biomedicines

MDPI

Review

New and Emerging Biomarkers in Chronic Kidney Disease

Mikołaj Dopierała *, Nadja Nitz, Oliwia Król, Karolina Wasicka-Przewoźna, Krzysztof Schwermer and Krzysztof Pawlaczyk

Department of Nephrology, Transplantology and Internal Medicine, Poznan University of Medical Sciences, 61-701 Poznan, Poland; nadelek01@gmail.com (N.N.); oliwia.krol@usk.poznan.pl (O.K.); k.wasicka@gmail.com (K.W.-P.); kpawlac@ump.edu.pl (K.P.)

* Correspondence: mikolaj.dopierala2@usk.poznan.pl

Abstract: Chronic kidney disease (CKD) represents a major and widespread global health challenge. It affects over 800 million people worldwide, which is approximately 13% of the world's population. Over the past 20 years, it has consistently ranked among the leading causes of death. As a result of its typically painless and asymptomatic presentation in the early stages of the disease, CKD is frequently diagnosed late, when the patient is already suffering from serious complications. In recent years, studies have identified novel biomarkers associated with the pathophysiology of CKD, including chronic inflammation, tubular injury, and CKD-related outcomes such as bone and mineral metabolism disorders, cardiovascular events, and all-cause mortality. Identifying and using these emerging biomarkers—like kidney injury molecule, N-acetyl–D-glucosaminidase, ficolins, the NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) inflammasome, soluble suppression of tumorigenicity-2, galectin-3, growth differentiation factor-15, soluble urokinase-type plasminogen activator receptor, sclerostin, the Dick-kopf proteins, and indexes such as the systemic inflammation response index—may lead to a significant advancement in early diagnosis, risk stratification, and personalized treatment strategies for CKD patients. Despite their potential, the routine clinical use of these novel biomarkers remains limited due to challenges such as high costs and the lack of standardized testing methods. There is still considerable room for advancement in both the diagnosis and management of CKD. Hopefully, increasingly more new biomarkers will become usable in clinical practice, ultimately improving care quality and outcomes for patients with CKD.

Keywords: inflammation; kidney biomarkers; chronic kidney disease; cardiorenal syndrome risk; kidney physiopathology; kidney injury

check for updates

Academic Editors: Susana Coimbra and Silvio Maringhini

Received: 1 March 2025
Revised: 18 May 2025
Accepted: 22 May 2025
Published: 10 June 2025

Citation: Dopierała, M.; Nitz, N.; Król, O.; Wasicka-Przewoźna, K.; Schwermer, K.; Pawlaczyk, K. New and Emerging Biomarkers in Chronic Kidney Disease. *Biomedicines* **2025**, *13*, 1423. https://doi.org/10.3390/biomedicines13061423

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Chronic kidney disease (CKD) is a widespread global health issue affecting approximately 13% of the world's population, which means that it afflicts over 800 million people [1]. It has remained one of the most prominent causes of death over the past two decades [2,3]. The rise in risk factors, particularly diabetes mellitus, hypertension, cardiovascular disease, and obesity, compounds the burden of CKD in the population [1]. CKD is defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health [4]. The pathophysiology of CKD is complex, but the main pathological hallmarks include fibrosis, tubular atrophy, and chronic inflammation. The progression of this process is primarily driven by proteinuria, hypoxia, and oxidative stress [5]. Early detection of CKD provides opportunities to effectively attenuate

the progression of renal dysfunction and prevent outcomes associated with CKD. However, primarily due to its typically painless and initially asymptomatic presentation, CKD is frequently diagnosed in the later stages. Currently, in clinical practice, the diagnosis and staging of CKD are made by estimating glomerular filtration rate (GFR) using creatinine and cystatin C or by albuminuria (ACR) [4]. These diagnostic criteria reflect renal function based on glomerular filtration. However, studies from recent decades identified novel biomarkers associated with the pathophysiology of CKD, including chronic inflammation, tubular injury, and CKD-related outcomes. These markers enable a more specific representation of overall kidney function and CKD complications.

2. Methodology

In this narrative review, we attempted to provide a comprehensive overview of recent advances in the identification of novel biomarkers for CKD. We conducted a comprehensive search of the relevant literature, mainly studies published in the last decade. Both clinical studies (observational studies, cohort studies, clinical trials) and preclinical research (animal models, mechanistic studies) were included to provide a broad understanding of biomarker relevance from basic science to clinical application. Studies not available in English, conference abstracts without full texts, and data still awaiting publication were excluded.

We strived to include a wide array of biomarkers and present an integrated view on both established and newly emerging biomarkers, with special attention to those that are rarely mentioned in previous reviews, such as ficolins or Dick-kopf proteins, and others that have only recently gained attention in CKD research, like inflammatory indices. Through a comprehensible pathophysiological framework and extending the understanding of biomarkers' functions beyond their primary roles, we tried to place a focal point on the translation of these into clinical practice.

A major limitation of this review is the fact that, given our focus on covering a broad spectrum of biomarkers, the depth of discussion for each individual marker was necessarily limited.

3. Biomarkers of Tubular Secretion

Creatinine, cystatin C, and estimated glomerular filtration rate (eGFR) are the primary parameters used for the definition and staging of chronic kidney disease (CKD). These markers reflect renal function based on glomerular filtration. However, their utility is limited, particularly in detecting the early stages of CKD [6]. Consequently, there is an urgent need to identify more sensitive biomarkers for the early detection of CKD that may more comprehensively represent overall kidney function. Considering tubular injury as a key mechanism in the progression of CKD [7], biomarkers of tubular secretion may prove useful for diagnosing this condition.

Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein with undetectable expression in the normal kidney [8]. KIM-1 consists of an immunoglobulin-like domain and an extracellular mucin domain. Renal injury factors lead to the upregulation of KIM-1 expression by proximal tubule epithelial cells. The mucin domain is shed, resulting in elevated levels of KIM-1 in urine and plasma [9,10]. KIM-1 serves as a sensitive biomarker of proximal tubule injury in both acute kidney injury (AKI) and chronic kidney disease (CKD) [10–12]. In a cross-sectional study by Waikar et al. (2016), a strong positive correlation was demonstrated between urinary KIM-1 level and the albumin-to-creatinine ratio (ACR) in individuals with and at risk for CKD (95% CI: 0.15-0.17), suggesting its potential role in the diagnosis and prognosis of CKD [13]. Urinary KIM-1 levels increased progressively with declining eGFR, until eGFR fell below 15 mL/min/1.73 m², likely re-

flecting a reduction in tubular mass responsible for KIM-1 expression [13]. Waikar et al. also reported reduced urinary KIM-1 levels in users of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), which correlates with the nephroprotective properties of these classes of medications [13–15]. The upregulation of KIM-1 has also been observed in various glomerulopathies, including diabetic glomerulopathy and IgA nephropathy [16,17]. Chronic KIM-1 expression is a component of the pathogenesis of chronic kidney disease. It plays a significant role in the progression of inflammation and tubulointerstitial fibrosis in renal tissue, partly by promoting the secretion of monocyte chemoattractant protein-1 (MCP-1) [18]. In conclusion, KIM-1 is not only a sensitive biomarker for CKD but can also be a potential therapeutic target in kidney disease [18,19].

N-acetyl–D-glucosaminidase (NAG) represents another urinary biomarker of proximal tubular injury [20]. This lysosomal enzyme has been investigated as a potential predictor of diabetic nephropathy, highlighting the role of tubular injury in the early stages of diabetic kidney disease [21,22]. Urinary NAG excretion can be detected before the appearance of microalbuminuria and macroalbuminuria in diabetic kidney disease (DKD) [23]. NAG is not filtered through the glomerulus due to its relatively high molecular weight, but it may appear in the urine as a consequence of tubular injury, including exposure to high urinary glucose [24,25]. Urinary NAG levels are not only significantly higher in diabetic patients but also reflect renal impairment, indicating the promising utility of NAG in monitoring diabetic kidney disease (DKD) [26]. Furthermore, Kim et al. demonstrated that urinary NAG may reflect glycemic control in patients with type 2 diabetes mellitus due to its correlation with glucometabolic parameters [27]. More recently, the application of NAG in the real-time monitoring of kidney function in DKD was presented. Ten et al. fabricated a NAG-responsive NIR-II fluorescent nanoprobe that specifically interacts with NAG to produce NIR-II fluorescence signals, enabling the noninvasive detection of kidney dysfunction [28].

Uromodulin, also known as Tamm–Horsfall protein, is a renal-specific protein expressed exclusively by the thick ascending limb of the loop of Henle and the distal convoluted tubule [29]. It is a major protein present in the urine of healthy individuals [30,31]. Numerous studies demonstrated multiple physiological functions of uromodulin, including ion reabsorption in the thick ascending limb, blood pressure control, protection against kidney stone formation, and immunomodulation [32–37]. Additionally, uromodulin prevents bacterial urinary tract infections. It counteracts the adherence of Escherichia coli to the urothelial surface by binding specifically to type 1 fimbriated Escherichia coli [38,39].

Both urinary and serum uromodulin have been investigated in the context of CKD. Distal tubular damage leads to lessened urinary excretion of Tamm–Horsfall protein [40–42]. It is also modulated by common variants in the UMOD gene, which encodes uromodulin [43]. In a case–control study, Köttgen et al. identified an association between a single-nucleotide polymorphism in the UMOD region (rs4293393) and elevated uromodulin concentrations as a predictor of CKD onset [44]. Urinary uromodulin serves as a biomarker of kidney tubulointerstitial damage [45], a key pathological mechanism affecting CKD development [46]. Urinary uromodulin level has been shown to predict rapid progression to end-stage kidney disease (ESKD) in CKD patients within 1 year [47].

According to research, serum uromodulin may also serve as a biomarker for kidney function assessment [48–50]. In an observational study including 170 patients with CKD, Fedak et al. demonstrated a strongly positive correlation between serum uromodulin concentrations and eGFR [51]. Importantly, the relationship between serum uromodulin and eGFR was independent of age, sex, BMI, and body surface area, enhancing the potential diagnostic utility of this protein [51]. Serum uromodulin, as a marker of tubular secretion,

represents functional nephron mass and kidney function as a whole [49,52]. In this way, serum uromodulin can help identify the early stages of CKD, including the creatine-blind range of CKD [52,53]. Similarly to urinary uromodulin, serum uromodulin may be used to identify high-risk groups for the incidence of ESKD in CKD patients [54]. Its level is also associated with a common CKD outcome—cardiovascular disease [55].

What is more, uromodulin has been implicated in various health conditions associated with CKD. Low serum uromodulin levels may be correlated with kidney function and renal disease activity in lupus nephritis and ANCA-associated glomerulonephritis [56,57]. In the course of Fabry disease, uromodulin excretion is also disturbed, ranging from normal to markedly decreased or even absent. However, a study of 15 male Fabry disease patients has shown that enzyme replacement therapy leads to the normalization of urinary uromodulin excretion [58]. Mutations in the gene encoding uromodulin underlie medullary cystic kidney disease type 2 and familial juvenile hyperuricemic nephropathy [59]. In these kidney diseases, impaired uromodulin export dynamics lead to an intracellular accumulation of this protein in the tubular epithelium of the thick ascending limb of Henle's loop. Consistently, urinary uromodulin excretion is reduced [60].

In conclusion, uromodulin is a promising biomarker for CKD, including the early stage of CKD. Furthermore, given its important role in maintaining kidney function, this protein may serve as a predictor of CKD onset and progression and could represent a novel target for therapeutic intervention.

The Klotho protein, another potential biomarker for CKD, was first identified in 1997 as an anti-aging molecule [61]. Subsequent research has established the role of Klotho deficiency in the aging process and the pathogenesis of age-related diseases [62–65]. This protein is predominantly expressed in the kidney, specifically in both the proximal and distal tubules [66]. Additionally, it has also been detected in the epithelium of the choroid plexus in the brain, as well as in the heart, pituitary gland, parathyroid gland, and other tissues [67]. Klotho is a transmembrane protein that functions as a coreceptor for fibroblast growth factor (FGF) [68]. Its extracellular domain undergoes shedding, resulting in the release of a soluble form into the bloodstream and urine [69]. Many studies have investigated the correlation between circulating soluble Klotho levels and kidney function. The majority indicated a positive correlation between serum and urine Klotho levels and estimated glomerular filtration rate (eGFR) in CKD [70–72]. In contrast, Seiler et al. reported no link between plasma Klotho and kidney function [73]. These divergences are likely due to variability in assay methods and the heterogeneity of CKD populations. However, Klotho is a substantiated renoprotective molecule, and its deficiency plays an important role in CKD progression [74–76]. It may serve as a potential biomarker for the early stages of CKD and a therapeutic target, and it can also predict CKD complications, though there is a requirement for the standardization of measurement methods for its clinical application.

Proteins in the Dickkopf (DKK) family are antagonists and modulators of the Wnt/beta-catenin signaling pathway [77]. This family encompasses four key proteins: Dick-kopf-1, Dick-kopf-2, Dick-kopf-3, and Dick-kopf-4 [77]. Of these, Dick-kopf-1 and Dick-kopf-3 have recently emerged as potentially significant novel biomarkers in the course of not only the diagnosis and progression of CKD complications due to their direct mechanism of action, as well as their involvement in "cross-talk" with other body tissues, but also as a potential prognostic marker [78,79].

Dickkopf-3 (DKK-3) is a urinary glycoprotein secreted as a response to stress and is expressed in tubular cells after injury [80], serving as a marker for ongoing tubular stress with the potential of serving as a biomarker of CKD progression; currently, several studies have confirmed its potential as an ongoing biomarker of renal injury [81]. Urinary levels of DKK-3 (uDKK-3) have been associated with poor renal survival in CKD and estimated

eGFR decline [82]. High urinary levels of DKK-3 have demonstrated increased eGFR loss [83] in resistant hypertension CKD patients, where eGFR loss was higher even up to 24 months later [82]. This was especially the case when uDDK-3 was greater than or equal to 400 pg/mL, resulting in a statistically significant eGFR decline as well as the more frequent appearance of proteinuria [82]. uDDK-3 has also been correlated with an increased risk of CKD progression in patients diagnosed with chronic obstructive pulmonary disease (COPD) [83].

Dickkopf-1, as a protein involved in the regulation of bone metabolism, will be further discussed in subsequent sections of this review.

The biomarkers mentioned in the text are presented in Table 1.

Table 1. Biomarkers of tubular secretion.

Biomarker	Origin/Source	Mechanism/Function	Clinical Relevance
KIM-1 (Kidney Injury Molecule-1)	Proximal tubule epithelial cells	Marker of proximal tubule injury	Elevated in AKI and CKD; correlates with ACR, associated with inflammation and fibrosis
NAG (N-acetyl-â-D-glucosaminidase)	Lysosomes of proximal tubule cells	Enzyme indicating tubular injury	Early marker of diabetic nephropathy (before albuminuria); reflects renal impairment and glycemic control
Uromodulin (Tamm–Horsfall Protein)	Thick ascending limb of Henle's loop and distal convoluted tubule	Involved in ion transport, immunity, and prevention of kidney stones	Urinary and serum levels predict CKD onset and progression; reflects tubular damage and nephron mass
Klotho	Proximal and distal renal tubules; other tissues	Anti-aging and renoprotective molecule	Positive correlation with eGFR; deficiency promotes CKD progression
Dickkopf-3 (DKK-3)	Tubular epithelial cells in kidneys (expressed in response to injury)	Urinary stress glycoprotein marker; reflects ongoing renal tubular stress and injury	Elevated urinary DKK-3 linked to eGFR decline and CKD progression; associated with proteinuria and poor renal outcomes; predictor of CKD progression in COPD and resistant hypertension

Abbreviations: AKI, acute kidney injury; ACR, albumin–creatinine ratio; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

4. Inflammatory Biomarkers

Impaired kidney function leads to the accumulation of uremic toxins and oxidative stress, activating pro-inflammatory pathways. Over the years, many inflammatory markers have been associated with chronic kidney disease. They are not only indicators of systemic inflammation but can also be used as predictors of cardiovascular disease, stroke, progression of kidney damage, and loss of renal function, as well as overall mortality [84–92]. Elevated levels of biomarkers such as C-reactive protein (CRP) [93–103], tumor necrosis factor alpha (TNF-a) [93,94,104–114], interleukin-6 (IL-6) [93,99,101,113,115–120], interleukin-1b (IL-1b) [102,103,113,121,122], interleukin-10 (IL-10) [93,123–125], fibrinogen [103,114,115,126,127], serum amyloid A (SAA) [128–131], and Transforming Growth Factor-Beta (TGF-β) [132,133] are well known to be correlated with CKD.

On the other hand, a high concentration of some inflammatory markers may seem to play a therapeutic role. For example, interleukin-10 (IL-10) may reduce fibrosis and inflammation [123,124].

In recent years, new inflammatory molecules and indexes have emerged as biomarkers for CKD. Below are some key findings regarding their potential role in CKD.

Ficolins are pattern recognition molecules. They play a role in pathogen recognition, complement activation, and inflammation regulation. There are three main types of ficolins: M-ficolin (ficolin-1), L-ficolin (ficolin-2) and H-ficolin (ficolin-3). Mainly, L-ficolin and

H-ficolin were studied in relation to CKD. The pattern recognition molecules within the complement system, such as H-ficolin and mannan-binding lectin (MBL), recognize specific molecular patterns on the surface of microorganisms and, by binding them, can activate the lectin pathway of the complement system. This, in turn, leads to inflammation. Hyperglycemia alters glycans enzymatically and non-enzymatically by the formation of advanced glycation end-products. These glycan alterations may be the cause of a harmful complement auto-attack initiated by pattern recognition molecules. Østergaard et al., in their article, suggested that higher levels of H-ficolin were associated with diabetic kidney disease progression. However, while the association with DKD progression was independent of other well-established risk factors, the effect disappeared after adjusting for triglyceride levels. Furthermore, in the studied cohort, high concentrations of H-ficolin predicted diabetes-related mortality but were not connected to all-cause mortality and cardiovascular events [134]. Elevated H-ficolin levels at the time of kidney transplantation were found to be an independent and significant risk factor for shorter graft survival [135]. What is more, L-ficolin gene polymorphism was shown to influence kidney allograft functions [136].

The NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) inflammasome is a multiprotein complex and a component of the innate immune system. By triggering the release of pro-inflammatory cytokines such as IL-1B and IL-18, it plays a role in inflammation, fibrosis, and the progression of CKD. Research has shown that through damaged mitochondria and an elevated production of reactive oxygen species (ROS), the NLRP3 inflammasome is activated in uremic patients treated with dialysis [137]. Other authors have suggested that NLRP3 inflammasome inhibition may be a promising therapeutic target in hyperoxaluria and nephrocalcinosis [121], as well as reducing renal fibrosis [138].

Serum tumor necrosis factor receptor 1 and 2 (TNFR1 and TNFR2) levels are related to eGFR in healthy subjects, which highlights their potential as early biomarkers for CKD [139]. In a study by Oh et al., elevated concentrations of tumor necrosis factor receptors (TNFRs) were correlated with an increased risk of progression in immoglobulin A nephropathy (IgAN). Circulating TNRFs can be early biomarkers to predict the severity and clinical outcome of IgAN [140]. TNFRs can also be a prognostic biomarker for diabetic kidney disease [107]. Further studies focused on TNFRs evaluated Black individuals with hypertension-attributed CKD and older adults with type 2 diabetes and albuminuria, proving that increases in TNFR1 and TNFR2 were associated with worsening kidney function in those groups [141].

Calprotectin is circulation damage-associated molecular pattern protein, considered an acute-phase protein. It originates mainly from myeloid cells and is released during neutrophil degranulation. Higher levels of circulating calprotectin are linked to increased risk of new-onset CKD [142]. Plasma calprotectin was also identified as a contributor to vascular calcification, cardiovascular (CV) outcomes, and mortality in patients with CKD [143,144].

The systemic inflammation response index (SIRI) is a novel predictive biomarker derived from the ratio of peripheral neutrophil, monocyte, and lymphocyte counts, calculated as (neutrophil count × monocyte count/lymphocyte count). The SIRI, as well as other indexes like the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the systemic immune-inflammation index (SII), were found to be significantly increased in CKD stage 5 compared to other CKD stages [145,146]. A high SIRI is linked to a greater risk of CKD in patients with hypertension. As the SIRI increases, the risk of CKD in hypertensive patients also rises [147]. Furthermore, an elevated SIRI is linked to an increased risk of both all-cause and cardiovascular mortality in patients with CKD. Regular monitoring of the SIRI can aid in the early identification of high-risk patients, enabling

prompt and targeted interventions [148]. Some studies have shown that it can be especially significant in the early stages (I-III) of CKD [87].

An elevated NLR is linked to increased proteinuria, higher serum creatinine levels, reduced eGFR, and a greater prevalence of advanced CKD. Therefore, a high NLR indicates a more advanced stage of CKD and may serve as a biomarker for predicting its progression [149]. NLR can also be used as a complementary prognostic marker for cardiovascular risk evaluation in patients with moderate-to-severe chronic kidney disease [150] and a predictor of cardiovascular and all-cause mortality in hemodialysis patients [151].

Hypoalbuminemia, a well-known sign of protein-energy wasting (PEW) or malnutrition, is frequently seen in individuals with CKD and is linked to an increased risk of cardiovascular complications. Recently, the C-reactive protein to albumin ratio (CAR) has emerged as a novel marker for PEW, as this condition appears to stem not only from insufficient dietary intake but also from persistent systemic inflammation. Measurement of CAR may be useful in clinical practice because this newly introduced surrogate marker of the PEW is simple and can be easily obtained in routine practice. In their research, Takahashi et al. showed that the pre-procedural CRP/albumin ratio could predict both the risk of amputation and mortality after lower extremity revascularization and could stratify the risk in HD patients with PAD [152]. In other studies, a higher CAR was found to be an independent risk factor for diabetic nephropathy [153] and CKD in general [154]. CAR has the potential to become a key biomarker for offering new avenues for advancing early risk stratification, precision therapies, personalized management, and preventive strategies in CKD [155].

Although increased levels of inflammatory indices such as the SIRI or NLR correlate with the progression of CKD, as well as with worsening outcomes in CKD patients, it is important to note that this association does not always imply a direct causal relationship. Systemic inflammation may be a consequence of underlying conditions such as malignancies, infections, or autoimmune diseases, which also contribute to CKD progression. In those cases, the inflammation may not be primarily caused by CKD or be the main reason for CKD progression.

The biomarkers mentioned in the text are presented in Table 2.

Table 2. Inflammatory biomarkers.

Biomarker	Origin/Source	Mechanism/Function	Clinical Relevance
Ficolins	Liver, immune cells	Pattern recognition molecules; activate lectin pathway of the complement system	Elevated levels are associated with diabetic kidney disease progression and diabetes-related mortality; affect post-transplant graft outcomes
NLRP3 inflammasome	Immune system (intracellular complex)	Activates IL-1B and IL-18; stimulated by ROS and mitochondrial damage	Promotes inflammation, fibrosis, and CKD progression; considered a therapeutic target in hyperoxaluria, nephrocalcinosis, and renal fibrosis
TNFR1 and TNFR2 (tumor necrosis factor receptor 1 and 2)	Circulating receptors of TNF-alpha	Mediate inflammatory signaling; correlate with renal function	Early CKD biomarkers; predict progression in IgA nephropathy and DKD; prognostic in hypertension-related CKD
Calprotectin	Myeloid cells (especially neutrophils)	Acute-phase protein; released during neutrophil degranulation	Associated with new-onset CKD, vascular calcification, and increased cardiovascular and all-cause mortality in CKD patients
SIRI (systemic inflammation response index)	Derived from blood cell counts	Systemic inflammation index (Neutrophil × Monocyte/ Lymphocyte)	Elevated in hypertensive patients at risk of CKD; predicts cardiovascular and all-cause mortality—especially useful in early CKD stages (I–III)

Table 2. *Cont.*

Biomarker	Origin/Source	Mechanism/Function	Clinical Relevance
NLR (neutrophil-to-lymphocyte ratio)	Derived from blood cell counts	Marker of immune imbalance (Neutrophil/Lymphocyte)	High NLR correlates with advanced CKD, proteinuria, and decreased eGFR; predictive of cardiovascular risk and mortality in CKD and dialysis patients
CAR (CRP/albumin ratio)	Serum protein levels	Reflects systemic inflammation and nutritional status (PEW marker)	Reliable, accessible PEW and risk stratification marker

Abbreviations: Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; DKD, diabetic kidney disease; NLR, neutrophil-to-lymphocyte ratio IL; interleukin, PEW, protein-energy wasting

5. Cardiovascular Biomarkers

CKD is a common condition associated with significant cardiovascular morbidity and mortality. Cardiovascular disease (CVD) is a leading cause of death in CKD, accounting for 40% to 50% of all deaths among individuals with advanced and end-stage kidney disease [156]. Novel cardiovascular biomarkers may aid in the early detection of cardiovascular complications and the prediction of CKD progression.

Troponin is a component of cardiac muscle thin filaments and consists of three isoforms: Troponin T (TnT), Troponin I (TnI), and Troponin C (TnC). These isoforms are associated with cardiac injury and various cardiovascular diseases, such as stroke, pulmonary embolism, acute perimyocarditis, and arrhythmias. Circulating troponin levels are widely used in diagnosing these conditions, particularly acute coronary syndromes. [157] Several studies have reported that elevated levels of cardiac troponin T (cTnT) and I (cTnI) are frequently observed in CKD patients, not related to the presence of acute coronary syndromes [158,159]. Furthermore, increased high-sensitivity troponin T (hsTnT) is associated with a higher risk for CKD progression and greater cardiovascular mortality in CKD participants [160,161].

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a well-established biomarker of heart failure used for diagnosis, risk assessment, and monitoring of disease progression. Studies have demonstrated that higher NT-proBNP levels strongly predict heart failure, and decreased NT-proBNP levels are associated with a lower risk of mortality in CKD populations [160,162]. A recent study has shown a negative correlation between NT-proBNP levels and kidney function in CKD patients. Furthermore, the same study revealed an association between NT-proBNP and an increased risk of kidney disease progression in CKD patients at stages 1–3 without heart failure (HF) [163]. The latest research uncovered that the same NT-proBNP concentration in patients with heart failure and impaired kidney function predicts a higher absolute risk of complications compared to those with normal kidney function [164].

Galectin-3 is a β-galactoside-binding lectin implicated in various biological processes involved in inflammation, fibrosis, cardiac dysfunction, and remodeling. Elevated levels of galectin-3 have been associated with an increased risk of heart failure and its morbidity. Furthermore, several studies suggest that galectin-3 plays a potential role in identifying patients at high risk of cardiac dysfunction before clinical symptoms manifest [165–167]. In renal disease, elevated serum galectin-3 concentrations are associated with the onset of CKD, development of renal fibrosis, and rapid renal function decline [168]. According to Kim et al., serum galectin-3 levels showed a direct correlation with both serum creatinine (Cr) levels and the urine protein-to-Cr ratio in CKD patients [169]. Recent studies reveal the potential of galectin-3 as a biomarker for kidney disease progression and its implications in cardiovascular morbidity and mortality among CKD patients [170,171].

Soluble suppression of tumorigenicity-2 (sST-2) is a soluble isoform of ST2, an interleukin-1 receptor-like 1 and member of the interleukin-1 receptor family. Interaction between interleukin -33 (IL-33), the transmembrane ST2 receptor (ST2L), and sST-2 plays a significant role in the inflammatory response to cardiac stress, and sST-2 is strongly associated with myocardial fibrosis, remodeling, and heart failure progression [172,173]. Several studies have reported that elevated serum levels of sST-2 are correlated with progression and higher risk of mortality in CKD participants [169,174] and increased risk of cardiovascular mortality in dialysis patients. Furthermore, sST-2 levels are not correlated with eGFR in CKD patients, indicating that sST2 is the least impacted by declining kidney function. These findings suggest its potential as a reliable biomarker for patients with cardiovascular disease and coexisting chronic kidney disease [175].

Recent reports reveal that elevated concentrations of sST2 and Gal-3 are associated with an increased cardiothoracic ratio (CTR) in CKD patients. This relationship may enable better cardiovascular risk evaluation for CKD patients [176].

Growth differentiation factor-15 (GDF-15) is a stress-responsive cytokine elevated in conditions associated with inflammation and oxidative stress, as well as in different types of cardiovascular events like heart failure and atrial fibrillation. Recently, GDF-15 has been described as a promising biomarker of atherosclerosis [177]. In terms of kidney disease, available studies indicate that GDF-15 is involved in the pathophysiology of CKD, diabetic nephropathy, and kidney cancer [178]. Furthermore, elevated levels of GDF-15 are associated with adverse renal outcomes and may serve as a potential biomarker for predicting the progression of chronic kidney disease (CKD) and its cardiovascular complications [179,180].

Soluble urokinase-type plasminogen activator receptor (suPAR) is a soluble form of urokinase-type plasminogen activator receptor (uPAR) involved in systemic inflammation and immune activation [181]. suPAR is a membrane bound receptor that interacts with and activates integrins in diverse cell types, such as podocytes, tubular epithelial cells (TECs), and fibroblasts, leading to a loss of glomerular filtration barrier integrity and podocyte damage.

Elevated suPAR levels have been associated with an increased risk of cardiovascular disease and kidney function decline in CKD patients [182,183]. Recent studies suggest that higher suPAR levels correlate with greater mortality and cardiovascular events, making suPAR a significant predictor for improving risk stratification and early intervention in CKD populations.

The combination of NT-proBNP, cardiac troponins, galectin-3, sST-2, GDF-15, and suPAR represents a promising approach for a more comprehensive cardiovascular risk assessment and mortality prediction in CKD patients. These biomarkers also demonstrate the potential of predicting CKD progression and guiding future therapeutic strategies.

The biomarkers mentioned in the text are presented in Table 3.

Table 3. Cardiovascular biomarkers.

Biomarker	Origin/Source	Mechanism/Function	Clinical Relevance
Galectin-3	Macrophages, epithelial cells, fibroblasts	â-galactoside-binding lectin; mediates inflammation, fibrosis, cardiac remodeling	Elevated in CKD and heart failure. Predicts renal fibrosis, rapid renal function decline, and CV mortality. Correlates with serum creatinine and proteinuria. Potential early biomarker of both renal and cardiac complications.
sST2 (soluble suppression of tumorigenicity-2)	Cardiomyocytes, endothelial cells	Soluble form of ST2 receptor; binds IL-33, modulating inflammatory responses to cardiac stress	Predicts CKD progression and cardiovascular mortality. Especially valuable in dialysis patients.

Table 3. *Cont.*

Biomarker	Origin/Source	Mechanism/Function	Clinical Relevance
GDF-15 (Growth differentiation factor-15)	Cardiomyocytes, kidneys, immune cells	Stress-induced cytokine involved in inflammation and oxidative stress	Associated with heart failure, atherosclerosis, and CKD progression. Predicts adverse renal and cardiovascular outcomes.
suPAR (soluble urokinase-type plasminogen activator receptor)	Immune system (monocytes, neutrophils), endothelium	Activates integrins, disrupting podocyte structure and filtration barrier	High levels linked with systemic inflammation, kidney function decline, and cardiovascular events. Predictive of mortality and CV risk in CKD.

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; IL, interleukin.

6. Bone and Mineral Metabolism Biomarkers

Chronic kidney disease (CKD) is associated with a variety of complications either secondary to its progression or as a consequence of the worsening renal function characterizing the disorder. Amongst these, cardiovascular diseases (CVDs), endocrine disorders, metabolic imbalances, mineral and bone disorders (CKD-MBD), and cognitive impairments have been identified [184]. All of the aforementioned have their own established biomarkers used for diagnosis and disease monitoring. However, recent research suggests that these biomarkers may also be used to predict CKD progression and improve prognostic accuracy [185].

Traditional biomarkers for CKD-MBD have included parathyroid hormone (PTH), calcium, alkaline phosphatase, cholecalciferol, and vitamin D [186]. Yet, emerging evidence suggests the presence of novel biomarkers that may provide insights into disease progression and these associated complications [185]. This includes Fibroblast Growth Factor 23 (FGF-23), Sclerostin, Dickkopf-1, and Dickkopf-3, which have emerged as promising biomarkers for CKD-MBD.

PTH, the parathyroid hormone, an 84-amino-acid single-chain peptide, plays a key role in bone metabolism by promoting calcium reabsorption in the kidneys, stimulating osteoclast activity in the bones, as well as enhancing intestinal calcium absorption through the activation of calcitriol.

The parathyroid hormone can be assessed in several forms, including whole PTH, intact PTH, and via the whole/intact PTH ratio [187]. In CKD, the impairment of renal function disrupts its mechanism, leading to secondary hyperparathyroidism (SHPT) [188]. Due to declining renal function and the subsequent decline in GFR, phosphate accumulates, and this stimulates the release of PTH and binds free calcium in the blood reducing its levels. This mechanism also reduces the activation of calcitriol [189].

Worsening renal function reduces the conversion of 25(OH)D -25-hydroxyvitamin D- to 1,25$(OH)_2$D (1,25-dihydroxyvitamin D) and limits vitamin D receptor (VDR) activation in the parathyroid gland, subsequently reducing negative feedback for PTH and ensuing gland hyperplasia and excess PTH production. The triad of low calcium, low calcitriol, and high phosphate triggers stimulation and causes parathyroid cell proliferation. This metabolic imbalance decreases the responsiveness of PTH to calcium and vitamin D, and worsening renal function prevents effective compensation, which leads to the appearance of bone mineral disorders (CKD-MBD) and vascular calcifications [190].

While PTH has been a long-established biomarker for measuring and monitoring the progression of secondary hyperparathyroidism, it has also been proposed as a biomarker for CKD [188]. The whole/intact PTH ratio (w/i PTH) has been demonstrated to correlate with eGFR in stage 3 of chronic kidney disease (CKD3), CKD4, and CKD5, as well as correlating with serum calcium in CKD5 [191]. The inflection point that was demonstrated in the correlation resides at 24.1 mL/min/1.73 m2 [191]. Studies further show that the w/i

PTH ratio declines as CKD develops, and these changes in the ratio are associated with worsening kidney function, abnormal mineral metabolism, and renal outcome [191].

PTH has been recognized as an important independent risk factor for the increased incidence of CVD in CKD and overall mortality in this patient group [192]. Currently, second and third generation immuno-assays are the most commonly employed methods to measure PTH in clinical practice [192]. Seiler-Mussler et al. clearly demonstrated that second-generation PTH assays were more closely related to CV events, CKD progression, and overall all-cause mortality than non-oxidized PTH measurements in CKD patients not on dialysis [193].

Fibroblast Growth Factor 23 is a growth factor that is heavily involved in phosphate synthesis and vitamin D metabolism. Fibroblast Growth Factor 23 is a phosphotropic hormone that is predominantly secreted by osteocytes and, to a lesser degree, by mature osteoblasts [194]. It is part of the FGF family, which consists of two main subtypes: intracellular and extracellular FGF. Extracellular FGF is subdivided into endocrine and canonical, otherwise called paracrine [190]. These FGFs depend on heparin or heparan sulfate to act as a cofactor; however, endocrine FGFs 15/19/21 and FGF23 have a low affinity for heparin and heparan sulfate and so require Klotho proteins to act as coreceptors [195].

FGF23 itself is composed of three exons and two introns, which codify a 32 kDa glycoprotein composed of 251 amino acids [196]. The FGF23 gene is located on chromosome 12p3.3 and plays a major role as a crucial regulator of phosphate homeostasis through its effects on various organs.

FGF-23 is primarily secreted as a response to increased phosphate levels, where it proceeds to bind to FGFR1–Klotho complexes in the kidneys, resulting in the downregulation of the sodium phosphate co-transporters NaPi-IIa and NaPi-IIc [194]. Thus, it elevates the excretion of renal phosphate, thereby lowering serum phosphate levels.

It also acts as an inhibitor of renal 1-alpha-hydroxylase (CYP27B1) [197]. This limits the conversion of 25(OH)D to active $1,25(OH)_2D$ (calcitriol) [195]. There is a continued upregulation of 24-hydroxylase, causing an enhanced degradation of the already synthesized $1,25(OH)_2D$ (11), consequently reducing intestinal calcium and phosphate absorption and acting as an indirect factor of hypocalcemia [198]. The aforementioned FGFR–Klotho signaling also acts on the parathyroid glands inhibiting PTH [199]. Yet, in chronic kidney disease, there is a development of resistance to FGF-23 signaling, so PTH is persistently elevated, contributing to secondary hyperparathyroidism (SHPT).

Recently, other effects of FGFs-23 have been more intensely monitored. It has been shown that, outside of phosphate regulation, it also stimulates lung inflammation, is associated with elevated interleukin-6 and CRP in the liver [200] and with bone mineralization, increases synaptic density, and alters the morphology of hippocampal cells [195].

In CKD, FGF23 is of significant interest as a biomarker due to its elevation early in the course of the disease. Higher FGF 23 is associated with CKD progression in patients with established chronic kidney disease [197]. Yet, Stubbs et al. (2011) showed that significant increases in FGF23 gene expression in the bone do not occur until later CKD stages [201]. It is important to note that FGF23 levels in CKD rise [198] when calcium, phosphate, and PTH are not yet significantly changed [202].

While definite conclusions as to its usefulness in the clinical field would require dedicated clinical trials, there is significant potential for this biomarker, as it has already been demonstrated that high FGF23 is associated with an increased risk of new-onset CKD and higher all-cause mortality afterwards [203]. Furthermore, studies also show a close correlation between elevated FGF23 levels and a higher incidence of infection, as well as hospitalization, myocardial infarction, heart failure, and death in the CKD patient population [190].

Another significantly promising biomarker is sclerostin. Like FGF-23, it is also produced by osteocytes and has been associated with chronic kidney disease–mineral bone disorder (CKD-MBD) [204].

Sclerostin, a 22 kDa glycoprotein and a product of the SOST gene, is a soluble antagonist of the classical Wnt-beta signaling pathway [205] and regulates bone mass via Wnt-chain signaling. Like FGF-23, sclerostin has been found to be positively correlated with stages of CKD, beginning at CKD stage 2, and its levels increase with disease progression. Both FGF-23 and Sclerostin have been associated with bone turnover parameters [204]. However, unlike FGF-23, sclerostin's presence is greater in cortical bone than in cancellous bone.

Overall, sclerostin has been linked with fewer osteoblasts and osteoclasts, and its elevation results in a thinner trabecular bone and a lower osteoid surface because of its correlation with decreased bone building, demonstrated through a lower activation frequency and bone formation rate, which occurs at high sclerostin levels [204]. Ji et al. (2018) have shown that sclerostin is elevated in serum in CKD3-CKD5 and is positively correlated with serum creatinine, blood phosphate [206], PTH, vitamin D, alkaline phosphatase, and calcium–phosphate products [207]. Sclerostin has been shown to be related to the calcium and phosphate mechanism, but there is still a lack of specific research regarding the exact mechanism of the correlation between calcium and phosphate in CKD-MBD. On the other hand, it has been negatively correlated with eGFR and blood calcium [207].

Serum sclerostin has been predicted as a potential sensitive indicator of the occurrence of CKD-MBD, and due to its close relationship to the prognosis of CKD, there has been a proposed association of sclerostin's involvement in CKD pathogenesis [205]. Moreover, sclerostin has been shown to be related to metabolic disturbances, and a recent study demonstrated its relationship to hyperglycemia in non-dialysis CKD males specifically [206]. In pre-dialysis end-stage kidney failure (ESKD), serum sclerostin has been shown to have a positive correlation with pulmonary hypertension [208].

Dick-kopf-1 is a secreted antagonist of the Wnt pathway and inhibits the formation of the Wnt-Fzd-LRP5/6 trimeric complex [209]. It has an established role in embryonic development and bone formation in adults, where it is increasingly recognized as a major modulator of the metabolism of bone [210]. Elevated levels of DKK1 have also been observed in numerous human cancers.

However, more recently, it has emerged as a potential therapeutic target for CKD progression and the development of complications. DKK1 has been independently associated with low bone turnover, and in stages 3 and 4 of CKD, circulating levels of DKK1 and sclerostin have appeared to be predictive of bone disease [200]; however, further research is required to assess its efficacy as a potential biomarker in the diagnosis, treatment, and monitoring of renal osteodystrophy [209]. Serum levels of DKK1 were positively associated with faster progression to end-stage renal disease [209]. Several studies have reported lower levels of DKK1 in CKD as compared to controls, with levels dropping even early in the course of CKD [210], with the lowest being reported in CKD-4 [209]. Yet, Fang et al. (2014) demonstrated that increased renal production of DKK1 and circulating DKK1 levels were positively associated, and they hypothesized their relationship to CKD pathogenesis [211]. Further studies to gain a more precise insight into this mechanism and its relationship to CKD-MBD are required to validate it as a potential biomarker.

The biomarkers mentioned in the text are presented in Table 4.

Table 4. Bone and mineral metabolism biomarkers.

Biomarker	Origin / Source	Mechanism / Function	Clinical Relevance
Parathyroid Hormone (PTH)	Parathyroid glands	Regulates calcium homeostasis	Established marker of SHPT and bone mineral disorder (CKD-MBD). A predictor of CKD progression, cardiovascular events, and mortality.
Fibroblast Growth Factor 23 (FGF-23)	Osteocytes and mature osteoblasts	Regulates phosphate metabolism. Suppresses 1-á-hydroxylase activity, reducing calcitriol production. Acts on parathyroid glands to suppress PTH.	Elevated early in CKD, before changes in phosphate, calcium, or PTH. Predicts CKD progression, all-cause mortality, and CV events.
Sclerostin	Osteocytes (mainly in cortical bone)	Reduces osteoblast activity and bone formation rate. Affects calcium–phosphate homeostasis.	Negatively correlated with eGFR. Promising marker for CKD-MBD and disease progression. Linked with hyperglycemia and pulmonary hypertension in CKD patients.
Dickkopf-1 (DKK-1)	Various tissues including bone; secreted protein	Regulates bone metabolism and embryonic development. Proposed involvement in "cross-talk" between tissues.	Emerging marker for CKD-related bone disorders and CKD-MBD. Levels correlate with disease severity and lower levels reported in advanced CKD. Associated with low bone turnover. Predictive of progression to ESKD.

Abbreviations: CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral bone disorder; CV, cardiovascular; ESKD, end-stage kidney disease, PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism.

7. Conclusions

There is a multitude of biomarkers related to CKD, with new ones emerging every year. The identification and implementation of novel biomarkers in CKD in clinical practice can result in significant advancements in early diagnosis, risk stratification, and personalized treatment strategies. These arising biomarkers may offer superior sensitivity in the detection of early kidney dysfunction and provide deeper insights into disease progression, correlated comorbidities, and potential therapeutic targets. However, the widespread clinical integration of these biomarkers faces challenges, mainly related to high costs and the necessity for standardized assays. The growing relevance of biomarkers in assessing kidney disease progression has been increasingly emphasized in the recent literature. Several reviews have explored advances in biomarker research for CKD [212–215], underscoring their potential in the comprehensive management of the disease, while also addressing the substantial challenges associated with their clinical implementation. It is essential to note that, whilst specific biomarkers are linked to differing CKD mechanisms and comorbidities, it is vital to recognize that many of the aforementioned biomarkers exhibit associations with multiple complications of CKD. This intersection is a reflection of the inherent complexity and multi-morbid nature that is characteristic of CKD. Due to this, the proposed division of biomarkers cannot be regarded as either definitive or exclusive. Acknowledging this inter-related nature of CKD is crucial for the appropriate interpretation of current and new biomarker data and for the successful development of comprehensive management strategies. The extension and continuation of research is pivotal for advancements in the diagnosis and treatment of CKD, and hopefully, as a result, a wider array of biomarkers will become accessible for use in daily clinical practice, enhancing the quality of healthcare delivered and improving patient outcomes for CKD.

Author Contributions: Writing—original draft: M.D., O.K., N.N. and K.W.-P.; Writing—review and editing: K.P. and K.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Poznan University of Medical Sciences.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Evans, M.; Lewis, R.D.; Morgan, A.R.; Whyte, M.B.; Hanif, W.; Bain, S.C.; Davies, S.; Dashora, U.; Yousef, Z.; Patel, D.C.; et al. A Narrative Review of Chronic Kidney Disease in Clinical Practice: Current Challenges and Future Perspectives. *Adv. Ther.* **2022**, *39*, 33–43. [CrossRef] [PubMed]
2. Rhee, C.M.; Kovesdy, C.P. Epidemiology: Spotlight on CKD deaths–Increasing mortality worldwide. *Nat. Rev. Nephrol.* **2015**, *11*, 199–200. [CrossRef] [PubMed]
3. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* **2020**, *395*, 709–733. [CrossRef] [PubMed]
4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int.* **2024**, *105*, S117–S314. [CrossRef]
5. Yamaguchi, J.; Tanaka, T.; Nangaku, M. Recent advances in understanding of chronic kidney disease. *F1000Research* **2015**, *4*. F1000 Faculty Rev-1212. [CrossRef]
6. Levey, A.S.; Inker, L.A. GFR as the "Gold Standard": Estimated, Measured, and True. *Am. J. Kidney Dis.* **2016**, *67*, 9–12. [CrossRef]
7. Liu, B.C.; Tang, T.T.; Lv, L.L.; Lan, H.Y. Renal tubule injury: A driving force toward chronic kidney disease. *Kidney Int.* **2018**, *93*, 568–579. [CrossRef]
8. Bonventre, J.V. Kidney injury molecule-1 (KIM-1): A urinary biomarker and much more. *Nephrol. Dial. Transplant.* **2009**, *24*, 3265–3268. [CrossRef]
9. Ichimura, T.; Bonventre, J.V.; Bailly, V.; Wei, H.; Hession, C.A.; Cate, R.L.; Sanicola, M. Kidney Injury Molecule-1 (KIM-1), a Putative Epithelial Cell Adhesion Molecule Containing a Novel Immunoglobulin Domain, Is Up-regulated in Renal Cells after Injury. *J. Biol. Chem.* **1998**, *273*, 4135–4142. [CrossRef]
10. Vaidya, V.S.; Ozer, J.S.; Dieterle, F.; Collings, F.B.; Ramirez, V.; Troth, S.; Muniappa, N.; Thudium, D.; Gerhold, D.; Holder, D.J.; et al. Kidney injury molecule-1 outperforms traditional biomarkers of kidney injury in preclinical biomarker qualification studies. *Nat. Biotechnol.* **2010**, *28*, 478–485. [CrossRef]
11. Schmidt, I.M.; Srivastava, A.; Sabbisetti, V.; McMahon, G.M.; He, J.; Chen, J.; Kusek, J.W.; Taliercio, J.; Ricardo, A.C.; Hsu, C.Y.; et al. Plasma Kidney Injury Molecule 1 in CKD: Findings From the Boston Kidney Biopsy Cohort and CRIC Studies. *Am. J. Kidney Dis.* **2022**, *79*, 231–243.e1. [CrossRef] [PubMed]
12. Han, W.K.; Bailly, V.; Abichandani, R.; Thadhani, R.; Bonventre, J.V. Kidney Injury Molecule-1 (KIM-1): A novel biomarker for human renal proximal tubule injury. *Kidney Int.* **2002**, *62*, 237–244. [CrossRef] [PubMed]
13. Waikar, S.S.; Sabbisetti, V.; Ärnlöv, J.; Carlsson, A.C.; Coresh, J.; Feldman, H.I.; Foster, M.C.; Fufaa, G.D.; Helmersson-Karlqvist, J.; Hsu, C.Y.; et al. Relationship of proximal tubular injury to chronic kidney disease as assessed by urinary kidney injury molecule-1 in five cohort studies. *Nephrol. Dial. Transplant.* **2016**, *31*, 1460–1470. [CrossRef] [PubMed]
14. Ruggenenti, P.; Perna, A.; Gherardi, G.; Garini, G.; Zoccali, C.; Salvadori, M.; Scolari, F.; Schena, F.P.; Remuzzi, G. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* **1999**, *354*, 359–364. [CrossRef]
15. Lewis, E.J.; Hunsicker, L.G.; Bain, R.P.; Rohde, R.D. The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy. *New Engl. J. Med.* **1993**, *329*, 1456–1462. [CrossRef]
16. Zhao, X.; Zhang, Y.; Li, L.; Mann, D.; Imig, J.D.; Emmett, N.; Gibbons, G.; Jin, L.M. Glomerular Expression of Kidney Injury Molecule-1 and Podocytopenia in Diabetic Glomerulopathy. *Am. J. Nephrol.* **2011**, *34*, 268–280. [CrossRef]
17. Kwon, S.H.; Park, M.Y.; Jeon, J.S.; Noh, H.; Choi, S.J.; Kim, J.K.; Hwang, G.S.; Jeon, H.J.; Han, D.C. KIM-1 expression predicts renal outcomes in IgA nephropathy. *Clin. Exp. Nephrol.* **2013**, *17*, 359–364. [CrossRef]
18. Humphreys, B.D.; Xu, F.; Sabbisetti, V.; Grgic, I.; Naini, S.M.; Wang, N.; Chen, G.; Xiao, S.; Patel, D.; Henderson, J.M.; et al. Chronic epithelial kidney injury molecule-1 expression causes murine kidney fibrosis. *J. Clin. Investig.* **2013**, *123*, 4023–4035. [CrossRef]
19. Rees, A.J.; Kain, R. Kim-1/Tim-1: From biomarker to therapeutic target? *Nephrol. Dial. Transplant.* **2008**, *23*, 3394–3396. [CrossRef]
20. Bazzi, C.; Petrini, C.; Rizza, V.; Arrigo, G.; Napodano, P.; Paparella, M.; D'Amico, G. Urinary N-acetyl-β-glucosaminidase excretion is a marker of tubular cell dysfunction and a predictor of outcome in primary glomerulonephritis. *Nephrol. Dial. Transplant.* **2002**, *17*, 1890–1896. [CrossRef]
21. Patel, D.N.; Kalia, K. Efficacy of urinary N-acetyl-β-D-glucosaminidase to evaluate early renal tubular damage as a consequence of type 2 diabetes mellitus: A cross-sectional study. *Int. J. Diabetes Dev. Ctries.* **2015**, *35*, 449–457. [CrossRef]
22. Wang, Y.; Jin, M.; Cheng, C.K.; Li, Q. Tubular Injury in Diabetic kidney Disease: Molecular Mechanisms and Potential Therapeutic Perspectives. *Front. Endocrinol.* **2023**, *14*, 1238927. [CrossRef] [PubMed]
23. Kern, E.F.O.; Erhard, P.; Sun, W.; Genuth, S.; Weiss, M.F. Early Urinary Markers of Diabetic Kidney Disease: A Nested Case-Control Study From the Diabetes Control and Complications Trial (DCCT). *Am. J. Kidney Dis.* **2010**, *55*, 824–834. [CrossRef] [PubMed]
24. Kadokura, T.; Saito, M.; Utsuno, A.; Kazuta, K.; Yoshida, S.; Kawasaki, S.; Toda, Y.; Ashida, A.; Tsukada, T.; Yokoyama, H.; et al. Ipragliflozin (ASP1941), a selective sodium-dependent glucose cotransporter 2 inhibitor, safely stimulates urinary glucose excretion without inducing hypoglycemia in healthy Japanese subjects. *Diabetol. Int.* **2011**, *2*, 172–182. [CrossRef]

25. Ellis, E.N.; Brouhard, B.H.; Lagrone, L.; Travis, L.B. Urinary Excretion of N-Acetyl-Beta-D-Glucosaminidase in Children with Type I Diabetes Mellitus. *Diabetes Care* **1983**, *6*, 251–255. [CrossRef]
26. Sheira, G.; Noreldin, N.; Tamer, A.; Saad, M. Urinary biomarker N-acetyl-β-D-glucosaminidase can predict severity of renal damage in diabetic nephropathy. *J. Diabetes Metab. Disord.* **2015**, *14*, 4. [CrossRef]
27. Kim, S.R.; Lee, Y.H.; Lee, S.G.; Kang, E.S.; Cha, B.S.; Kim, J.H.; Lee, B.W. Urinary N-acetyl-β-D-glucosaminidase, an early marker of diabetic kidney disease, might reflect glucose excursion in patients with type 2 diabetes. *Medicine* **2016**, *95*, e4114. [CrossRef]
28. Tan, J.; Yin, K.; Ouyang, Z.; Wang, R.; Pan, H.; Wang, Z.; Xu, C.; Li, Y.; Wang, H.; Fan, C.; et al. Real-Time Monitoring Renal Impairment Due to Drug-Induced AKI and Diabetes-Caused CKD Using an NAG-Activatable NIR-II Nanoprobe. *Anal. Chem.* **2021**, *93*, 16158–16165. [CrossRef]
29. Sikri, K.L.; Foster, C.L.; MacHugh, N.; Marshall, R.D. Localization of Tamm-Horsfall glycoprotein in the human kidney using immuno-fluorescence and immuno-electron microscopical techniques. *J. Anat.* **1981**, *132 Pt 4*, 597–605.
30. Hunt, J.S.; McGiven, A.R.; Groufsky, A.; Lynn, K.L.; Taylor, M.C. Affinity-purified antibodies of defined specificity for use in a solid-phase microplate radioimmunoassay of human Tamm-Horsfall glycoprotein in urine. *Biochem. J.* **1985**, *227*, 957–963. [CrossRef]
31. Prasadan, K.; Bates, J.; Badgett, A.; Dell, M.; Sukhatme, V.; Yu, H.; Gittes, G.K. Nucleotide sequence and peptide motifs of mouse uromodulin (Tamm-Horsfall protein)—The most abundant protein in mammalian urine. *Biochim. Biophys. Acta BBA Gene Struct. Expr.* **1995**, *1260*, 328–332. [CrossRef]
32. Mutig, K.; Kahl, T.; Saritas, T.; Godes, M.; Persson, P.; Bates, J.; Raffi, H.; Rampoldi, L.; Uchida, S.; Hille, C.; et al. Activation of the Bumetanide-sensitive Na^+,K^+,$2Cl^-$ Cotransporter (NKCC2) Is Facilitated by Tamm-Horsfall Protein in a Chloride-sensitive Manner. *J. Biol. Chem.* **2011**, *286*, 30200–30210. [CrossRef]
33. You, R.; Chen, L.; Xu, L.; Li, H.; Shi, X.; Zheng, Y.; Zhang, Z.; Wu, Y.; Wang, Y.; Wang, M.; et al. High Level of Uromodulin Increases the Risk of Hypertension: A Mendelian Randomization Study: PO1777. *J. Am. Soc. Nephrol.* **2021**, *32*, 550. [CrossRef]
34. Gudbjartsson, D.F.; Holm, H.; Indridason, O.S.; Thorleifsson, G.; Edvardsson, V.; Sulem, P.; de Vegt, F.; d'Ancona, F.C.; den Heijer, M.; Wetzels, J.F.; et al. Association of Variants at UMOD with Chronic Kidney Disease and Kidney Stones—Role of Age and Comorbid Diseases. *PLoS Genet.* **2010**, *6*, e1001039. [CrossRef] [PubMed]
35. Schmid, M.; Prajczer, S.; Gruber, L.N.; Bertocchi, C.; Gandini, R.; Pfaller, W.; Jennings, P.; Joannidis, M. Uromodulin Facilitates Neutrophil Migration Across Renal Epithelial Monolayers. *Cell Physiol. Biochem.* **2010**, *26*, 311–318. [CrossRef] [PubMed]
36. LaFavers, K.A.; Hage, C.A.; Gaur, V.; Micanovic, R.; Hato, T.; Khan, S.; Dagher, P.C.; Wu, X.R.; El-Achkar, T.M. The kidney protects against sepsis by producing systemic uromodulin. *Am. J. Physiol.-Ren. Physiol.* **2022**, *323*, F212–F226. [CrossRef]
37. Micanovic, R.; Khan, S.; Janosevic, D.; Lee, M.E.; Hato, T.; Srour, E.F.; Winfree, S.; Ghosh, J.; Tong, Y.; Rice, S.E.; et al. Tamm-Horsfall Protein Regulates Mononuclear Phagocytes in the Kidney. *J. Am. Soc. Nephrol.* **2018**, *29*, 841. [CrossRef]
38. Pak, J.; Pu, Y.; Zhang, Z.T.; Hasty, D.L.; Wu, X.R. Tamm-Horsfall Protein Binds to Type 1 Fimbriated *Escherichia coli* and Prevents *E. coli* from Binding to Uroplakin Ia and Ib Receptors. *J. Biol. Chem.* **2001**, *276*, 9924–9930. [CrossRef]
39. Weiss, G.L.; Stanisich, J.J.; Sauer, M.M.; Lin, C.W.; Eras, J.; Zyla, D.S.; Trück, J.; Devuyst, O.; Aebi, M.; Pilhofer, M.; et al. Architecture and function of human uromodulin filaments in urinary tract infections. *Science* **2020**, *369*, 1005–1010. [CrossRef]
40. Lynn, K.L.; Marshall, R.D. Excretion of Tamm-Horsfall glycoprotein in renal disease. *Clin. Nephrol.* **1984**, *22*, 253–257.
41. Prajczer, S.; Heidenreich, U.; Pfaller, W.; Kotanko, P.; Lhotta, K.; Jennings, P. Evidence for a role of uromodulin in chronic kidney disease progression. *Nephrol. Dial. Transplant.* **2010**, *25*, 1896–1903. [CrossRef] [PubMed]
42. Youhanna, S.; Weber, J.; Beaujean, V.; Glaudemans, B.; Sobek, J.; Devuyst, O. Determination of uromodulin in human urine: Influence of storage and processing. *Nephrol. Dial. Transplant.* **2014**, *29*, 136–145. [CrossRef] [PubMed]
43. Olden, M.; Corre, T.; Hayward, C.; Toniolo, D.; Ulivi, S.; Gasparini, P.; Pistis, G.; Hwang, S.J.; Bergmann, S.; Campbell, H.; et al. Common Variants in UMOD Associate with Urinary Uromodulin Levels: A Meta-Analysis. *J. Am. Soc. Nephrol.* **2014**, *25*, 1869. [CrossRef]
44. Köttgen, A.; Hwang, S.J.; Larson, M.G.; Van Eyk, J.E.; Fu, Q.; Benjamin, E.J.; Dehghan, A.; Glazer, N.L.; Kao, W.H.; Harris, T.B.; et al. Uromodulin Levels Associate with a Common UMOD Variant and Risk for Incident CKD. *J. Am. Soc. Nephrol.* **2010**, *21*, 337. [CrossRef]
45. Melchinger, H.; Calderon-Gutierrez, F.; Obeid, W.; Xu, L.; Shaw, M.M.; Luciano, R.L.; Kuperman, M.; Moeckel, G.W.; Kashgarian, M.; Wilson, F.P.; et al. Urine Uromodulin as a Biomarker of Kidney Tubulointerstitial Fibrosis. *Clin. J. Am. Soc. Nephrol.* **2022**, *17*, 1284. [CrossRef]
46. Humphreys, B.D. Mechanisms of Renal Fibrosis. *Annu. Rev. Physiol.* **2018**, *80*, 309–326. [CrossRef]
47. Steubl, D.; Block, M.; Herbst, V.; Nockher, W.A.; Schlumberger, W.; Kemmner, S.; Bachmann, Q.; Angermann, S.; Wen, M.; Heemann, U.; et al. Urinary uromodulin independently predicts end-stage renal disease and rapid kidney function decline in a cohort of chronic kidney disease patients. *Medicine* **2019**, *98*, e15808. [CrossRef]

48. Scherberich, J.E.; Gruber, R.; Nockher, W.A.; Christensen, E.I.; Schmitt, H.; Herbst, V.; Block, M.; Kaden, J.; Schlumberger, W. Serum uromodulin—A marker of kidney function and renal parenchymal integrity. *Nephrol. Dial. Transplant.* **2018**, *33*, 284–295. [CrossRef]
49. Risch, L.; Lhotta, K.; Meier, D.; Medina-Escobar, P.; Nydegger, U.E.; Risch, M. The serum uromodulin level is associated with kidney function. *Clin. Chem. Lab. Med. CCLM* **2014**, *52*, 1755–1761. [CrossRef]
50. Usui, R.; Ogawa, T.; Takahashi, H.; Iwasaki, C.; Koike, M.; Morito, T.; Arai, K.; Sakurada, T.; Sato, T.; Otsuka, Y.; et al. Serum uromodulin is a novel renal function marker in the Japanese population. *Clin. Exp. Nephrol.* **2021**, *25*, 28–36. [CrossRef]
51. Fedak, D.; Kuźniewski, M.; Fugiel, A.; Wieczorek-Surdacka, E.; Przepiórkowska-Hoyer, B.; Jasik, P.; Miarka, P.; Dumnicka, P.; Kapusta, M.; Solnica, B.; et al. Serum uromodulin concentrations correlate with glomerular filtration rate in patients with chronic kidney disease. *Pol. Arch. Med. Wewn.* **2016**, *126*, 995–1004. [CrossRef] [PubMed]
52. Steubl, D.; Block, M.; Herbst, V.; Nockher, W.A.; Schlumberger, W.; Satanovskij, R.; Angermann, S.; Hasenau, A.L.; Stecher, L.; Heemann, U.; et al. Plasma Uromodulin Correlates With Kidney Function and Identifies Early Stages in Chronic Kidney Disease Patients. *Medicine* **2016**, *95*, e3011. [CrossRef] [PubMed]
53. Genov, D.; Kundurdgiev, A.; Ivanova, I.; Nikolova, M.; Pencheva, V.; Hristova, M.; Vazelov, E. Role of Serum Uromodulin in the Early Diagnosis of Chronic Kidney Disease. *Acta. Medica Bulg.* **2021**, *48*, 13–16. [CrossRef]
54. Lv, L.; Wang, J.; Gao, B.; Wu, L.; Wang, F.; Cui, Z.; He, K.; Zhang, L.; Chen, M.; Zhao, M.H. Serum uromodulin and progression of kidney disease in patients with chronic kidney disease. *J. Transl. Med.* **2018**, *16*, 316. [CrossRef]
55. Ikeme, J.C.; Scherzer, R.; Garimella, P.S.; Hallan, S.I.; Katz, R.; Estrella, M.M.; Shlipak, M.G.; Ix, J.H. The Association of Plasma and Urine Uromodulin With Cardiovascular Disease in Persons With Hypertension and CKD. *Am. J. Kidney Dis.* **2024**, *84*, 799–802. [CrossRef]
56. David, B.L.; Ivan, G.N.J.; Emilio, P.G.E.; Daniela, M.S.J.; Betsabe, C.H.; Luisa, V.V.M.; Santiago, A.V.J.; Jose, L.P.I.; Caballero-Islas, A.E.; Zuniga-Curiel, S.; et al. Low serum uromodulin levels and their association with lupus flares. *PLoS ONE* **2022**, *17*, e0276481. [CrossRef]
57. Tachibana, S.; Iyoda, M.; Suzuki, T.; Kanazawa, N.; Iseri, K.; Wada, Y.; Matsumoto, K.; Shibata, T. Serum uromodulin is associated with the severity of clinicopathological findings in ANCA-associated glomerulonephritis. *PLoS ONE* **2019**, *14*, e0224690. [CrossRef]
58. Vylet'al, P.; Hůlková, H.; Živná, M.; Berná, L.; Novák, P.; Elleder, M.; Kmoch, S. Abnormal expression and processing of uromodulin in Fabry disease reflects tubular cell storage alteration and is reversible by enzyme replacement therapy. *J. Inherit. Metab. Dis.* **2008**, *31*, 508–517. [CrossRef]
59. Hart, T.C.; Gorry, M.C.; Hart, P.S.; Woodard, A.S.; Shihabi, Z.; Sandhu, J.; Shirts, B.; Xu, L.; Zhu, H.; Barmada, M.M.; et al. Mutations of the UMOD gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricaemic nephropathy. *J. Med. Genet.* **2002**, *39*, 882–892. [CrossRef]
60. Rampoldi, L.; Caridi, G.; Santon, D.; Boaretto, F.; Bernascone, I.; Lamorte, G.; Tardanico, R.; Dagnino, M.; Colussi, G.; Scolari, F.; et al. Allelism of MCKD, FJHN and GCKD caused by impairment of uromodulin export dynamics. *Hum. Mol. Genet.* **2003**, *12*, 3369–3384. [CrossRef]
61. Kuro-o, M.; Matsumura, Y.; Aizawa, H.; Kawaguchi, H.; Suga, T.; Utsugi, T.; Ohyama, Y.; Kurabayashi, M.; Kaname, T.; Kume, E.; et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature* **1997**, *390*, 45–51. [CrossRef] [PubMed]
62. Arking, D.E.; Becker, D.M.; Yanek, L.R.; Fallin, D.; Judge, D.P.; Moy, T.F.; Becker, L.C.; Dietz, H.C. KLOTHO Allele Status and the Risk of Early-Onset Occult Coronary Artery Disease. *Am. J. Hum. Genet.* **2003**, *72*, 1154–1161. [CrossRef] [PubMed]
63. Arking, D.E.; Atzmon, G.; Arking, A.; Barzilai, N.; Dietz, H.C. Association Between a Functional Variant of the KLOTHO Gene and High-Density Lipoprotein Cholesterol, Blood Pressure, Stroke, and Longevity. *Circ. Res.* **2005**, *96*, 412–418. [CrossRef] [PubMed]
64. Ichikawa, S.; Imel, E.A.; Kreiter, M.L.; Yu, X.; Mackenzie, D.S.; Sorenson, A.H.; Goetz, R.; Mohammadi, M.; White, K.E.; Econs, M.J. A homozygous missense mutation in human KLOTHO causes severe tumoral calcinosis. *J. Clin. Investig.* **2007**, *117*, 2684–2691. [CrossRef]
65. Arroyo, E.; Leber, C.A.; Burney, H.N.; Narayanan, G.; Moorthi, R.; Avin, K.G.; Moe, S.M. Relationship between klotho and physical function in healthy aging. *Sci. Rep.* **2023**, *13*, 21158. [CrossRef]
66. Kuro-o, M. The Klotho proteins in health and disease. *Nat. Rev. Nephrol.* **2019**, *15*, 27–44. [CrossRef]
67. Wang, Y.; Sun, Z. Current understanding of klotho. *Ageing Res. Rev.* **2009**, *8*, 43–51. [CrossRef]
68. Kurosu, H.; Ogawa, Y.; Miyoshi, M.; Yamamoto, M.; Nandi, A.; Rosenblatt, K.P.; Baum, M.G.; Schiavi, S.; Hu, M.C.; Moe, O.W.; et al. Regulation of Fibroblast Growth Factor-23 Signaling by Klotho. *J. Biol. Chem.* **2006**, *281*, 6120–6123. [CrossRef]
69. Hu, M.C.; Shi, M.; Zhang, J.; Addo, T.; Cho, H.J.; Barker, S.L.; Ravikumar, P.; Gillings, N.; Bian, A.; Sidhu, S.S.; et al. Renal Production, Uptake, and Handling of Circulating αKlotho. *J. Am. Soc. Nephrol.* **2016**, *27*, 79–90. [CrossRef]
70. Shimamura, Y.; Hamada, K.; Inoue, K.; Ogata, K.; Ishihara, M.; Kagawa, T.; Inoue, M.; Fujimoto, S.; Ikebe, M.; Yuasa, K.; et al. Serum levels of soluble secreted α-Klotho are decreased in the early stages of chronic kidney disease, making it a probable novel biomarker for early diagnosis. *Clin. Exp. Nephrol.* **2012**, *16*, 722–729. [CrossRef]

71. Rotondi, S.; Pasquali, M.; Tartaglione, L.; Muci, M.L.; Mandanici, G.; Leonangeli, C.; Sales, S.; Farcomeni, A.; Mazzaferro, S. Soluble α-Klotho Serum Levels in Chronic Kidney Disease. *Int. J. Endocrinol.* **2015**, *2015*, 872193. [CrossRef] [PubMed]
72. Barker, S.L.; Pastor, J.; Carranza, D.; Quiñones, H.; Griffith, C.; Goetz, R.; Mohammadi, M.; Ye, J.; Zhang, J.; Hu, M.C.; et al. The demonstration of αKlotho deficiency in human chronic kidney disease with a novel synthetic antibody. *Nephrol. Dial. Transplant.* **2015**, *30*, 223–233. [CrossRef] [PubMed]
73. Seiler, S.; Wen, M.; Roth, H.J.; Fehrenz, M.; Flügge, F.; Herath, E.; Weihrauch, A.; Fliser, D.; Heine, G.H. Plasma Klotho is not related to kidney function and does not predict adverse outcome in patients with chronic kidney disease. *Kidney Int.* **2013**, *83*, 121–128. [CrossRef] [PubMed]
74. Hu, M.C.; Shi, M.; Zhang, J.; Quiñones, H.; Griffith, C.; Kuro-o, M.; Moe, O.W. Klotho Deficiency Causes Vascular Calcification in Chronic Kidney Disease. *J. Am. Soc. Nephrol.* **2011**, *22*, 124. [CrossRef]
75. Oishi, H.; Doi, S.; Nakashima, A.; Ike, T.; Maeoka, Y.; Sasaki, K.; Doi, T.; Arihiro, K.; Masaki, T. Klotho overexpression protects against renal aging along with suppression of transforming growth factor-β1 signaling pathways. *Am. J. Physiol.-Ren. Physiol.* **2021**, *321*, F799–F811. [CrossRef]
76. Li, S.S.; Sheng, M.J.; Sun, Z.Y.; Liang, Y.; Yu, L.X.; Liu, Q.F. Upstream and downstream regulators of Klotho expression in chronic kidney disease. *Metabolism* **2023**, *142*, 155530. [CrossRef]
77. Ibrahim, A.M.S.; Ghorab, A.A.; Ibrahim, M.; Ibrahim, A.M.S. Dickkopf 3 as a novel biomarker of the kidney injury. *Afr. J. Biol. Sci.* **2024**, *6*, 660–670.
78. Dincel, A.S.; Jørgensen, N.R.; on behalf of the IOF-IFCC Joint Committee on Bone Metabolism (C-BM). New emerging biomarkers for bone disease: Sclerostin and Dickkopf-1 (DKK1). *Calcif. Tissue Int.* **2022**, *112*, 243–257. [CrossRef]
79. Zewinger, S.; Rauen, T.; Rudnicki, M.; Federico, G.; Wagner, M.; Triem, S.; Schmidt, T.; Schunk, S.J.; Fliser, D.; Heine, G.H.; et al. Dickkopf-3 (DKK3) in urine identifies patients with short-term risk of eGFR loss. *J. Am. Soc. Nephrol.* **2018**, *29*, 2722–2733. [CrossRef]
80. Torigoe, K.; Muta, K.; Tsuji, K.; Yamashita, A.; Torigoe, M.; Abe, S.; Tanaka, M.; Nishimura, S.; Nakagawa, T.; Ueda, M. Association of urinary Dickkopf-3 with residual renal function decline in patients undergoing peritoneal dialysis. *Medicina* **2021**, *57*, 631. [CrossRef]
81. Dziamałek-Macioszczyk, P.; Winiarska, A.; Pawłowska, A.; Wojtacha, P.; Stompór, T. Patterns of Dickkopf-3 serum and urine levels at different stages of chronic kidney disease. *J. Clin. Med.* **2023**, *12*, 4705. [CrossRef] [PubMed]
82. Schäfer, A.K.C.; Pieper, D.; Dihazi, H.; Dihazi, G.H.; Lüders, S.; Koziolek, M.J.; Müller, G.A.; Sörensen-Zender, I.; Haller, H. Urinary Dickkopf-3 (DKK3) is associated with greater eGFR loss in patients with resistant hypertension. *J. Clin. Med.* **2023**, *12*, 1034. [CrossRef] [PubMed]
83. Schunk, S.J.; Beisswenger, C.; Ritzmann, F.; Herr, C.; Wagner, M.; Triem, S.; Hütter, G.; Schmit, D.; Zewinger, S.; Sarakpi, T.; et al. Measurement of urinary Dickkopf-3 uncovered silent progressive kidney injury in patients with chronic obstructive pulmonary disease. *Kidney Int.* **2021**, *100*, 1081–1091. [CrossRef]
84. Cao, Y.; Wang, W.; Xie, S.; Xu, Y.; Lin, Z. Joint association of the inflammatory marker and cardiovascular-kidney-metabolic syndrome stages with all-cause and cardiovascular disease mortality: A national prospective study. *BMC Public. Health* **2025**, *25*, 10. [CrossRef] [PubMed]
85. Danaei, G.; Lu, Y.; Singh, G.M.; Carnahan, E.; Stevens, G.A.; Cowan, M.J.; Farzadfar, F.; Lin, J.K.; Finucane, M.M.; Azizi, F.; et al. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: A comparative risk assessment. *Lancet Diabetes Endocrinol.* **2014**, *2*, 634–647.
86. Li, N.; Li, Y.; Cui, L.; Shu, R.; Song, H.; Wang, J.; Chen, Y.; Di, X.; Li, J.; Wang, L.; et al. Association between different stages of cardiovascular-kidney-metabolic syndrome and the risk of all-cause mortality. *Atherosclerosis* **2024**, *397*, 118585. [CrossRef]
87. Gu, L.; Xia, Z.; Qing, B.; Wang, W.; Chen, H.; Wang, J.; Chen, Y.; Gai, Z.; Hu, R.; Yuan, Y. Systemic Inflammatory Response Index (SIRI) is associated with all-cause mortality and cardiovascular mortality in population with chronic kidney disease: Evidence from NHANES (2001–2018). *Front. Immunol.* **2024**, *15*, 1338025. [CrossRef]
88. Bonaccio, M.; Di Castelnuovo, A.; Pounis, G.; De Curtis, A.; Costanzo, S.; Persichillo, M.; Cerletti, C.; Donati, M.B.; de Gaetano, G.; Iacoviello, L.; et al. A score of low-grade inflammation and risk of mortality: Prospective findings from the Moli-sani study. *Haematologica* **2016**, *101*, 1434–1441. [CrossRef]
89. Zhang, Y.; Xing, Z.; Zhou, K.; Jiang, S. The Predictive Role of Systemic Inflammation Response Index (SIRI) in the Prognosis of Stroke Patients. *Clin. Interv. Aging* **2021**, *16*, 1997–2007. [CrossRef]
90. Wang, P.; Guo, X.; Zhou, Y.; Li, Z.; Yu, S.; Sun, Y.; Hou, Y. Monocyte-to-high-density lipoprotein ratio and systemic inflammation response index are associated with the risk of metabolic disorders and cardiovascular diseases in general rural population. *Front. Endocrinol.* **2022**, *13*, 944991. [CrossRef]
91. Han, Y.; Lin, N. Systemic Inflammatory Response Index and the Short-Term Functional Outcome of Patients with Acute Ischemic Stroke: A Meta-analysis. *Neurol. Ther.* **2024**, *13*, 1431–1451. [CrossRef] [PubMed]

92. Lai, W.; Zhao, X.; Gao, Z.; Huang, H.; Huang, D.; Zhou, Y.; Chen, G.; Zhang, L.; Zhang, Z.; Jin, Z.; et al. Association of Systemic Inflammation Level on Admission with Total and Cardiovascular-Specific Death in Heart Failure with Preserved Ejection Fraction: A Large Multi-Center Retrospective Longitudinal Study. *J. Inflamm. Res.* **2024**, *17*, 5533–5542. [CrossRef] [PubMed]
93. Yadav, R.; Sangha, S.S.; Yadav, S.; Sharma, P.; Shah, H.; Bhowmik, D. A Clinical Study to Evaluate the Anti-inflammatory Effect of Lactoferrin + Disodium Guanosine Monophosphate Therapy in the Patients with Chronic Kidney Disease. *J. Assoc. Physicians India* **2025**, *73*, 18–22.
94. Yeo, E.S.; Hwang, J.Y.; Park, J.E.; Choi, Y.J.; Huh, K.B.; Kim, W.Y. Tumor Necrosis Factor (TNF-α) and C-reactive Protein (CRP) are Positively Associated with the Risk of Chronic Kidney Disease in Patients with Type 2 Diabetes. *Yonsei Med. J.* **2010**, *51*, 519. [CrossRef]
95. Menon, V.; Greene, T.; Wang, X.; Pereira, A.A.; Marcovina, S.M.; Beck, G.J.; Kusek, J.W.; Collins, A.J.; Levey, A.S.; Sarnak, M.J. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney Int.* **2005**, *68*, 766–772. [CrossRef]
96. Jalal, D.; Chonchol, M.; Etgen, T.; Sander, D. C-reactive protein as a predictor of cardiovascular events in elderly patients with chronic kidney disease. *J. Nephrol.* **2012**, *25*, 719–725. [CrossRef]
97. Gao, J.; Wang, A.; Li, X.; Li, J.; Zhao, H.; Zhang, J.; Chen, S.; Su, Z.; Zhang, Y.; Wu, S. The Cumulative Exposure to High-Sensitivity C-Reactive Protein Predicts the Risk of Chronic Kidney Diseases. *Kidney Blood Press. Res.* **2020**, *45*, 84–94. [CrossRef]
98. Menon, V.; Wang, X.; Greene, T.; Beck, G.J.; Kusek, J.W.; Marcovina, S.M.; Levey, A.S.; Sarnak, M.J. Relationship between C-reactive protein, albumin, and cardiovascular disease in patients with chronic kidney disease. *Am. J. Kidney Dis.* **2003**, *42*, 44–52. [CrossRef]
99. Panichi, V.; Migliori, M.; De Pietro, S.; Taccola, D.; Bianchi, A.M.; Giovannini, L.; Norpoth, M.; Metelli, M.R.; Cristofani, R.; Bertelli, A.A.; et al. C-Reactive Protein and Interleukin-6 Levels Are Related to Renal Function in Predialytic Chronic Renal Failure. *Nephron* **2002**, *91*, 594–600. [CrossRef]
100. Lee, J.E.; Choi, S.Y.; Huh, W.; Kim, Y.G.; Kim, D.J.; Oh, H.Y. Metabolic Syndrome, C-Reactive Protein, and Chronic Kidney Disease in Nondiabetic, Nonhypertensive Adults. *Am. J. Hypertens.* **2007**, *20*, 1189–1194.
101. Prodhan, M.J.A.; Al Mahmud, M.; Saha, S.K.; Salauddin, S.M.; Ali, M. Association of Inflammatory Marker C-Reactive Protein and Interleukin-6 with Stages 3-5 of Chronic Kidney Disease. *Saudi J. Med.* **2024**, *9*, 344–353. [CrossRef]
102. Ridker, P.M.; MacFadyen, J.G.; Glynn, R.J.; Koenig, W.; Libby, P.; Everett, B.M.; Lefkowitz, M.; Thuren, T.; Cornel, J.H. Inhibition of Interleukin-1β by Canakinumab and Cardiovascular Outcomes in Patients With Chronic Kidney Disease. *J. Am. Coll. Cardiol.* **2018**, *71*, 2405–2414. [CrossRef] [PubMed]
103. Kurella Tamura, M.; Tam, K.; Vittinghoff, E.; Raj, D.; Sozio, S.M.; Rosas, S.E.; Makos, G.; Lora, C.; He, J.; Go, A.S.; et al. Inflammatory Markers and Risk for Cognitive Decline in Chronic Kidney Disease: The CRIC Study. *Kidney Int. Rep.* **2017**, *2*, 192–200. [CrossRef]
104. Vázquez-Huerta, D.I.; Alvarez-Rodríguez, B.A.; Topete-Reyes, J.F.; Muñoz-Valle, J.F.; Fuentes-Ramírez, F.; Salazar-López, M.A.; Valle, Y.; Mendoza-Carrera, F.; Moran-Moguel, M.C.; Peña-Rodríguez, M.; et al. Tumor necrosis factor alpha -238 G/A and -308 G/A polymorphisms and soluble TNF-α levels in chronic kidney disease: Correlation with clinical variables. *Ren. Fail.* **2014**, *7*, 2111–2119.
105. Ernandez, T.; Mayadas, T. Immunoregulatory role of TNFα in inflammatory kidney diseases. *Kidney Int.* **2009**, *76*, 262–276. [CrossRef]
106. Li, G.; Wu, W.; Zhang, X.; Huang, Y.; Wen, Y.; Li, X.; Gao, R. Serum levels of tumor necrosis factor alpha in patients with IgA nephropathy are closely associated with disease severity. *BMC Nephrol.* **2018**, *19*, 326. [CrossRef]
107. Murakoshi, M.; Gohda, T.; Suzuki, Y. Circulating Tumor Necrosis Factor Receptors: A Potential Biomarker for the Progression of Diabetic Kidney Disease. *Int. J. Mol. Sci.* **2020**, *21*, 1957. [CrossRef]
108. Li, H.; Li, M.; Liu, C.; He, P.; Dong, A.; Dong, S.; Zhang, M. Causal effects of systemic inflammatory regulators on chronic kidney diseases and renal function: A bidirectional Mendelian randomization study. *Front. Immunol.* **2023**, *14*, 1229636. [CrossRef]
109. Therrien, F.J.; Agharazii, M.; Lebel, M.; Larivière, R. Neutralization of Tumor Necrosis Factor-Alpha Reduces Renal Fibrosis and Hypertension in Rats with Renal Failure. *Am. J. Nephrol.* **2012**, *36*, 151–161. [CrossRef]
110. Egli-Spichtig, D.; Imenez Silva, P.H.; Glaudemans, B.; Gehring, N.; Bettoni, C.; Zhang, M.Y.H.; Pastor-Arroyo, E.M.; Schönenberger, D.; Rajski, M.; Hoogewijs, D.; et al. Tumor necrosis factor stimulates fibroblast growth factor 23 levels in chronic kidney disease and non-renal inflammation. *Kidney Int.* **2019**, *96*, 890–905. [CrossRef]
111. Zhang, J.; Patel, M.B.; Griffiths, R.; Mao, A.; Song, Y.S.; Karlovich, N.S.; Sparks, M.A.; Jin, H.; Wu, M.; Lin, E.E.; et al. Tumor Necrosis Factor-α Produced in the Kidney Contributes to Angiotensin II–dependent Hypertension. *Hypertension* **2014**, *64*, 1275–1281. [CrossRef] [PubMed]
112. Ramseyer, V.D.; Garvin, J.L. Tumor necrosis factor-α: Regulation of renal function and blood pressure. *Am. J. Physiol.-Ren. Physiol.* **2013**, *304*, F1231–F1242. [CrossRef] [PubMed]

113. Agharazii, M.; St-Louis, R.; Gautier-Bastien, A.; Ung, R.V.; Mokas, S.; Larivière, R.; Richard, D.E. Inflammatory Cytokines and Reactive Oxygen Species as Mediators of Chronic Kidney Disease-Related Vascular Calcification. *Am. J. Hypertens.* **2015**, *28*, 746–755. [CrossRef] [PubMed]
114. Amdur, R.L.; Feldman, H.I.; Dominic, E.A.; Anderson, A.H.; Beddhu, S.; Rahman, M.; Wolf, M.; Reilly, M.; Ojo, A.; Townsend, R.R.; et al. Use of Measures of Inflammation and Kidney Function for Prediction of Atherosclerotic Vascular Disease Events and Death in Patients With CKD: Findings From the CRIC Study. *Am. J. Kidney Dis.* **2019**, *73*, 344–353. [CrossRef]
115. Banaszkiewicz, M. Fibrinogen and interleukin-6 as meaningful biomarkers of cardiovascular-related death in chronic kidney disease patients treated with renal replacement therapy under 60 years of age. *Przegl. Lek.* **2017**, *74*, 621–626.
116. Akchurin, O.; Patino, E.; Dalal, V.; Meza, K.; Bhatia, D.; Brovender, S.; Zhu, Y.S.; Cunningham-Rundles, S.; Perelstein, E.; Kumar, J.; et al. Interleukin-6 Contributes to the Development of Anemia in Juvenile CKD. *Kidney Int. Rep.* **2019**, *4*, 470–483. [CrossRef]
117. Durlacher-Betzer, K.; Hassan, A.; Levi, R.; Axelrod, J.; Silver, J.; Naveh-Many, T. Interleukin-6 contributes to the increase in fibroblast growth factor 23 expression in acute and chronic kidney disease. *Kidney Int.* **2018**, *94*, 315–325. [CrossRef]
118. Chen, W.; Yuan, H.; Cao, W.; Wang, T.; Chen, W.; Yu, H.; Fu, Y.; Jiang, B.; Zhou, H.; Guo, H.; et al. Blocking interleukin-6 trans-signaling protects against renal fibrosis by suppressing STAT3 activation. *Theranostics* **2019**, *9*, 3980–3991. [CrossRef]
119. Li, X.; Qureshi, A.R.; Suliman, M.E.; Heimburger, O.; Barany, P.; Stenvinkel, P.; Lindholm, B. Interleukin-6-to-Albumin Ratio as a Superior Predictor of Mortality in End-Stage Kidney Disease Patients. *Am. J. Nephrol.* **2023**, *54*, 268–274. [CrossRef]
120. Amdur, R.L.; Mukherjee, M.; Go, A.; Barrows, I.R.; Ramezani, A.; Shoji, J.; Reilly, M.P.; Gnanaraj, J.; Deo, R.; Rahman, M.; et al. Interleukin-6 Is a Risk Factor for Atrial Fibrillation in Chronic Kidney Disease: Findings from the CRIC Study. Aguilera AI, redaktor. *PLoS ONE* **2016**, *11*, e0148189. [CrossRef]
121. Anders, H.J.; Suarez-Alvarez, B.; Grigorescu, M.; Foresto-Neto, O.; Steiger, S.; Desai, J.; Marschner, J.A.; Honarpisheh, M.; Shi, C.; Jordan, J.; et al. The macrophage phenotype and inflammasome component NLRP3 contributes to nephrocalcinosis-related chronic kidney disease independent from IL-1–mediated tissue injury. *Kidney Int.* **2018**, *93*, 656–669. [CrossRef] [PubMed]
122. Libby, P. Interleukin-1 Beta as a Target for Atherosclerosis Therapy. *J. Am. Coll. Cardiol.* **2017**, *70*, 2278–2289. [CrossRef] [PubMed]
123. Steen, E.H.; Wang, X.; Balaji, S.; Butte, M.J.; Bollyky, P.L.; Keswani, S.G. The Role of the Anti-Inflammatory Cytokine Interleukin-10 in Tissue Fibrosis. *Adv. Wound Care* **2020**, *9*, 184–198. [CrossRef] [PubMed]
124. Neumann, C.; Scheffold, A.; Rutz, S. Functions and regulation of T cell-derived interleukin-10. *Semin. Immunol.* **2019**, *44*, 101344. [CrossRef]
125. Gao, C.; Peng, F.; Xie, X.; Peng, L. The Relationship Between Blood Interleukin-10 and Cardiovascular Mortality and All-Cause Mortality After Kidney Transplantation. *Risk Manag. Healthc Policy* **2021**, *14*, 1481–1489. [CrossRef]
126. Yu, J.; Lin, T.; Huang, N.; Xia, X.; Li, J.; Qiu, Y.; Yang, X.; Mao, H.; Huang, F. Plasma fibrinogen and mortality in patients undergoing peritoneal dialysis: A prospective cohort study. *BMC Nephrol.* **2020**, *21*, 349. [CrossRef]
127. Wang, H.; Zheng, C.; Lu, Y.; Jiang, Q.; Yin, R.; Zhu, P.; Zhou, M.; Liu, Z. Urinary Fibrinogen as a Predictor of Progression of CKD. *Clin. J. Am. Soc. Nephrol.* **2017**, *12*, 1922–1929. [CrossRef]
128. Mao, J.Y.; Sun, J.T.; Yang, K.; Shen, W.F.; Lu, L.; Zhang, R.Y.; Tong, X. Serum amyloid A enrichment impairs the anti-inflammatory ability of HDL from diabetic nephropathy patients. *J. Diabetes Complicat.* **2017**, *31*, 1538–1543. [CrossRef]
129. Saulnier, P.J.; Dieter, B.P.; Tanamas, S.K.; McPherson, S.M.; Wheelock, K.M.; Knowler, W.C.; Lemley, K.V.; Mauer, M.; Yee, B.; Nelson, R.G.; et al. Association of Serum Amyloid A with Kidney Outcomes and All-Cause Mortality in American Indians with Type 2 Diabetes. *Am. J. Nephrol.* **2017**, *46*, 276–284. [CrossRef]
130. Gao, A.; Gupta, S.; Shi, H.; Liu, Y.; Schroder, A.L.; Witting, P.K.; Kwan, T.; Trevillyan, J.M.; Celermajer, D.; Heather, A.K. Pro-Inflammatory Serum Amyloid a Stimulates Renal Dysfunction and Enhances Atherosclerosis in Apo E-Deficient Mice. *Int. J. Mol. Sci.* **2021**, *22*, 12582. [CrossRef]
131. Anderberg, R.J.; Meek, R.L.; Hudkins, K.L.; Cooney, S.K.; Alpers, C.E.; Leboeuf, R.C.; Tuttle, K.R. Serum amyloid A and inflammation in diabetic kidney disease and podocytes. *Lab. Investig.* **2015**, *95*, 250–262. [CrossRef] [PubMed]
132. Xavier, S.; Vasko, R.; Matsumoto, K.; Zullo, J.A.; Chen, R.; Maizel, J.; Chander, P.N.; Goligorsky, M.S. Curtailing Endothelial TGF-β Signaling Is Sufficient to Reduce Endothelial-Mesenchymal Transition and Fibrosis in CKD. *J. Am. Soc. Nephrol.* **2015**, *26*, 817–829. [CrossRef] [PubMed]
133. Mehta, T.; Buzkova, P.; Kizer, J.R.; Djousse, L.; Chonchol, M.; Mukamal, K.J.; Shlipak, M.; Ix, J.H.; Jalal, D. Higher plasma transforming growth factor (TGF)-β is associated with kidney disease in older community dwelling adults. *BMC Nephrol.* **2017**, *18*, 98. [CrossRef]
134. Østergaard, J.A.; Jansson Sigfrids, F.; Forsblom, C.; Dahlström, E.H.; Thorn, L.M.; Harjutsalo, V.; Bjerre, M.; Hansen, T.K.; Flyvbjerg, A.; Groop, P.H.; et al. The pattern-recognition molecule H-ficolin in relation to diabetic kidney disease, mortality, and cardiovascular events in type 1 diabetes. *Sci. Rep.* **2021**, *11*, 8919. [CrossRef]
135. Smedbråten, Y.V.; Sagedal, S.; Mjøen, G.; Hartmann, A.; Fagerland, M.W.; Rollag, H.; Mollnes, T.E.; Thiel, S. High Ficolin-3 Level at the Time of Transplantation Is an Independent Risk Factor for Graft Loss in Kidney Transplant Recipients. *Transplantation* **2015**, *99*, 791–796. [CrossRef]

136. Dabrowska-Zamojcin, E.; Czerewaty, M.; Malinowski, D.; Tarnowski, M.; Słuczanowska-Głabowska, S.; Domanski, L.; Safranow, K.; Pawlik, A. Ficolin-2 Gene rs7851696 Polymorphism is Associated with Delayed Graft Function and Acute Rejection in Kidney Allograft Recipients. *Arch. Immunol. Ther. Exp.* **2018**, *66*, 65–72. [CrossRef]
137. Granata, S.; Masola, V.; Zoratti, E.; Scupoli, M.T.; Baruzzi, A.; Messa, M.; Sallustio, F.; Gesualdo, L.; Lupo, A.; Zaza, G. NLRP3 Inflammasome Activation in Dialyzed Chronic Kidney Disease Patients. *PLoS ONE* **2015**, *10*, e0122272. [CrossRef]
138. Li, S.; Lin, Q.; Shao, X.; Mou, S.; Gu, L.; Wang, L.; Zhang, Z.; Shen, J.; Zhou, Y.; Qi, C.; et al. NLRP3 inflammasome inhibition attenuates cisplatin-induced renal fibrosis by decreasing oxidative stress and inflammation. *Exp. Cell Res.* **2019**, *383*, 111488. [CrossRef]
139. Gohda, T.; Murakoshi, M.; Shibata, T.; Suzuki, Y.; Takemura, H.; Tsuchiya, K. Circulating TNF receptor levels are associated with estimated glomerular filtration rate even in healthy individuals with normal kidney function. *Sci. Rep.* **2024**, *14*, 7245. [CrossRef]
140. Oh, Y.J.; An, J.N.; Kim, C.T.; Yang, S.H.; Lee, H.; Kim, D.K.; Joo, K.W.; Paik, J.H.; Kang, S.W.; Park, J.T.; et al. Circulating tumor necrosis factor α receptors predict the outcomes of human IgA nephropathy: A prospective cohort study. *PLoS ONE* **2015**, *10*, e0132826. [CrossRef]
141. Chen, T.K.; Coca, S.G.; Estrella, M.M.; Appel, L.J.; Coresh, J.; Philbrook, H.T.; Obeid, W.; Fried, L.F.; Heerspink, H.J.L.; Ix, J.H.; et al. Longitudinal TNFR1 and TNFR2 and kidney outcomes: Results from AASK and VA NEPHRON-D. *J. Am. Soc. Nephrol.* **2022**, *33*, 996–1010. [CrossRef] [PubMed]
142. Bourgonje, A.R.; Bourgonje, M.F.; la Bastide-van Gemert, S.; Nilsen, T.; Hidden, C.; Gansevoort, R.T.; Mulder, D.J.; Hillebrands, J.-L.; Bakker, S.J.L.; Dullaart, R.P.F.; et al. A prospective study of the association between plasma calprotectin levels and new-onset chronic kidney disease in the general population. *Kidney Int. Rep.* **2024**, *9*, 1265–1275. [CrossRef] [PubMed]
143. Amaya-Garrido, A.; Brunet, M.; Buffin-Meyer, B.; Piedrafita, A.; Grzesiak, L.; Agbegbo, E.; Del Bello, A.; Ferrandiz, I.; Ardeleanu, S.; Bermudez-Lopez, M.; et al. Calprotectin is a contributor to and potential therapeutic target for vascular calcification in chronic kidney disease. *Sci. Transl. Med.* **2023**, *15*, eabn5939. [CrossRef]
144. Løfblad, L.; Hov, G.G.; Åsberg, A.; Videm, V. Calprotectin and CRP as biomarkers of cardiovascular disease risk in patients with chronic kidney disease: A follow-up study at 5 and 10 years. *Scand. J. Clin. Lab. Investig.* **2023**, *83*, 258–263. [CrossRef]
145. Elangovan, D.; Sowmya, S. Association of NLR, MLR, PLR, SII, and SIRI with the stages of chronic kidney disease: A cross-sectional study. *Int. J. Med. Biochem.* **2024**, *7*, 186–194. [CrossRef]
146. Petrović, M.; Rabrenović, V.; Rančić, N. The significance of determining biomarkers of inflammation in chronic kidney failure. *Vojnosanit. Pregl.* **2024**, *81*, 498–504. [CrossRef]
147. Wang, Y.; Liao, L.; Guo, Q.; Liao, Y.; Lin, X.; Li, H.; Zhang, M.; Chen, J.; Huang, Z.; Zhao, L.; et al. The systemic inflammatory response index is associated with chronic kidney disease in patients with hypertension: Data from the National Health and Nutrition Examination Survey 1999–2018. *Ren. Fail.* **2024**, *46*, 2396459. [CrossRef]
148. Wei, L.; Mao, S.; Liu, X.; Zhu, C.; Zhang, Y.; Wang, H.; Chen, L.; Zhao, Q.; Li, J.; Xu, T.; et al. Association of systemic inflammation response index with all-cause mortality as well as cardiovascular mortality in patients with chronic kidney disease. *Front. Cardiovasc. Med.* **2024**, *11*, 1363949. [CrossRef]
149. Kim, J.; Song, S.H.; Oh, T.R.; Suh, S.H.; Choi, H.S.; Kim, C.S.; Ma, S.K.; Kim, S.W.; Bae, E.H.; Lee, J.H. Prognostic role of the neutrophil-to-lymphocyte ratio in patients with chronic kidney disease. *Korean J. Intern. Med.* **2023**, *38*, 725–733. [CrossRef]
150. Solak, Y.; Yilmaz, M.I.; Sonmez, A.; Saglam, M.; Cakir, E.; Unal, H.U.; Gok, M.; Caglar, K.; Oguz, Y.; Yenicesu, M.; et al. Neutrophil to lymphocyte ratio independently predicts cardiovascular events in patients with chronic kidney disease. *Clin. Exp. Nephrol.* **2013**, *17*, 532–540. [CrossRef]
151. Neuen, B.L.; Leather, N.; Greenwood, A.M.; Gunnarsson, R.; Cho, Y.; Mantha, M.L.; Smith, T.J.; Lee, K.H.; Brown, M.J.; Patel, R.S.; et al. Neutrophil–lymphocyte ratio predicts cardiovascular and all-cause mortality in hemodialysis patients. *Ren. Fail.* **2016**, *38*, 70–76. [CrossRef] [PubMed]
152. Takahashi, H.; Kumada, Y.; Kawai, N.; Ishida, N.; Nakamura, Y.; Ito, R.; Sato, M.; Fujimoto, K.; Yamamoto, T.; Suzuki, H.; et al. Prognostic value of C-reactive protein/albumin ratio for amputation and/or mortality after lower extremity revascularization in haemodialysis patients with peripheral artery disease. *Eur. Heart J.* **2024**, *45* (Suppl. 1), ehae666.3249. [CrossRef]
153. Bilgin, S.; Kurtkulagi, O.; Atak Tel, B.M.; Duman, T.T.; Kahveci, G.; Khalid, A.; Aktas, G.; Yilmaz, A.; Demir, S.; Ozkan, S. Does C-reactive protein to serum albumin ratio correlate with diabetic nephropathy in patients with type 2 diabetes mellitus? The CARE TIME study. *Prim. Care Diabetes* **2021**, *15*, 1071–1074. [CrossRef] [PubMed]
154. Zhang, Z.; Liu, P.; Yang, L.; Zhao, N.; Ou, W.; Zhang, X.; Wang, Y.; Chen, S.; Wu, J.; Li, M.; et al. Association between the high-sensitivity C-reactive protein/albumin ratio and new-onset chronic kidney disease in Chinese individuals. *Nephron* **2024**, *148*, 160–170. [CrossRef]
155. Huang, Q.; Lu, X.; Liang, Y.; Zhu, W.; Chen, J.; Yang, Y. Nonlinear relationship between the C-reactive protein to albumin ratio and chronic kidney disease: A cross-sectional analysis using the NHANES database. *bioRxiv* **2025**. [CrossRef]

156. Saeed, D.; Reza, T.; Shahzad, M.W.; Karim Mandokhail, A.; Bakht, D.; Qizilbash, F.H.; Ahmed, N.; Khan, S.; Ali, M.; Hussain, R. Navigating the crossroads: Understanding the link between chronic kidney disease and cardiovascular health. *Cureus* **2023**, *15*, e51362. [CrossRef]
157. Salaun, E.; Drory, S.; Coté, M.-A.; Tremblay, V.; Bédard, E.; Steinberg, C.; Paré, D.; O'Connor, K.; Cieza, T.; Coté, N.; et al. Role of antitroponin antibodies and macrotroponin in the clinical interpretation of cardiac troponin. *J. Am. Heart Assoc.* **2024**, *13*, e035128. [CrossRef]
158. Geladari, E.V.; Vallianou, N.G.; Evangelopoulos, A.; Koufopoulos, P.; Panagopoulos, F.; Margellou, E.; Katsiki, N.; Dalamaga, M.; Tsigalou, C.; Karamouzis, M.; et al. Cardiac troponin levels in patients with chronic kidney disease: "Markers of high risk or just noise"? *Diagnostics* **2024**, *14*, 2316. [CrossRef]
159. Braghieri, L.; Badwan, O.Z.; Skoza, W.; Fares, M.; Menon, V. Evaluating troponin elevation in patients with chronic kidney disease and suspected acute coronary syndrome. *Cleve Clin. J. Med.* **2023**, *90*, 483–489. [CrossRef]
160. Wang, K.; Zelnick, L.R.; Anderson, A.; Cohen, J.; Dobre, M.; Deo, R.; Christenson, R.; Shlipak, M.; Feldman, H.; Go, A.; et al. Cardiac biomarkers and risk of mortality in CKD (the CRIC Study). *Kidney Int. Rep.* **2020**, *5*, 2002–2012. [CrossRef]
161. Bansal, N.; Zelnick, L.; Shlipak, M.G.; Anderson, A.; Christenson, R.; Deo, R.; Feldman, H.; Lash, J.P.; Go, A.S.; Robinson-Cohen, C.; et al. Cardiac and stress biomarkers and chronic kidney disease progression: The CRIC Study. *Clin. Chem.* **2019**, *65*, 1448–1457. [CrossRef] [PubMed]
162. Bansal, N.; Hyre Anderson, A.; Yang, W.; Christenson, R.H.; deFilippi, C.R.; Deo, R.; Feldman, H.I.; Go, A.S.; Shlipak, M.G.; Lash, J.P. High-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and risk of incident heart failure in patients with CKD: The Chronic Renal Insufficiency Cohort (CRIC) Study. *J. Am. Soc. Nephrol.* **2015**, *26*, 946–956. [CrossRef] [PubMed]
163. Lu, Y.; Chen, J.; Su, L.; Lukwaro, A.F.; Zhou, S.; Zheng, S.; Wang, Y.; Fan, X.; Tang, C.; Yang, J.; et al. N-terminal pro-B-type natriuretic peptide, eGFR, and progression of kidney disease in chronic kidney disease patients without heart failure. *Clin. Kidney J.* **2024**, *17*, sfae298. [CrossRef] [PubMed]
164. Neuen, B.L.; Vaduganathan, M.; Claggett, B.L.; Beldhuis, I.; Myhre, P.; Desai, A.S.; Solomon, S.D.; Zile, M.R.; Packer, M.; McMurray, J.J.V. Natriuretic peptides, kidney function, and clinical outcomes in heart failure with preserved ejection fraction. *Heart Fail.* **2025**, *13*, 28–39. [CrossRef]
165. Ho, J.E.; Liu, C.; Lyass, A.; Courchesne, P.; Pencina, M.J.; Vasan, R.S.; Larson, M.G.; Levy, D.; Ghorbani, A.; Benjamin, E.J. Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. *J. Am. Coll. Cardiol.* **2012**, *60*, 1249–1256. [CrossRef]
166. McEvoy, J.W.; Chen, Y.; Halushka, M.K.; Christenson, E.; Ballantyne, C.M.; Blumenthal, R.S.; Coresh, J.; Selvin, E.; Nambi, V. Galectin-3 and risk of heart failure and death in Blacks and Whites. *J. Am. Heart Assoc.* **2016**, *5*, e003079. [CrossRef]
167. Echouffo-Tcheugui, J.B.; Zhang, S.; Florido, R.; Pankow, J.S.; Michos, E.D.; Goldberg, R.B.; Selvin, E.; Folsom, A.R.; Ballantyne, C.M.; Coresh, J. Galectin-3, metabolic risk, and incident heart failure: The ARIC Study. *J. Am. Heart Assoc.* **2024**, *13*, e031607. [CrossRef]
168. Chen, S.C.; Kuo, P.L. The role of Galectin-3 in the kidneys. *Int. J. Mol. Sci.* **2016**, *17*, 565. [CrossRef]
169. Kim, A.J.; Ro, H.; Kim, H.; Chang, J.H.; Lee, H.H.; Chung, W.; Park, J.T.; Yoo, T.H.; Kang, S.W.; Han, S.H. Soluble ST2 and Galectin-3 as predictors of chronic kidney disease progression and outcomes. *Am. J. Nephrol.* **2021**, *52*, 119–130. [CrossRef]
170. Alam, M.L.; Katz, R.; Bellovich, K.A.; Bhat, Z.Y.; Brosius, F.C.; De Boer, I.H.; Rosamond, W.D.; Sarnak, M.J.; Zelnick, L.R.; Robinson-Cohen, C. Soluble ST2 and Galectin-3 and progression of CKD. *Kidney Int. Rep.* **2019**, *4*, 103–111. [CrossRef]
171. Wang, F.; Zhou, L.; Eliaz, A.; Hu, C.; Qiang, X.; Ke, L.; Liu, W.; Zhang, M.; Zhao, Y.; Li, X. The potential roles of Galectin-3 in AKI and CKD. *Front. Physiol.* **2023**, *14*, 1090724. [CrossRef] [PubMed]
172. Januzzi, J.L. ST2 as a cardiovascular risk biomarker: From the bench to the bedside. *J. Cardiovasc. Transl. Res.* **2013**, *6*, 493–500. [CrossRef] [PubMed]
173. Weinberg, E.O.; Shimpo, M.; De Keulenaer, G.W.; MacGillivray, C.; Tominaga, S.I.; Solomon, S.D.; Rouleau, J.L.; Lee, R.T.; Huang, C. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. *Circulation* **2002**, *106*, 2961–2966. [CrossRef]
174. Tuegel, C.; Katz, R.; Alam, M.; Bhat, Z.; Bellovich, K.; De Boer, I.; Kestenbaum, B.; Sarnak, M.J.; Shlipak, M.G.; Ix, J.H. GDF-15, Galectin 3, Soluble ST2, and risk of mortality and cardiovascular events in CKD. *Am. J. Kidney Dis.* **2018**, *72*, 519–528. [CrossRef]
175. Mirna, M.; Topf, A.; Wernly, B.; Rezar, R.; Paar, V.; Jung, C.; Lichtenauer, M.; Hoppe, U.C.; Edlinger-Stanger, A.; Weber, T. Novel biomarkers in patients with chronic kidney disease: An analysis of patients enrolled in the GCKD-Study. *J. Clin. Med.* **2020**, *9*, 886. [CrossRef]
176. Chen, Y.J.; Chou, C.Y.; Er, T.K. Correlations of sST2 and Gal-3 with cardiothoracic ratio in patients with chronic kidney disease. *Biomedicines* **2024**, *12*, 791. [CrossRef]

177. Nyárády, B.B.; Kiss, L.Z.; Bagyura, Z.; Merkely, B.; Dósa, E.; Láng, O.; Tóth, K.; Molnár, A.; Takács, J.; Szabó, A. Growth and differentiation factor-15: A link between inflammaging and cardiovascular disease. *Biomed. Pharmacother.* **2024**, *174*, 116475. [CrossRef]
178. Lasaad, S.; Crambert, G. GDF15, an emerging player in renal physiology and pathophysiology. *Int. J. Mol. Sci.* **2024**, *25*, 5956. [CrossRef]
179. Nair, V.; Robinson-Cohen, C.; Smith, M.R.; Bellovich, K.A.; Bhat, Z.Y.; Bobadilla, M.; Brosius, F.C.; de Boer, I.H.; Ix, J.H.; Kestenbaum, B.; et al. Growth differentiation factor–15 and risk of CKD progression. *J. Am. Soc. Nephrol.* **2017**, *28*, 2233–2240. [CrossRef]
180. Tang, Y.; Liu, T.; Sun, S.; Peng, Y.; Huang, X.; Wang, S.; Zhang, X.; Zhou, H.; Li, Q.; Wu, J.; et al. Role and mechanism of growth differentiation factor 15 in chronic kidney disease. *J. Inflamm. Res.* **2024**, *17*, 2861–2871. [CrossRef]
181. Rasmussen, L.J.H.; Petersen, J.E.V.; Eugen-Olsen, J. Soluble urokinase plasminogen activator receptor (suPAR) as a biomarker of systemic chronic inflammation. *Front. Immunol.* **2021**, *12*, 780641. [CrossRef] [PubMed]
182. Hayek, S.S.; Ko, Y.A.; Awad, M.; Ahmed, H.; Gray, B.; Hosny, K.M.; Reiser, J.; Quyyumi, A.A.; Brown, J.M.; Collins, B.; et al. Cardiovascular disease biomarkers and suPAR in predicting decline in renal function: A prospective cohort study. *Kidney Int. Rep.* **2017**, *2*, 425–432. [CrossRef] [PubMed]
183. Meijers, B.; Poesen, R.; Claes, K.; Dietrich, R.; Bammens, B.; Sprangers, B.; Naesens, M.; Verbeke, K.; Vanholder, R.; Evenepoel, P.; et al. Soluble urokinase receptor is a biomarker of cardiovascular disease in chronic kidney disease. *Kidney Int.* **2015**, *87*, 210–216. [CrossRef]
184. Raphael, K.L. Metabolic acidosis in CKD: Core Curriculum 2019. *Am. J. Kidney Dis.* **2019**, *74*, 263–275. [CrossRef]
185. Bello, A.K.; Alrukhaimi, M.; Ashuntantang, G.E.; Basnet, S.; Rotter, R.C.; Douthat, W.G.; Dos Santos, J.P.; Kazancioglu, R.; Levin, A.; Okpechi, I.G.; et al. Complications of chronic kidney disease: Current state, knowledge gaps, and strategy for action. *Kidney Int. Suppl.* **2017**, *7*, 122–129. [CrossRef]
186. Ammirati, A.L. Chronic kidney disease. *Rev. Assoc. Médica Bras.* **2020**, *66* (Suppl. 1), s03–s09. [CrossRef]
187. Koda, R.; Kazama, J.J.; Matsuo, K.; Kawamura, K.; Yamamoto, S.; Wakasugi, M.; Iseki, K.; Fujimoto, S.; Tsubakihara, Y.; Nangaku, M.; et al. Intact parathyroid hormone and whole parathyroid hormone assay results disagree in hemodialysis patients under cinacalcet hydrochloride therapy. *Clin. Exp. Nephrol.* **2015**, *19*, 710–717. [CrossRef]
188. Kritmetapak, K.; Pongchaiyakul, C. Parathyroid hormone measurement in chronic kidney disease: From basics to clinical implications. *Int. J. Nephrol.* **2019**, *2019*, 1–9. [CrossRef]
189. Brandenburg, V.; Ketteler, M. Vitamin D and secondary hyperparathyroidism in chronic kidney disease: A critical appraisal of the past, present, and the future. *Nutrients* **2022**, *14*, 3009. [CrossRef]
190. Vogt, I.; Haffner, D.; Leifheit-Nestler, M. FGF23 and phosphate–cardiovascular toxins in CKD. *Toxins* **2019**, *11*, 647. [CrossRef]
191. Okamoto, K.; Fujii, H.; Goto, S.; Kono, K.; Watanabe, K.; Nishi, S. Changes in the whole/intact parathyroid hormone ratio and their clinical implications in patients with chronic kidney disease. *J. Nephrol.* **2020**, *33*, 795–802. [CrossRef] [PubMed]
192. Zhang, L.; Cao, H. Unlocking the mysteries of n-oxPTH: Implications for CKD patients. *Front. Endocrinol.* **2025**, *15*, 1455783. [CrossRef] [PubMed]
193. Seiler-Mussler, S.; Limbach, A.S.; Emrich, I.E.; Pickering, J.W.; Roth, H.J.; Fliser, D.; Martus, P.; Krane, V.; Eckardt, K.U.; Titze, S.; et al. Association of nonoxidized parathyroid hormone with cardiovascular and kidney disease outcomes in chronic kidney disease. *Clin. J. Am. Soc. Nephrol.* **2018**, *13*, 569–576. [CrossRef] [PubMed]
194. Bonewald, L.F.; Wacker, M.J. FGF23 production by osteocytes. *Pediatr. Nephrol.* **2013**, *28*, 563–568. [CrossRef]
195. Rausch, S.; Föller, M. The regulation of FGF23 under physiological and pathophysiological conditions. *Pflüg Arch. Eur. J. Physiol.* **2022**, *474*, 281–292. [CrossRef]
196. Ho, B.B.; Bergwitz, C. FGF23 signalling and physiology. *J. Mol. Endocrinol.* **2021**, *66*, R23–R32. [CrossRef]
197. Heijboer, A.C.; Cavalier, E. The measurement and interpretation of fibroblast growth factor 23 (FGF23) concentrations. *Calcif. Tissue Int.* **2022**, *112*, 258–270. [CrossRef]
198. Erben, R.G. Physiological actions of fibroblast growth factor-23. *Front. Endocrinol.* **2018**, *9*, 267. [CrossRef]
199. Van Der Vaart, A.; Yeung, S.M.H.; Van Dijk, P.R.; Bakker, S.J.L.; De Borst, M.H. Phosphate and fibroblast growth factor 23 in diabetes. *Clin. Sci.* **2021**, *135*, 1669–1687. [CrossRef]
200. Mihai, S.; Codrici, E.; Popescu, I.D.; Enciu, A.M.; Rusu, E.; Zilisteanu, D.; Tanase, C.; Mihaila, M.; Cucu, N.; Preda, M.; et al. Inflammation-related patterns in the clinical staging and severity assessment of chronic kidney disease. *Dis. Markers* **2019**, *2019*, 1–12. [CrossRef]
201. Stubbs, J.R.; He, N.; Idiculla, A.; Gillihan, R.; Liu, S.; David, V.; Hong, Y.; Quarles, L.D. Longitudinal evaluation of FGF23 changes and mineral metabolism abnormalities in a mouse model of chronic kidney disease. *J. Bone Miner. Res.* **2011**, *27*, 38–46. [CrossRef] [PubMed]
202. Simic, P. Bone and bone derived factors in kidney disease. *Front. Physiol.* **2024**, *15*, 1356069. [CrossRef] [PubMed]

203. De Jong, M.A.; Eisenga, M.F.; Van Ballegooijen, A.J.; Beulens, J.W.J.; Vervloet, M.G.; Navis, G.; Bakker, S.J.L.; Gansevoort, R.T.; Van Vliet-Ostaptchouk, J.V.; De Borst, M.H.; et al. Fibroblast growth factor 23 and new-onset chronic kidney disease in the general population: The Prevention of Renal and Vascular Endstage Disease (PREVEND) study. *Nephrol. Dial. Transplant.* **2021**, *36*, 121–128. [CrossRef] [PubMed]
204. Lima, F.; Monier-Faugere, M.C.; Mawad, H.; David, V.; Malluche, H.H. FGF-23 and sclerostin in serum and bone of CKD patients. *Clin. Nephrol.* **2023**, *99*, 209–218. [CrossRef]
205. Dreyer, T.J.; Keen, J.A.; Wells, L.M.; Roberts, S.J. Novel insights on the effect of sclerostin on bone and other organs. *J. Endocrinol.* **2023**, *257*, e220209. [CrossRef]
206. Romejko, K.; Rymarz, A.; Szamotulska, K.; Bartoszewicz, Z.; Niemczyk, S. Relationships between sclerostin, leptin and metabolic parameters in non-dialysis chronic kidney disease males. *J. Pers. Med.* **2022**, *13*, 31. [CrossRef]
207. Ji, Y.Q.; Guan, L.N.; Yu, S.X.; Yin, P.Y.; Shen, X.Q.; Sun, Z.W.; Wu, H.Y.; Chen, J.L.; Li, D.X.; Zhang, Y.; et al. Serum sclerostin as a potential novel biomarker for heart valve calcification in patients with chronic kidney disease. *Eur. Rev. Med. Pharmacol. Sci.* **2018**, *22*, 8822–8829.
208. Lee, J.; Cho, D.H.; Min, H.J.; Son, Y.B.; Kim, T.B.; Oh, S.W.; Han, S.H.; Yoo, T.H.; Kim, Y.S.; Choi, K.H.; et al. Higher sclerostin is associated with pulmonary hypertension in pre-dialysis end-stage kidney disease patients: A cross-sectional prospective observational cohort study. *BMC Pulm. Med.* **2024**, *24*, 78. [CrossRef]
209. Hsu, Y.C.; Chang, C.C.; Hsieh, C.C.; Huang, Y.T.; Shih, Y.H.; Chang, H.C.; Tsai, Y.L.; Lin, Y.J.; Wu, M.C.; Chiang, T.I.; et al. Dickkopf-1 acts as a profibrotic mediator in progressive chronic kidney disease. *Int. J. Mol. Sci.* **2023**, *24*, 7679. [CrossRef]
210. Neto, R.; Pereira, L.; Magalhães, J.; Quelhas-Santos, J.; Martins, S.; Carvalho, C.; Ribeiro, S.; Frazão, J.M.; Macário, F. Sclerostin and DKK1 circulating levels associate with low bone turnover in patients with chronic kidney disease stages 3 and 4. *Clin. Kidney J.* **2021**, *14*, 2401–2408. [CrossRef]
211. Fang, Y.; Ginsberg, C.; Seifert, M.; Agapova, O.; Sugatani, T.; Register, T.C.; Freedman, B.I.; Monier-Faugere, M.-C.; Malluche, H.; Hruska, K.A. CKD-induced Wingless/Integration1 inhibitors and phosphorus cause the CKD–mineral and bone disorder. *J. Am. Soc. Nephrol.* **2014**, *25*, 1760. [CrossRef] [PubMed]
212. Gupta, A.; Sontakke, T.; Acharya, S.; Kumar, S. A comprehensive review of biomarkers for chronic kidney disease in older individuals: Current perspectives and future directions. *Cureus* **2024**, *16*, e70262. [CrossRef] [PubMed]
213. Maringhini, S.; Zoccali, C. Chronic kidney disease progression—A challenge. *Biomedicines* **2024**, *12*, 2203. [CrossRef] [PubMed]
214. Mizdrak, M.; Kumrić, M.; Kurir, T.T.; Božić, J. Emerging biomarkers for early detection of chronic kidney disease. *J. Pers. Med.* **2022**, *12*, 548. [CrossRef]
215. Lopez-Giacoman, S.; Madero, M. Biomarkers in chronic kidney disease, from kidney function to kidney damage. *World J. Nephrol.* **2015**, *4*, 57–73. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.