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Review Paper

Biomarker-Guided Pharmacotherapy Across the Ckm Continuum: From Subclinical Inflammation to Established Cardiorenal Disease

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ABSTRACT

Cardiovascular–kidney–metabolic (CKM) syndrome is a progressive disorder driven by the interplay of metabolic dysfunction, chronic inflammation, cardiovascular disease, and chronic kidney disease. Biomarker-guided pharmacotherapy has emerged as a promising approach for early diagnosis, risk stratification, and personalized treatment across the CKM continuum. This review summarizes the clinical utility of established biomarkers, including glycated hemoglobin (HbA1c), estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR), natriuretic peptides, and cardiac troponins, together with emerging biomarkers such as galectin-3, soluble ST2, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), growth differentiation factor-15 (GDF-15), and soluble urokinase plasminogen activator receptor (suPAR). Current evidence supports biomarker-guided use of SGLT2 inhibitors, GLP-1 receptor agonists, finerenone, renin–angiotensin system inhibitors, and guideline-directed heart failure therapies to improve cardiovascular and renal outcomes. The review also highlights the growing role of composite biomarker panels, multi-omics technologies, and artificial intelligence in enhancing precision pharmacotherapy and individualized patient care. Although these advances are encouraging, further prospective studies are needed to validate emerging biomarkers, establish standardized clinical thresholds, and evaluate their cost-effectiveness before routine implementation. Overall, biomarker-guided pharmacotherapy offers significant potential to improve early intervention, optimize therapeutic decisions, and enhance outcomes in patients across the CKM continuum.

INTRODUCTION

The progressive continuum known as cardiovascular-kidney-metabolic (CKM) illness is characterized by a combination of metabolic dysfunction, chronic inflammation, vascular injury, and renal impairment that accelerates

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damage to the heart and kidneys. Biomarkers can assist identify patients at risk, improve prognosis, and promote earlier intervention throughout the CKM spectrum because these processes frequently start prior to overt organ failure. Since natriuretic peptides continue to be the most reliable markers for directing treatment and tracking response, biomarker-guided pharmacotherapy is particularly pertinent in heart failure and cardiorenal illness. Although their routine clinical usage still needs more validation, emerging biomarkers as galectin-3, soluble ST2, NGAL, and inflammatory markers may further enhance customized therapy.[1]

Stage 1:

Excess adipose tissue becomes inflamed and releases cytokines and adipokines that create a low-grade chronic inflammatory state. This inflammation disrupts normal insulin signaling and promotes oxidative stress, which is the first step toward metabolic dysfunction.[1][2]

Stage 2:

Insulin resistance Because inflammatory mediators obstruct the action of insulin in muscle, liver, and adipose tissue, circulating free fatty acids increase and glucose absorption decreases. This creates a self-amplifying cycle by exacerbating metabolic imbalance and raising inflammatory activity.[2][3][5]

Stage 3:

Hypertension Inflammation causes vasoconstriction, salt retention, and endothelial dysfunction by activating the sympathetic nervous system and renin-angiotensin-aldosterone system. As a result, blood pressure increases and becomes more difficult to manage, particularly in those who are obese and insulin resistant.[3][4]

Stage 4:

The renal microvasculature and glomeruli are harmed by chronic inflammation and hypertension, which results in hyperfiltration, albuminuria, and progressive fibrosis. This weakens kidney function over time and exacerbates the inflammatory condition.[3]

Stage 5:

A negative spiral of deteriorating cardiac and renal function is created in severe disease when inflammation from the heart and kidneys exacerbates congestion, tissue damage, and more cytokine production. At this point, established cardiorenal syndrome appears and the consequences worsen.[1][2][3]

PATHOPHYSIOLOGY:

A chronic inflammatory state that impacts the cardiovascular and renal systems is a key link between obesity, hypertension, and insulin resistance. The renin-angiotensin-aldosterone system is activated, pro-inflammatory cytokines and adipokines are released, oxidative stress is increased, and endothelial dysfunction, salt retention, and high blood pressure are all caused by excess adipose tissue.The kidneys are subject to increasing hemodynamic stress, glomerular hyperfiltration, and gradual structural damage as long as hypertension lasts. By hindering arterial relaxation, encouraging metabolic imbalance, and increasing renal salt reabsorption, insulin resistance exacerbates this process and makes controlling hypertension more difficult.[6]

These interrelated processes eventually produce a self-sustaining cardiorenal cycle that raises the risk of heart failure, resistant hypertension, and chronic kidney disease. Early identification of this inflammatory-metabolic pathway is crucial because it promotes prompt blood pressure management, lifestyle modification, and treatment of metabolic risk factors before irreversible organ damage occurs.[7]

Stage 0

There are no significant metabolic, renal, or cardiovascular risk factors. The objective is prevention by a healthy diet, exercise, and weight control because the body has not yet experienced the inflammatory or metabolic alterations that initiate CKM illness.[6]

Stage 1

The primary cause of this stage is excess or dysfunctional obesity, particularly central obesity. Insulin resistance, oxidative stress, and early vascular dysfunction all start when fat tissue becomes inflamed and produces cytokines**.[7]**

Stage 2

This stage encompasses kidney illness and/or metabolic risk factors, such as prediabetes, diabetes, hypertension, dyslipidemia, or chronic kidney disease. Increased endothelium damage, glomerular stress, salt retention, and progressive renal injury are all consequences of inflammation.[8]

Stage 3

This stage of cardiovascular disease is subclinical. Inflammation and metabolic damage have already resulted in hidden atherosclerosis, cardiac remodeling, or biomarker indications of heart stress even though the patient may not yet exhibit symptoms.[9]

Stage 4

Heart failure, coronary artery disease, stroke, and peripheral arterial disease are examples of [recognized cardiovascular diseases. Chronic inflammation exacerbates tissue damage, and renal failure frequently exacerbates heart disease, resulting in a complete cardiorenal cycle.[10][11]

THE CKM CONTINUUM: STAGING (0–4) AND BIOMARKER-BASED RISK STRATIFICATION

Stage 0: No CKM risk factors

There is no kidney or cardiovascular problems, and the body weight, blood pressure, glucose, and lipids are all normal in this early stage. While biomarkers are typically normal, low risk can be confirmed by baseline screening markers such BMI, waist circumference, fasting glucose, HbA1c, lipid profile, serum creatinine, and urine albumin-to-creatinine ratio.[12]

Stage 1: Excess or dysfunctional adiposity

At this point, low-grade inflammation starts and obesity or central adiposity is present. Waist circumference, BMI, HbA1c, fasting glucose, hs-CRP, adiponectin, leptin, and IL-6 are useful early indicators because they show early metabolic and inflammatory stress prior to organ damage being apparent.[12][13]

Stage 2: Metabolic risk factors and/or CKD

Metabolic syndrome, dyslipidemia, diabetes, hypertension, and early chronic kidney disease are all included in this stage. Blood pressure, HbA1c, fasting glucose, triglycerides, LDL-C, serum creatinine, cystatin C, eGFR, and urine albumin-to-creatinine ratio are significant biomarkers because they indicate early kidney involvement and metabolic burden**.[13]**

Stage 3: Subclinical cardiovascular disease

At this point, there are no obvious signs and a quiet cardiovascular injury. NT-proBNP, hs-troponin T, hs-troponin I, and occasionally hs-CRP are biomarkers that aid in identifying this stage, in addition to imaging markers such coronary artery calcium or structural heart abnormalities on echocardiography**.[14]**

Stage 4: Clinical cardiovascular disease

This includes well-known conditions such atrial fibrillation, peripheral artery disease, heart failure, stroke, coronary artery disease, and kidney failure. NT-proBNP, troponin, creatinine, eGFR, and

urine albumin-to-creatinine ratio are frequently used biomarkers in this context, primarily for severity evaluation, prognosis, and therapy response monitoring.[14]

PHARMACOTHERAPY OF CARDIOVASCULAR–KIDNEY–METABOLIC (CKM) SYNDROME (LATEST GUIDELINES 2025–2026)

Initiate an SGLT2 inhibitor (empagliflozin or dapagliflozin) in patients with **type 2 diabetes, chronic kidney disease (eGFR ≥20 mL/min/1.73 m²), heart failure, or albuminuria**, regardless of HbA1c, to reduce CKD progression, heart failure hospitalization, and cardiovascular mortality. To achieve substantial weight loss, enhance glycemic control, and lower severe adverse cardiovascular events, patients with obesity and/or established atherosclerotic cardiovascular disease (ASCVD) should start using a GLP-1 receptor agonist (semaglutide or liraglutide).For patients with type 2 diabetes and obesity who need to lose more weight and have better cardiometabolic results, tirzepatide (a dual GIP/GLP-1 receptor agonist) may be a good option.

Patients with eGFR ≥30 mL/min/1.73 m² should start metformin as first-line glucose-lowering therapy unless it is contraindicated; however, patients with CKM syndrome should start SGLT2 inhibitors or GLP-1 receptor agonists right away.[13]

To lower blood pressure, halt the progression of chronic kidney disease, and lower cardiovascular risk, patients with hypertension and albuminuria should be prescribed ACE inhibitors or ARBs.

To further lower renal fibrosis and cardiovascular events, add finerenone to individuals who have persistent albuminuria even after receiving optimal ACE inhibitor or ARB therapy.[15]

To minimize LDL cholesterol and cardiovascular risk in individuals with diabetes or known ASCVD, start high-intensity statin therapy; if LDL-C stays above target, think about ezetimibe or PCSK9 inhibitors.[16]

Use biomarkers such the TyG index, estimated glucose disposal rate (eGDR), galectin-3, GDF-15, suPAR, and albuminuria to identify high-risk patients so that organ-protective treatments can be started early.[17]

RENAL INFLAMMATION AND BIOMARKER-DIRECTED KIDNEY-PROTECTIVE THERAPY IN CHRONIC KIDNEY DISEASE (CKD)

Optimize renin-angiotensin system (RAS) inhibition with an ACE inhibitor or angiotensin receptor blocker (ARB) in patients with chronic kidney disease (CKD) and albuminuria (UACR ≥30 mg/g) to reduce intraglomerular pressure, suppress renal inflammation, lessen proteinuria, and stop the progression of CKD. These medications remain the primary line of treatment for kidney protection.[18]

Patients with CKD and an eGFR ≥20 mL/min/1.73 m² should begin taking an SGLT2 inhibitor (empagliflozin, dapagliflozin, or canagliflozin) regardless of their diabetes status because these drugs reduce tubular inflammation, oxidative stress, albuminuria, CKD progression, hospitalization for heart failure, and cardiovascular mortality.

Finerenone, a non-steroidal mineralocorticoid receptor antagonist (ns-MRA), should be added to patients with type 2 diabetes, chronic kidney disease (CKD), and persistent albuminuria in spite of maximally tolerated ACE inhibitor or ARB treatment. Finerenone inhibits fibrotic and inflammatory pathways, slowing the progression of cardiovascular events and renal illness.[19]

GLP-1 receptor agonists (semaglutide or liraglutide) should be considered in those with type 2 diabetes and chronic kidney disease (CKD), particularly if additional glycemic control or weight loss are required. These drugs indirectly

protect the kidneys by improving metabolic control and reducing systemic inflammation and cardiovascular risk.[19]

Use biomarker-directed risk stratification for the diagnosis, staging, prognosis, and treatment monitoring of chronic kidney disease (CKD) by routinely assessing the ratio of urine albumin to creatinine (UACR) and the estimated glomerular filtration rate (eGFR). New indications of inflammation include.[13]

Renal inflammation may be detected by Kidney Injury Molecule-1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), soluble urokinase plasminogen activator receptor (suPAR), Tumor Necrosis Factor Receptors (TNFR-1 and TNFR-2), Galectin-3, Growth Differentiation Factor-15 (GDF-15), and Interleukin-6 (IL-6).[16]

Since CKD is intimately related to cardiovascular illness across the cardiovascular–kidney–metabolic (CKM) continuum, aggressively manage cardiovascular risk with high-intensity statins, optimal blood pressure control (<130/80 mmHg when appropriate), and comprehensive lifestyle measures.[17]

CARDIAC BIOMARKERS AND TREATMENT INTENSIFICATION IN HEART FAILURE (HFREF/HFPEF) (UPDATED GUIDELINES 2024–2025)

All patients with suspected heart failure should have their natriuretic peptides (B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP)) measured in order to determine the diagnosis, gauge the severity of the condition, predict the prognosis, and direct the escalation of treatment. BNP/NT-proBNP values that are consistently high or rising suggest that heart failure is getting worse and that guideline-directed medical therapy (GDMT) needs to be optimized.

Measure cardiac troponins (cTnI or cTnT) to determine whether myocardial damage is still present and to categorize the risk of death and hospitalization. Because elevated troponin levels in chronic heart failure are linked to unfavorable outcomes, heart failure therapy should be aggressively optimized and closely monitored.[20]

Unless contraindicated, start the four core therapy for HFrEF as soon as feasible. These include a mineralocorticoid receptor antagonist (spironolactone or eplerenone), an SGLT2 inhibitor (dapagliflozin or empagliflozin), an angiotensin receptor-neprilysin inhibitor (ARNI; sacubitril/valsartan) or an ACE inhibitor/ARB if ARNI is not tolerated, and an evidence-based β-blocker (bisoprolol, carvedilol, or metoprolol succinate).

These treatments dramatically lower mortality, heart failure hospitalization, and disease progression when started early and quickly increased.[22]

Regardless of diabetes status, individuals with HFpEF should start taking an SGLT2 inhibitor since it is the only treatment that has substantial evidence of lowering heart failure hospitalization.

Current guidelines should be followed to optimize blood pressure, treat atrial fibrillation correctly, and manage obesity, diabetes, chronic renal disease, and other comorbidities. In certain HFpEF patients, especially those with LVEF at the lower end of the preserved range, mineralocorticoid receptor antagonists and ARNI may be taken into consideration.[23][16]

To detect persistent myocardial stress, inflammation, and fibrosis, combine BNP/NT-proBNP with new biomarkers like high-sensitivity cardiac troponin (hs-cTn), soluble suppression of tumorigenicity-2 (sST2), galectin-3, Growth Differentiation Factor-15 (GDF-15), soluble urokinase plasminogen activator receptor (suPAR), and high-sensitivity C-reactive protein (hs-CRP). Because they are more likely to experience negative consequences, patients with elevated biomarker levels may benefit from tighter

monitoring and an earlier start or escalation of GDMT.

After starting or titrating GDMT, keep an eye on blood pressure, natriuretic peptide levels, serum potassium, and renal function to guarantee therapeutic efficacy, identify side effects, and maintain ideal dosages of heart failure drugs.[22]

COMPOSITE AND MULTI-OMIC BIOMARKER PANELS: TOWARD PRECISION PHARMACOTHERAPY

In order to enhance risk prediction and facilitate precision medication in cardiovascular-kidney-metabolic (CKM) syndrome, recent research supports the use of composite biomarker panels that incorporate metabolic, inflammatory, renal, and cardiovascular indicators. These panels offer a more thorough evaluation of disease development and enable customized treatment selection when compared to single biomarkers.[16]

To evaluate insulin resistance, inflammation, fibrosis, and renal injury, composite biomarker panels integrate established biomarkers (HbA1c, eGFR, UACR, lipid profile, BNP/NT-proBNP) with novel biomarkers (TyG index, eGDR, suPAR, Galectin-3, GDF-15, KIM-1, NGAL, hs-CRP, IL-6, and TNF-α).[17][13]

By identifying molecular changes prior to the onset of clinical disease, multi-omic technologies (genomics, transcriptomics, proteomics, metabolomics, lipidomics, and epigenomics) allow for earlier diagnosis and tailored treatment approaches.

By concurrently assessing several pathogenic pathways, combined metabolic, inflammatory, and renal biomarker panels perform better than single biomarkers in predicting the course of chronic kidney disease (CKD), heart failure, cardiovascular events, and death.

To identify CKM phenotypes, forecast the course of the disease, and direct the customized use of SGLT2 inhibitors, GLP-1 receptor agonists, finerenone, and ARNIs, artificial intelligence (AI)-assisted risk stratification integrates clinical and multi-omic biomarker data, supporting precision pharmacotherapy.[18]

EVIDENCE GAPS AND A PROPOSED FRAMEWORK FOR BIOMARKER-TRIGGERED THERAPY ACROSS THE CKM CONTINUUM

The routine application of biomarkers for cardiovascular-kidney-metabolic (CKM) syndrome in clinical practice is still restricted, despite significant advancements in their discovery. While many emerging biomarkers have not yet been integrated into guideline-directed management, current treatment recommendations still mainly rely on conventional biomarkers, such as HbA1c, estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR), and natriuretic peptides. Despite the promising prognostic value of biomarkers like the triglyceride-glucose (TyG) index, estimated glucose disposal rate (eGDR), soluble urokinase plasminogen activator receptor (suPAR), Growth Differentiation Factor-15 (GDF-15), Galectin-3, Kidney Injury Molecule-1 (KIM-1), and Neutrophil Gelatinase-Associated Lipocalin (NGAL). Further multicenter studies are needed to establish standardized cut-off values, validate their clinical utility, and assess their cost-effectiveness across various populations.[23]

To improve precision pharmacotherapy across the CKM continuum, a biomarker-triggered therapeutic approach has been put forth. Instead of relying only on conventional clinical measures, this method suggests customizing treatment based on a person's biomarker profile. Early introduction of GLP-1 receptor agonists or tirzepatide may be beneficial for patients who exhibit signs of insulin resistance, such as higher TyG index or decreased eGDR.[24]

Similar to this, patients who have falling eGFR or increased albuminuria should be treated as soon as possible with SGLT2 inhibitors in addition to ACE inhibitors or angiotensin receptor blockers (ARBs); nevertheless, if albuminuria persists after optimal therapy, finerenone may be added. Early adjustment of guideline-directed therapy for heart failure may enhance clinical outcomes in individuals with increased BNP/NT-proBNP, high-sensitivity cardiac troponin, Galectin-3, or GDF-15. It is anticipated that future integration of multi-omic technologies with artificial intelligence (AI)-based predictive models would improve patient stratification, identify those most likely to benefit from targeted medicines, and enable genuinely individualized therapy of CKM syndrome.[25]

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