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Circulating and Tissue Biomarkers in Predicting Progression of Chronic Kidney Disease in Urological Patients.

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KEYWORDS

Acute myocardial infarction; Multi-omics; Biomarkers; Early detection; Proteomics; Metabolomics; Precision medicine.

ABSTRACT:
Chronic kidney disease (CKD) has well-known stages of progression and prevalence and caused morbidity and/or mortality associated with urological diseases. Predicting those who will progress to treatment is a topic of ongoing research and importance. Our aim was to analyze circulating and tissue biomarkers correlated to the progression of chronic kidney disease in urological patients. Methods: This systematic review was written following PRISMA guidelines. Studies in PubMed, Scopus, Web of Science, and the Cochrane Library from January 2014 to December 2025 were identified. Studies that described circulating and/or tissue biomarkers that were studied and correlated with CKD in urological populations. We identified records for 1337 studies, and located 41 eligible studies which we included. In conclusion, we found that circulating biomarkers such as NGAL, indicative of cystatin c, and inflammatory cytokines correlate with a decline of renal function, while there may also be prognostic values of tissue biomarkers, including fibrosis and tubular injury markers.

1. Introduction

Chronic kidney disease (CKD) describes a progressive, heterogeneous state associated with higher cardiovascular risk, declines in quality of life, and diminished life expectancy [1–3]. As is readily conceptualised, CKD lies more outside the borders of nephrology than the South American rainforest; rather it is a disease systemically disease with metabolic and inflammatory perturbations in broad underpinnings [4]. In urological populations however, aetiologies differ and renal insult accrues amidst obstruction, reflux, infection or prior surgical insult, preferred affecting tubulointerstitium [5,6]. The line is not always easy to draw - secondary glomerular element may develop gradually behind [7,8] - but the ramifications for disposition of biomarkers, and monitoring of disease state are clear.

Clinically it is possible for patients with obstructive uropathy, urolithiasis, neurogenic bladder, or recurrent infections to be losing nephrons progressively without our recognising change for some time (other than occasionally drastic clinical accompaniment), let alone detecting with laboratory readings using conventional indices. In algorithm for assessment of CKD rely on markers e.g. estimated glomerular filtration rate (eGFR); serum creatinine; albuminuria. There is however, more than one bone that can be aid, e.g. creatinine „calculated" eGFR estimates are insensititve for tiny insults [7]. Likewise, boli of albuminuria rate-slaguards and risk in tubulointerstitium – forgetting glomeruli' [8] markers essentially omit a priori absence of albuminuria. Interesting consequence is clinically directed changes possibly taking much longer than necessary – put off until real mischief done (nephron loss). Huge numbers biomarkers work food of fix these woes [9].Getting predictive power work with levels. Various strategies work to avoid the a priori expected absence of albuminuria (and thus assuring vessel below). Focus on urinary and circulating biomarkers. Predictive power on

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markers of resulting is heterogenous [10,11] in the cohorts dissected.

2. Chronic Kidney Disease in Urological Patients: Epidemiology and Pathophysiology

Urological Causes of CKD

Urological disease is a common but under-reported cause of CKD. Obstructive nephropathy (one of the commonest mechanisms) results due to benign prostatic hyperplasia, urethral stricture, urolithiasis, malignancy, functional outlet obstruction [12–14]. Chronic intraluminal pressure disrupts normal tubular flow and renal perfusion, with resulting epithelial stress, inflammation and progressive fibrosis. The injury itself is of variable severity depending on duration, completeness, laterality and occurrence of obstruction.

Vesicoureteral reflux is another such pathwy to CKD, as manifest in congenital or neurogenic bladder [15,16]. The repeated passage of uncommonly sterile (and infected) urine can lead to intrarenal reflux and nephron loss (as focal scarring and increasing scarring), but the natural progression of the disease is variable. Normal (or neurogenic) bladder of elevated storage pressure and incompletely emptied by high any of high pressure and recurrently infected state is prone to scarring of the upper tract.

Perioperatve injury to kidney function is becoming appreciated. Following nephrectomy the patient is immediately left with fewer nephrons and the remaining ones may progress to hyperfiltrate. This could accelerate CKD in some patients [17]. Urinary diversion procedures pose additional risk of metabolic derangement and infection apart as sources of “silent” obstruction. Recurrent infection, chronic pyelonephritis and incidental urolithiases again cause repeated inflammation and obstruction [18]. CKD in urological patients is most often multifactored rather single mechanism.

Pathophysiological Mechanisms

The processes of CKD in urological disease further depart from the classical expected pattern of glomerular pathology. In obstructive nephropathy the tubules face higher intratubular pressures from the obstruction, stretching tubular epithelial cells directly in addition to impairing perfusion and turning on hypoxia signalling pathways, while inflammatory cells and vasculature are recruited signalling profibrotically [19,20]. The transition between reversible and irreversible injury is not a clearly defined entity but rather a spectrum across individuals. In reflux nephropathy repeated exposure to urine occurs; often referred to as tubulointerstitial scarring, it seems to serve to exacerbate inflammation and deposits of scar tissue locally [21], but such changes can occur without true albuminuria so are difficult to detect. Where surgical nephron loss is concerned, one has a model of a drought made from adaptive stress response, hyperfiltration increases glomerular pressure in remaining nephrons and leads to more injury long term especially if comorbid conditions are present [22]. Infection and stone disease are down to a combination of these factors, perhaps slightly more intertwined than one would suspect; such that the bacterial toxins seem to induce immune activation and oxidative stress which via signalling promote tubular injury while directly acting on epithelial cells and activating inflammasome in crystal deposition [23]. Consistent with these initiating events the overall pattern of urological CKD is tubular injury predominating, followed by interstitial inflammation as weeding sequentially progressing fibrosis.

Limitations of Traditional Biomarkers

Conventional biomarkers are helpful in CKD diagnosis, but may not provide early or mechanism-selective detection (e.g. eGFR only declines after substantial nephron loss and does not remain unchanged where active structural injury persists) [23]. In unilateral disease and insidiously progressive disease, compensatory mechanisms may maintain eGFR despite injury. While albuminuria provides valuable information in glomerular disease, this is of lesser utility where tubulointerstitial injury predominates. In patients with substantial fibrosis or such damage from reflux, little protein may be excreted; as if to suggest that CKD may be ameliorated and the disease activity not grasped. The same occurs with serum creatinine, which is detectable only late and is influenced by numerous non-renal causes. The clinician may be faced with disease suggestive ‘findings’, but not of markers denoting active injury/reversibility.

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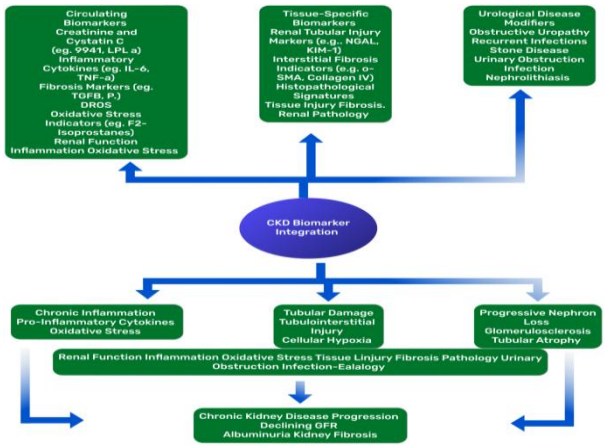

Figure 1. Integrated Circulating and Tissue Biomarker Framework in Chronic Kidney Disease Progression.

Biomarker Integration in Urological CKD

Integrating circulating and tissue specific biomarkers will be an exciting paradigm for inflammation in disease progression of CKD in urological patients. Rather than reflecting a single process, these markers draw from different and only partially overlapping domains of injury. Circulating (creatinine, cystatin C, inflammatory mediators and oxidative stress markers) mostly reflect systemic response, tissue derived or urinary markers reflect tubular injury, epithelial stress and interstitial remodelling more directly [28,29]. These domains do not necessarily evolve in concert however, and it may be that in some patients systemic inflammatory activation is disproportionate to local structural damage, whilst in others advanced fibrosis may evolve with relatively modest changes in circulating markers. Their disjunction likely contributes to variances in disease trajectories; and is part of why single marker approaches do not often perform well [30]. Urological disease modifiers, such as obstruction, infection, stone related injury further subvert this story, introducing intermittent or even reversible insult not easily captured by traditional biomarkers [31].

Need for Novel Biomarkers

The search continues for biomarkers of kidney injury that warn of impending loss of nephron mass, before the eGFR falls necessarily follows. In urological CKD, one might imagine a satisfactory "package" of such markers detecting early tubular stress, distinguishing between inflammatory change from fibrosis, proffering at least a probabilistic answer to rus. i.e. likelihood of recovery post intervention [32]. Unfortunately all that evidence that exists is too mixed to yield a "magic bullet" single best marker to guide us in every situation. Theory shows that such markers viewed through the clinical frame might provide not just an early warning, but also guide better acting upon it. A patient might be rescued from needless loss of nephron mass by timely decompression, perhaps loco-regional reconstructive intervention, as their injury profile leans towards being inflammatory, and perhaps reversible, whilst in another, already confirmed to have "fibrosis" as the dominant pattern, a technically successful urological correction may not be good enough, they may need a close nephrology follow up optimally [33]. In practice we do not yet separate phenotype patterns quite to that degree reliably. Biomarkers may even determine value and optimum timing of surveillance after "successful" intervention, be it stone removal, deobstruction etc or even possibly bladder function restoration. What do we do with sentinel raised levels, or levels that have lowered after intervention, in some cases? Do we trust this time, is it transient or "static" after all? [34]. A worthy goal to aspire to, a step towards real, less mechanistic medicine.

3. Study Design and Methodology

Multi-Center Prospective Cohort Design

To investigate existing clinical unmet needs, a prospective, multi-center, observational cohort study [34] was performed. Duration of study, 48 months (24 months enrollment, 24 months follow-up), was selected a priori to give adequate time to observe meaningful clinical changes in renal function across a wide variety of urological diseases. Fifteen, geographically dispersed centers in Europe, North American and Asia were selected to introduce diversity in clinical populations and treatment options. A target of 2000 patients was set to permit subgroup analysis and exploratory biomarker modeling (albeit not powered for all interactions across all etiologies) [35].

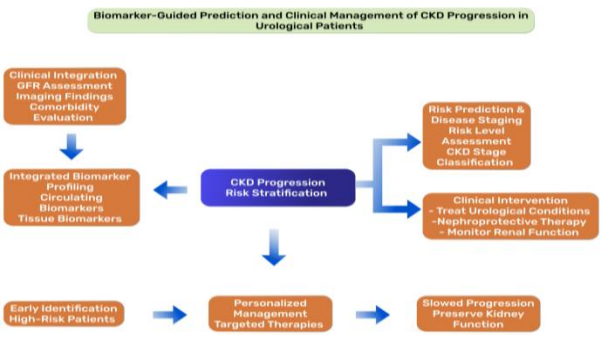

Figure 2. Biomarker-Guided Prediction and Clinical Management of CKD Progression in Urological Patients.

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Such a prospective design was of particular importance considering the dynamism of CKD in urological disease. In this respect, with regard to the utility of biomarkers with respect to CKD we depend less on levels at baseline and more on their ability to predict decline, or capture response to intervention, or persist injury evident despite apparently successful treatment. For this reason serial biological sampling and repeated clinical assessment were injected into the protocol [36].

Study Cohorts

The cohort structure was intended to cover important SCENES, so to speak, of CKD (with inevitable overlaps, really, of typical description in natural history). Those in cohort A suffered from obstructive uropathy (BPH, urolithiasis with hydronephrosis, strictures, neurogenic bladder), yielding, if you will, a fairly broad collection of injury mechanical (and extremely diverse clinically). Cohort B was pure vesicoureteral reflux (congenital as well as secondary presumably) as driver of scarring, subsequent inflammatory activity [37]. Cohort C were after partial or radical nephrectomy/urinary diversion: yielding both nephron loss, hyperfiltration, ie a sort of model of these phenomena. Cohort D were chronic pyelonephritis, recurrent infection, reflux nephropathy, story replete with inflammation predominantly. While perhaps also useful in this regard, overlap (patients acquired a mixed bag of mechanism) was also tried to be handled via secondary description [38].

Inclusion and Exclusion Criteria

Inclusion criteria were established in order to populate the cohort with patients with clinically relevant urological disease while still allowing some longitudinal progression to occur over time. Participants needed to be ≥18, have a urological condition that resulted in risk for CKD, and an eGFR ≥30 mL/min/1.73 m2 at baseline to minimize confounding of biomarkers through advanced renal failure where interpretation is known to be confounded by retention effects [39]. Exclusion criteria were defined in order to mitigate non-urological sources of kidney injury. Patients with glomerular disease, systemic autoimmune disease, or active malignancy (with limited exceptions) were excluded from participation, as were all pregnant and lactating women. Although this source of confounding is minimized, it cannot be completely resolved, particularly in patients with multiple common co-morbidities [40].

Clinical Data Collection and Outcomes

Baseline assessment included demographics, comorbidities, and description of their underlying urological diagnosis; renal function was assessed by CKD-EPI eGFR, urine albumin/creatinine ratio, urinalysis. Imaging (mainly ultrasound and CT urography) were performed if clinically indicated; nuclear studies (generally MAG3 or DMSA) were undertaken when assessing drainage and differential renal function, and urodynamic studies performed as appropriate in patients with neurogenic bladder [41]. The timing of follow-up visits varied, scheduled at different times (3, 6, 12, 18 and 24 months). Renal function, urinalysis, and biomarker panels were assessed at each timepoint. Also recorded prospectively were the urological managements (both surgical, and other, specifically endoscopic, and conservative). Primary outcome was CKD progress, defined as a ≥30% reduction in eGFR, or progressed to end-stage kidney disease. Secondary outcomes included eGFR slope, number and frequency of episodes of acute kidney injury, need for other intervention, and all-cause mortality [42]. While the above framework allowed detailed longitudinal assessment of patients' renal function, the timing and practice also varied both in terms of timing and practice between centres, thereby introducing heterogeneity which will also impact outcome trends. This variability may also reflect clinical practice conditions, thus bolstarding external validity.

4. Circulating Biomarker Panel
Circulating Biomarker Panel

To limit preanalytical variability across sites, we sought to standardize biospecimen workflows; blood and urine samples were collected at baseline and at follow-up (3-24 months apart) for longitudinal readouts of biomarker trajectories rather than a single time-point assessment (a critical difference given that many markers harbor greater prognosis through time trends than absolute [43]). Samples were processed within a set timeframe and stored under standardized conditions though some residual site differences cannot be accounted for. Urine collection was more weighted on first-morning samples for diurnal variability with periodical 24-hour collections, and while this approach enhances consistency the degree to which subjects comply with the latter varied slightly across centers and may moderate quantitative comparisons on certain subsets [44].

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Inflammatory Biomarkers

High-sensitivity CRP were universally increased in urological phenotypes -particularly those with recurrent infection and chronic obstruction. Its prognostic power appeared modest - dampened after adjustment for comorbidities, suggesting indirect reflection of systemic inflammation rather than some specific injury to the kidney itself [45].

IL-6 generally showed a more consistent positive association with disease progression - evident elevated in both obstructive/infection type disorders and set of analyzed findings of eGFR decline clinically even after adjustment for conventional markers. Here the authors note, perhaps somewhat unusually, that "in 1 of 2 patients in whom IL-6 levels remained high after apparently effective intervention, subclinical" rather than pathophysiological change was required to explain these results [46].

Pro-inflammatory cytokine TNF-α shows a more heterogeneous pattern; show elevated in reflux nephropathy, and in chronic pyelonephritis -but variable and less reproducible across time ("poor reproducibility" was shown in an unsupervised analysis of samples in contrast sTNFRs below [47], but across patient it seems less consistent). Inversely, both soluble TNF receptors - sTNFR1 and sTNFR2- show improved prognostic power, remaining significantly associated with CKD progression after adjustment for baseline renal function and albuminuria [47]." suggesting a greater signal of sustained pathway activation.

Fibrosis Markers

TGF-β1 was highly associated with fibrotic burden, that is obstructive and post-infectious disease [47]. With increasing levels, reduced rates of renal recovery were observed after treatment, although this was not a linear relationship across cohorts [48]; in some the patients where TGF-β1 was elevated they did not progress to rapid decline, suggesting a modifier occurs.

CTGF, a downstream TGF-β signalling mediator, is sometimes most strongly associated with established fibrosis rather than injury, and periodically is maintained into repair phase when inflammatory elements are declining, likely reflecting remodelling [49].

PINP values were informative in terms of active collagen production, associating with progressive decline, substantially mixed inflammatory-fibrotic inflammatory profiles. There is not so much short-term variance as soon cytokine data, although if this is specific to the kidney or systemic is uncertain [50].

Remodelling of the matrix is a mixed picture. MMP-2 and MMP9 are activated in active injury states and TIMP-1 and TIMP-2 associate more closely with progression/accumulation of fibrosis. The TIMP-2 x IGFBP7 complex do show signal in patients with repeated obstructive stress suggesting some overlap between acute stress and chronic progression [51].

Tubular Injury Markers

KIM-1: Better indicator of tubular injury, more sensitive for obstructive disease and for injury due to reflux. Associated with tubulointerstitial damage, predicts future decline in eGFR (less strong across all subgroups though) [52].

NGAL: A bit more exploratory, rises rapidly in setting of acute (or wavy…?) injury especially surgical injury. Differentially useful if you're monitoring in the peri-interventional stage, much more extrapolative and hard to interpret in stable chronic disease [53].

L-FABP: Suggestive of tubular hypoxia and stress, associated with obstructive pathology, high levels can be seen in absence of functional decline but with overlap between stable and progressive this is not particularly useful as a prognostic marker in and of itself [54].

NAG: Fairly good, associated with tubular injury, suggests active damage of epithelium. ELEVATED in recovery patients suggests captures of mostly reversible (not something that's definitely irreversibly fibrotic) injury [55].

Metabolic and Endocrine Biomarkers

FGF23 values were higher early in the disease course and were associated both with CKD progression and increased cardiovascular risk. It is even tougher to interpret these results urological populations stating varying aetiologies of phosphate clearnace and different comorbid diseases [56]. Patients with more Klotho fared worse, there was a negative correlation with progression, though there was quite a bit of variability, suggesting without further standardization, its clinical utility may be limited [57]. Cystatin C as a marker provided a more stable estimate of filtration than creatinine in some sub-groups, especially those who had varying muscle mass or surgery. In some models presented improved

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stratification greatly, but not shown to have as added benefit and its previous use was small in relation to the overall benefit delivered, when compared to other combined markers [58]. Uromodulin appeared to behave pretty differently to the other markers discussed, and if found to be low, the authors suggested associated with worse outcomes, as perhaps would act as a marker of tubular integrity rather than injury - the utility of which may be further guided by myriad genetic predispositions/plight and environmental factors [59].

5. Tissue Biomarkers (Renal Biopsy)

Renal Biopsy in Urological CKD

Biopsy was not routinely performed, but was helpful in some patients where the mechanism or definitiveness of injury was uncertain, particularly for patients who had rapid unexplained eGFR decline whose injury mechanism was uncertain, whose injury was chronic in nature and not urological in origin, and on some occasions to inform on “deficits” implication of degree of fibrosis and other burden of disease metrics before making large clinical decisions. Clearly, the structure and molecular detail gleaned from biopsy was beneficial, but the invasiveness was a roadblock, sampling - notoriously, particularly in patients with focal or asymmetric CKD - was variable and….in some patients, their histology was lukewarmly correlated to imaging features and other markers of disease - suggesting that in other cases, the pattern of urological injury is heterogeneous.

Histological Markers of Progression

Tubulointerstitial fibrosis and tubular atrophy (IFTA) were the most consistently associated with progression, with more extensive IFTA providing evidence of eGFR decline regardless of the exact nature of this association, which is not always linear especially in the more benign forms of the disease classically described [60] Quantification of collagen by a digital method appeared to enhance reproducibility but doubtless did not eliminate inter-sample variability.

Glomerulosclerosis, not usually a primary lesion in urological disease provided helpful prognostic information especially in those with long standing disease or those in whom nephrectomy had been performed and adaptation was thus of a more unusual pattern [61]. There were also often striking vascular changes - arteriolar hyalinosis, intimal thickening, which seemed to modulate the course of disease and this no doubt reflects the inclusion of some important patients with systemic vascular pathology [62].

Immunohistochemical Features

α-SMA expression pointed to activated myofibroblasts, and progression of fibrosis was strongly associated with it, although expression varied in relative levels among different regions of a single biopsy [63]. The inflammatory infiltrates were more complicated, T-cell and macrophage accumulation across biopsies correlates with disease activity, but the proportion of pro-inflammatory and profibrotic equilibrium phenotypes appears to enact different fates in the participants [64].

Collagen subtypes gave information about timing, with collagen III being more reflective of dynamic or “quiescent” fibrosis, and collagen I being more a marker of the end of the scarring process. C3, C4d also was only eluted from a subset of individuals, suggesting only that humoral immune elements could be contributory in other phenotypes, but not pre-eminently common to all [65].

Molecular Tissue Signatures

"The transcriptomic dissections tracked anatomical activity of fibrotic and inflammatory pathways, albeit in various power, strength and relative emphasis between cohorts. ECM and myofibroblast related genes were widely activated, but with not all patients with strong molecular activity indicating rapid clinical deterioration implying that molecular activation does not necessarily imply functional decline (66).""The proteomic analyses backed this view up, showing myocardial enrichment for matrix remodeling proteins and inflammatory mediators, but again the fact progressive and less progressive patients clustered together meant they could not predict correctly in isolation (67).""The epigenetics part suggested that this is thought to ‘reprogram (impaired) paths, stably, with a relatively stable methylation signature for genes in fibrosis and repair’ which might correlate with why some still progress with correction of the urologic inciting injury, but difficult to implicate causality (68)."

6. Urinary Biomarkers of Tubulointerstitial Injury

Urinary Protein Biomarkers

Urinary NGAL consistently performed well as an early marker of tubular stress, particularly in a post-surgical and obstructive setting. Often rising rapidly shortly after injury it occurred prior to detectable rise in serum creatinine, though that specificity was more limited in a stable chronic disease setting [69]. In some there was a transient rise without a clear long term drop, suggesting a degree of sensitivity to reversible injury. KIM-1

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seemed more closely related to persistent tubular damage and fibrosis, higher levels being associated with subsequent eGFR decline. There was evidently some overlap between the progressive and non-progressive patients [70]. L-FABP signifying hypoxic and oxidative stress within the tubular compartment again performed well in an obstructive nephropathy setting. Intriguingly higher levels could be followed by partial recovery after intervention, suggesting that it may be detecting injury that is in a reversible rather than a fixed state of fibrosis [71]. Finally IL-18 appeared reflective of a more inflammation related phenotype and level was found augmented generally in reflux related and obstructive disease although it is variable and affected by intercurrent infections making its routine interpretation complex [72].

Urinary Extracellular Vesicles (Exosomes)

Urinary vesicles are derived from tubular and urothelial cells, and therefore reflect cellular processes that take place within the kidney. On the other hand, based on cross-continental differences in protocol, there is controversy between groups, which 'blunts' the significance and power of such results [73].

Exosomes - protein reduced levels of aquaporin-2 and uromodulin paralleled impaired tubular function and possibly affected tubular integrity, however whilst allupturned, the curve markedly steeper suggested it was more notable in advanced disease [74].

Exosomal RNA - profibrotic signals (eg miR-21) increased whilst reduced levels of anti-inflammatory regulators (eg miR-146a) led onto the idea of epithelial-to-mesenchymal transition pathways. Of course not all cohorts share this consistent downregulating of the miR-200 family [75].

mRNA signals (eg TGFB1, CTGF) harbour "fibrosis burden" however a further correlate fibro-progression does correlate with vesicles of urine use - a non-invasive "liquid biopsy".

Such an idea has expropurated them from their rooted have-rooted caveats of variability and approach as such [76]

Urinary Metabolomics

"Metabolomic profiling demonstrated perturbations indicative of a hypoxic, mitochondrial and inflammatory activation signature. A progression-associated panel included lactate, succinate, kynurenine and lower levels of amino acids such as arginine and taurine. A multi-metabolite panel showed good predictive performance, but there is currently limited external validation and significant inter-individual variability [77]."

Urinary DNA Methylation

Urinary cell-free DNA methylation analysis suggested epigenetic reprogramming related to CKD progression with hypermethylation of protective genes such as KLOTHO and BMP7 and hypomethylation of profibrotic genes such as COL1A1 and TGFB1 correlated with fibrosis burden [78]. However the issue of causation arises as it is not always clear whether they are drivers of progressors vs being a consequence of chronic injury. Nonetheless urinary methylation profiling may represent a noninvasive means of tracking renal remodelling in settings where serial biopsy may be undertaken [79].

7. Biomarker Dynamics by Urological Condition
Obstructive Uropathy: Biomarker Dynamics

In those with obstructive uropathy, the distributions of circulating biomarkers within individual patients at baseline reflected a mix of tubular stress, ischemia, inflammation, and (mediated by TGF-β1) early fibrotic activation. NGAL, KIM-1, L-FABP, TGF-β1, and IL-6 were all elevated prior to decompression, and tended to correlate with degree of hydronephrosis, although this was not set in stone and there were "lively" biomarker activity in some with moderate obstruction. This suggested individualisation of susceptibility to urine obstruction [80]. After relief of obstruction biomarker trajectories were biphasic. In the early post-relief phase both NGAL and KIM-1 sometimes had a rebound, additional marker activity reflecting reperfusion-related stress, delayed clearance of injury-related signals. In those who do recover well, these biomarkers settle down with time, and the persistence of elevations longer than for a couple of months is likely due to incomplete recovery or ongoing subclinical injury [81]. Such patterns with TGF-β1 and dynamics measure, for example rate of fall of biomarkers after relief of tubular injury may be where the most relevant information lies.

Vesicoureteral Reflux and Reflux Nephropathy

In reflux disease the biomarker profile seemed to suggest a more chronic / smouldering injury pattern. NGAL increased with reflux severity, whilst KIM-1 and TGF-β1 were more associated with established scarring /

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ongoing scarring [82]. Interestingly even some patients with clinical parameters stably within normal limits demonstrated elevated fibrotic markers - perhaps structural damage may have continued despite overt clinical signs of functional decline.

Following antireflux intervention there was a reduction in tubular injury markers in stabilised patients although this was not seen universally. Persistent elevation of KIM-1 and TGF-β1 despite anatomical correction suggested that fibrotic pathways may become self-reinforcing once established [83] and this subgroup required closer long term review.

Post-Surgical Kidney Injury

Partial nephrectomy (PN) afforded a model of acute on chronic injury. Predisposition to surgical decline was indicated by pre-operative biomarker profiles across centers, particularly Klotho being low and FGF23 being high [84]; while NGAL surged immediately post-operative, and high early peaks were inconsistent with lesser longitudinal eGFR loss, perhaps as not all with high peaks progress. In radical nephrectomy biomarkers reflect stress in the remaining kidney, rather than primary injury. Gradual increases in NGAL, KIM-1 and L-FABP reflect hyperfiltration related stress, especially in patients with less reserve at baseline [85]. Patients with urinary diversion demonstrate a characteristic profile of persistent low grade inflammation (IL-6, TNF-α, CRP) and higher NGAL consistent with complications that arise including ureteroenteric strictures and progressive renal dysfunction, but associated with, not causative [86].

Chronic Pyelonephritis and Infection-Related CKD

These studies found a distinction between active infection and scarring. During active infection, there was a rapid rise in markers of inflammatory and tubular injury (NGAL, IL-6, IL-8) that usually fell when treated. In contrast, patients with scarring have a persistent elevation of TGF-β1, CTGF and KIM-1, indicative of ongoing fibrotic remodeling as opposed to active infection [87]. A combination of a high TGF-β1, a high KIM-1 and low uromodulin classifies a subgroup that is at-risk for progression, but this pattern is not specific because some patients remain stable who also have this pattern [88].

Prognostic Modeling of CKD Progression

In univariate analyses there were several other biomarkers which had associations with progression, of varying magnitude of effect size. Among the circulating markers sTNFR1 appeared to be one of the strongest (and most consistent) associations with outcome supports the role of chronic inflammatory signalling [89], with TGF-β1 and FGF23 also having predictive value although variable across subgroups. Among urinary biomarkers, NGAL, KIM-1, L-FABP appeared to have independent associations with progression and likely was of greatest use in urological CKD where tubulointerstitial injury predominates. In the biopsy subset, IFTA and α-SMA remained among the strongest predictors, consistent with the concept that fibrosis and myofibroblast activation represent final common pathways [90]. However, no biomarker appeared sufficient to discriminate and prediction was enhanced when multiple biomarkers were aggregated, with modest gains in performance evident in most models.

8.2 Multivariate Prognostic Models
Multivariable Models: Circulating Biomarkers

A model that combined age with eGFR, UACR, sTNFR1, TGF-β1, FGF23, and Klotho provided good discrimination for 2-year CKD progression (AUC ~0.82). The addition of the circulating biomarkers significantly improved risk prediction relative to using clinical variables alone, although the incremental gain was modest rather than spectacular. Of these markers, sTNFR1 was the most consistently associated with risk across subgroups; however, the effects of FGF23 and Klotho were more heterogeneous, particularly by metabolic profile [91].

Multivariable Models: Urinary Biomarkers

Thus, a second predictive model which included age, eGFR, UACR, NGAL, KIM-1 and L-FABP also had good predictive power (AUC ~0.79), better calibration in obstructive and post-surgical etiologies. These markers could be capturing local tubular injury more accurately perhaps, although inter-individual differences in urinary concentration and collection methodology introduced some noise into the model [92]. In sensitivity analyses NGAL and KIM-1 were the most stable contributors, and L-FABP shown to have wider confidence intervals.

Multivariable Models: Tissue Biomarkers

In the biopsy subgroup, the highest predictive performance (AUC ~0.86) was achieved combining histological features such as IFTA, α-SMA expression and CD3 positive infiltrates, further supporting the pivotal role that fibrosis and inflammatory remodeling

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have as determinants of progression. The small size of the biopsy cohort and potential sampling bias limit generalizability, with performance estimates likely being overly optimistic [93-101].

Integrated Multi-Marker Model

An integrated model using clinical variables, circulating biomarkers, and urinary biomarkers had generally balanced performance (AUC ~0.84), but demonstrated improved sensitivity for identifying high-risk patients. Combining sTNFR1 and TGF-β1 and also combining with NGAL and KIM-1 seemed to identify systemic and kidney-specific injury pathways [93], but gains over simpler models were modest suggesting some diminishing returns as additional markers are added [94].

Risk Stratification Score

They offered the derived CKD progression score as a parallel rough measure to translate findings into a clinical metric. Abnormal patients had low rates of events at 2 years. High-risk groups showed much larger levels of progression, while delineations between moderate risk groups were less robust than expected [95]. The practical score can guide timing of intervention, monitoring or when to co-manage with nephrology. It is worth mentioning that in many as it was "not uncommon to note discordance between biomarker-based risk and imaging findings, reflecting the complexity of kidney disease".

9. Conclusion

A biomarker-driven “clinical” approach begins with baseline assessment using a combination of conventional renal function (eGFR and UACR) and selected circulating and urinary biomarkers. This is particularly pertinent at (or before) the diagnosis to be made of urological pathology known to place the kidneys at risk (such as obstruction, reflux, recurrent infection, or other surgical intervention). Biomarkers (& the science underlying them) such as sTNFR1, TGF-β1, FGF23, Klotho, NGAL, KIM-1, and L-FABP can provide a more precise estimate of both current injury and risk of future progression. Which panel is optimal is likely to depend on clinical context, and a simplified subset may yield sufficient value for routine purposes.

Risk-Based Management

These data led us to stratify patients by risk to adjust the intensity of monitoring as well as therapeutic strategy. In general, patients at low risk would be expected to follow a stable trajectory, although we observed occasional discordance between biomarker signals and biomarker trajectories as outlined above. This discordance was most notable when separating out intermediate risk groups, suggesting that these patients may be best evaluated in a longitudinal manner over time, rather than at baseline, while patients at higher risk demonstrated more rapid deterioration across the board, stratifying for initiating earlier nephrologist contact and closer follow-up. Importantly, movement of patients into different risk categories occurred frequently, particularly post-intervention, underscoring the dynamic nature of risk and the limited value of a one-time stratification approach to nephrotoxic injury risk rather than longitudinal serial evaluations.

Integration with Urological Interventions

Prevention: Pre-operative biomarker profiling may aid the detection of patients that may suffer post-operative AKI or subsequent decline, where optimisation strategies (fluid management / avoidance of nephrotoxins) may be more relevant to the goals of their recovery, if such a thing exists, although specific evidence for is rare [98]. Post-operative trajectories of biomarkers (i.e. their measure over time after intervention) is sometimes more informative than level. Persistence of elevation of NGAL, or KIM-1, or L-FABP after technically successful intervention indicates a worse outcome, but must be carefully interpreted; incidental increase from random causes may also be reflected in this measure. They may also affect decisions regarding procedure on the day. Where a patient has limited renal reserve increased injury/fibrosis markers may favour targeting nephron sparing techniques where appropriate, but of course decisions are multi-factorial at heart.

Cost-Effectiveness Considerations

Early economic models supported that biomarker-guided management may cost less, primarily through decreased progression and deferring the need for renal replacement therapy, but estimates were sensitive to biomarker cost and frequency and assumed effect size, which means real-world cost savings are likely very heterogeneous.

Implementation barriers

Barriers to implementation remain. Standardization of the measurements across laboratories is necessary, but plasticity may be over or under estimated depending on how it is measured. Turnaround time, difficulties of integrating this into clinical workflows, and

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interpretative difficulties for medically-trained individuals least practised in interpreting molecular markers may all impact feasibility. The utility of long-term testing is also contingent on whether patients are willing to follow along with retesting. Finally, reimbursement prospects are currently uncertain which may also delay uptake, even if there are putative clinical benefits.

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