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Laboratory Biomarkers for Early Screening of Metabolic Kidney Disease Risk in Older Adults

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Abstrak

Background: Population aging and the increasing prevalence of metabolic disorders have substantially increased the burden of chronic kidney disease (CKD) among older adults. Because metabolic kidney disease develops gradually and often remains asymptomatic during its early stages, early identification using laboratory biomarkers has become an important strategy for preventing disease progression. **Objective:** This review aimed to summarize current evidence regarding conventional and emerging laboratory biomarkers for the early screening of metabolic kidney disease risk in older adults and to discuss the clinical value of an integrated multimarker approach for risk stratification and preventive nephrology. **Methods:** A narrative review was conducted by synthesizing recent evidence from peer-reviewed literature on laboratory biomarkers associated with metabolic kidney disease. Conventional biomarkers, including glycemic, lipid, renal, inflammatory, metabolic, and hematological parameters, as well as selected novel renal biomarkers, were evaluated with emphasis on their biological rationale, clinical applicability, and limitations. **Results:** Individual laboratory biomarkers reflect different stages of the pathophysiological continuum from metabolic dysregulation to subclinical kidney injury. Glycemic and lipid biomarkers identify upstream metabolic abnormalities, inflammatory and hematological biomarkers indicate systemic immune activation and oxidative stress, whereas renal biomarkers reflect structural and functional kidney impairment. Evidence suggests that integrating these routinely available laboratory biomarkers provides better risk stratification than single-marker assessment and may facilitate earlier identification of high-risk older adults before clinically overt CKD develops. **Conclusion**: An integrated laboratory biomarker approach represents a practical, accessible, and promising strategy for early screening of metabolic kidney disease in older adults. Incorporating multimarker assessment into primary healthcare, geriatric services, and routine medical check-up programs may improve early risk prediction, support personalized preventive interventions, and advance the implementation of predictive, preventive, and precision nephrology.

Keywords: Older adults; metabolic kidney disease; laboratory biomarkers; chronic kidney disease; risk stratification.

Abstrak

Latar Belakang: *Peningkatan populasi lanjut usia disertai tingginya prevalensi gangguan metabolik telah meningkatkan beban penyakit ginjal kronik (PGK). Penyakit ginjal metabolik berkembang secara bertahap dan sering kali tidak bergejala pada tahap awal, sehingga identifikasi dini melalui biomarker laboratorium menjadi strategi penting untuk mencegah progresivitas penyakit.* ***Tujuan****: Artikel tinjauan ini bertujuan merangkum bukti terkini mengenai biomarker laboratorium konvensional dan biomarker baru untuk skrining dini risiko penyakit ginjal metabolik pada lanjut usia, serta mengkaji peran pendekatan multimarker terintegrasi dalam stratifikasi risiko dan pencegahan penyakit ginjal.* ***Metode****: Narrative review dilakukan dengan mensintesis literatur ilmiah terkini mengenai biomarker laboratorium yang berkaitan dengan penyakit ginjal metabolik. Biomarker glikemik, lipid, ginjal, inflamasi, metabolik, hematologi, serta biomarker ginjal baru dievaluasi*

berdasarkan dasar patofisiologi, aplikasi klinis, dan keterbatasannya. ***Hasil****: Setiap kelompok biomarker merefleksikan tahapan yang berbeda dalam perjalanan penyakit, mulai dari disfungsi metabolik hingga cedera ginjal subklinis. Biomarker glikemik dan lipid menggambarkan gangguan metabolik awal, biomarker inflamasi dan hematologi mencerminkan aktivasi inflamasi sistemik dan stres oksidatif, sedangkan biomarker ginjal menunjukkan perubahan struktural dan fungsional ginjal. Bukti yang ada menunjukkan bahwa integrasi biomarker laboratorium rutin memberikan kemampuan stratifikasi risiko yang lebih baik dibandingkan penggunaan biomarker tunggal, sehingga memungkinkan identifikasi dini individu lanjut usia yang berisiko tinggi sebelum terjadi PGK yang nyata.* ***Kesimpulan****: Pendekatan biomarker laboratorium terintegrasi merupakan strategi yang praktis, mudah diterapkan, dan menjanjikan untuk skrining dini risiko penyakit ginjal metabolik pada lanjut usia. Implementasi pendekatan multimarker pada pelayanan primer, klinik geriatri, dan program pemeriksaan kesehatan berkala berpotensi meningkatkan prediksi risiko, mendukung pencegahan yang lebih personal, serta memperkuat penerapan predictive, preventive, and precision nephrology.*

Kata kunci: *lanjut usia; penyakit ginjal metabolik; biomarker laboratorium; penyakit ginjal kronik; stratifikasi risiko.*

I. INTRODUCTION

The rapid growth of the global older adult population has profoundly altered the epidemiological landscape of chronic diseases, particularly chronic kidney disease (CKD). Population aging is accompanied by progressive structural and functional changes in the kidney, including nephron loss, glomerulosclerosis, tubular atrophy, vascular rarefaction, and reduced renal reserve. These physiological alterations increase susceptibility to kidney injury and reduce the organ's capacity to respond to metabolic stress. Consequently, CKD has become one of the most prevalent chronic conditions among older adults and is associated with increased cardiovascular morbidity, frailty, hospitalization, and mortality.

Beyond chronological aging, the increasing prevalence of metabolic disorders including type 2 diabetes mellitus, hypertension, obesity, dyslipidemia, and hyperuricemia has substantially accelerated the development and progression of kidney disease in older adults. These metabolic abnormalities contribute to insulin resistance, oxidative stress, chronic low-grade inflammation, endothelial dysfunction, and renal fibrosis, creating a complex pathophysiological network that culminates in metabolic kidney disease. Rather than acting independently, aging and metabolic dysfunction interact synergistically, amplifying the risk of progressive renal impairment and cardiovascular complications.

One of the greatest clinical challenges is that kidney dysfunction often remains asymptomatic during its early stages. Many older adults are diagnosed only after substantial nephron loss has occurred, limiting opportunities for preventive intervention. Since CKD progression is frequently irreversible, identifying individuals at increased risk before significant decline in kidney function develops has become an important objective of contemporary nephrology. Early risk stratification enables timely lifestyle modification, optimization of metabolic control, and implementation of renoprotective therapies that may delay disease progression and reduce adverse clinical outcomes.

Laboratory biomarkers play a central role in this early identification process because they provide objective, accessible, and relatively inexpensive information regarding metabolic status, renal function, and systemic inflammation. Conventional biomarkers such as fasting plasma glucose, glycated hemoglobin (HbA1c), serum creatinine, estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR), blood urea nitrogen, lipid profile, and serum uric acid remain fundamental components of CKD screening. However, interpretation of these biomarkers in older adults is often complicated by age-related changes in muscle mass, nutritional status, chronic inflammation, multimorbidity, and polypharmacy, all of which may influence biomarker performance and diagnostic accuracy.

To overcome these limitations, increasing attention has been directed toward emerging biomarkers reflecting tubular injury, fibrosis, oxidative stress, and inflammation, including cystatin C, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), inflammatory cytokines, and metabolomic signatures. Although these novel biomarkers demonstrate promising diagnostic and prognostic potential, their routine clinical implementation remains constrained by limited availability, high costs, and insufficient validation across diverse populations. Consequently, there remains a critical need to determine how conventional laboratory biomarkers can be optimally utilized either individually or in combination to improve early screening and risk stratification in older adults.

Recent advances in laboratory medicine have shifted the paradigm from diagnosing established CKD toward predicting future kidney disease risk. Rather than relying on a single biomarker, accumulating evidence supports the integration of multiple laboratory parameters representing glycemic control, lipid metabolism, renal function, hematologic status, and systemic inflammation to identify individuals with subclinical metabolic kidney injury. Such multimarker approaches may better capture the multifactorial nature of metabolic kidney disease and provide a stronger foundation for precision risk prediction and individualized preventive strategies.

Therefore, this narrative review aims to summarize current evidence regarding conventional and emerging laboratory biomarkers for the early screening of metabolic kidney disease risk in older adults. In addition, this review discusses the biological rationale, clinical applicability, limitations, and future perspectives of biomarker-based risk stratification to support earlier identification and prevention of kidney disease in the aging population.

II. PATHOPHYSIOLOGICAL BASIS FOR LABORATORY BIOMARKER-BASED EARLY SCREENING

Kidney aging is characterized by a gradual decline in nephron number, renal blood flow, and glomerular filtration rate, accompanied by structural changes such as glomerulosclerosis, tubulointerstitial fibrosis, vascular rarefaction, and impaired regenerative capacity. These physiological alterations reduce renal functional reserve, rendering older adults more susceptible to metabolic insults than younger individuals. At the cellular level, aging is associated with mitochondrial dysfunction, cellular senescence, impaired autophagy, oxidative stress, and chronic low-grade inflammation (inflammaging), all of which accelerate renal vulnerability and contribute to progressive kidney dysfunction. Importantly, these age-related processes often precede clinically apparent chronic kidney disease (CKD), creating a prolonged subclinical phase during which biological alterations are already occurring despite preserved conventional measures of kidney function.

The coexistence of metabolic disorders including type 2 diabetes mellitus, hypertension, obesity, dyslipidemia, and hyperuricemia further amplifies these age-related changes. Persistent hyperglycemia promotes the formation of advanced glycation end-products, activation of protein kinase C, and excessive production of reactive oxygen species, leading to endothelial dysfunction and mesangial expansion. Meanwhile, dyslipidemia induces lipid accumulation within podocytes and tubular epithelial cells, resulting in lipotoxicity, mitochondrial injury, and inflammatory activation. Hypertension increases intraglomerular pressure and mechanical stress, whereas obesity contributes to insulin resistance and adipose tissue-derived inflammatory cytokine production. Collectively, these metabolic abnormalities initiate glomerular hyperfiltration, tubular injury, endothelial dysfunction, and progressive extracellular matrix deposition long before irreversible nephron loss becomes clinically evident.

These pathological processes are accompanied by measurable biochemical alterations that appear earlier than overt reductions in estimated glomerular filtration rate (eGFR). Disturbances in glucose metabolism are reflected by elevated fasting plasma glucose and glycated hemoglobin (HbA1c), whereas insulin resistance and altered lipid metabolism lead to abnormalities in triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. Simultaneously, low-grade systemic inflammation is associated with changes in inflammatory and hematological markers such as C-reactive

protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and red cell distribution width (RDW). Although these biomarkers are not kidney-specific, they represent upstream metabolic and inflammatory mechanisms that contribute directly to renal injury and therefore provide valuable information regarding future kidney disease risk rather than established kidney damage.

As renal injury progresses from functional adaptation to structural damage, conventional renal biomarkers begin to change. Albuminuria reflects early disruption of the glomerular filtration barrier and may occur before a significant decline in glomerular filtration rate. Serum creatinine and eGFR remain the most widely used indicators of kidney function; however, their sensitivity for detecting early renal impairment in older adults is limited because creatinine concentration is strongly influenced by age-related reductions in muscle mass, nutritional status, and frailty. Consequently, an older individual may already experience significant renal structural injury despite having serum creatinine concentrations within the normal reference range. These limitations have stimulated growing interest in complementary biomarkers such as cystatin C, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and biomarkers reflecting inflammation, oxidative stress, and fibrosis, which may detect subclinical kidney injury earlier than conventional renal function tests.

Rather than functioning independently, laboratory biomarkers should therefore be viewed as components of an integrated biological continuum. Metabolic biomarkers indicate the presence of upstream metabolic dysregulation, inflammatory biomarkers reflect ongoing tissue injury and immune activation, while renal biomarkers demonstrate the transition toward structural and functional kidney impairment. Integrating these biomarker domains provides a more comprehensive assessment of metabolic kidney disease risk than reliance on a single laboratory parameter. Such a multimarker approach aligns with the contemporary paradigm of predictive and preventive nephrology, in which laboratory findings are utilized not merely to diagnose established CKD but to identify high-risk older adults during the preclinical stage, thereby enabling timely lifestyle intervention, optimization of metabolic control, and implementation of renoprotective strategies before irreversible kidney damage occurs.

Pathophysiological framework illustrating the progression from aging-related biological alterations to metabolic disorders, subclinical kidney injury, and subsequent changes in laboratory biomarkers. The integration of metabolic, inflammatory, and renal biomarkers enables early risk stratification of metabolic kidney disease in older adults, facilitating timely preventive interventions before clinically overt chronic kidney disease develops (Figure 1).

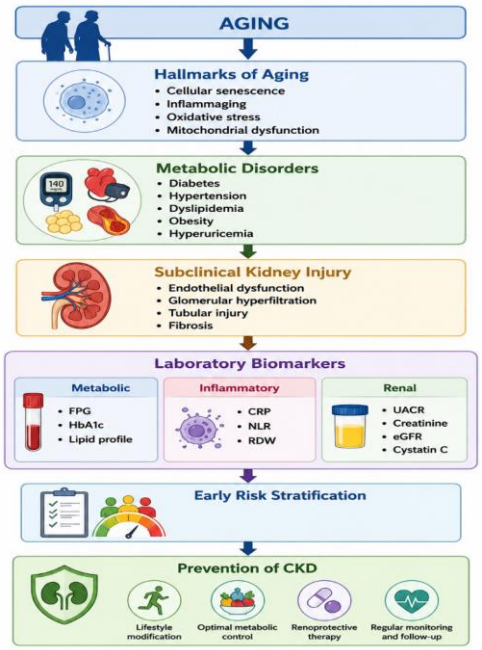

FIGURE 1. PATHOPHYSIOLOGICAL FRAMEWORK OF LABORATORY BIOMARKERS FOR EARLY SCREENING OF METABOLIC KIDNEY DISEASE RISK IN OLDER ADULTS

III. LABORATORY BIOMARKERS FOR EARLY SCREENING OF METABOLIC KIDNEY DISEASE RISK IN OLDER ADULTS

3.1 GLYCEMIC BIOMARKERS

Glucose homeostasis is essential for maintaining normal renal physiology and preserving nephron integrity throughout the aging process. In older adults, physiological aging is accompanied by progressive insulin resistance, impaired pancreatic β-cell function, reduced insulin sensitivity in peripheral tissues, and alterations in glucose metabolism. These metabolic disturbances increase the likelihood of chronic hyperglycemia, even in individuals without previously diagnosed diabetes mellitus. The aging kidney is particularly vulnerable to these metabolic insults because age-related nephron loss, decreased renal reserve, endothelial dysfunction, and chronic low-grade inflammation (inflammaging) reduce its capacity to maintain structural and functional homeostasis. Consequently, disturbances in glucose metabolism may accelerate renal injury well before clinically overt chronic kidney disease (CKD) becomes apparent.

Persistent hyperglycemia initiates multiple interconnected molecular pathways that contribute to diabetic and metabolic kidney injury. Excess intracellular glucose stimulates the formation of advanced glycation end-products (AGEs), which interact with their receptor (RAGE) and activate nuclear factor-kappa B (NF-κB), resulting in increased production of pro-inflammatory cytokines and reactive oxygen species. Simultaneously, activation of the polyol pathway, protein kinase C signaling, and the hexosamine biosynthetic pathway further amplifies oxidative stress, endothelial dysfunction, and mitochondrial injury. These molecular events promote mesangial cell proliferation, podocyte apoptosis, thickening of the glomerular basement membrane, extracellular matrix accumulation, and progressive tubulointerstitial fibrosis. Importantly, these pathological alterations often develop during a prolonged subclinical phase in which conventional indicators of renal function, such as serum creatinine and estimated glomerular filtration rate (eGFR), may remain within the normal range. Therefore, biomarkers reflecting disturbances in glucose metabolism provide an opportunity to identify individuals at increased risk of metabolic kidney disease before irreversible nephron loss occurs.

Among routinely available laboratory parameters, fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) remain the cornerstone biomarkers for evaluating glycemic status. FPG reflects short-term glucose homeostasis and provides a snapshot of hepatic glucose production and insulin sensitivity at the time of blood collection. In contrast, HbA1c reflects cumulative glycemic exposure over approximately 8–12 weeks by measuring the proportion of glycated hemoglobin within circulating erythrocytes. Compared with single glucose measurements, HbA1c exhibits lower intra-individual variability and is less influenced by short-term dietary intake or acute physiological stress, making it particularly useful for long-term metabolic assessment.

Growing epidemiological evidence indicates that glycemic biomarkers are associated not only with diabetes diagnosis but also with future kidney disease risk. Elevated HbA1c has consistently been associated with albuminuria, accelerated decline in eGFR, incident CKD, and increased cardiovascular morbidity, even among individuals without established diabetes mellitus. Similarly, higher FPG concentrations have been associated with an increased risk of renal function decline, suggesting that mild disturbances in glucose metabolism may already reflect ongoing microvascular injury affecting the kidneys. These findings support the concept that glycemic biomarkers should

be interpreted as indicators of cumulative metabolic stress rather than merely diagnostic markers of diabetes.

Recent studies have also highlighted the importance of insulin resistance as an upstream driver of metabolic kidney disease. Beyond hyperglycemia itself, insulin resistance promotes systemic inflammation, endothelial dysfunction, activation of the renin–angiotensin–aldosterone system, and altered lipid metabolism, all of which contribute to glomerular hyperfiltration and progressive nephron injury. In a community-based cohort, indices of insulin resistance, particularly the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), demonstrated stronger predictive performance for incident CKD than traditional glycemic parameters such as FPG or HbA1c, suggesting that insulin resistance may precede measurable deterioration in renal function. Although HOMA-IR is not routinely measured in primary care, these findings emphasize the importance of early metabolic dysregulation in CKD pathogenesis.

3.2 LIPID BIOMARKERS

Dyslipidemia is increasingly recognized as a key contributor to metabolic kidney disease through mechanisms collectively known as renal lipotoxicity, in which excessive lipid accumulation within renal parenchymal cells disrupts cellular homeostasis and accelerates kidney injury. Unlike physiological lipid storage that supports membrane integrity and energy metabolism, pathological lipid deposition results from an imbalance between lipid uptake, de novo lipogenesis, fatty acid oxidation, and cholesterol efflux. This imbalance promotes intracellular accumulation of triglycerides, free fatty acids, ceramides, cholesterol esters, and toxic lipid intermediates within podocytes, mesangial cells, proximal tubular epithelial cells, and renal endothelial cells. These lipid species induce mitochondrial dysfunction, endoplasmic reticulum stress, oxidative stress, inflammasome activation, and apoptosis, ultimately leading to glomerulosclerosis, tubulointerstitial fibrosis, and progressive nephron loss. Recent experimental and translational studies have established renal lipotoxicity as a central pathogenic mechanism linking obesity, diabetes mellitus, metabolic syndrome, and chronic kidney disease (CKD).

The aging kidney is particularly susceptible to lipid-mediated injury because aging is accompanied by impaired mitochondrial fatty acid β-oxidation, reduced autophagic activity, increased oxidative stress, and chronic low-grade inflammation. These age-related alterations reduce the kidney's ability to metabolize intracellular lipids efficiently, thereby facilitating lipid droplet accumulation within renal cells. Moreover, metabolic disorders commonly observed in older adults including insulin resistance, obesity, hypertension, and type 2 diabetes mellitus further exacerbate renal lipid dysregulation by increasing circulating free fatty acids and stimulating de novo lipogenesis. Consequently, lipid accumulation is no longer considered merely a consequence of CKD but rather an early pathogenic event that precedes measurable deterioration in renal function.

Routine lipid biomarkers including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and non-HDL cholesterol remain widely available laboratory parameters that provide valuable information regarding systemic metabolic health and cardiovascular risk. Although these biomarkers are not specific indicators of kidney injury, increasing epidemiological evidence suggests that abnormal lipid profiles are associated with early renal dysfunction independent of traditional cardiovascular risk factors. Elevated triglycerides and LDL-C promote endothelial

dysfunction, increased vascular permeability, and mesangial lipid accumulation, whereas reduced HDL-C impairs reverse cholesterol transport and diminishes its anti-inflammatory and antioxidant functions. Together, these abnormalities facilitate chronic renal inflammation and progressive structural injury, particularly in metabolically vulnerable older adults.

Among conventional lipid biomarkers, hypertriglyceridemia appears to have the strongest association with early kidney injury. Elevated triglyceride concentrations reflect impaired clearance of triglyceride-rich lipoproteins and increased circulating free fatty acids, both of which contribute directly to renal lipotoxicity. Excess fatty acids activate inflammatory pathways through nuclear factor-κB (NF-κB), transforming growth factor-β (TGF-β), and the NLRP3 inflammasome, thereby promoting extracellular matrix deposition and renal fibrosis. Several population-based cohort studies have demonstrated that elevated triglycerides are independently associated with albuminuria, accelerated decline in estimated glomerular filtration rate (eGFR), and incident CKD, even among individuals without diabetes. These findings suggest that triglycerides may serve as an early indicator of metabolic stress affecting the kidney rather than merely reflecting dyslipidemia.

In contrast, HDL-C exerts multiple renoprotective effects beyond cholesterol transport. Functional HDL possesses antioxidant, anti-inflammatory, anti-apoptotic, and endothelial-protective properties that help maintain glomerular integrity and preserve microvascular function. However, aging and chronic metabolic disorders alter HDL composition and functionality, resulting in dysfunctional HDL with diminished antioxidant capacity and impaired cholesterol efflux. Consequently, reduced HDL-C concentrations, or impaired HDL function despite normal concentrations, have been associated with increased albuminuria, vascular stiffness, and progressive renal impairment. These observations indicate that qualitative changes in HDL may be as clinically relevant as quantitative measurements when assessing metabolic kidney disease risk.

Low-density lipoprotein cholesterol (LDL-C) also contributes to renal injury through oxidative modification and intracellular cholesterol accumulation. Oxidized LDL (oxLDL) is readily internalized by podocytes, mesangial cells, and macrophages through scavenger receptors such as CD36, leading to foam cell formation, oxidative stress, and activation of pro-fibrotic signaling pathways. Experimental studies further demonstrate that dysregulation of lipid transport proteins—including CD36, ATP-binding cassette transporters (ABCA1 and ABCG1), sterol regulatory element-binding proteins (SREBPs), and peroxisome proliferator-activated receptor-α (PPAR-α)—plays a pivotal role in renal lipid accumulation and progression of CKD. These molecular mechanisms have emerged as promising therapeutic targets in metabolic kidney disease.

3.3 Renal Biomarkers

Renal biomarkers remain the cornerstone of chronic kidney disease (CKD) detection, staging, and longitudinal monitoring because they directly reflect structural and functional alterations within the kidney. In the context of metabolic kidney disease, renal injury develops gradually through glomerular hyperfiltration, endothelial dysfunction, podocyte loss, tubular injury, and progressive interstitial fibrosis. These pathological changes may evolve over several years before clinically overt CKD becomes apparent. Consequently, laboratory biomarkers capable of identifying these early alterations are essential for recognizing high-risk individuals and initiating timely preventive interventions, particularly among

older adults who have reduced renal functional reserve and increased susceptibility to metabolic stress.

Conventional renal biomarkers—including serum creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR), and albuminuria—continue to serve as the foundation of routine kidney function assessment. Serum creatinine is the most frequently used endogenous marker for estimating glomerular filtration rate because of its wide availability, low cost, and standardized measurement. Current clinical practice recommends interpreting serum creatinine together with eGFR calculated using the CKD-EPI equation, which provides a more accurate estimation of kidney function than serum creatinine alone. However, serum creatinine primarily reflects filtration capacity rather than structural kidney injury and typically rises only after substantial nephron loss has already occurred. Therefore, reliance solely on serum creatinine may delay recognition of early metabolic kidney disease.

Among conventional renal biomarkers, albuminuria is widely regarded as the earliest clinically detectable manifestation of glomerular injury. Increased urinary albumin excretion reflects disruption of the glomerular filtration barrier resulting from endothelial dysfunction, glycocalyx injury, podocyte damage, and basement membrane remodeling. Importantly, albuminuria frequently precedes measurable reductions in eGFR and has consistently been associated with both CKD progression and cardiovascular morbidity. For this reason, current international guidelines recommend combined assessment of eGFR and UACR rather than either parameter alone for CKD screening and risk stratification. This combined approach substantially improves prediction of kidney disease progression, cardiovascular events, and all-cause mortality, particularly in older adults with diabetes, hypertension, or metabolic syndrome.

Despite their widespread clinical use, conventional renal biomarkers possess several important limitations when applied to aging populations. Serum creatinine is highly dependent on skeletal muscle mass, dietary protein intake, sex, ethnicity, hydration status, and frailty. Because aging is commonly accompanied by sarcopenia and reduced muscle mass, serum creatinine concentrations may remain within the normal reference range despite significant reductions in nephron number and glomerular filtration. Consequently, kidney dysfunction may be substantially underestimated in older adults when serum creatinine is interpreted in isolation. Likewise, BUN is influenced by protein intake, liver function, gastrointestinal bleeding, and hydration status, limiting its specificity as a marker of renal impairment. These age-related physiological changes complicate interpretation of conventional biomarkers and underscore the need for complementary indicators capable of detecting subclinical kidney injury.

Among emerging biomarkers, cystatin C has received considerable attention as an alternative endogenous marker of glomerular filtration. Unlike serum creatinine, cystatin C is produced at a relatively constant rate by all nucleated cells and is much less affected by skeletal muscle mass or dietary protein intake. Numerous studies have demonstrated that cystatin C-based eGFR provides improved risk stratification for cardiovascular events, frailty, and mortality in older adults. Nevertheless, interpretation of cystatin C also requires caution because its concentration may be influenced by systemic inflammation, thyroid dysfunction, smoking, obesity, and corticosteroid use. Recent discussions have therefore emphasized that cystatin C should complement rather than completely replace serum creatinine in routine clinical practice. Combined creatinine–cystatin C equations

generally provide the highest diagnostic accuracy for estimating kidney function and predicting adverse renal outcomes.

Increasing interest has also focused on biomarkers reflecting tubular injury, which may identify kidney damage before substantial impairment of glomerular filtration occurs. Neutrophil gelatinase-associated lipocalin (NGAL) is one of the best-characterized tubular biomarkers and is rapidly released from injured tubular epithelial cells following ischemic or metabolic injury. Elevated urinary and plasma NGAL concentrations have been associated with early tubular dysfunction, accelerated CKD progression, and future decline in kidney function. Similarly, kidney injury molecule-1 (KIM-1), a transmembrane glycoprotein expressed in dedifferentiated proximal tubular epithelial cells after injury, has demonstrated strong associations with tubular damage, interstitial fibrosis, and CKD severity. These biomarkers are particularly attractive because tubular dysfunction often precedes measurable declines in eGFR in metabolic kidney disease.

3.4 Inflammatory Biomarkers

Chronic low-grade inflammation, commonly referred to as inflammaging, is now recognized as one of the fundamental hallmarks of biological aging and a major driving force in the development of metabolic kidney disease. Unlike acute inflammation, inflammaging is characterized by persistent activation of the innate immune system, accompanied by modest but sustained elevations in circulating inflammatory mediators. Age-related immune dysregulation results from cumulative oxidative stress, mitochondrial dysfunction, cellular senescence, impaired autophagy, and activation of the senescence-associated secretory phenotype (SASP), which collectively promote continuous production of pro-inflammatory cytokines and chemokines. In older adults, these inflammatory processes are further amplified by metabolic disorders such as obesity, insulin resistance, type 2 diabetes mellitus, hypertension, and dyslipidemia, creating a chronic inflammatory milieu that accelerates renal aging and predisposes individuals to chronic kidney disease (CKD).

Inflammation contributes to kidney injury through multiple interconnected mechanisms involving both glomerular and tubulointerstitial compartments. Persistent activation of inflammatory signaling pathways, particularly nuclear factor-kappa B (NF-κB), nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome, Janus kinase/signal transducer and activator of transcription (JAK/STAT), and transforming growth factor-β (TGF-β), promotes endothelial dysfunction, increased vascular permeability, leukocyte recruitment, macrophage infiltration, podocyte injury, and extracellular matrix accumulation. These events stimulate fibroblast activation and progressive renal fibrosis, ultimately leading to irreversible nephron loss. Importantly, inflammatory activation often precedes measurable reductions in estimated glomerular filtration rate (eGFR), indicating that inflammatory biomarkers may serve as early indicators of metabolic kidney injury before conventional renal biomarkers become abnormal.

Among routinely available inflammatory biomarkers, C-reactive protein (CRP) remains the most extensively investigated marker of systemic inflammation. Synthesized primarily by hepatocytes in response to interleukin-6 (IL-6), CRP reflects activation of the acute-phase response and has consistently been associated with incident CKD, albuminuria, accelerated decline in kidney function, cardiovascular disease, and all-cause mortality. High-sensitivity CRP (hs-CRP), capable of detecting low-grade

inflammation, has attracted increasing attention because even modest elevations are associated with metabolic syndrome and subclinical renal dysfunction in community-dwelling older adults. Although CRP is not specific to kidney disease, its widespread availability and standardized measurement make it an attractive component of population-based screening strategies.

Pro-inflammatory cytokines, particularly interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), play central roles in mediating renal inflammation and fibrosis. IL-6 stimulates hepatic CRP synthesis while simultaneously promoting mesangial cell proliferation, endothelial dysfunction, and activation of profibrotic pathways within the kidney. TNF-α contributes to apoptosis of podocytes and tubular epithelial cells, disruption of endothelial integrity, and increased oxidative stress. Elevated circulating concentrations of IL-6 and TNF-α have been associated with albuminuria, rapid eGFR decline, frailty, cardiovascular events, and increased mortality among older adults. Experimental evidence further suggests that persistent cytokine activation accelerates progression from subclinical kidney injury to established CKD through sustained inflammatory signaling and extracellular matrix remodeling.

Composite inflammatory indices derived from routine hematological testing have emerged as practical and inexpensive alternatives for assessing systemic inflammation. Among these, the neutrophil-to-lymphocyte ratio (NLR) has received considerable attention because it integrates two complementary aspects of immune regulation: neutrophilia reflecting innate immune activation and relative lymphopenia indicating impaired adaptive immunity. Elevated NLR has been independently associated with albuminuria, reduced eGFR, CKD progression, cardiovascular complications, and mortality across diverse populations. Similarly, the platelet-to-lymphocyte ratio (PLR) and the systemic immune-inflammation index (SII) have shown promising associations with metabolic syndrome, vascular dysfunction, and renal impairment, although evidence regarding their routine application in CKD screening remains limited. Their major advantage lies in being calculated from a standard complete blood count without additional laboratory costs, making them attractive candidates for large-scale screening programs.

3.5 METABOLIC BIOMARKERS

Metabolic biomarkers provide important complementary information beyond conventional renal function tests by reflecting systemic metabolic homeostasis, nutritional status, endocrine regulation, and mineral metabolism, all of which influence kidney health. In older adults, metabolic dysregulation frequently precedes structural kidney damage and contributes to the initiation of chronic kidney disease (CKD) through multiple interconnected mechanisms, including oxidative stress, endothelial dysfunction, mitochondrial impairment, insulin resistance, activation of the renin–angiotensin–aldosterone system (RAAS), chronic low-grade inflammation, and disturbances in calcium-phosphate metabolism. Unlike renal biomarkers that primarily indicate established kidney dysfunction, metabolic biomarkers capture upstream biological processes that predispose the aging kidney to injury, making them particularly valuable for early risk stratification of metabolic kidney disease. Recent evidence increasingly supports the concept that metabolic abnormalities should be viewed as modifiable risk factors rather than merely consequences of declining kidney function.

Among currently available metabolic biomarkers, serum uric acid (SUA) has received considerable attention because of its dual role as both a metabolic product and a

potential mediator of kidney injury. Hyperuricemia is common among older adults owing to reduced renal urate excretion, increased oxidative stress, metabolic syndrome, and insulin resistance. Experimental studies have demonstrated that elevated uric acid concentrations stimulate activation of the renin–angiotensin system, endothelial dysfunction, vascular smooth muscle proliferation, oxidative stress, and inflammatory signaling through nuclear factor-kappa B (NF-κB) and NLRP3 inflammasome activation. These mechanisms promote glomerular hypertension, microvascular rarefaction, tubular injury, and progressive renal fibrosis. Epidemiological studies published over the last five years consistently report that elevated SUA is independently associated with incident CKD, albuminuria, accelerated decline in estimated glomerular filtration rate (eGFR), and increased cardiovascular mortality, even after adjustment for diabetes and hypertension. These findings suggest that serum uric acid represents an early indicator of metabolic kidney vulnerability rather than simply a consequence of impaired renal excretion.

Serum albumin is another clinically important metabolic biomarker because it reflects multiple physiological processes, including nutritional status, hepatic protein synthesis, systemic inflammation, and vascular permeability. Albumin possesses antioxidant, anti-inflammatory, and endothelial-protective properties that contribute to maintenance of microvascular integrity. In older adults, hypoalbuminemia frequently reflects chronic inflammation, protein-energy wasting, frailty, or occult systemic disease rather than isolated nutritional deficiency. Numerous cohort studies have demonstrated that lower serum albumin concentrations are associated with accelerated CKD progression, increased hospitalization, cardiovascular events, and all-cause mortality. Furthermore, hypoalbuminemia may coexist with albuminuria, indicating simultaneous impairment of systemic protein metabolism and glomerular barrier function. Consequently, serum albumin provides prognostic information extending beyond conventional assessment of nutritional status and should be interpreted within the broader context of systemic metabolic health.

Disturbances in electrolyte and mineral metabolism also represent important metabolic alterations associated with early kidney dysfunction. Although abnormalities in sodium and potassium are often observed in advanced CKD, subtle changes in electrolyte homeostasis may occur during the early stages of renal injury due to impaired tubular handling and hormonal dysregulation. Similarly, alterations in calcium and phosphate metabolism become increasingly prevalent with aging because of declining nephron number, reduced vitamin D activation, secondary hyperparathyroidism, and fibroblast growth factor-23 (FGF-23) activation. Even before overt CKD develops, disruption of mineral metabolism contributes to vascular calcification, endothelial dysfunction, oxidative stress, and chronic inflammation, thereby increasing both cardiovascular and renal risk. Recent evidence suggests that elevated phosphate concentrations, even within the upper normal range, are associated with faster kidney function decline and increased cardiovascular morbidity in older populations.

Increasing attention has also focused on vitamin D metabolism as a potential indicator of metabolic kidney health. Vitamin D deficiency is highly prevalent among older adults due to reduced skin synthesis, decreased dietary intake, impaired intestinal absorption, and diminished renal conversion of 25-hydroxyvitamin D to its active form, 1,25-dihydroxyvitamin D. Beyond its classical role in calcium homeostasis, vitamin D modulates immune function, suppresses renin expression, attenuates oxidative stress, and inhibits renal

fibrogenesis. Observational studies have demonstrated associations between vitamin D deficiency and albuminuria, reduced eGFR, increased inflammation, and progression of CKD. However, intervention trials evaluating vitamin D supplementation have produced inconsistent results, indicating that serum vitamin D is currently more valuable as a biomarker of metabolic health than as an established therapeutic target for CKD prevention.

3.6 HEMATOLOGICAL BIOMARKERS

Routine hematological parameters have emerged as promising adjunctive biomarkers for the early identification of metabolic kidney disease because they reflect several fundamental biological processes involved in renal aging, including chronic inflammation, oxidative stress, endothelial dysfunction, impaired erythropoiesis, and immune dysregulation. Complete blood count (CBC) parameters including hemoglobin concentration, hematocrit, red blood cell distribution width (RDW), leukocyte count, platelet count, and leukocyte-derived inflammatory indices are inexpensive, widely available, standardized, and routinely measured in both primary and tertiary healthcare settings. Unlike kidney-specific biomarkers that primarily reflect structural or functional renal damage, hematological biomarkers capture systemic alterations that often precede measurable impairment in renal filtration, making them attractive candidates for early risk stratification in older adults. Recent reviews have highlighted that hematological indices not only change with aging but also integrate signals from metabolic dysfunction, chronic inflammation, and vascular aging, all of which contribute to chronic kidney disease (CKD).

The biological basis for using hematological biomarkers in metabolic kidney disease lies in the close interaction between the hematopoietic system, immune system, and kidney. Aging is accompanied by immunosenescence and persistent low-grade inflammation (inflammaging), resulting in altered erythropoiesis, increased oxidative stress, shortened erythrocyte lifespan, and changes in leukocyte activation. Simultaneously, metabolic disorders such as diabetes mellitus, obesity, hypertension, and insulin resistance amplify inflammatory signaling through activation of the NF-κB pathway, increased production of reactive oxygen species, and endothelial injury. These systemic alterations are reflected in routine hematological indices long before overt deterioration of renal function becomes evident. Consequently, CBC-derived biomarkers provide indirect but clinically meaningful information regarding the biological environment that promotes renal injury.

Among erythrocyte indices, red cell distribution width (RDW) has received increasing attention as a marker of biological aging and chronic disease. RDW represents the variability in erythrocyte size (anisocytosis) and has traditionally been used in the differential diagnosis of anemia. However, accumulating evidence indicates that elevated RDW reflects chronic inflammation, oxidative stress, nutritional deficiencies, impaired iron metabolism, and ineffective erythropoiesis rather than hematological disorders alone. Oxidative stress damages erythrocyte membranes and shortens erythrocyte survival, whereas inflammatory cytokines impair bone marrow erythropoiesis, resulting in increased heterogeneity of circulating red blood cells. In patients with CKD, elevated RDW has consistently been associated with albuminuria, reduced estimated glomerular filtration rate (eGFR), vascular calcification, cardiovascular events, frailty, and increased mortality. Importantly, RDW appears to predict adverse outcomes independently of hemoglobin concentration, suggesting that it captures biological processes beyond anemia itself.

Another CBC-derived biomarker that has gained considerable attention is the neutrophil-to-lymphocyte ratio (NLR), which reflects the balance between innate inflammatory activation and adaptive immune regulation. Neutrophilia represents activation of the innate immune response, whereas relative lymphopenia reflects impaired adaptive immunity and chronic physiological stress. Elevated NLR has been associated with persistent systemic inflammation, endothelial dysfunction, renal fibrosis, and accelerated decline in kidney function. Recent systematic reviews and meta-analyses have demonstrated that individuals with elevated baseline NLR have significantly lower eGFR and an almost two-fold greater risk of progression to end-stage kidney disease (ESKD), even after adjustment for conventional renal risk factors. Because NLR can be calculated directly from routine CBC results without additional laboratory cost, it represents an attractive biomarker for population-based screening and longitudinal risk assessment.

Hemoglobin concentration remains one of the most clinically relevant hematological biomarkers in kidney disease. Although anemia is classically regarded as a complication of advanced CKD resulting from inadequate erythropoietin production, accumulating evidence suggests that subtle reductions in hemoglobin may occur much earlier during kidney disease progression. Chronic inflammation suppresses erythropoietin synthesis, impairs iron utilization through hepcidin-mediated pathways, and shortens erythrocyte survival, resulting in progressive anemia even before severe reductions in eGFR develop. Furthermore, anemia contributes to renal hypoxia, increased oxidative stress, and activation of profibrotic signaling pathways, thereby accelerating CKD progression. Recent observational studies have demonstrated that declining hemoglobin levels independently predict worsening CKD stage, cardiovascular complications, and mortality among older adults, emphasizing that hemoglobin should be interpreted not only as a marker of oxygen-carrying capacity but also as an indicator of systemic metabolic and inflammatory burden.

IV. Toward Precision Screening and Clinical Decision Support

The increasing availability of electronic laboratory data creates opportunities to develop integrated risk prediction models capable of identifying older adults at high risk for metabolic kidney disease. Rather than relying on a single laboratory abnormality, predictive algorithms may combine glycemic, lipid, inflammatory, metabolic, hematological, and renal biomarkers into individualized risk scores. Such models could be incorporated into clinical decision support systems (CDSS), automatically identifying high-risk patients and providing evidence-based recommendations for monitoring, referral, and preventive management.

This integrated laboratory-based approach represents a transition from conventional disease detection toward predictive, preventive, and precision nephrology, where routinely available laboratory data are used not only to diagnose established CKD but also to anticipate future kidney disease risk and guide individualized preventive interventions.

V. Conclusion

Metabolic kidney disease in older adults results from the complex interaction between biological aging and metabolic disturbances, including hyperglycemia, dyslipidemia, chronic inflammation, oxidative stress, and endothelial dysfunction. Because these pathological processes develop gradually and often remain asymptomatic, early identification before clinically overt chronic

kidney disease (CKD) is essential for timely prevention and intervention.

This review highlights that routinely available laboratory biomarkers—including glycemic, lipid, renal, inflammatory, metabolic, and hematological parameters—provide complementary information reflecting different stages of disease progression. Rather than being interpreted individually, these biomarkers should be integrated into a multimarker approach to improve early risk stratification, identify subclinical kidney injury, and support more personalized preventive strategies. Their wide availability and low cost make them particularly suitable for implementation in primary healthcare, geriatric clinics, and routine medical check-up programs.

Overall, an integrated laboratory biomarker approach represents a practical and promising strategy for shifting kidney care from the diagnosis of established CKD toward earlier risk prediction and prevention, thereby supporting the transition to predictive, preventive, and precision nephrology

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