiovascular system and kidneys, known as cardiorenal syndrome, in which dysfunction of one organ causes dysfunction of the other, is well known. There is an equally widespread understanding of cardiometabolic syndrome. Thus, in the general population of patients with AH, overt, treatment-resistant AH occurs in [7.9–13.4]% of cases, however, its frequency increases significantly in certain groups of people with obesity, metabolic syndrome, T2DM, and especially in patients with CKD, where its prevalence can reach 31% [3; 4]. Excessive and dysfunctional adipose tissue (especially visceral obesity and other ectopic fat deposits) can cause inflammation, insulin resistance, metabolic risk factors, and a variety of systemic consequences, including increased risk of CVD [5]. Although these syndromes are well known, there is a growing understanding that metabolic abnormalities play a key pathophysiological role in the bidirectional interactions of the cardiovascular system and the kidneys. In addition, kidney dysfunction is increasingly recognized as a key mediator of the relationship between metabolic risk factors and CVD, especially HF [6]. Thus, rather than viewing cardiorenal syndrome and cardiometabolic diseases as separate processes, it is becoming increasingly clear that their intersections need to be viewed as a broader concept CaReMe.

In October 2023, the AHA for the first time officially defined what is called CKM syndrome, defined as a systemic disease characterized by pathophysiological interactions between metabolic risk factors, CKD and the cardiovascular system, leading to multiple organ dysfunction and high rates of adverse cardiovascular outcomes [7; 8]. It is emphasized that CKM syndrome is a progressive condition that often begins at a relatively early age under the influence of biological, social or environmental factors [9].

The CKM syndrome includes both individuals at risk for CVD due to the presence of metabolic RF, CKD, or both, and individuals with existing CVD that are potentially associated with or complicate metabolic RF or CKD. According to experts from the AASLD and the EASL, CKM syndrome most often results from excess adipose tissue, adipose tissue dysfunction, or both. Inflammation, oxidative stress, insulin resistance and vascular dysfunction are identified as central processes leading to the development of metabolic RF, progression of kidney diseases, potentiation of cardiorenal interactions and development of CVD. Metabolic RF and CKD additionally predispose to CVD through several direct and indirect pathways, including potentiated MASLD (*Fig.*) [7; 10]. In this regard, it is very important to identify signs of CKM in the early stages in order to carry out preventive measures.

The mechanisms of vascular, cardiac, and renal injury associated with these processes can be broadly classified as hemodynamic, metabolic, inflammatory, and fibrotic. Hyperglycemia causes glomerular hyperfiltration and hypertension – hemodynamic mechanisms that have long been recognized to initiate and exacerbate renal damage. Along with obesity and systemic hypertension, glomerular hemodynamics and arterial injury are caused by overt stress and endothelial damage, which contribute to both atherosclerosis and glomerulosclerosis [11; 12].

Hypertension and obesity are also major etiological factors underlying the development of left ventricular hypertrophy and HF [12]. Hyperglycemia in T2DM initiates a series of intracellular processes that contribute to renal and vascular damage through inflammation and fibrosis [11].

Evidence of CKD, albuminuria, low glomerular filtration rate, or both are associated with a progressive increase in the risk of major atherosclerotic vascular events and cardiovascular events, as well as CVD death. Consequently, the most common causes of death in individuals with T2DM and CKD are HF and ASCVD, and only ~10% of patients with CKD survive to renal failure [10]. CKD and diabetes are more likely to cause below-knee peripheral arterial disease, which is often more difficult to revascularize and is associated with more ischemic damage. CKD also leads to anemia and disorders of bone and mineral metabolism, which worsen CVD. Decreased oxygen carrying capacity increases myocardial demand and may aggravate HF [13]. HF can reduce the glomerular filtration rate as a result of impaired cardiac output, high venous pressure, activation of the renin-angiotensin-aldosterone system and the

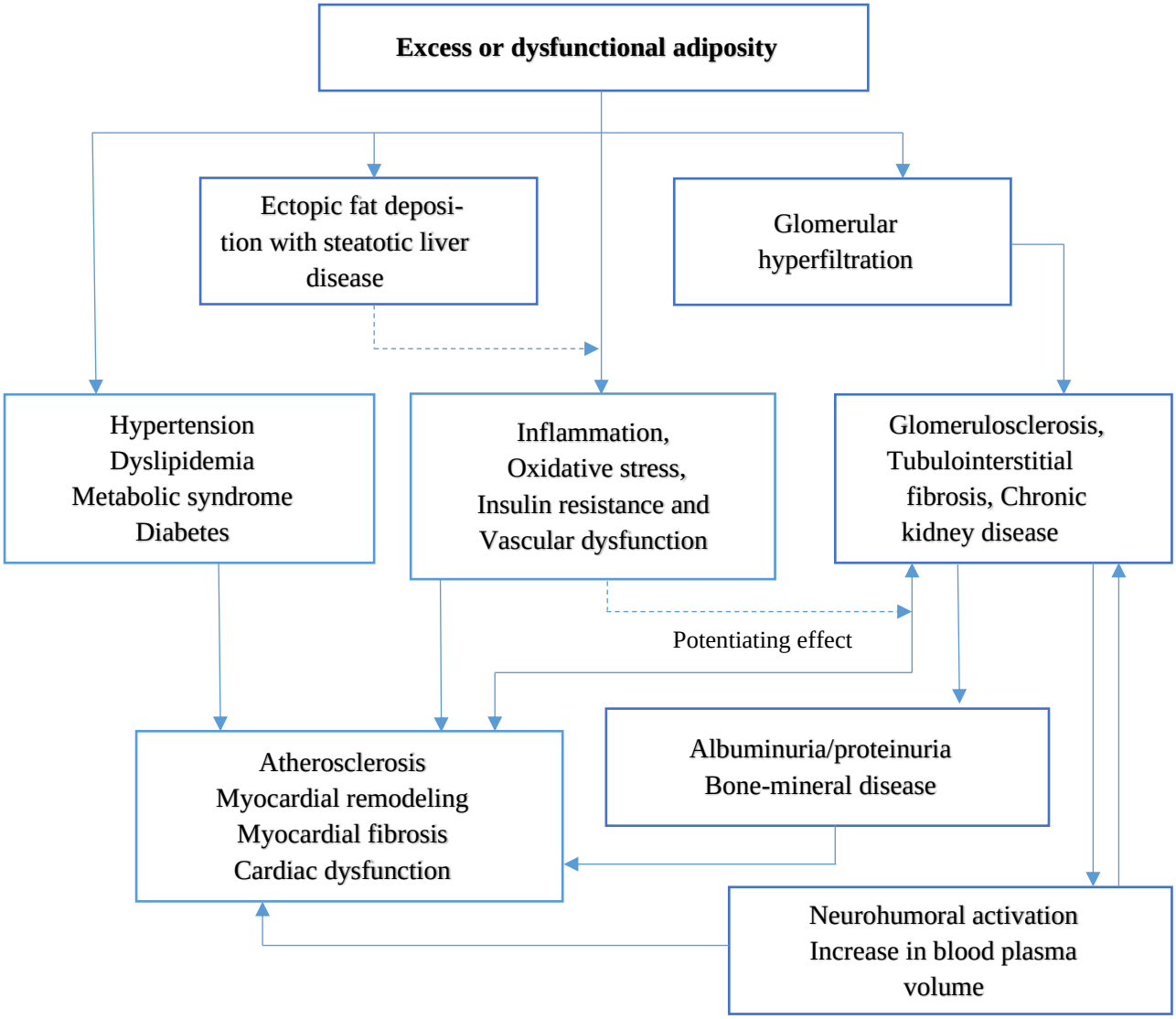

Fig. Scheme of the cardiovascular-kidney-metabolic syndrome

sympathetic nervous system [13]. Therefore, it is very important to identify the signs of CKM syndrome at early stages to carry out preventive measures.

The principles of staging and the algorithm for treating CKM syndrome reflect the pathophysiological aspects, the degree of risk and the possibilities for prevention and optimization of medical care.

The authors have identified four stages of the CKM syndrome [7].

Stage 0 is the absence of CKM risk factors with normal body mass index (BMI) and waist circumference, normotension, normoglycemia, normal lipid profile and no signs of CKD or subclinical/clinical CVD. The aim is to prevent CKM syndrome (especially unhealthy weight gain) by achieving and maintaining ideal health based on the 8 AHA Life's Essentials (diet, physical activity, smoking, BMI, fasting blood glucose, total cholesterol and BP, healthy sleep) [14]. In this case, the fight against obesity is a major aspect in the prevention of CKM syndrome due to its role in the development of T2DM, hypertension and dyslipidemia. It is also emphasized that to maintain a healthy lifestyle and prevent the development of risk factors for CKM syndrome with age, it is necessary to optimize maternal health (even before pregnancy) to reduce the likelihood of CKM syndrome in offspring, implement healthy lifestyle recommendations and use resources to prevent the development of risk factors for CKM syndrome in young patients. Adults at this stage should be examined every 3–5 years to assess lipid levels, BP and blood sugar levels.

Stage 1: excessive or dysfunctional accumulation of adipose tissue (clinically manifested as impaired glucose tolerance or prediabetes) without other metabolic RF or CVD [7]. The criteria for this stage are a BMI ≥25 kg/m^2 (or ≥23 kg/m^2 if of Asian descent); waist circumference ≥88/102 cm in women/men (or ≥80/90 cm in women/men if of Asian descent) and/or fasting blood glucose ≥[5.5–6.8] mmol/L or HbA1c 5.7% to 6.4% [4]. Those with stage 1 also include women with a history of gestational diabetes, who are at risk of developing diabetes and should be monitored for the occurrence of impaired glucose tolerance after pregnancy [15].

Treatment includes support for healthy lifestyle changes (healthy diet and regular physical activity) with the goal of at least 5% weight loss and correction of glucose intolerance, if necessary [16]. For individuals with persistent/progressive IGT despite lifestyle modification, metformin may also be considered to prevent the development of T2DM. It is recommended to screen adults with stage 1 CKM syndrome every 2–3 years to assess BP, TG levels, cholesterol, and blood sugar [7].

Stage 2: metabolic risk factors and CKD. Stage 2 is characterized by the presence of metabolic RF (hypertriglyceridemia (≥1.5 mmol/l), AH, metabolic syndrome, T2DM), moderate or high risk CKD, or a combination of these factors with their annual screening. CKD is defined by decreased GFR or albuminuria that persists for ≥3 months [17].

The goal of treatment in the second stage is the comprehensive elimination of metabolic risk factors and CKD in order to prevent the progression of CVD to subclinical and clinical forms. Optimal reduction of cardiovascular risk in metabolic syndrome includes lifestyle changes followed by targeted pharmacotherapy to control BP, glycemia, and lipid levels. Target parameters for glycemic and BP control for most patients are: HbA1c <7%, BP <130/80 mmHg. Although thiazide-type diuretics and calcium channel blockers are equally effective, ACE inhibitors/ARBs should be a priority in patients with T2DM and albuminuria or in patients with other CKDs given their effect on preventing deterioration of renal function [18; 19].

In individuals with intermediate and high risk of ASCVD, statin therapy moderately reduces TG levels and reduces the risk of ASCVD. In individuals with TG levels ≥2.3 mmol/L and an increased risk of pancreatitis, fibrate therapy is recommended, with fenofibrate being preferred when combined with statins due to fewer side effects. In individuals with moderate hypertriglyceridemia ([1.5–5.6] mmol/L), diabetes, and associated RF, icosapent ethyl (a purified form of eicosapentaenoic acid) reduces the risk of cardiovascular events [20]. In diabetes and/or HF, SGLT2 inhibitors (empagliflozin, dapagliflozin) or a GLP-1 receptor agonist (GLP-1Ra) reduce the risk of deterioration in renal function and are probably preferred in patients with CKD [21]. GLP-1 Ra (liraglutide, semaglutide) may be preferred in individuals with severe obesity (BMI ≥35 kg/m^2), given their powerful effect on weight loss. In individuals with diabetic nephropathy and proteinuria taking ACE inhibitors/ARBs, finerenone, a highly selective non-steroidal mineralocorticoid receptor antagonist, may be considered to reduce the risk of adverse cardiovascular and renal events [22].

Stage 3: Subclinical CVD, equivalent CVD risk factors, or very high risk of CKD. Subclinical HF is defined by elevated levels of cardiac biomarkers (NT-proBNP ≥125 pg/mL, high-sensitivity troponin T ≥14 ng/L for women and ≥22 ng/L for men, high-sensitivity troponin I ≥10 ng/L for women and ≥12 ng/L for men) or echocardiographic parameters, with the combination indicating the highest risk of HF. There is a high risk of ASCVD within 10 years and a very high risk of CKD stages 4–5. The goal is to intensify efforts to prevent progression to symptomatic CVD and kidney failure. This may include increasing or changing medications and additional attention to lifestyle changes. Measurement of coronary artery calcium score in some adults is recommended to assess possible arterial narrowing when treatment decisions are unclear [7].

The addition of β-blocker therapy to ACE inhibitors in patients with asymptomatic left ventricular dysfunction is associated with lower rates of the composite endpoint of death or hospitalization for HF [23]. SGLT2 inhibitors reduce the likelihood of hospitalization for HF or CVD mortality, especially in patients with diabetes. However, combination therapy with SGLT2 inhibitors and GLP-1Ra may have a greater effect on major adverse cardiac events and HF manifestations than either drug alone [24].

Stage 4: CVD with or without renal insufficiency. Stage 4 CKM syndrome is divided into two subcategories: (4a) without renal insufficiency and (4b) with renal insufficiency. It includes clinical CVD (coronary artery disease, HF, stroke, peripheral arterial disease, atrial fibrillation) among individuals with excessive/dysfunctional obesity, other metabolic RF and CKD [7]. The aim of treatment is individualized CVD treat-

ment taking into account the conditions of CKM syndrome. Treatment of patients with HF is carried out with an emphasis on four main components of therapy: β-blockers, angiotensin/neprilysin receptor inhibitors, mineralocorticoid receptor antagonists and SGLT2 inhibitors in case of reduced left ventricular ejection fraction [25]. The use of ACE inhibitors/ARBs and mineralocorticoid receptor antagonists may be challenging in CKD due to concerns about hypotension, hyperkalemia, and worsening renal function [26]. An analysis of 6 randomized trials showed that concomitant use of SGLT2 inhibitors reduces the risk of severe hyperkalemia [27]. GLP-1Ra reduces the risk of myocardial infarction, stroke, and cardiovascular mortality in people with diabetes and causes significant weight loss ([12–18]%) [28].

Several risk factors for CKM syndrome, including AH, obesity, CKD, and dyslipidemia, are associated with a higher likelihood and severity of AF, so comprehensive RF management is recommended in such patients [29; 30]. In addition, RF CKM syndrome in DM and AH increases the risk of stroke in AF, which necessitates the use of anticoagulants for prophylaxis. When anticoagulant therapy is indicated, recent guidelines support the use of DOACs or warfarin in patients with CKM syndrome, including those with severe obesity or CKD. However, with progressive kidney disease, dose adjustment of direct oral anticoagulants is required. Weight loss, regular physical activity, and improvement of cardiorespiratory fitness are recommended to improve the course of AF. Treatment of obstructive sleep apnea, which is closely associated with obesity, may help reduce the severity of AF [29].

The risk of CVD is disproportionately increased in patients with renal failure on maintenance dialysis, with HF and atherosclerotic CVD representing the two main phenotypes in this population [31]. Although there are limited high-quality data to guide optimal treatment of HF and ACVD in renal failure, several therapies have shown beneficial effects, particularly on HF-related outcomes. Consideration should be given to frequent dialysis sessions to reduce left ventricular hypertrophy/left ventricular mass index and HF hospitalizations, and to improve quality of life [32; 33]. When using drug classes such as β-blockers or ACE inhibitors, their dialyzability and synchrony with the dialysis cycle should be considered [34]. The role of routine initiation of statins in dialysis patients without known ACVD is limited, but continuation of statins started before dialysis is reasonable [35]. Finally, given the high rates of pulmonary hypertension and right heart failure that are characteristic of renal failure and the renal replacement therapy process, an early multidisciplinary approach involving leading HF specialists is recommended [36].

There is heterogeneity in the rate and extent of progression across the stages of CKM syndrome. Progression through the stages of CKM syndrome is associated with increased relative and absolute risk of CVD, renal failure, and mortality. Factors such as genetics, behavioral factors, and environmental factors may collectively significantly influence the progression of CKM syndrome across all its stages [7].

Discussion

The most effective strategy for CKM syndrome management that ensures both multifactorial therapeutic effect and higher patient compliance is an interdisciplinary approach to providing care to such patients. It is proposed to create an interdisciplinary group for the treatment of CKM syndrome, which, together with primary care physicians, will develop protocolized recommendations for the care of patients with two or more co-occurring diseases within the framework of CKM syndrome to maintain an integrated approach to ensuring high-quality and timely access to treatment. The interdisciplinary team will be supported by a coordinator and will also include representatives of primary care, cardiologists, nephrologists, endocrinologists, pharmacy and nursing, care navigators, social workers or community health workers. At the same time, depending on the severity and associated risks, patients should be timely referred to related specialists to ensure holistic management of CKM syndrome and optimize treatment methods. It is proposed to differentiate the principles of patient management depending on the stage of CKM syndrome.

Potential thresholds for referring a patient for consultation with a specialist have been identified:

- nephrologist – in case of increased risk according to KDIGO: stages 3a (A3, especially if there is no response to ACE inhibitors/ARBs), 3b (A2/A3), 4 and 5 [37];
- endocrinologist – in case of DM with poor glycemic control (HbA1c >9%) or microvascular diseases and/or target organ damage;
- cardiologist – if CVD is present, consultation may be considered in the presence of subclinical high-risk CVD, such as markedly elevated coronary calcium (≥ 300 in non-elderly adults (men <65 years or women <75 years) and/or multiple RF

for CKM syndrome or coronary calcium ≥ 1,000) or a combination of elevated cardiac biomarker and abnormal echocardiography.

Conclusions

CKM syndrome reflects the influence of multisystem pathophysiological interactions nested within a multilevel socially and clinically determined entity, the confluence of which determines clinical outcomes. It is important that clinical trials include the full spectrum of patients with CKM syndrome, with a particular need to include patients with CKD, who have traditionally been underrepresented in cardiovascular research. Numerous knowledge gaps necessitate targeted research in key areas. In relation to the development of the CKM syndrome concept, there is an incomplete understanding of sex differences, the genetic basis and application of genetic testing, the mechanisms of vascular, myocardial and renal dysfunction, and environmental and societal RF. Strategies for the use of combination therapy, as well as evidence-based approaches to its initiation, monitoring and maintenance, are important and represent areas of future research. Improved lifelong CKM syndrome screening strategies, particularly for those at highest risk, will facilitate early intervention to avoid progression to CKM syndrome and reduce the risk of cardiovascular events and renal failure.

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Authors' Contributions

Contribution / Authors	A	B	C	D	E	F
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Herasymchuk N.M.	+	+	+	+	+	+
Ambrosova T.M.	+				+	+
Kochubiei O.A.		+			+	+
Herasymchuk U.S.	+	+	+	+	+	+

Notes: A – concept; B – design; C – data collection;
D – statistical processing and interpretation of data;
E – writing or critical editing of the article;
F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

Declarations

Conflict of interest is absent.

All authors have given their consent to the publication of the article, to the processing and publication of their personal data.

The authors of the manuscript state that in the process of conducting research, preparing, and editing this manuscript, they did not use any generative AI tools or services to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of work (from the development of the research concept to the final editing) were carried out without the involvement of generative artificial intelligence, exclusively by the authors.

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