*Review Paper:*

# Navigating CKD Diagnosis: Biomarkers as Predictive Tools for Early Detection

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***Abstract***

*The prevalence of CKD worldwide is a significant health concern, considering its estimated incidence in 13.4% of the world population and millions who require renal replacement therapy. This review about early CKD detection by traditional biomarkers like GFR and albuminuria focuses on the importance of this issue, mainly due to the limitations of these indicators, particularly in early CKD stages. The review promises several new emerging biomarkers like beta-trace protein, or BTP, beta-2-microglobulin, or B2M, klotho, neutrophil gelatinase-associated lipocalin, or NGAL and liver-type fatty acid-binding protein, or L-FABP. Such markers would identify kidney dysfunction, tubulointerstitial damage and endothelial dysfunction more promptly and are thus crucial for improved patient outcomes.*

*While these advances will eventually take place in the standardization of the use of biomarkers for clinical practice, especially in resource-limited settings, where this overdiagnoses and overtreats. It also makes it difficult to have a "universal" gold standard of biomarkers for early CKD, thus making validation and implementation difficult. Future studies should validate these biomarkers in terms of their cost-effectiveness and long-term consequences in the management of CKD and patient care.*

**Keywords:** Chronic kidney disease, biomarkers, GFR, albuminuria, BTP, B2M, klotho, NGAL, L-FABP, early detection.

## Introduction

Chronic kidney disease is low kidney function and is expressed by a glomerular filtration rate of less than 60 mL/min/1.73m$^2$ and/or presence of damage in the kidney for 3 or more months duration[36]. CKD has been recognized as one of the leading public health problems all over the world.

An estimated 4.902 to 7.083 million persons have ESKD that need renal replacement treatment, while 13.4% (11.7–15.1%) of the world's population has CKD. CKD burden is likely to continue to increase worldwide as diabetes, the leading cause of CKD worldwide, increases in prevalence. This growing burden is most likely to occur in Asia, which will harbor >4.5 billion people or 60% of the worldwide population[48].

Estimated to increase by over 150% between 2000 and 2035 across South Asia alone, by 2035 China and India will be the countries with the most people with diabetes, 251.7 million, in total. Another concern is an increase in clusters of CKD of unknown aetiology, which is reported in parts of South Asia including Sri Lanka and India[45].

The worldwide burden of illness and mortality is impacted by CKD because of its influence on cardiovascular risk and ESKD[48]. Cardiovascular disease is the primary cause of morbidity and death, even in people with end-stage renal disease (ESRD). It remains the most common cause of death for dialysis and transplant recipients.

Based on both conventional and disease-specific risk factors, there is growing evidence that patients are actually experiencing a rise in the burden of CVD before beginning dialysis. The discovery that the risk for cardiovascular events and death is elevated even in the initial stages of CKD in comparison to those who do not exhibit any signs of CKD, is particularly noteworthy[41].

**Etiology:** Diabetes, high blood pressure and elevated body mass index are recognized risk factors in the industrialized world, in poor nations. Infectious glomerulonephritis and interstitial nephritis also cause kidney disease, along with urolithiasis, long-term drug abuse and environmental conditions[6].

In the absence of these risk factors, CKDs have been shown to originate in Central America, Sri Lanka and India, among other regions of the world, known as CKDu, or chronic kidney disease of unclear etiology.

**Box 1**: The 3 levels of albuminuria include an ACR[31]:

- A1: ACR less than 30 mg/g (<3.4 mg/mmol)
- A2: ACR 30 to 299 mg/g (3.4-34 mg/mmol)
- A3: ACR greater than 300 mg/g (>34 mg/mmol)

| Stages of CKD Based on eGFR[31] | |
|---|---|
| G1 | G1: GFR 90 mL/min/1.73 $m^2$ and above with evidence of kidney disease, such as hematuria or proteinuria. |
| G2 | GFR 60 to 89 mL/min/1.73 $m^2$ |
| G3b | GFR 45 to 59 mL/min/1.73 $m^2$ |
| G3b | GFR 30 to 44 mL/min/1.73 $m^2$ |
| G4 | GFR 15 to 29 mL/min/1.73 $m^2$ |
| G5 | GFR less than 15 mL/min/1.73 $m^2$ or treatment by dialysis. |

**Figure 1: Stages of CKD based on eGFR**

| SYMPTOMS OF CKD[79] |
|---|
| **1. Hypertension** |
| **2. Nausea and Vomiting** |
| **3. Loss of appetite** |
| **4. Oliguria** |
| **5. Sleep disturbance** |
| **6. Muscle cramps** |
| **7. Decrease mental sharpness** |
| **8. Swelling of feet and ankles** |
| **9. Chest pain due to uremic pericarditis** |
| **10. Shortness of breath due to pulmonary edema** |

**Figure 2: Symptoms of CKD**

| RISK FACTORS OF CKD |
|---|
| **1. Non-Modifiable**: Old age, male gender and non-white ethnicity including Black Americans, Afro-Caribbean individuals, Hispanics and Asians, all adversely affect CKD progression[49]. |
| **2. Modifiable**: Systemic Hypertension, Metabolic factors and Proteinuria[42]. |

**Figure 3: Showing Risk factor of CKD**

**Pathophysiology:** Chronic and ongoing damage from increasing nephropathies leads to enduring kidney fibrosis and the deterioration of normal kidney structure, unlike acute kidney injury (AKI), which usually results in full functional recovery. The injury is likely to impact the glomeruli, tubules, interstitium and arteries, which are the three primary components of the kidney. Histologically, it will manifest as vascular sclerosis, tubulointerstitial fibrosis and glomerulosclerosis. Scarring and fibrosis arise from a sequence of interrelated processes:

(1) Kidneys compromised by infiltration of inflammatory cells. (2) Intrinsic renal cell activation and proliferation, followed by their eventual demise, mesangiolysis, podocytopenia and necrosis. (3) Myofibroblasts and fibroblasts, along with other extracellular matrix-producing cells, get stimulated and proliferate. The conventional architecture is supplanted by the deposition of extracellular matrix. Glomerulosclerosis is a histological entity that represents the culmination of these processes[4]. Proteinuria, hypertension, African descent and hyperglycemia are all associated factors. The acceleration of chronic kidney disease (CKD) has been associated with environmental factors including lead exposure, smoking, metabolic syndrome, certain analgesics and obesity[26].

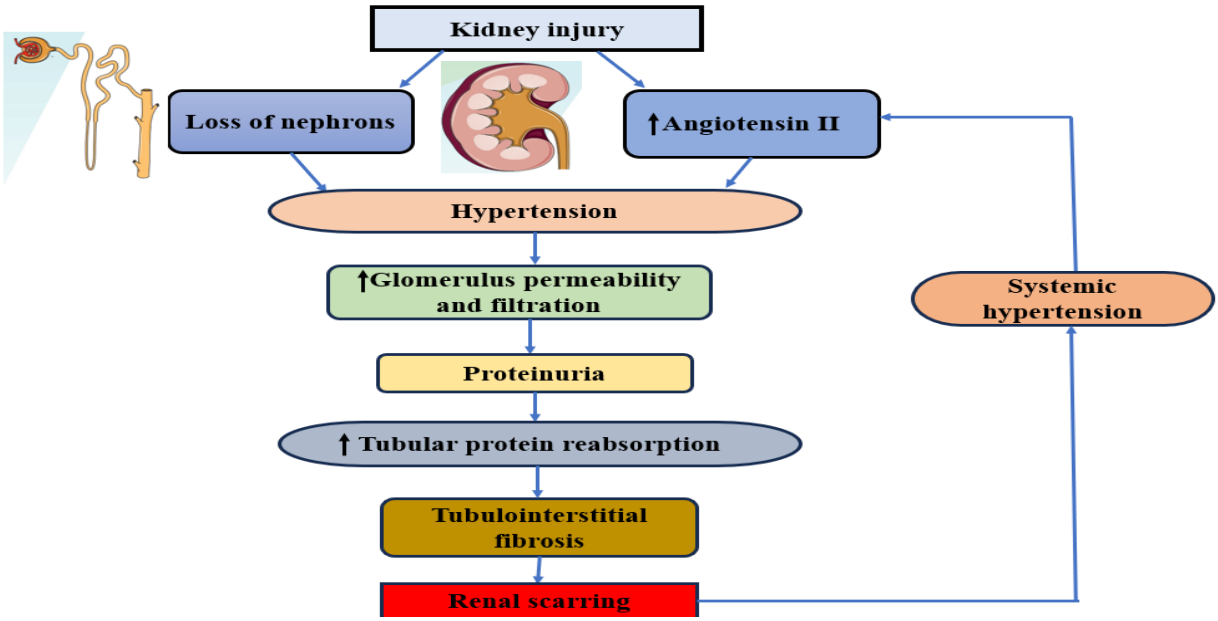


**Figure 4: Pathophysiology of Chronic Kidney Disease**

## Biomarkers for measurement of renal function

Estimating albuminuria and glomerular filtration rate is a routine procedure in the diagnosis and prognosis of chronic kidney disease (CKD). Albuminuria indicates renal impairment, serving as a reliable measure of the extent of kidney disease. Conversely, traditional indicators gain prominence only once renal disease has advanced and filtration capacity has markedly diminished[87]. Consequently, they escalate after many instances of renal cell injury have occurred[42,43]. Over the past two decades, various novel biomarkers have surfaced as promising instruments in combating chronic kidney disease[47]. Future research should prioritise enhanced biomarkers of renal dysfunction beyond GFR and specific serum and urine-based markers of kidney injury. The pathophysiological mechanisms underlying kidney damage including alterations in kidney function, tubulointerstitial injury, endothelial dysfunction, inflammation and cardiovascular risk factors, require further exploration of specific biomarkers that can detect kidney injury and can correlate with these mechanisms[69].

**Beta Trace Protein (BTP) and Beta -2-Microglobulin (B2M):** The proximal tubules re-absorb more than 90% of the low-molecular-weight proteins filtered by the glomeruli such as beta trace protein and beta-2-microglobulin. These proteins have been suggested as serum markers of diminished GFR and in instances of elevated urinary excretion, as indicators of tubular damage due to their predominantly sustained urinary excretion[22]. Prostaglandin H2 is metabolized through prostaglandin D2 synthase, also known as BTP. Due to its importance in cerebrospinal fluid (CSF) and its significantly lower concentrations in blood, it has been utilized as a diagnostic for CSF leakage[19]. Numerous researchers have investigated BTP and compared its diagnostic efficacy to conventional markers of chronic renal disease[10,75]. The findings indicated a robust correlation between elevated BTP levels in urine and systemic circulation and increased concentrations of creatinine and cystatin C. Furthermore, BTP concentrations in urine escalated over time, corresponding with decreasing glomerular filtration rate (GFR) and the elevation in serum concentrations[16]. BTP and B2M have been linked in numerous studies to the progression of end-stage renal disease (ESRD), the onset of cardiovascular disease (CVD) and mortality[21,66]. A 14-year cohort study of 250 T2D Pima Indians revealed that while both BTP and B2M are linked to end-stage renal disease (ESRD), B2M was the sole predictor demonstrating an independent linkage with mortality.

Findings from a cohort analysis involving 9,703 individuals from the Atherosclerosis risk in communities experiment confirmed the viability of utilising B2M variations as an indicator of ESRD progression. The onset of end-stage renal disease (ESRD) was significantly associated with a 30% reduction in renal function, as indicated by this innovative filtration marker. A meta-analysis of 23,318 individuals from 6 trials assessed the benefits of reclassifying eGFR, predicting the risk of kidney failure and mortality, utilising eGFR equations based on BTP and B2M respectively. Considering established risk variables, the eGFR equations utilising BTP and B2M demonstrated superior performance compared to traditional creatinine-based models in forecasting kidney failure and mortality. Furthermore, this yielded the most precise outcomes for predicting eGFR by an equation incorporating both markers[32].

**Klotho:** The transmembrane protein klotho is predominantly expressed by cells in the proximal and distal tubules[8]. Blood klotho concentrations are diminished in CKD patients. Stages 1 and 2 CKD patients exhibited a direct association between Klotho deficiency and the extent of kidney function deterioration[28,88]. Klotho has been identified as a highly sensitive and early biomarker for chronic kidney disease (CKD), since its levels correspond

with the severity of renal insufficiency[28].

The study revealed that alongside diminished klotho levels, CKD patients had an elevated risk of cardiovascular disease (CVD)[30], mortality[72], inflammation and albumin excretion (ACE)[56]. Zhang et al[86] noted that in a cohort of 125 patients receiving hemodialysis, serum klotho levels were associated with the severity of mineral bone disease. A study including 152 CKD patients revealed a negative correlation between serum klotho levels and serum phosphate levels. This indicates that diminished klotho levels exacerbate the problem of urinary phosphate excretion[44].

**Biomarkers for tubular lesions**

**Neutrophil Gelatinase-Associated Lipocalin (NGAL), Kidney Injury Molecule-1 (KIM-1) and N-acetyl-_-D-glucosaminidase (NAG):** In the course of bacterial infections, activated neutrophils secrete NGAL, a ubiquitous lipocalin protein that transports iron. It is expressed within damaged renal tubular epithelial cells released by them. In 45 people with CKD, due to renal dysplasia, obstructive uropathy, glomerular and cystic diseases, blood NGAL levels exhibited an inverse correlation with GFR[58]. No patients in the CKD trial with measured NGAL levels had previously administered steroids, immunosuppressants, ACE inhibitors, or angiotensin 2 receptor blockers (ARB). Proteinuria over 1 g/day for minimum 6 months was a characteristic of all patients. Twenty healthy individuals were recruited to serve as controls. All subjects had given informed consent following the approval of the study by the local ethics committee.

Results were presented in nanograms per milliliter and were acquired using a commercially sold Elisa kit from the Antibody Shop in Gentofte, Denmark, to assess NGAL in urine. The data was statistically analyzed using GraphPad Prism (version 4.0) software. Pearson correlation coefficient was employed to identify correlations and the unpaired two-tailed t-test to compare the groups. If $P<0.05$, the results were deemed statistically significant. The findings indicate that uNGAL concentrations were markedly elevated in patients exhibiting macroproteinuria compared to controls ($378.28 \pm 111.13$ vs $7.38 \pm 3.26$ ng/ml; $P=0.01$). Furthermore, these concentrations demonstrated a direct correlation with urinary protein excretion ($r=0.294$, $P=0.01$) and an inverse correlation with residual renal function (uNGAL/GFR: $r=0.528$, $P=0.04$; uNGAL/Creatinine: $r=0.588$, $P=0.02$)[14].

KIM-1 is a cellular receptor that controls how the immune system reacts to viral infections. It is imperceptible in healthy kidneys but manifests at increased levels in renal damage investigations and clinical applications[29]. Urinary levels serve as a valuable complement to blood KIM-1 levels in evaluating acute or chronic kidney injury, since they reflect the cumulative impact of damage to the kidney's proximal tubules over time. In instances of persistent chronic damage, plasma KIM-1 may prove to be an indispensable resource[68]. Zhang et al[86] discovered that in a cohort of 324 persons with hypertension and no prior kidney illness, baseline KIM-1 concentrations were positively correlated with the risk of developing incident chronic kidney disease (CKD). NGAL, rather than KIM-1, was associated with the UACR and the occurrence of reduction in eGFR in a follow-up research involving 527 individuals with type 1 diabetes[64].

Glycosidase NAG is predominantly found in the lysosomes of cells situated at the distal end of the proximal tubule[73]. An increase in N-acetyl-β-D-glucosaminidase (NAG) levels in urine signifies proximal tubular damage, as the molecule cannot be filtered by the glomeruli due to its substantial molecular weight of 130,000 Dalton. Jungbauer et al[35] evaluated the levels of urinary NAG, NGAL and KIM-1 in 149 patients with chronic heart failure (CHF) over a 5-year follow-up to predict the advancement of chronic kidney disease (CKD). These patients illustrated the efficacy of NAG and KIM-1 as cardiorenal biomarkers by establishing robust correlations between CKD progression and these variables, but no such link was seen with NGAL.

However, in a prospective cohort study involving 250 patients spanning all stages of chronic kidney disease (CKD), NGAL exhibited a stronger association with CKD progression than KIM-1 and NAG. NGAL was the exclusive predictor of kidney failure and mortality. The varying outcomes may indicate that NGAL, KIM-1 and NAG respond differently based on the etiology of CKD[46]. Future research should investigate the dynamics of NGAL, KIM-1 and NAG as kidney disease biomarkers in chronic kidney disease (CKD) of various etiologies.

**Liver-Type Fatty Acid Binding Protein (L-FABP):** The 14-kDa mammalian intracellular fatty acid-binding protein (FABP) belongs to the superfamily of lipid-binding proteins (LBP) and is encoded by 89-gene family[74]. L-FABP is expressed in liver as well as in several tissues including the intestines, pancreas, stomach, lungs and kidneys. Albumin is mainly reabsorbed in the proximal tubules, attached to free fatty acids, under normal conditions following filtration by the glomeruli[83]. Chronic kidney disease 273 (CKD 273) patients are characterized by significant proteinuria and an excess of fatty acids. Moreover, an excess of fatty acids may manifest in CKD 275 patients with hypertriglyceridemia.

In contrast to patients with minimal change nephrotic syndrome (MCNS), individuals with chronic kidney disease (CKD) excrete linoleic and arachidonic acids in their urine at significantly elevated rates[37]. A clinical trial identified a link between urinary excretion of L-FABP and the severity of tubulointerstitial damage as well as the rate of progression of chronic kidney disease. Furthermore, a multicenter study indicated that urine L-FABP had greater sensitivity than urinary protein in forecasting the progression of chronic renal illness[69]. Urine L-FABP has been proposed as an early marker for detection of acute kidney injury and an indicator

of the progression of diabetic nephropathy in individuals with type 2 diabetes. Urinary L-FABP serves as a promising clinical marker for screening kidney impairment and identifying patients at risk for renal function deterioration[54].

Elevated urine L-FABP levels were associated with the development of end-stage renal disease (ESRD) and cardiovascular disease (CVD), independent of diabetes in a prospective observational multicentre study that included 244 Japanese patients with chronic kidney disease (CKD). Reduced eGFR and increased L-FABP were associated with cardiovascular events, regardless of their fatality[50]. Maeda et al[50] established that L-FABP, in conjunction with the urinary albumin-to-creatinine ratio (UACR), may serve as a marker of cardiovascular injury in stages 1 and 2 of chronic kidney disease (CKD) in patients with type 2 diabetes due to its association with elevated cardiac markers and electrocardiogram abnormalities[15].

**Uromodulin (UMOD):** Uromodulin, often referred to as UMD or Tamm-Horsfall protein, is a protein primarily released by the tubular part of kidney which regulates water-electrolyte balance and serves as a host defense mechanism in the urinary system against microbial invasion[40]. The predominant protein found in the urine of healthy individuals is UMOD. The reduction of tubular atrophy and interstitial fibrosis in chronic kidney disease patients results in reduced UMOD levels in both urine and serum. Familial tubulointerstitial diseases are attributed to rare mutations in the UMOD gene[40]. Recent genome-wide association studies have demonstrated that variations of the UMOD gene are linked to hypertension, nephrolithiasis and chronic kidney disease (CKD). Uromodulin-associated SNPs may either elevate a patient's chance of developing chronic kidney disease (CKD) or accelerate its progression[18].

In an observation involving 170 pre-dialysis CKD patients, serum UMOD levels were considerably decreased in patients with chronic kidney disease (CKD) at stages 1–5, as well as in 30 healthy individuals. The levels were negatively correlated with serum creatinine and cystatin C levels, while directly associated with estimated glomerular filtration rate (eGFR)[78]. Steubl et al[78] asserted that plasma UMOD, unlike creatinine and cystatin C, serves as a distinguishing metric for patients without CKD or with stage 1 CKD compared to those exhibiting this protein. A reduction in serum UMOD levels, without altering creatinine levels, correlates with a reduction of renal function in persons with autoimmune kidney diseases, stages 1–5 and chronic kidney disease (CKD). Evidence indicates a connection between reduced serum UMOD levels and healthy renal parenchyma[35].

## Biomarkers of endothelial dysfunction

The integrity of the endothelial cell layer is vital for various vascular processes such as the regulation of vasomotor tone and permeability and it serves as a "guardian" for molecular transport between the blood and adjacent tissue. Endothelial dysfunction and disintegration, often induced by cardiovascular risk factors like hypertension, can ultimately lead to the loss of small arteries (vascular rarefaction) and tissue hypoxia[51]. A primary cause of renal impairment in individuals with chronic kidney disease is vascular rarefaction, characterized by ongoing endothelial injury within the capillary network of the renal medulla[52].

Endothelial dysfunction in chronic kidney disease (CKD) remains inadequately elucidated; nonetheless, it is posited to arise from oxidative stress which diminishes nitric oxide (NO) synthesis and bioavailability as well as from complications in the production, transport and utilization of L-arginine, the principal substrate for NO synthesis. As chronic kidney disease progresses, the importance of these processes appears to change, leading to endothelial dysfunction that is far less reversible in severe uremic conditions[53]. Since these biomarkers indicate different pathophysiological changes that impact the integrity of the endothelium, we concentrated our investigation on fetuin-A and asymmetric dimethylarginine (ADMA).

**Asymmetric Dimethylarginine (ADMA):** Research shows that nitric oxide (NO) generation is decreased in people with end-stage renal disease (ESRD). Furthermore, ADMA is a potent inhibitor of NO generation in both biological systems and experimental environments, potentially leading to many adverse effects such as vasoconstriction, hypertension and immune dysfunction. Furthermore, it is established that supplementary cardiovascular risk factors such as high triglycerides, hyperglycemia, homocysteine, low-density lipoprotein cholesterol and proinflammatory mediators, correlate with increased levels of ADMA[62]. Plasma ADMA levels were associated with deteriorating renal function in a cross-sectional research involving 176 CKD patients. The most significant elevation in ADMA plasma levels was noted in stage 5 individuals.

Two risk factors for cardiovascular disease, anemia and an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m², were associated with an elevation in asymmetric dimethylarginine (ADMA)[80]. The cross-sectional research revealed that out of 651 individuals, 269 were male and 382 were female. The proportion of men having an eGFR below 60 mL/min/1.73m$^2$ ranged from 21.6% to 30.4%. No difference that is statistically significant in ADMA concentrations, was observed between the sexes. ADMA concentrations had a positive correlation with age and serum creatinine, while demonstrating a significant negative correlation with GFR in a prospective research involving 227 people with mild to severe kidney impairment.

Moreover, the mean ADMA concentrations in patients with a GFR ≤ 30 ml/min/1.73 m$^2$ were significantly elevated compared to those in CKD patients with a GFR of 90 ml/min/1.73 m$^2$ or higher. This study indicates that an increase in ADMA is a contributing factor to the progression of CKD[11]. In a cross-sectional study which was conducted

including 145 Australian people aged 40 to 74 with coronary artery disease, individuals in the low GFR cohort (GFR < 81 ml/min/1.73 $m^2$) had significantly elevated ADMA concentrations relative to those in the high GFR cohort (GFR ≥ 81 ml/min/1.73 $m^2$), despite the study only comprising patients with a GFR of 45 ml/min/1.73 $m^2$ or greater. The association between GFR and ADMA levels remained significant after adjusting for age, sex and smoking status[81].

In the multivariate analysis, normoalbuminuria exhibited a 43% reduced LDF response to PORH and a 39% diminished LDF response to TH when compared to macroalbuminuria. The relative β values are: 0.42, p = 0.009 and -0.37, p = 0.01. After adjustment, the reaction to PORH was 23.9% diminished in CKD patients relative to controls (p = 0.02). Individuals with chronic kidney disease and those without exhibited no disparity in their TH responses. Regardless of diabetes and blood pressure, a strong association existed between microvascular endothelial function and increased albuminuria and chronic kidney disease (CKD). These findings may help to explain the increased systemic cardiovascular risk linked to albuminuria and chronic renal diseases[71].

**Fetuin-A:** The liver produces fetuin-A, a 62 kDa glycoprotein is negatively charged and externally dispersed, during the acute phase response. Although it prevents apatite formation in cell cultures and *in vitro*, it does not influence the end product of this chemical[13]. Vascular calcification, carotid intima-media thickness (CIMT), high-sensitivity C-reactive protein (hs-CRP), body mass index (BMI) and albumin levels were all positively correlated with diminished fetuin-A levels. A critical element of MIAC syndrome may be fetuin-A deficiency[60]. During the initial phase of chronic renal disease (stage 2), serum fetuin-A levels were reduced. Therefore, it is probable that arterial calcification and cardiovascular illness will develop early in the course of chronic renal disease. Endothelial dysfunction concurrently arises in these patients, substantiating this observation.

Serum fetuin-A levels and endothelial dysfunction are significantly correlated in this specific group of nondiabetic CKD patients. Reduced fetuin-A levels may represent a novel risk factor for the onset of endothelial dysfunction in chronic kidney disease (CKD)[9]. Elevated mortality in persons with chronic kidney disease (CKD) is typically attributed to problems including inflammation and nutritional status, all of which seem to be linked to fetuin-A[5,12,13,62,85]. A potential explanation for the differences in fetuin-A levels between dialyzed and non-dialyzed patients is that the former exhibits a poorer nutritional status[33].

## Biomarkers of inflammation

Inflammation has been identified as a critical factor in the onset and progression of chronic kidney disease (CKD) from the initial pioneering theory proposed in the late 1990s. This idea proposed that inflammation, particularly the release of the principal inflammatory cytokine interleukin-1 (IL-1) by monocytes, initiated the severe complications and increased mortality rate seen in patients undergoing chronic dialysis[25]. The elevated generation of proinflammatory cytokines, oxidative stress, acidosis, persistent infections, altered adipose tissue metabolism, intestinal dysbiosis and other factors all contribute to the chronic inflammatory state in chronic kidney disease (CKD)[3]. Genetic and epigenetic variables seem to influence inflammatory activation in chronic kidney disease (CKD).

Numerous approaches such as medication, behavioural changes and dialysis optimization, have been put forth to manage inflammation in chronic kidney disease (CKD)[1]. Kaminska et al[38] discovered that in the late stages of chronic kidney disease (CKD), blood concentrations of VCAM1, TNF and IL-6 were significantly higher; however, no association with TNF was found. A robust association was discovered among VCAM1, ICAM1, TNF and IL-6. A robust association was identified between TNF and IL-6. No noticeable alteration occurred in the other indices. A robust association existed between IL-6 and CS, age, renal function and C-reactive protein. When CS and IL-6 levels were elevated, the risk of cardiovascular and all-cause mortality was five times higher for patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD) at baseline[59].

Chronic kidney disease (CKD) is directly linked to the development and progression of microinflammation brought on by tumor necrosis factor alpha (TNF-α). TNF-α is a dualistic cytokine that has both immunoregulatory and proinflammatory characteristics[39]. It is a functioning 26 kDa homotrimeric transmembrane protein. The TNF-a pathway attracts inflammatory cells, causes alterations in the tubulointerstitial area and encourages cellular damage and apoptosis[6]. A large multicentre prospective cohort study showed that cTNFRs are linked to cardiovascular disease in individuals with chronic kidney disease, regardless of age, sex, inflammatory markers and other risk factors in patients with chronic kidney disease.

Pentraxins are a class of cyclic multimeric proteins that have been conserved throughout evolution[24]. The extended pentraxin group includes a prototype protein known as pentraxin 3 (PTX3). While the liver primarily synthesizes CRP and serum amyloid P in response to IL-6 stimulation[77], a number of organs and cells produce PTX3, with endothelium and innate immune cells being the main contributors[2,5].

PTX3 levels are considered a true independent marker of disease activity produced in inflammatory sites, in contrast to CRP, due to its extrahepatic synthesis[17]. Growth differentiation factor 15 (GDF-15) is a member of the transforming growth factor ß (TGF-ß) cytokine family, which has a molecular mass of 34,140 Da and standard reference values of 310 ± 10 pg/mL.

GDF-15 is generated in response to tissue damage or by proinflammatory cytokines[23] and it plays a role in both inflammatory and apoptotic processes[57]. In recent years, elevated GDF-15 plasma levels have been associated with an increased risk of death in patients with coronary artery disease and chronic heart failure[84,86]. Patients with chronic kidney disease (CKD) had higher plasma levels of GDF-15, which was linked to impaired renal function[61].

## Challenges in early CKD diagnosis

Preventing kidney failure might theoretically be accomplished by identifying chronic kidney disease (CKD) in its asymptomatic stage. Nonetheless, patient care may remain unchanged with a CKD diagnosis[58]. Research indicates that CKD screening carries inherent hazards, particularly in Nations with low and moderate incomes (LMICs), the opportunity costs associated with screening outweigh any potential benefits[20]. The early identification of chronic kidney disease carries significant risks, particularly the potential for unnecessary invasive procedures resulting in adverse outcomes. Imaging procedures intended for early detection may reveal lesions that are clinically insignificant such as isolated cysts or incidentalomas, resulting in superfluous testing and treatment. Initially, this appears beneficial; however, empirical evidence indicates otherwise[58].

Moreover, patients incur increased costs, inconvenience and worry stemming from the requirement for several professional consultations, follow-up appointments and diagnostic testing[82]. According to a single study, 58% of senior patients' prescriptions could be stopped and doing so improved their quality of life, demonstrating the idea that less is more [67]. Regrettably, there is presently no definitive standard or reliable comparator for the assessment of CKD biomarkers. This is arguably the principal disadvantage of the field. Most doctors believe that kidney biopsies are usually necessary, even though they are aware of the dangers associated with this intrusive surgery and the possible "trap" of a diagnosis that has little bearing on therapy[58].

In the initial phases of chronic kidney disease (CKD), neither estimated glomerular filtration rate (eGFR) nor microalbuminuria serves as a dependable measure of renal function, presenting a considerable obstacle to the identification of viable biomarkers. P30 fluctuated between 60% and 90% in cross-sectional studies whereas P10 averaged 40%. The bulk of eGFR readings did not concur with mGFR values by more than 30%. Discordance with mGFR surpassed ±30% in 10-40% of subjects, which is a significant factor. The accuracy of eGFR estimates did not improve when cystatin C replaced creatinine, as the margin of error was similar for both equation sets[65]. The sole study employing agreement statistics revealed minimal concordance between mGFRs and eGFRs calculated via the MDRD, CKD-EPI and Cockcroft-Gault equations[27]. A comparison with a reliable GFR indicator is crucial before evaluating a biomarker for practical application.

## Discussion

Chronic kidney disease continues to be one of the most significant issues in global health today, especially since its prevalence appears to be increasing-facilitated not only by diabetes and hypertension but also by environmental agents in low- and middle-income countries. Despite much progress being achieved on the etiology of CKD, especially with CKD of unknown etiology occurring in Central America and South Asia, many cases remain difficult to diagnose early because conventional biomarkers like GFR and albuminuria become detectable only after considerable damage has occurred in the kidneys and hence lag behind early intervention. It is in this previous work that researchers have already been able to identify novel biomarkers to allow for an earlier and more sensitive and specific detection of CKD.

The proposed biomarkers include beta-trace protein (BTP), beta-2-microglobulin (B2M), klotho, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and liver-type fatty acid binding protein (L-FABP) with potential for reflecting earlier states of kidney dysfunction, tubulointerstitial damage and endothelial dysfunction. These biomarkers might even deliver more sensitive and effective markers for the disease progression as well as the amount of cardiovascular risks that is closely related to outcome in CKD. However, with such promising potential, several obstacles stand before these biomarkers. So far, no "gold standard" biomarker is recognized as universally accepted for the early detection of CKD, therefore making it difficult to validate and use them in everyday clinical setting.

It also becomes problematic for LMICs in terms of cost and risk of inappropriate tests. Detection of early biomarkers at times leads to image techniques and invasive procedures that could sometimes result in overdiagnosis or unnecessary intervention, complicating management further for the patient. Screening of asymptomatic populations is challenging both on ethical grounds and economically for CKD. Although theoretically, early detection would ensure timely intervention, there is little evidence that mass screening is of any benefit. It is, therefore, essential to maintain a balanced approach wherein priority remains for high-risk populations but keeping sight of over-treatment and resource use in healthcare.

## Conclusion

Chronic kidney disease is becoming a more serious worldwide health concern, particularly in regions characterized by very high prevalence rates of diabetes and CKD of unknown etiology. Novel biomarkers such as BTP, B2M, klotho and NGAL are poised to revolutionize earlier for more precise detection of CKD. The new biomarkers reflect multiple aspects of kidney damage that could potentially be helpful for increasing early detection, offer better risk stratification and are likely to yield better predictions of the disease course. Despite all these advances,

the wide application of new biomarkers in clinical settings would be prohibited by a lack of harmonization standard of early CKD diagnosis and the risk of too much testing and over-treatment.

Therefore, future research should validate these biomarkers adequately across different populations with respect to cost-effectiveness and long-term impact on patient outcomes. It is through this more precise and evidence-based diagnosis and management of CKD which has consequently improved patient care at every juncture as the world continues to battle to cut the huge burden that CKD poses.

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(Received 22nd October 2024, accepted 21st December 2024)

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