S100 proteins in kidney disease: Inflammatory biomarkers, pathogenic mechanisms and therapeutic prospects (Review)

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Abstract. The S100 protein family, particularly the calprotectin heterodimer S100A8/A9, is increasingly recognized as both an inflammatory readout and a context-dependent mediator of kidney injury. Selected extracellular S100 proteins function as damage-associated molecular patterns released during cellular stress, leukocyte activation and tissue injury. They can amplify sterile inflammation through the receptor for advanced glycation end-products (RAGE), Toll-like receptor 4 (TLR4) and related downstream pathways, although receptor usage and biological effects vary by cell type and disease setting. The present review examines S100 proteins in kidney disease across three related domains: Clinical biomarkers, disease mechanisms and therapeutic translation. Current evidence most strongly supports urinary S100A8/A9 for distinguishing intrinsic from pre-renal acute kidney injury; circulating S100A8/A9 and S100A12 have mainly been studied as markers of inflammatory and cardiovascular risk in chronic kidney disease. S100-associated signaling has been implicated in leukocyte recruitment, mesangial and macrophage activation, podocyte injury, tubular stress, tubulointerstitial fibrosis and uremia-associated vascular calcification. Emerging studies also describe stress-regulated and intracellular S100 functions, including gasdermin E (GSDME)-regulated signal transducer and activator of transcription 3 (STAT3) signaling that controls S100A7A, S100-annexin complexes and S100A16-driven Wnt/β-catenin or endoplasmic reticulum stress. However, therapeutic evidence remains largely preclinical, and clinical translation is constrained by ligand redundancy, disease heterogeneity and incomplete prospective validation. S100 proteins may therefore contribute to biomarker panels and targeted interventions, but their clinical utility requires prospective validation and clear separation of receptor-mediated from intracellular effects.

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Abbreviations: AAV, ANCA-associated vasculitis; AKI, acute kidney injury; CKD, chronic kidney disease; DAMP, damage-associated molecular pattern; DKD, diabetic kidney disease; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; EMT, epithelial-to-mesenchymal transition; ESRD, end-stage renal disease; FSP1, fibroblast-specific protein 1; GSDME, gasdermin E; IgA, immunoglobulin A; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κB; NGAL, neutrophil gelatinase-associated lipocalin; RAGE, receptor for advanced glycation end-products; STAT3, signal transducer and activator of transcription 3; TLR4, Toll-like receptor 4

Key words: S100 proteins, RAGE, calprotectin, AKI, CKD, DN, renal fibrosis, vascular calcification

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1. Introduction

Kidney diseases, including acute kidney injury (AKI) and chronic kidney disease (CKD), impose a growing global burden and often converge on inflammation, fibrosis and loss of functional nephron mass. Diabetic nephropathy (DN),

immune-mediated glomerulonephritis, ischemia-reperfusion injury (IRI) and toxic tubular injury differ in their initiating triggers, but each can activate sterile inflammatory programs that contribute to persistent tubulointerstitial remodeling and kidney failure (1-3). Damage-associated molecular patterns (DAMPs), released by stressed, activated or necrotic cells, can mediate this transition, although their relative contribution varies across disease models and patient populations.

The S100 family of calcium-binding proteins includes selected extracellular DAMPs implicated in kidney disease. Members such as S100A8/A9, S100A12, S100A4, S100A6, S100A7A, S100A10, S100A16 and S100B have distinct intracellular and extracellular functions; alarmin activity is best characterized for selected members such as S100A8/A9 and S100A12 (4-7). Extracellular forms of selected S100 proteins engage pattern-recognition receptors, especially the receptor for advanced glycation end-products (RAGE) and Toll-like receptor 4 (TLR4), thereby activating nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways depending on cell type and disease context; intracellular signal transducer and activator of transcription 3 (STAT3), Wnt/β-catenin and endoplasmic reticulum stress (ERS) mechanisms do not necessarily require RAGE (1,5,7,8). Experimental studies show that the effects of selected S100 pathways can be injurious or reparative. In diabetic kidney disease (DKD), circulating high-molecular-weight RAGE ligands activate pathways associated with nephropathy (1). In cisplatin nephrotoxicity, S100A7A promotes macrophage infiltration via RAGE in male mice (6). After ischemia-reperfusion, S100A8/A9 influences macrophage-mediated inflammation and repair (5).

Clinically, this biology has created interest in S100 proteins as biomarkers and therapeutic targets. Serum creatinine may rise after tissue injury has occurred, while albuminuria provides limited information about the underlying inflammatory pathway. Urinary and circulating S100 proteins may reflect leukocyte activation, tubular inflammation, vascular inflammation or fibrotic remodeling. The present review examines three aspects of S100 biology in nephrology: Their diagnostic and prognostic potential, their context-dependent roles in kidney and vascular injury, and their therapeutic potential in carefully selected patients. The conceptual framework linking injury triggers, cellular S100 sources, receptor engagement, downstream signaling and renal pathological outcomes is summarized in Fig. 1. Throughout the present review, S100/RAGE and S100/TLR4 are used only when involvement of the corresponding receptor is supported, whereas the broader term S100-associated mechanisms encompasses intracellular functions. Clinical kidney disease was also distinguished from tissue injury and the renal or vascular compartment relevant to each mechanism was identified. This framework guides our assessment of the settings in which S100 measurements may have clinical value, the mechanisms that may justify target selection, and the evidence still needed for therapeutic translation.

2. Biology of the S100 protein family and receptor signaling

The S100 protein family comprises more than 20 small, acidic calcium-binding proteins characterized by two EF-hand calcium-binding motifs. These proteins serve diverse intracellular functions, and some members can act as DAMPs after extracellular release (9). Myeloid cells such as neutrophils and activated macrophages are major sources of S100A8/A9 (calprotectin), which can engage cell surface receptors to propagate inflammatory responses (9,10). Members implicated in kidney disease include S100A8/A9, S100A12, S100A4, S100A6 and S100B. Non-myeloid sources include stressed tubular cells, mesangial cells, podocytes and interstitial or vascular cells; expression alone does not establish extracellular release (6,11-14). S100A2 is an emerging regulator of tubular stress involving forkhead box O1 (FoxO1) (15).

S100A8/A9, a heterodimer of S100A8 and S100A9, is the best-characterized S100 complex in kidney disease. In nephrotoxic nephritis, S100A9 deficiency protects mice from glomerular injury, and *in vitro* S100A8/A9 stimulation induces interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and C-X-C motif chemokine ligand 1 (CXCL1) production by macrophages and mesangial cells (10). These data support a pathogenic role in interactions between leukocytes and renal cells. The effects nevertheless depend on context: S100A8/A9 may participate in both injury amplification and repair-associated macrophage responses depending on timing, cellular source and disease model (5,10). Recent studies also implicate calprotectin in CKD-associated vascular calcification and diabetic renal interstitial fibrosis, but clinical causality remains to be established (11,16).

S100A12, a pro-inflammatory S100 protein released by activated neutrophils, is elevated in myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA)-associated glomerulonephritis (17) and has also been associated with vascular pathology in CKD (18,19). Serum S100A12 levels are elevated in patients with CKD stages 4-5, especially in those with cardiovascular comorbidity (18). Increased S100A12 mRNA transcription in peripheral leukocytes supports increased production without excluding altered renal clearance (18). Animal models suggest that S100A12 can contribute to vascular remodeling and arterial calcification in the uremic environment (19).

S100A4, also known as fibroblast-specific protein 1 (FSP1), has been used as a marker of fibroblasts and myofibroblasts, although it is not specific to fibroblasts (20). Increased numbers of S100A4-positive interstitial cells are observed in renal fibrosis across kidney diseases, including immunoglobulin A (IgA) nephropathy, obstructive nephropathy and polycystic kidney disease (20-22). S100A4/FSP1 has also been examined in vascular-access smooth-muscle remodeling (23), podocyte or tubular epithelial-to-mesenchymal transition (EMT)-like phenotypes (24,25), and CKD arteriovenous-fistula endothelial remodeling (26). Lineage-tracing studies challenge the interpretation of complete epithelial conversion into myofibroblasts (27), while transplant-biopsy SNAI1 findings support interpreting mesenchymal-marker expression as a diseased epithelial phenotype rather than proof of lineage conversion (28).

Other S100 proteins also play distinct roles. S100A6 (calcyclin) expression is upregulated in the glomeruli of diabetic mice (29). In acute renal failure, S100A6 mRNA and protein levels are markedly elevated in the renal cortex during the peak of tubular injury and early recovery, supporting its

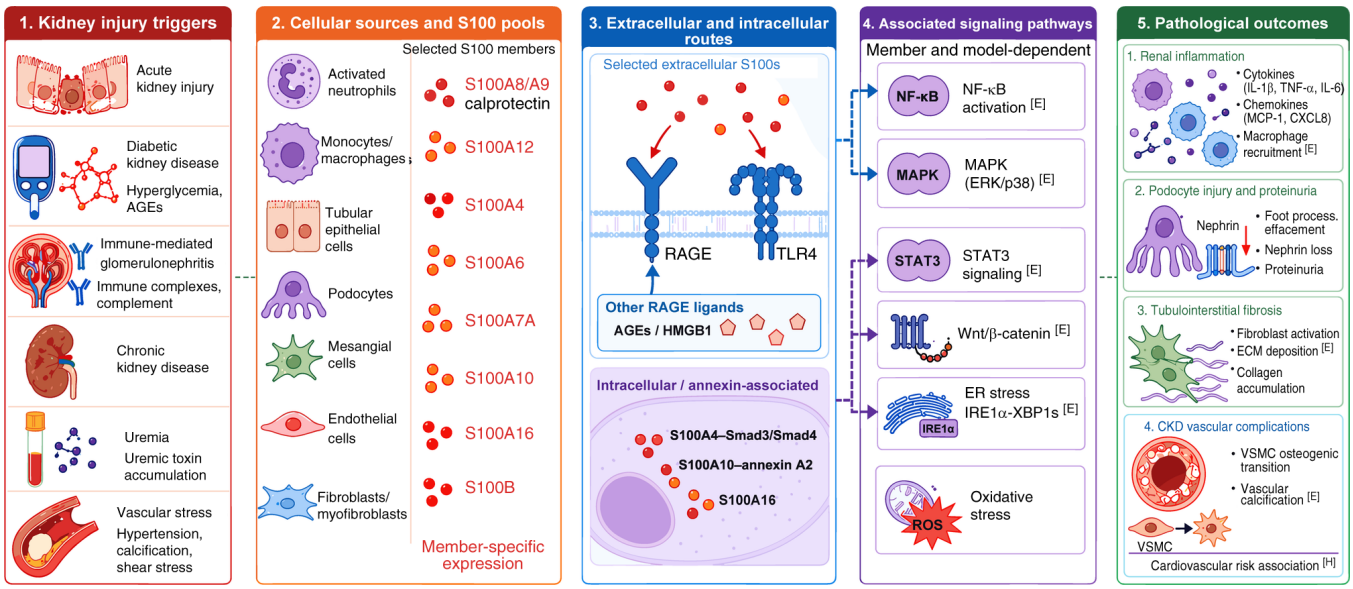

Figure 1. Overview of S100-associated mechanisms in kidney disease. Selected extracellular S100-receptor routes are distinguished from intracellular and annexin-associated pathways. Cellular sources and proteins are illustrative groups: Expression alone does not establish secretion, and connections depend on the S100 member and experimental model. Non-S100 RAGE ligands are shown separately. Dashed connectors indicate conceptual relationships across studies. H, human observational association; E, functional experimental support. Labels apply to adjacent findings, without validating every grouped connection or establishing clinical benefit. AGEs, advanced glycation end-products; CKD, chronic kidney disease; ECM, extracellular matrix; ER, endoplasmic reticulum; HMGB1, high-mobility group box 1; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κB; RAGE, receptor for advanced glycation end-products; STAT3, signal transducer and activator of transcription 3; TLR4, Toll-like receptor 4; VSMC, vascular smooth muscle cell.

investigation as a marker of tubular injury and recovery (30). S100B, a protein best known as a marker of glial cell activity, is also a RAGE ligand (8,12,31). In kidney disease, elevated serum S100B has been investigated as a biomarker for cognitive impairment in patients with end-stage renal disease (ESRD) (32). S100B has also been studied after cardiac arrest, a distinct prognostic setting (33). Mechanistically, high glucose stimulates S100B expression in mesangial cells; S100B then drives pro-fibrotic gene expression, including transforming growth factor-β1 (TGF-β1) and type IV collagen, and induces cellular hypertrophy (12).

RAGE mediates some of the pro-inflammatory and pro-fibrotic effects of selected extracellular S100 proteins. RAGE is a multi-ligand transmembrane receptor belonging to the immunoglobulin superfamily, expressed on numerous cell types, including macrophages, endothelial cells and podocytes (12,31). Its ligands are not limited to S100 proteins but also include advanced glycation end-products (AGEs) and high-mobility group box 1, both of which are elevated in conditions such as diabetes and CKD (1). High-molecular-weight RAGE ligands isolated from the serum of patients with diabetes are particularly potent activators of downstream signaling (1). Because RAGE recognizes non-S100 ligands, protection following RAGE blockade alone does not identify the responsible S100 protein.

After ligand engagement, the short cytoplasmic domain of RAGE triggers intracellular signaling that sustains inflammatory gene expression. The best-established downstream effects include NF-κB activation, MAPK signaling through extracellular signal-regulated kinases 1/2 (ERK1/2) and p38, oxidative stress, cytokine and chemokine release, and extracellular matrix (ECM) production (1,8,12,31). For example, RAGE ligand preparations and S100B stimulation promote profibrotic responses in mesangial cells (1,12,31). These findings support a feed-forward model in which tissue injury releases S100 ligands, receptor activation amplifies inflammation, and persistent inflammation accelerates fibrosis and vascular damage.

3. S100 proteins as clinical biomarkers in nephrology

Selected S100 proteins, including members with extracellular DAMP activity, are candidate biomarkers in several kidney diseases. Blood and urine measurements of selected S100 proteins have been investigated as indicators of acute tubular injury, chronic inflammation, fibrosis and vascular damage. This section reviews the clinical evidence for key S100 proteins across nephrological settings. The disease-specific evidence is summarized in Fig. 2, and representative biomarker applications are listed in Table I. Blood, urine and tissue measurements are not interchangeable, and an association with disease does not establish clinical decision value.

S100A8/A9 in AKI. S100A8/A9 is abundantly expressed in neutrophils and monocytes and serves as a sensitive marker of innate immune activation. Its most extensively studied clinical application in nephrology is differentiating intrinsic (structural) from pre-renal (functional) AKI. This distinction is clinically useful, but urinary calprotectin should be interpreted as a marker of urinary tract or kidney inflammation rather than as a stand-alone diagnostic test. Its performance may be influenced by urinary tract infection, systemic inflammation, sampling time and the assay platform (34-36).

Multiple studies have evaluated urinary calprotectin for differentiating intrinsic from pre-renal AKI. An adult comparison study evaluated calprotectin together with

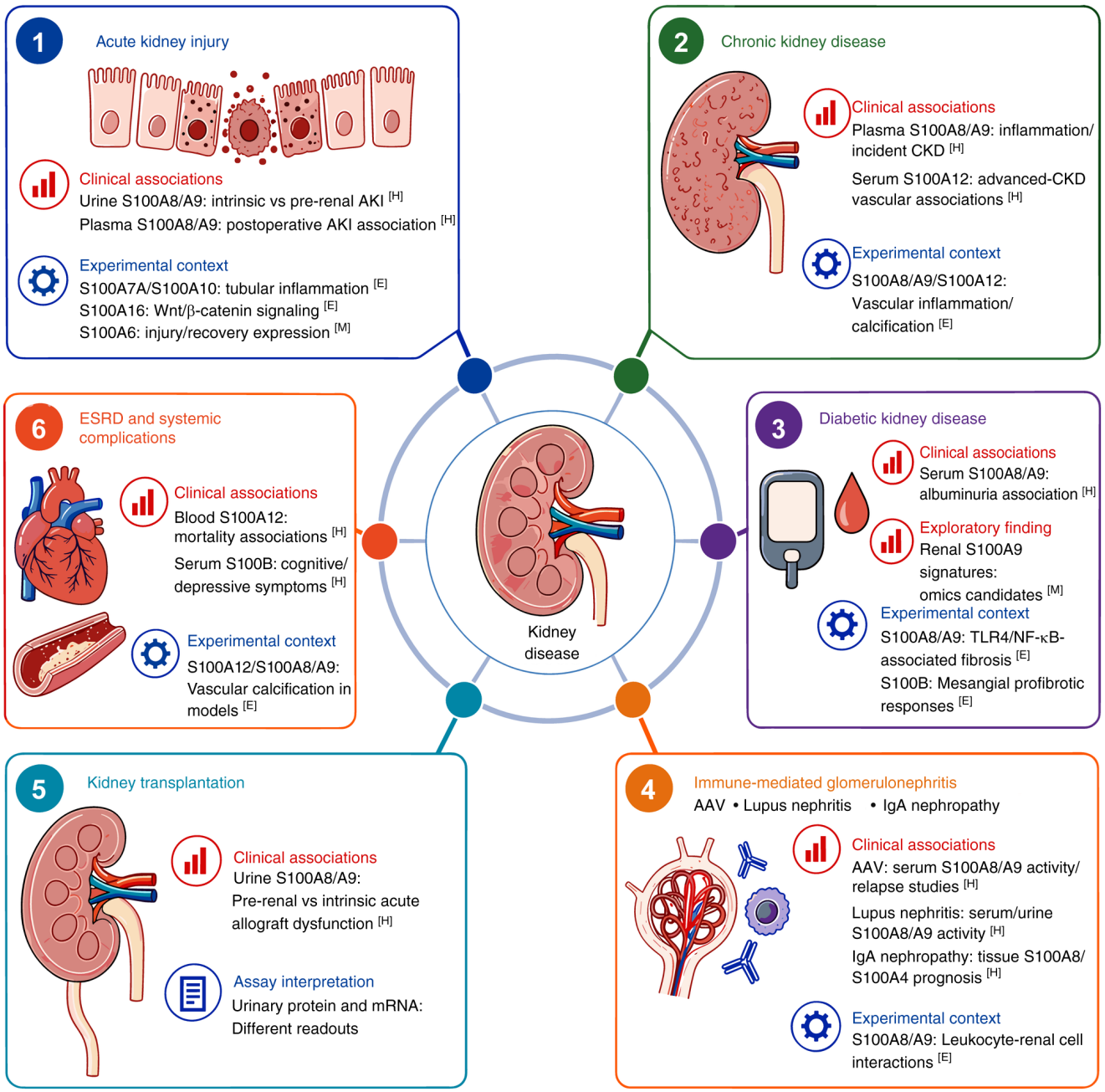

Figure 2. Clinical associations and experimental contexts of S100 proteins across kidney diseases. H denotes human observational evidence, including diagnostic cohorts; E, functional experimental support; M, exploratory or model-limited evidence, including expression and omics findings. These labels describe adjacent findings rather than formal evidence grades. Urine, serum, plasma, tissue and mRNA measurements are distinct readouts. Transplant findings concern acute graft dysfunction; human S100B associations concern systemic complications. Tissue S100A8 and S100A4 findings in IgA nephropathy derive from separate studies, and S100A9 omics candidates require protein-level validation. Ring connections group disease settings without implying causality. Clinical utility requires further validation. AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; AAV, antineutrophil cytoplasmic antibody-associated vasculitis; IgA, immunoglobulin A; mRNA, messenger RNA.

neutrophil gelatinase-associated lipocalin (NGAL) (35). A cardiopulmonary-bypass proteomics study detected urinary S100A8 and provides perioperative biomarker data, but it did not evaluate calprotectin diagnostic accuracy (37). A meta-analysis and critical-care cohorts report favorable discrimination, although thresholds differ and external validation and standardization remain limited (38,39). In renal transplant recipients, urinary calprotectin can help distinguish pre-renal graft dysfunction from intrinsic acute allograft injury (40).

S100A8/A9 has also been studied in several clinical settings associated with AKI. In pediatric populations, urinary calprotectin has been investigated for differentiating AKI etiologies (41,42) and for predicting adverse outcomes. However, one pediatric AKI cohort reported poor mortality discrimination, with areas under the receiver operating characteristic curve (AUCs) of 0.55 for 30-day and 0.61 for 3-month mortality, whereas prediction of renal replacement therapy (RRT) yielded an AUC of 0.72 (43). After cardiac surgery, elevated plasma S100A8/A9 levels immediately

Table I. S100 measurements in kidney disease: specimen, clinical question and evidence limitations.

S100 protein	Sample type	Clinical question	Key supporting evidence	Evidence and interpretation limit	(Refs.)
S100A8/A9	Urine protein	Intrinsic vs. pre-renal AKI	Adult, pediatric and allograft diagnostic cohorts	H: candidate adjunct; UTI and assay thresholds limit transferability	(34,35,38-41)
S100A8/A9	Plasma protein	Postoperative AKI risk	Cardiopulmonary bypass and aortic dissection cohorts	H: timing-specific association; does not validate urine thresholds	(44,45)
S100A8/A9	Urine protein	Adverse outcomes in pediatric AKI	Mortality AUC 0.55-0.61; kidney replacement therapy AUC 0.72	H: poor mortality prediction; endpoint-specific performance	(43)
S100A8/A9	Urine protein	Cisplatin-associated kidney injury	Exploratory nephrotoxicity cohort	H: limited validation; not an established treatment rule	(48)
S100A8/A9	Plasma or feces	Incident CKD or intestinal inflammation	Plasma CKD association; fecal mortality association	H: distinct compartments; confounding and causality unresolved	(50,51,53)
S100A8/A9	Serum; urine CD163 in a panel	Active AAV kidney disease	Disease-activity cohort and combined biomarker model	H: external validation and incremental value needed	(54,55)
S100A8/A9	Serum and urine protein	Lupus nephritis activity	Associations with clinical kidney activity	H: systemic autoimmune activity can confound blood results	(56,57)
S100A8	Glomerular macrophages	IgAN progression	MRP8-positive cells associated with sclerotic change	H: biopsy association; not a non-invasive test	(58)
S100A8/A9	Serum; kidney immune-cell transcripts	DKD severity or early inflammatory signatures	Albuminuria associations and omics candidates	H/M: protein measurements and transcripts are not equivalent	(4,61-63)
S100A12	Serum or plasma	Vascular risk in advanced CKD	Associations with vascular disease and mortality	H: account for inflammation, kidney function and dialysis timing	(18,75-78)
S100A4/FSP1	Kidney biopsy	IgAN prognosis and fibrosis	Cell density associated with kidney survival and steroid response	H: historical name does not confer fibroblast specificity	(21,74)
S100B	Serum protein	Systemic neurologic complications	Cognitive, depressive or neuropathy associations	H: not specific for kidney injury or DKD progression	(32,65-67)
S100A6 and annexin A2	Kidney tissue	Tubular injury and recovery	Co-expression over experimental injury and recovery	M: experimental marker association, not a validated clinical assay	(30)

H, human observational evidence; E, functional experimental support; M, exploratory or model-limited evidence. These descriptive labels are not formal evidence grades and do not imply clinical validation. AUC, area under the receiver operating characteristic curve; CKD, chronic kidney disease; DKD, diabetic kidney disease; AKI, acute kidney injury.

following cardiopulmonary bypass are associated with subsequent AKI (44). Plasma S100A8/A9 has also been investigated for predicting postoperative AKI after high-risk procedures such as acute type A aortic dissection surgery (45). Mechanistic experiments in this setting implicate S100A8/A9-high macrophages in renal tubular epithelial cell damage (46). In sepsis-associated AKI, S100A8/A9 expression is time-dependently elevated in the kidney, and its inhibition ameliorates renal dysfunction in murine models, supporting a pathogenic role in that model (47). In drug-induced nephrotoxicity, urinary calprotectin has also been evaluated for detecting acute cisplatin-induced nephrotoxicity (48). Urinary calprotectin has additionally been studied in relation to kidney damage and mortality in COVID-19 (49). These plasma and urine studies use different sampling times and endpoints; thus a common diagnostic threshold cannot be assumed.

S100A8/A9 in CKD and glomerulonephritis. In CKD, S100A8/A9 has been studied primarily as a marker of systemic low-grade inflammation associated with disease progression and complications. Higher plasma calprotectin levels are prospectively associated with an increased risk of new-onset CKD in the general population, particularly when defined by urinary albumin excretion (50). CKD-related systemic inflammation has also been examined in relation to the gut-kidney axis: Elevated fecal calprotectin, a marker of intestinal inflammation, has been associated with higher mortality in patients with CKD, independent of traditional inflammatory markers (51). Related exploratory findings in children on RRT and elderly patients with moderate CKD support further investigation of this relationship (52,53). Intestinal barrier dysfunction and microbial products or uremic solutes may increase systemic inflammatory exposure. However, fecal calprotectin indicates intestinal inflammation; it does not establish transport of S100 proteins to the kidney or causation of CKD progression.

S100A8/A9 has also been studied in inflammatory glomerular diseases. In ANCA-associated vasculitis (AAV), serum and leukocyte surface S100A8/A9 reflect disease activity, decrease with treatment and may help predict relapse (54). A predictive model combining serum calprotectin, urinary soluble CD163 and hematuria has been proposed to improve detection of active renal vasculitis (55). In lupus nephritis, serum and urinary S100A8/A9 levels correlate with renal activity in the available cohorts (56,57). In IgA nephropathy, the accumulation of myeloid-related protein 8 (MRP8; S100A8)-expressing macrophages in glomeruli has been associated with sclerotic progression and unfavorable prognosis in children (58). These observations support S100A8/A9 as a marker of active myeloid inflammation, but larger prospective studies are needed to define its role in routine decision-making.

Evidence linking calprotectin to vascular calcification may be relevant to CKD-associated cardiovascular risk. A primary experimental study indicates that S100A8/A9 can promote osteochondrogenic differentiation of vascular smooth muscle cells (VSMCs) through RAGE and TLR4 signaling (16). Reviews and commentary provide broader mechanistic and clinical context (59,60). The extent to which circulating calprotectin is a causal mediator, a marker of vascular inflammation or both may vary among patient subgroups and requires prospective interventional study.

S100 proteins in DKD. In DN, S100A8/A9 and S100B have been associated with disease status, progression and systemic complications. The evidence is most consistent for associations with albuminuria, inflammatory cell infiltration and diabetic complications, whereas their incremental value beyond established clinical markers remains insufficiently defined. DKD is used for the clinical disease category; DN is retained when describing studies that use that designation.

Serum S100A8/A9 levels increase across worsening stages of DN, from normo-albuminuria to macroalbuminuria, and correlate positively with urinary albumin-to-creatinine ratio and serum creatinine (4). The association with microalbuminuria has prompted evaluation of calprotectin as an early marker of microvascular damage and inflammation in type 2 diabetes (61). Single-cell sequencing studies have identified S100A9 as a candidate early molecular marker that is highly expressed in pro-inflammatory myeloid-derived suppressor cells that infiltrate the kidney in early DN (62). Machine-learning analyses have also nominated S100A9 as a candidate diagnostic biomarker for DKD (63). The gut-kidney axis is also relevant in DN, but a study of patients with type 1 diabetes found that fecal calprotectin did not differ significantly between progressive and stable DKD groups (64). These omics-derived signatures require independent protein-level validation and comparison with estimated glomerular filtration rate (eGFR) and albuminuria.

S100B, which is primarily expressed in glial cells, has been studied in relation to systemic complications of diabetes (65). Elevated serum S100B has been associated with diabetic peripheral neuropathy, a common comorbidity of DN (65). In patients with ESRD, which can result from DN, higher serum S100B levels are associated with neurologic and psychiatric complications, including cognitive impairment and depression (32,65-67). In high-glucose-stimulated mesangial cells, S100B contributes to pro-fibrotic responses (12). S100B is also under investigation as a potential marker for long-term complications in patients with DN who have a history of COVID-19 (68). These systemic associations do not establish S100B as a kidney-specific predictor of DKD progression. Studies of activated leukocyte cell adhesion molecule in DN and IgA nephropathy provide non-S100 biomarker comparators (69,70), not evidence of S100B signaling.

S100A4 and S100A12 as prognostic markers. S100A4 and S100A12 are two S100 proteins with distinct candidate prognostic roles in kidney disease, related primarily to fibrosis and cardiovascular complications, respectively.

S100A4/FSP1 is a widely used marker of fibroblast activation in fibrotic kidneys, but its biological interpretation requires caution. In animal models of kidney fibrosis, including obstructive and remnant-kidney models, S100A4/FSP1 expression increases in interstitial fibroblast-like cells (71,72). Hypoxia and fibroblast-epithelial crosstalk may further promote FSP1-positive cell accumulation and fibrotic remodeling (71,73). In IgA nephropathy, interstitial FSP1-positive cell density has been associated with renal survival and corticosteroid responsiveness (21,74). However, extracellular FSP1 may also exert context-dependent protective effects through antioxidant pathways, indicating that FSP1 does not act solely as a fibrosis-promoting factor (13). Intracellular fibrogenic

functions and extracellular protective effects should therefore be distinguished.

S100A12 (also known as EN-RAGE) is a pro-inflammatory RAGE ligand and a candidate marker of cardiovascular risk in advanced CKD. Plasma S100A12 levels are elevated in patients with ESRD undergoing hemodialysis or peritoneal dialysis (75,76), and several cohorts link higher levels to all-cause or cardiovascular mortality (77,78). These findings may have prognostic value, but they do not show that S100A12-directed therapy will improve outcomes. ABCC6 genetics provides non-S100 calcification context (79); the distinction between S100A12 as a risk marker and a causal factor remains important (80). Experimental studies support S100-associated vascular remodeling and calcification mechanisms (19,81).

Comparative value of S100 biomarkers. The potential clinical value of S100 proteins should be assessed against established biomarkers, both individually and in combined panels. In AKI, urinary calprotectin provides information about inflammatory parenchymal injury that differs from tubular stress markers such as NGAL, kidney injury molecule-1 (KIM-1) and interleukin-18 (IL-18) (35,41,43). Its principal value may be etiological classification rather than universal AKI prediction. In CKD, S100 proteins are unlikely to replace albuminuria, estimated glomerular filtration rate or histology, but may add pathway-level information on inflammation, fibrosis or vascular risk.

In chronic and inflammatory kidney diseases, combining S100 proteins with other markers may improve diagnostic performance. In AAV, a model combining serum calprotectin with the macrophage marker urinary CD163 performed better for detecting active renal disease than either biomarker alone (55). In renal transplant recipients, urinary mRNA levels of NGAL, KIM-1 and IL-18 correlated with histological findings of rejection, whereas S100A8/A9 mRNA did not, indicating that biomarker choice may depend on the clinical question within the same patient population (82). In stable CKD, plasma calprotectin levels correlate with other inflammatory markers such as IL-6 and monocyte chemoattractant protein-1, as well as with levels of protein-bound uremic toxins, supporting its investigation as an indicator of the systemic inflammatory state associated with uremia (83). Integration of S100 proteins into panels for AKI differentiation, CKD assessment or prediction of inflammatory flares requires external validation and evidence of clinical benefit. Urinary transcript findings should not be extrapolated directly to calprotectin protein assays.

Across biomarker studies, the evidence base is heterogeneous. Urinary S100A8/A9 in AKI is supported by multiple clinical cohorts and meta-analytic evidence, whereas several other S100 members are supported mainly by small cohorts, tissue studies, animal models or bioinformatic analyses. Future studies should therefore report standardized assays, prespecified cutoffs, external validation cohorts and incremental predictive value beyond conventional markers.

Assay standardization and confounders. Most urinary AKI studies used enzyme-linked immunosorbent assays with cohort- and assay-specific cut-offs (34,35,38). The 300 ng/ml value from the original adult study is a diagnostic threshold, not a normal range or treatment-selection threshold (34). Antibody specificity, calibrators, molecular forms, dilution, analytical range and urine-matrix effects limit comparability. A serum assay comparison required substantial calibration adjustment; this finding demonstrates the need for harmonization but does not quantify inter-assay bias in urine (84). Validation should address precision, recovery, linearity, interference and quantification limits, followed by independent validation of clinical thresholds and incremental value. Urinary concentrations and creatinine-normalized values should be reported separately.

Urinary tract infection, pyuria and contamination can confound interpretation. Bacteriuria can raise urinary calprotectin even without dipstick pyuria, thus a negative dipstick alone does not exclude infection-related elevation (36). Studies should document the collection method, catheter status, hematuria and suspected contamination, with urine culture or repeat sampling when indicated. Systemic infection, surgery and autoimmune activity also affect circulating markers independently of kidney injury (44,54,85). Studies should record eGFR, residual kidney function, dialysis status and sampling relative to dialysis; increased leukocyte S100A12 transcription does not exclude altered clearance (18).

Serum and plasma results should not be pooled: Specimen-dependent concentrations and delayed-processing effects have been demonstrated for circulating calprotectin (86). Collection-to-processing time, temperature, centrifugation, storage and freeze-thaw exposure should be controlled for each matrix and assay. Findings in blood cannot establish analyte stability in urine. Sampling should be defined relative to injury, surgery, treatment and recovery because these time points address different clinical questions (30,43,44).

4. S100-associated mechanisms in kidney injury and progression

S100-associated signaling is best viewed as one component of a broader sterile inflammatory network in kidney disease. After release from stressed or necrotic cells, selected extracellular S100 proteins act as DAMPs by engaging pattern-recognition receptors, including RAGE and TLR4. These interactions can activate downstream signaling events that promote inflammation, fibrosis and cellular injury and thereby contribute to AKI and CKD progression. However, the magnitude and direction of S100 effects depend on ligand concentration, cellular source, receptor availability and disease stage. The principal compartment-specific mechanisms are illustrated in Fig. 3. Similar endpoints may also arise from intracellular S100 functions without established RAGE dependence.

Kidney inflammation. A hallmark of kidney injury is inflammatory cell recruitment and activation. S100A8/A9 and S100A12 can act as chemo-attractants and immune activators, but their functions are not uniformly deleterious. In glomerulonephritis models, S100A8/A9 promotes inflammatory leukocyte-renal cell interactions, whereas in IRI it has been linked to macrophage-mediated repair responses (5,10). Distinguishing injury-amplifying from repair-associated S100 signaling is therefore essential for interpreting therapeutic studies.

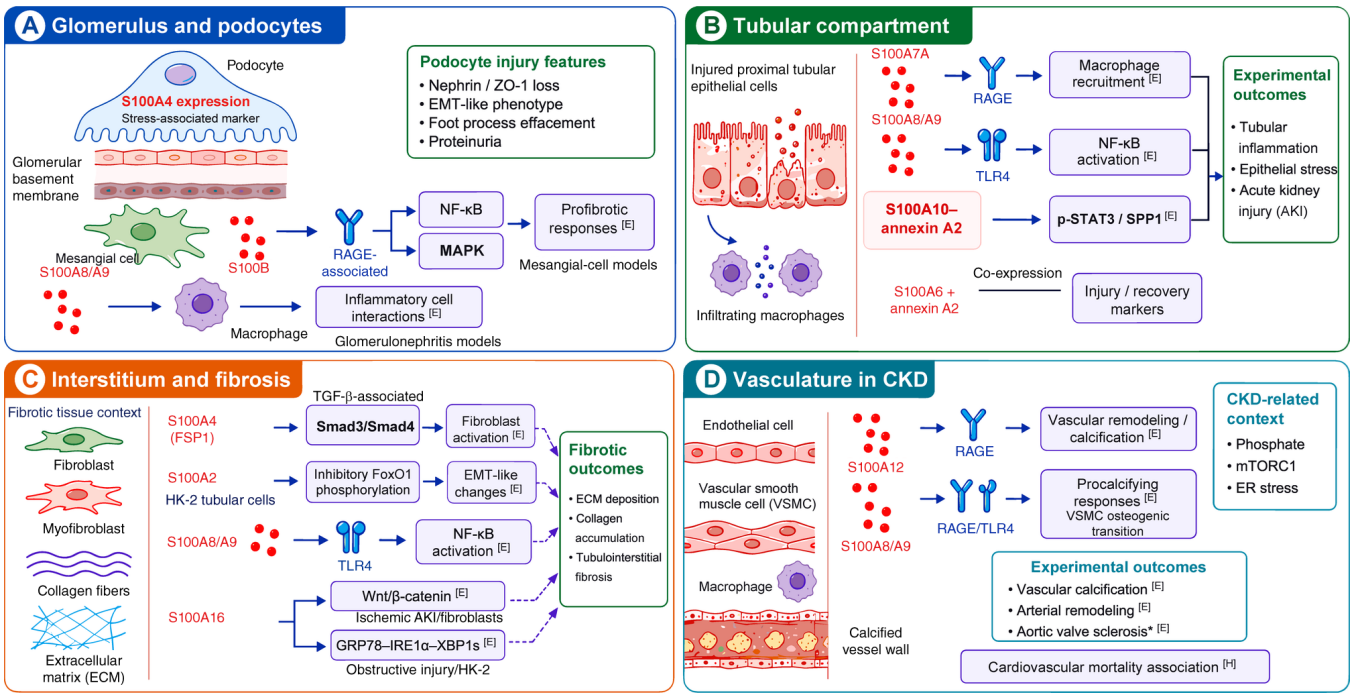

Figure 3. S100-associated mechanisms in glomerular, tubular, interstitial and vascular compartments. (A) Podocyte S100A4 expression does not establish extracellular release or S100A4-RAGE causality. (B) S100A7A findings derive from male-mouse cisplatin AKI. S100A10-annexin A2 signaling has no established RAGE requirement, whereas S100A6/annexin A2 denotes co-expression. (C) S100A2-associated inhibitory FoxO1 phosphorylation and EMT-like changes concern HK-2 cells. S100A16-Wnt findings derive from ischemic AKI/interstitial fibroblast models, and GRP78/IRE1α/XBP1s findings from obstructive injury/HK-2 models. Tissue illustrations do not assign a shared cellular origin or demonstrate epithelial conversion into fibroblasts. (D) The asterisk denotes aortic valve sclerosis in a humanized S100A8/A9/A12 cluster model. CKD-related factors provide context from separate studies; human mortality associations remain observational. Solid arrows indicate effects supported within the stated models; dashed connectors indicate cross-study synthesis. H, human association; E, functional experimental support. Labels apply to adjacent findings and are not formal grades or evidence of clinical benefit. CKD, chronic kidney disease; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; ER, endoplasmic reticulum; FSP1, fibroblast-specific protein 1; RAGE, receptor for advanced glycation end-products; SPP1, secreted phosphoprotein 1; TLR4, Toll-like receptor 4; VSMC, vascular smooth muscle cell; AKI, acute kidney injury.

These mechanisms occur across several nephropathies. In systemic lupus erythematosus, serum S100A8/A9 and S100A12 are elevated in patients with high disease activity and are associated with the presence of glomerulonephritis (85). In DKD, S100A8/A9-associated TLR4/NF-κB signaling contributes to inflammation and interstitial fibrosis in experimental models (11). In septic AKI, blockade of the S100A8/A9-TLR4 interaction with paquinimod ameliorates renal dysfunction and inflammatory injury (47). Human biomarker associations and experimental receptor effects provide different levels of evidence. S100A8- and S100A9-derived B-cell epitopes have also been evaluated as serological biomarkers in DN (87), but that diagnostic study does not establish a pathogenic signaling mechanism.

Recent single-cell transcriptomic studies have provided a more detailed cellular map of S100 expression. In IRI-induced AKI, inflammatory macrophage subsets with high S100A9 expression have been proposed as potential therapeutic targets (88). In DKD, S100A8/A9-high macrophages are also enriched in inflammatory niches (89). These datasets are valuable for hypothesis generation, but transcript abundance does not necessarily establish protein activity or causal function. Validation at the protein level and with spatial and functional studies remains important.

Together, these studies implicate myeloid recruitment and tubular stress as distinct contributors to inflammation. The relevant receptor, cell population and timing vary; an intervention should therefore be assessed for both early injury and later recovery (5,6,10,88).

Tubulointerstitial fibrosis (TIF). TIF is a common feature of progressive kidney disease and contributes to irreversible loss of renal function. It is characterized by excessive accumulation of ECM, produced primarily by activated myofibroblasts. S100-associated mechanisms are implicated in this fibrotic process, with S100A4 and S100A8/A9 playing prominent roles.

S100A4/FSP1 is associated with fibroblast activation in fibrotic kidneys, although its expression is not fibroblast-specific. Niclosamide treatment, together with genetic S100A4 perturbation, attenuates fibroblast activation, collagen deposition and ECM accumulation in experimental renal fibrosis (90). *In vitro*, S100A4 overexpression promotes TGF-β1-induced fibroblast activation, whereas S100A4 knockdown is protective (90). S100A2 and S100A8/A9 are associated with additional profibrotic mechanisms: S100A2 promotes inhibitory FoxO1 phosphorylation and EMT-like changes in HK-2 cells, S100A8/A9 promotes fibrosis in obstructive nephropathy, and S100A8/A9 inhibition ameliorates diabetic renal interstitial fibrosis by suppressing TLR4/NF-κB signaling (11,15,91). S100A4 interacts with Smad3, stabilizes the Smad3/Smad4 complex and promotes its nuclear translocation, although niclosamide is not a selective mechanistic probe (90). S100A2-associated FoxO1 inhibition does not establish a S100A2-RAGE pathway.

The cellular origin of scar-producing myofibroblasts remains a matter of debate. S100A4/FSP1 expression in tubular epithelial cells or podocytes has often been interpreted as evidence for EMT in DN and human immunodeficiency virus-associated podocyte injury (24,92,93). However, lineage-tracing studies have shown that resident interstitial cells, particularly pericytes, rather than epithelial cells, are the dominant source of myofibroblasts in several models of kidney fibrosis (27). Thus, S100A4 expression should be interpreted as a marker of injury, dedifferentiation and profibrotic signaling rather than proof that epithelial cells become matrix-producing myofibroblasts *in vivo*.

S100A4-Smad3/Smad4, S100A2-FoxO1 and S100A16-associated Wnt or ERS mechanisms contribute to fibroblast activation, epithelial stress and tissue remodeling (14,15,90,94). This conclusion synthesizes findings across studies and does not demonstrate direct interactions among all S100 proteins. The kidney studies discussed in the present review do not establish direct S100-specific coupling to Hippo/YAP/TAZ; this relationship remains a testable hypothesis.

Podocyte injury and proteinuria. Podocytes are essential for maintaining the glomerular filtration barrier, and injury to these cells can result in foot-process effacement, detachment, proteinuria and progressive glomerulosclerosis. RAGE signaling is implicated in glomerular injury, although AGE-containing ligand preparations do not isolate S100-specific effects (1,8). In diabetic settings, RAGE signaling intersects with oxidative stress, inflammatory cytokines and ECM remodeling, contributing to podocyte vulnerability.

An EMT-like podocyte phenotype links S100A4 expression to proteinuria-associated cellular stress. TGF-β1 can reduce podocyte junctional proteins such as nephrin and ZO-1 while inducing mesenchymal markers including desmin and S100A4/FSP1; these changes are associated with increased albumin permeability (24). In DN, podocyte FSP1 expression correlates with podocyte depletion and glomerulosclerosis (92). These findings support a stress-associated phenotype but neither prove complete lineage conversion nor establish extracellular S100A4-RAGE causality. PLA2R binding to the annexin A2-S100A10 complex in human podocytes is a separate molecular observation whose contribution to barrier injury remains unresolved (95).

These observations link S100A4 expression to podocyte stress but do not establish a causal extracellular ligand-receptor mechanism. Cell-specific receptor perturbation and ligand rescue would be needed to establish whether a specific S100 pathway directly contributes to proteinuria.

Vascular complications in CKD. Cardiovascular disease is the leading cause of mortality in patients with CKD, driven in part by accelerated atherosclerosis and vascular calcification (VC). The uremic environment, characterized by inflammatory mediators and mineral dysregulation, favors vascular remodeling. Within this setting, S100/RAGE-related signaling has been implicated in uremia-associated VC, an active, cell-mediated process that involves the osteogenic transition of VSMCs.

Mechanistic evidence supports a causal contribution of S100/RAGE signaling to vascular calcification. In CKD models, transgenic S100A12 expression directly mediates vascular remodeling and arterial calcification through RAGE-dependent pathways (19). Humanized mice expressing the S100A8/A9/A12 cluster develop left ventricular hypertrophy and aortic valve sclerosis with calcification during CKD, and this phenotype requires RAGE (81). Separate studies implicate RAGE in phosphate-associated calcification and mechanistic target of rapamycin complex 1 (mTORC1)/ERS in the uremic vascular environment; these findings do not establish one linear S100 pathway (96,97).

Calprotectin has emerged as a candidate mediator and therapeutic target in CKD-associated vascular calcification (16). Mechanistic experiments showed that calprotectin exacerbates calcification in human VSMCs and mouse aortic rings, whereas paquinimod reduced calcification by dampening inflammatory signaling (16). These findings link calprotectin measurements to an experimentally modifiable vascular mechanism, but clinical trials are needed before calprotectin can be regarded as a validated therapeutic target in CKD vascular disease. Pharmacological RAGE and TLR4 inhibition reduced pro-calcifying effects in that experimental setting, supporting receptor involvement without demonstrating treatment benefit in patients (16).

The vascular evidence links inflammatory ligand exposure to mineral stress in vascular cells. Human outcome associations remain observational, whereas intervention experiments provide support that is specific to each model; reduced inflammation or calcification in a model is not equivalent to improved cardiovascular outcomes.

5. Stress-regulated and intracellular S100 pathways

Although RAGE and TLR4 are central to the current framework, S100 biology in the kidney extends beyond a single inflammatory axis. Recent studies link S100 proteins to tubular stress responses, gasdermin regulation, annexin complexes, Wnt/β-catenin signaling and ERS. The position of each S100 protein within these pathways varies with the specific protein and experimental model. These findings broaden the mechanistic scope of the field and may explain disease-context specificity, but several remain early observations from animal or cell models and should be interpreted as emerging mechanisms rather than established clinical targets.

A recent study identified a protective, non-pyroptotic function of gasdermin E (GSDME) in cisplatin-induced nephrotoxicity (6). In this male-mouse AKI model, GSDME expression was reduced in kidney tissue, and tubule-specific GSDME deficiency exacerbated renal injury. Mechanistic experiments indicate that GSDME in proximal tubular cells normally prevents the degradation of O-linked N-acetylglucosamine (O-GlcNAc) transferase. Consequently, GSDME loss reduces STAT3 O-GlcNAcylation, which enhances STAT3 phosphorylation and activation. Activated STAT3 then drives the expression of its downstream target, S100a7a. The resulting increase in S100A7A protein promotes macrophage infiltration via RAGE activation, amplifying renal inflammation. These findings support a protective role for tubular GSDME through suppression of STAT3-dependent S100A7A production in this model (6). The non-pyroptotic upstream function of GSDME should therefore be distinguished from the downstream RAGE-associated S100A7A

effect. Janus kinase 2 (JAK2)/STAT3-directed treatment in DN provides broader pathway context (98), without establishing S100-specific efficacy.

Interactions between S100 proteins and annexin A2 (Anxa2), another calcium-dependent protein, further illustrate the context dependence of S100-related pathways in tubular injury. S100A6 and Anxa2 have been identified as markers associated with tubular injury and recovery in AKI (30). In experimental toxic and ischemic AKI, both proteins increase during injury and early recovery, consistent with roles in the injury response rather than uniformly pathogenic effects (30). By contrast, S100A10/Anxa2 complex activation was reported to aggravate cisplatin- and ischemia-reperfusion-induced AKI through phosphorylated STAT3 and secreted phosphoprotein 1 signaling (99). Co-expression does not establish a pathogenic S100A6-annexin A2 complex. The S100A10-annexin A2 experiments included complex inhibition and proximal-tubule knockdown, but do not establish a RAGE requirement (99).

S100A16, a less extensively characterized member of the S100 family, has been implicated in several stress pathways relevant to AKI and fibrosis. In experimental ischemic AKI and interstitial fibroblasts, S100A16 promotes Wnt/β-catenin activation by facilitating the degradation of glycogen synthase kinase 3β and casein kinase 1α, two negative regulators of β-catenin signaling, through the E3 ubiquitin ligase HRD1 (14). S100A16 also interacts with the endoplasmic reticulum chaperone glucose-regulated protein 78 (GRP78) and activates the inositol-requiring enzyme 1α/spliced X-box binding protein 1 pathway in renal TIF models (94). These findings support S100A16 as a mechanistic candidate, but its clinical relevance and druggability remain to be defined. The Wnt study used heterozygous S100A16 deficiency; the GRP78 study examined obstructive injury and HK-2 cells. Neither mechanism should be considered RAGE-dependent without receptor-specific evidence.

6. Therapeutic implications and future perspectives

The involvement of S100 proteins in inflammation, fibrosis and vascular injury supports their investigation as therapeutic targets, although the supporting evidence varies across diseases. Current evidence consists mainly of preclinical studies and human biomarker associations, while kidney-specific clinical trial evidence remains limited. Studies have examined inhibition of S100 ligands, RAGE signaling and downstream inflammatory pathways. Current therapeutic strategies and evidence gaps are summarized in Table II.

Interventions affecting S100 proteins and receptor signaling. Specific S100 proteins are potential therapeutic targets, but this strategy remains at an early stage. The S100A8/A9 heterodimer has been studied most extensively because of its biomarker performance and mechanistic links to vascular calcification and inflammation. Paquinimod reduced calprotectin-driven vascular calcification in experimental systems, providing preclinical proof of principle (16). However, the absence of clear efficacy in immune-mediated glomerulonephritis models indicates that S100A8/A9 inhibition may be disease- and compartment-specific rather than broadly renoprotective (100).

Preclinical studies have also examined pharmacological modulation of S100A4-associated renal fibrosis. In a mouse model of folic acid-induced nephropathy, niclosamide, an anthelmintic investigated as an S100A4 inhibitor, attenuated fibroblast activation, collagen deposition and ECM protein expression. S100A4 facilitated TGF-β1-induced fibroblast activation in this model, and niclosamide blocked this effect, supporting a link between S100A4 and a central fibrotic pathway (90). The pleiotropic effects of niclosamide limit attribution to selective S100A4 inhibition, and extracellular S100A4 can protect tubular cells in cisplatin injury models (13).

RAGE or its downstream pathways provide additional therapeutic targets. Preclinical studies have examined natural compounds that modulate RAGE-related signaling. For example, KIOM-79, a herbal extract, prevented S100B-induced expression of TGF-β1 and fibronectin in mouse mesangial cells by suppressing the activation of downstream effectors, including NF-κB and the MAP kinases p38 and ERK (31). An ethanolic extract from *Scrophularia striata* also produced protective effects in a rat model of DN by suppressing the renal expression of both RAGE and its ligand S100A8 (101). These studies show that RAGE-related expression or signaling can be reduced experimentally. These extracts are indirect modulators; reduced expression or downstream signaling does not establish direct receptor antagonism. Studies of sepsis-associated autophagy decline (102), β-chain-deficient complement component 4 binding protein [C4BP(β-)] and *Benincasa hispida* (103,104) provide broader injury and treatment context; none establishes selective S100 inhibition.

Challenges to clinical translation. Despite the promise of targeting S100-associated mechanisms, several challenges remain. One concern is inhibitor specificity. Numerous small molecules, including paquinimod and niclosamide, may have off-target effects that contribute to their observed efficacy or toxicity. The discrepancy in paquinimod's effectiveness against vascular calcification vs. glomerulonephritis illustrates the challenge of translating findings from animal models to human disease (16,100). Animal models often represent a single, acute pathological process, which may not fully recapitulate the multifactorial nature and chronicity of human kidney disease. Furthermore, S100-associated signaling involves multiple ligands and receptors, and this redundancy may allow other components to compensate when one is inhibited.

Elevated S100 concentrations may reflect systemic inflammation rather than a treatment-responsive kidney pathway. Biomarker associations therefore require independent evidence of target dependence before they can justify treatment selection.

Roadmap for clinical translation. A staged research strategy should begin with assay qualification and validation of repeated measurements against relevant clinical variables. No kidney-specific S100 threshold for selecting treatment is established. A prespecified upper quantile defined for the assay and study population could be an exploratory enrichment criterion, but it would require validation and continuous biomarker analysis. Candidate populations include CKD with documented vascular calcification and DKD with persistent albuminuria and inflammatory evidence despite stable

Table II. Classification of interventions affecting S100-associated mechanisms in kidney disease.

Intervention class	Agent or manipulation	Target or process	Experimental setting and finding	Main limitation	(Refs.)
Ligand-directed pharmacology	Paquinimod	S100A9 and calprotectin signaling	VSMCs, aortic rings and CKD mice: reduced calcification	E: preclinical efficacy; selectivity and kidney dosing require definition	(16)
Ligand-directed pharmacology	Paquinimod	S100A8/A9-associated inflammation	Septic AKI mice: improved injury; nephrotoxic nephritis: no successful prevention	E: disease-dependent response; not broad kidney protection	(47,100)
Receptor blockade	Pharmacological RAGE or TLR4 inhibition	Calprotectin-associated receptor effects	VSMCs and aortic rings: reduced pro-calcifying effects	E: receptors have other ligands; receptor efficacy is not S100 specificity	(16)
Genetic test and expression modulation	S100A8/A9 knockdown; AB38b	S100A8/A9; TLR4 and NF-κB	Diabetic models: reduced epithelial stress and fibrosis	E: knockdown and a compound reducing expression are distinct interventions	(11)
Pleiotropic pharmacology with genetic support	Niclosamide; S100A4 knockdown	S100A4; Smad3/ Smad4	Folic acid nephropathy and fibroblasts: reduced activation and matrix	E: niclosamide is not a selective probe; extracellular S100A4 may protect tubules	(13,90)
Indirect downstream modulation	KIOM-79	S100B-stimulated NF-κB/MAPK outputs	Cultured mesangial cells: reduced TGF-β1 and fibronectin	E: *in vitro* extract data; direct RAGE antagonism not established	(31)
Expression modulation	*Scrophularia striata* extract	RAGE and S100A8 expression	Diabetic rats: improved parameters and reduced expression	E: mixed constituents; expression change does not demonstrate binding	(101)
Intracellular complex disruption	A2ti; proximal tubular S100a10 knockdown	S100A10-annexin A2/STAT3/SPP1	Toxic and ischemic AKI models: reduced injury	M: limited models; no established RAGE requirement	(99)
Genetic mechanistic test	S100A16 heterozygous deficiency or knockdown	HRD1/GSK3β/CK1α and Wnt/β-catenin	Ischemic AKI and interstitial fibroblasts	M: no validated selective drug or human efficacy	(14)
Mechanistic perturbation	S100A16 expression manipulation	GRP78/IRE1α/XBP1s	Obstructive injury and HK-2 cells: ER-stress mechanism	M: mechanistic evidence, not demonstrated drug efficacy	(94)
Broad immune modulation	C4BP(β-)	Complement-related immune regulation	Experimental lupus nephritis: reduced disease	E: not an S100-directed inhibitor	(103)
Multi-component treatment and omics	*Benincasa hispida* extract	Candidate S100A6-associated changes	Diabetic mice: structural and molecular responses	M: candidate association; selective S100A6 inhibition unproven	(104)

H, human observational evidence; E, functional experimental support; M, exploratory or model-limited evidence. These descriptive labels are not formal evidence grades and do not imply clinical validation. AUC, area under the receiver operating characteristic curve; CKD, chronic kidney disease; DKD, diabetic kidney disease; AKI, acute kidney injury; VSMC, vascular smooth muscle cells.

standard-of-care therapy. Infection, mineral metabolism, eGFR and dialysis-related confounding should be assessed before enrollment.

Early randomized, placebo-controlled add-on studies should prioritize safety, pharmacokinetics in kidney impairment and target engagement. Prespecified high- and low-biomarker strata would allow treatment-by-biomarker interaction analysis; a study restricted to the high-biomarker group cannot establish differential treatment benefit. Adaptive enrichment would require prespecified rules, adequate sample size and control of false-positive results. Ligand inhibition, RAGE blockade, expression modulation and intracellular complex disruption should be selected according to the demonstrated mechanism, rather than treated as interchangeable interventions (Table II).

For receptor-directed agents, pharmacodynamic assessment should measure ligand-receptor engagement or receptor activity using a functional assay. For intracellular targets, pharmacodynamic assessment should measure pathway responses in the relevant tissue. Total circulating S100 concentration may not fall after ligand blockade. eGFR trajectory, albuminuria and standardized calcification imaging can provide exploratory outcomes, with clinical benefit tested in later trials with adequate power. Infection, hematologic effects and impaired injury recovery should be monitored. This roadmap is a research proposal, not a validated clinical algorithm.

7. Conclusion

S100 proteins should not be treated as interchangeable biomarkers or therapeutic targets. Clinical translation depends on resolving ligand identity, cellular source, receptor dependence and whether the evidence supports an association or a causal experimental effect.

Priorities include assay standardization, prospective validation beyond conventional clinical markers and appropriately controlled intervention studies. Target engagement, safety and benefit beyond existing care must be demonstrated before S100 measurements or inhibition can guide routine nephrology practice.

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Authors' contributions

HW wrote the original draft, organized the literature and prepared the figures and tables. ZL wrote the original draft and assisted with figure and table preparation. QL and YN contributed to literature collection and manuscript drafting. JL and LM wrote, reviewed and edited the manuscript, supervised the study and acquired funding. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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