Assessment of Galectin-3 in kidney diseases

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Abstract

Background:A lectin with a molecular weight of 30KDa, galectin-3 (Gal-3) is involved in various processes of pathophysiology, such as fibrosis and kidney injury. Gal-3 utilizes its carbohydrate-recognition domain to bind β-galactoside. Gal-3 is a multi-functional protein that may be found both within and outside of cells. It is involved in cell-to-cell adhesion, cell-to-extracellular matrix adhesion, and immunological chemoattractant protein, among other functions. Furthermore, clinical trials and experimental models have also connected Gal-3 to renal illness. The development of different pharmacological inhibitors of Gal-3 is justified because it appears to improve renal illness in several pathological circumstances. Gal-3 has several uses in renal pathophysiology, both as a biomarker and a possible therapeutic agent; this review will attempt to highlight the most recent research on this topic.

Keywords: Galectin-3, Kidney Diseases

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1. Introduction

In the early 1980s, researchers found the lectin galectin-3 (Gal-3) in tumor cells. Several organs and injuries related to them have since had this protein's function investigated [1,2,3]. The pathophysiology of these diseases is complex, whether they are cancer, heart disease, or kidney disease. Nevertheless, therapeutic implications of Gal-3 pharmacological suppression are worth exploring. Recently, researchers in both the basic and clinical sciences have begun to investigate Gal-3's role in kidney illnesses; elevated levels of this protein have been linked to certain types of renal damage and patient outcomes.

As a biomarker and prospective therapeutic target, Gal-3 pathophysiology in kidney disease is the goal of this review.

2. Gal-3: A Carbohydrate Binding Protein from the Lectin Family

2.1. The Lectin Family

A class of binding proteins known as lectins interact with various partners through a unique carbohydrate recognition domain (CRD) [4]. The Latin word "legere" means "to collect" in English. Lectins are involved in many processes (such as the transduction route and cell-to-cell interaction) due to these interactions [5,6].

Galectins are a subset of lectins that attach to β-galactose by their unique CRD. They are a family of fourteen proteins. Gal-3 is a chimeric protein that includes one CRD and one regulatory N-terminal domain connected with a collagen-like sequence [7]. Galectins 1, 2, 5, 7, 10, 11, 13, 14, 15, and 16 are composed of one unique CRD associated in monomer or dimer. Galectins 4, 6, 8, 9, and 12 are composed of two different united CRDs. The structure of galectins is illustrated in Figure 1a. Among the many biological activities in which galectins participate are cell-to-cell communication [11], immunological signaling that causes profibrotic effects [8,9,10], and early development.

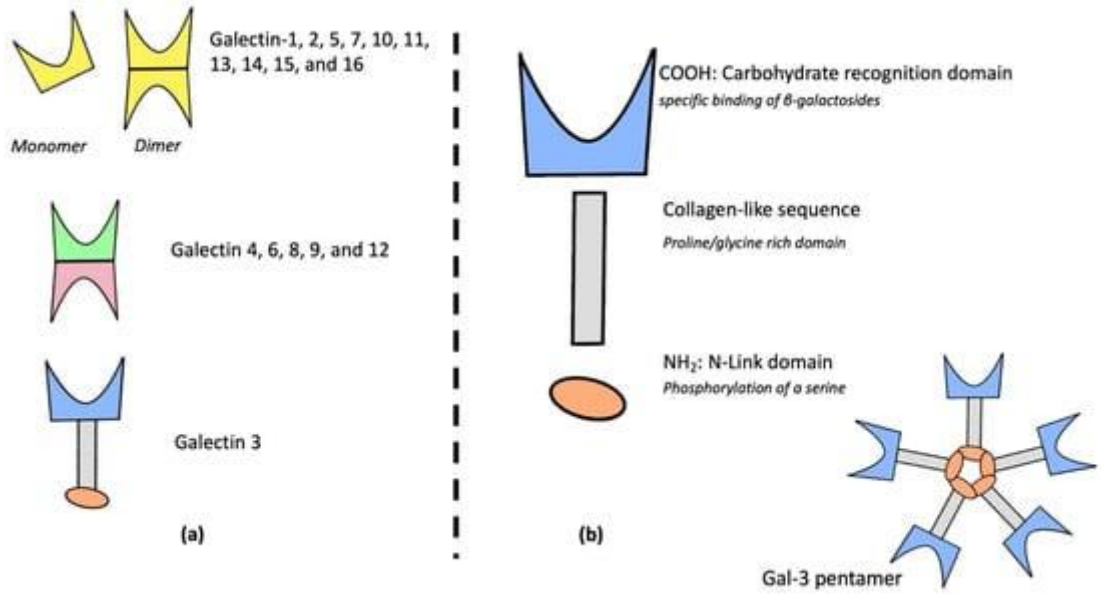

Figure 1. Galectins' family structure (a), galectin-3 chimeric and specific structure (b).

2.2. Galectin-3

2.2.1. Structure

Over the years, Gal-3 has gone by several names, including Mac-2 antigen, IgE-binding protein, carbohydrate-binding protein, and L-29 [12,13,14]. It is the sole galectin found in mammals. There are three separate domains that make up this soluble protein: a CRD, a collagen-like sequence, and a particular domain at the N-link terminus [15,16,17,18]. Figure 1b shows the galectin-3 structure.

- The CRD binds carbs through a polypeptide fold domain. Several signaling pathways are activated when Gal-3's CRD interacts with proteins that contain carbohydrates [19].

- Matrix metalloprotease can cleave the nine collagen-like sequences that comprise the proline/glycine rich domain, which connects the CRD to the N-link domain [20].

- The biological activity of Gal-3 is dependent on the N-link domain. Two serin-phosphorylation sites are located within this domain [21]. This domain undergoes biochemical modifications that cause kernel cells to internalize Gal-3 [22].

2.2.2. Expression and Role

The expression of Gal-3 by a wide variety of cells and organs (e.g., inflammatory, endothelial, muscle or tumor cells, and fibroblasts) leads to a wide variety of pathophysiological roles [23,24,25].

There are two forms of Gal-3 expression: internal, on the cell membrane, and extracellular, in a soluble form. Figure 2 provides a concise overview of the several functions of Gal-3.

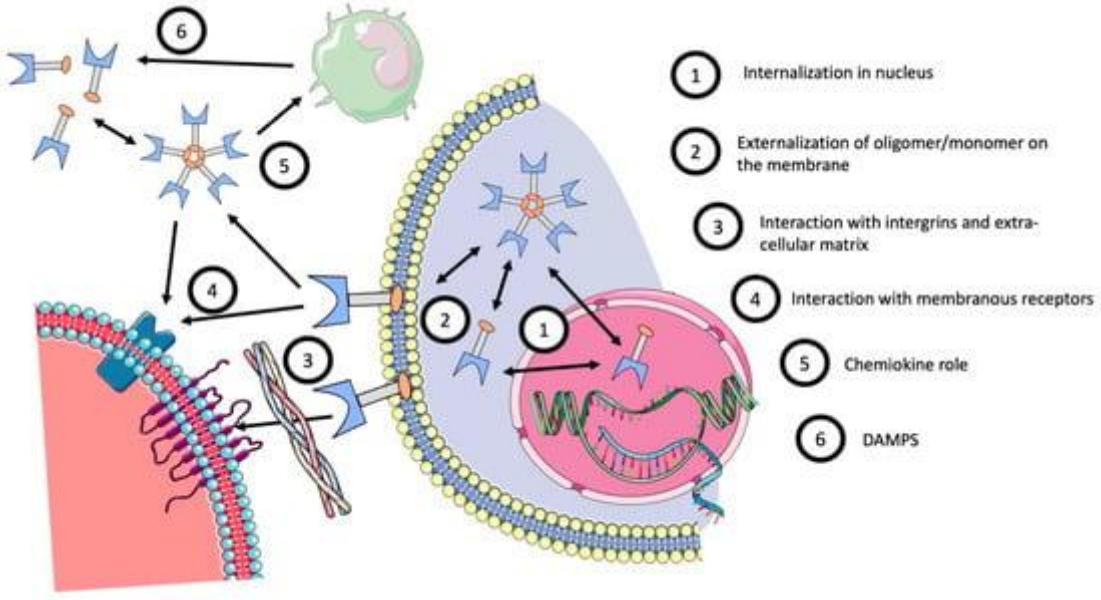

Figure 2. Galectin-3's role and localization.

- Gal-3 is produced in the cytoplasm of the cell and helps the cell to survive by regulating apoptosis [26]. Another way it can stimulate cell proliferation is by entering the nucleus through the digestive tract [27].

- Gal-3 regulates the interaction of epithelial cells with the extracellular matrix or other cells and is located in the plasma membrane of cells [28]. Cell adhesion or bond cell activation promotion is facilitated by its capacity to bind with integrins or endothelium sticky proteins [29,30,31,32]. In addition to bridging the gap between Gal-3 and cells, Gal-3 can connect with

glycoproteins to enhance binding to the extracellular matrix [28,33]. From the membrane to intracellular pathways, all of these processes foster a transduction cascade [22,35,36,37,38].

- In response to targeted injury, Gal-3 is released into the bloodstream or stored in organs as a soluble form; it then functions as a DAMP to elicit an immune response [39,40]. According to multiple studies, Gal-3 modulates immune cell infiltration of macrophages, which leads to fibrosis in the kidneys and lungs [41,42,43].

2.2.3. Galectin-3 Inhibitors

To assess its pathophysiological effect following damage, researchers have looked at genetic and pharmacological suppression of Gal-3. Gal-3 inhibitors are categorized according to the binding qualities of their carbohydrates [44]. Extracellular fixation and permeability capacities are critical for this lectin since it binds to various cellular locations. Nevertheless, there are a few studies that do not fully address the topic or relevance of Gal-3 inhibitors. Here, Gal-3 inhibitors have shown only little efficacy in clinical trials. To further explore this point, more research is required.

2.2.4. Galectin-3 in the Kidney

Gal-3 is mostly expressed during development in collecting ducts and on the apical membrane of α-intercalated cells. This provides more evidence that Gal-3 may play a role in tubular growth [54], maybe by promoting tubulogenesis via interactions with the extracellular matrix or cell-to-cell adhesion [55]. Adult kidneys show Gal-3 expression in ascending thick limb cells, proximal tubules, main and intercalated cells, and the tubules themselves [56].

Since Gal-3 can freely cross the glomerular membrane, some exploratory studies have suggested a renal clearance, although its exact pharmacokinetics remain unknown [27]. Despite its modest molecular weight (29–31 KDa), Gal-3 does not appear to be associated with albumin in extracellular spaces, according to previous research [57]. In their initial study, Meijers et al. determined that Gal-3 was entirely and freely eliminated from the body through the urine, with a distribution volume of 90 mL and a clearance of 0.92 mL/min, in a rat model. A Gal-3 fractional excretion rate of 3.0% and an estimated Gal-3 excretion rate of 3.9 mL/min (2.3 to 6.4) were determined in healthy humans, respectively. Lastly, at a slower pace than creatinine, the dialyzer can filter Gal-3 for hemodialysis patients [58].

Gal-3 expression changes in diseased states and has been investigated in both animal and human studies. Research on these topics is described in full below.

3. Gal-3 in Preclinical Models of Kidney Disease

The role of Galectin-3 is summarized in Figure 3.

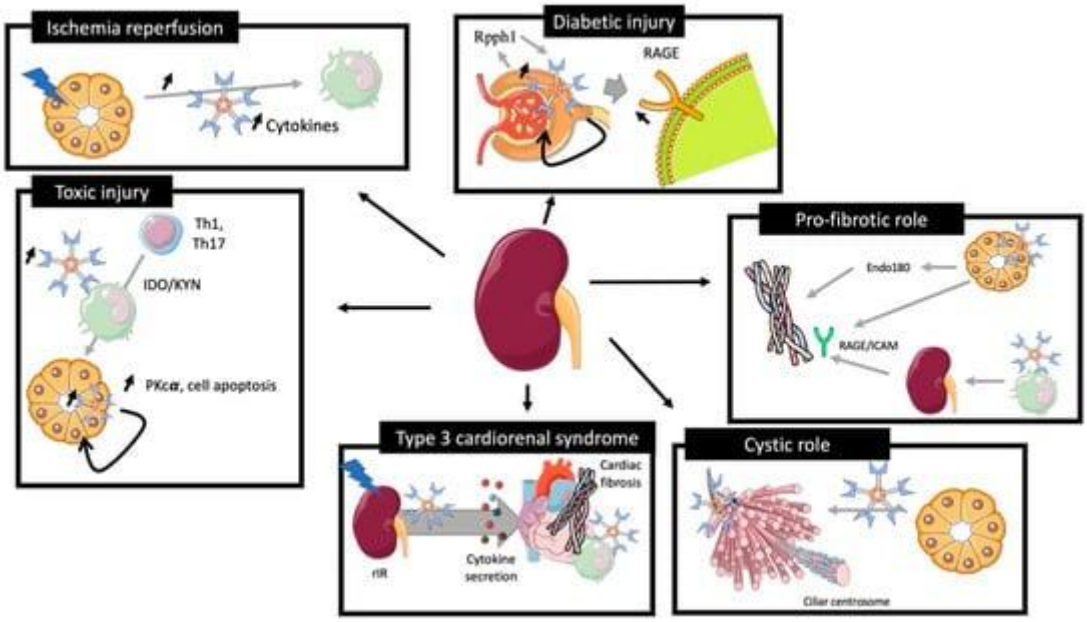

Figure 3. Role of galectin-3 in preclinical models of kidney injury. rIR leads to an increase of plasma and renal Gal-3 expression associated with acute tubular injury, promoting cytokine expression and immune cells recruitment. Toxic renal injury induces Gal-3 associated Th1 and Th17 recruitment for renal reparation and Gal-3 tissular associated PKc*αα* cell apoptosis. Diabetic models induce an overexpression of Gal-3 via the Rpph1 pathway, promoting AGE downregulation via an upregulation of RAGE. In the cystic model, Gal-3 was expressed in cystic centrosome cilia and its inhibition aggravates the development of cyst. Gal-3 expression induces collagen formation via the endo180 receptor and the RAGE/ICAM pathway. Gal-3 is increased in plasma during type 3 cardiorenal syndrome leading to cytokine secretion, cardiac Gal-3-associated immune cells, and fibrosis induction.

3.1. Ischemia/Reperfusion

A number of studies have documented Gal-3's function in renal ischemia/reperfusion (rIR).

Researchers Nishiyama et al. demonstrated that rIR quickly increased the expression of Gal-3 mRNA in rats and was negatively correlated with serum creatinine dose after 48 hours (R = −0.94). Within 48 hours following damage, distal tubules showed an extension of Gal-3 overexpression [59]. In addition, reduced macrophage infiltration and activation, decreased tissue damage (ROS generation, tubular necrosis), and enhanced renal function were all linked to genetic suppression of Gal-3 in this paradigm [60].

We recently documented an upregulation of Gal-3 plasmatic, mRNA, and protein expression 24 hours post-rIR as a result of inflammatory cell infiltration and tubular damage. The release of Gal-3 by immune cells and the overexpression of plasma soluble Gal-3 were linked to elevated levels of pro-inflammatory cytokines, including IL1b, IL6, TNFα, and IL10. Curiously, Gal-3

KO mice showed a reduction in elevated levels of pro-inflammatory cytokines [61]. Additionally, in the outer medulla surrounding necrotic tubules and in nearby capillaries following rIR, a population of renal interstitial cells Gal-3 (+), CD44 (+), and vimentin (+) were found. This suggests that Gal-3 mediates endothelial activation and kidney tubular regeneration under these experimental circumstances [62].

The results of these investigations pointed to a distinct function for Gal-3 following rIR, which promotes endothelial activation, cytokine release, and inflammation in the kidneys, which in turn causes tissue remodeling and further fibrosis. Inhibiting Gal-3 in this model prevented inflammation, fibrosis, and cytokine release, all of which are outcomes of renal illness [63].

3.2. Toxic Injury

Tubular damage seems to be less severe in toxic preclinical models of experimental nephropathy compared to rIR models. Rapid elevation of renal Gal-3 mRNA expression was noted by Nishiyama et al. in a toxic FA-induced nephropathy model [59]. A heterogeneous collection of tubules, including dilated collecting ducts, showed Gal-3 expression, which diffused from proximal ducts. In addition to being found in macrophages fourteen days after damage, Gal-3 inhibition slowed the onset of fibrosis and reduced inflammation and kidney apoptosis [64].

An increase of Gal-3 kidney expression, along with cell death, collagen type I production, and upregulation of PKC-α, was noted by Li et al. on day 3 in a model of cisplatin-induced AKI. Curiously, blocking Gal-3 slowed the progression of AKI to CKD [65]. But in a comparable AKI paradigm, Volarevic et al. showed that immunological cell Gal-3 expression regulated immunosuppression via renal dendritic cells, TLR-2 activation, and IL-10 release. Inhibiting Gal-3 may have a negative effect on immunological modulation, according to these results [66].

Therefore, Gal-3 may have conflicting functions following kidney injury, depending on the cell type that expresses it (macrophages make it anti-fibrotic, whilst tubular cells generate it pro-fibrotic).

3.3. Glomerular Injury

Several investigations have shown that damaged glomeruli have altered Gal-3 expression. Gal-3 was overexpressed in diabetic rats, namely in mesangial cells, from 2 to 12 weeks in a streptozotocin model of diabetic nephropathy in rats. The glomerular remodeling of the related advance-glycation-end-product (AGE) receptor (RAGE) was altered by overexpression of Gal-3 [67]. Gal-3 deficiency causes increased diabetic glomerulopathy and glomerular AGE buildup due to RAGE downregulation, as shown by these authors using the same experimental paradigm [68]. Furthermore, AGE buildup linked to glomerular damage was generated in mice by injection of N-carboxylmethyllysine. Increased circulating AGE levels and changed RAGE functions are additional mechanisms by which Gal-3 inhibition hastens glomerular disease [69]. According to Zhang et al., AGE-mediated damage occurs when the long non-coding sequence

Rpph1 interacts with Gal-3. This, in turn, promotes the MERF/ERK transduction pathway, which leads to MCP-1 overexpression and the proliferation of mesangial cells [70].

Increased plasma Gal-3 levels were associated with the advancement of glomerulopathy and accompanying proteinuria in another preclinical model employing transgenic Ren-2 rats that developed severe hypertension-induced glomerulosclerosis. Both renal damage and function were enhanced in this mouse by inhibiting Gal-3 [71].

Last but not least, we know that anti-Thy1.1 antibody injections in rats accelerated glomerulonephritis progression, which may be related to mesangial hypercellularity and elevated Gal-3 expression in infiltrating glomerular macrophages and distal tubules [72].

These findings highlight the multifaceted function of Gal-3 in glomerular injury. As glomerulopathy progresses, Gal-3 inhibition slows its reduction, which speeds up the disease. On the other hand, Gal-3 may protect against glomerulopathy by reducing the infiltration of immune cells associated with Gal-3 when its expression extends in tubule and mesangial cells.

Immune-Responsible Damage to the Kidneys (3.4)

3.4.1. Renal Disease Associated with Sepsis

Gal-3 was found to be elevated in septic-associated kidney injury in a rat peritonitis model (cecal ligature puncture). Additionally, modified citrus pectin (MCP) pharmacologically inhibited Gal-3, which enhanced renal function and survival while decreasing IL-6 plasma and inflammation [73].

3.4.2. Transplantation Model

Over the past few years, research has demonstrated that Gal-3 can regulate inflammation and immune cell infiltration in pathophysiological settings. Graft dysfunction due to immune cells is observed in grafted models. Researchers Dang et al. transplanted BM12 kidneys into wild-type (WT), genetically modified (GM) (WT), or genetically barren (Gal-3 null) mice. The graft caused an increase in Gal-3 tissular and plasmatic expression in wild-type mice. Less tubular damage, mild fibrosis, and immune cell infiltration were seen in Gal-3 deficient mice [42]. Inhibiting Gal-3 improved renal outcome, and these findings validated its function in immune cell recruitment in a diseased setting.

3.5. Polycystic Model

Cilia of enlarged collecting ducts showed Gal-3 expression in a mouse model of congenital polycystic kidney (CPK). Interestingly, mice who were injected with Gal-3 had a drop in cyst frequency, while mice that were not injected with Gal-3 displayed a larger ratio of kidney weight to bone length and a different structure for their cilia.

This research highlights the importance of tubular Gal-3 expression throughout tubule development and the structural effects of this expression [74].

3.6. Renal Fibrosis

According to reports, Gal-3 promotes fibrosis in various organs [1] and is involved in the progression of acute to chronic renal illness by activating inflammatory cells, releasing inflammatory factors, and injuring tissues [75]. Nevertheless, Gal-3's function in this regard remains debatable.

Extracellular matrix-producing cells (fibroblast and myofibroblast) proliferate in response to Gal-3, which may have a role in their migration and adherence [76].

Additionally, it has been noted that in Gal-3 null mice, there was an increase in total collagen and a decrease in myofibroblast and extra-cellular matrix synthesis due to a downregulation of endo180 receptors involved in collagen degradation [77]. This led to a more extensive degree of renal damage and fibrosis.

By employing a model of UUO, Gasparitsch et al. proved that there was a correlation between Gal-3 expression and an upregulation of collagen I. The authors noted that in RAGE−/− or RAGE−/− ICAM−/− mice, Gal-3 expression was considered less significant. According to these findings, the progression from acute injury to fibrosis may include the interaction of Gal-3 with RAGE/ICAM [78]. Macrophages that produced or secreted Gal-3 increased renal fibroblast activation to a profibrotic phenotype, as Henderson et al. discovered in the same experimental setting focusing on macrophage infiltration. Moreover, this paradigm showed that fibrosis severity was reduced when CD11b-DTR mice were used for selective macrophage depletion [63].

Lastly, pharmacological suppression of Gal-3 improved immune response and renal fibrosis in rats fed a high-fat diet, a model known to cause severe damage to the glomeruli and tubules. Another model of aortic occlusion-induced fibrosis found that pharmacological suppression of Gal-3 reduced fibrosis as well [79].

Research like this shows that Gal-3 expression plays a role in the pathophysiology of damage response that promotes fibrosis. Renal fibrosis appears to be linked to Gal-3 expression in immune cells. On the other hand, Gal-3 expression in tissues regulates collagen via particular receptors, leading to improved tissue regeneration and less fibrosis after renal injury.

3.7. Preclinical Model of Cardio-Renal Syndrome

Gal-3 may play a role in type 3 cardio-renal syndrome, which we have only just discovered. Mice were subjected to a left renal ischemia reperfusion following a right nephrectomy in order to create a temporary kidney malfunction. After 48 hours, the dysfunction quickly returned to normal, and neither water excess nor uremic syndrome were observed. The result is an increase in

cardiac fibrosis and a decrease in ventricular fraction shortening after 28 days. Unilateral ureteral blockage produced comparable outcomes. The significance of acute renal injury in the initiation of cardiac dysfunction was brought to light in this investigation. Following renal ischemia reperfusion, Gal-3 levels rose in the experimental model's plasma, kidneys, and heart. Heart failure was averted by blocking Gal-3. In a model of bone marrow transplant mice, we also found that immune cells expressing Gal-3 in the heart caused cardiac fibrosis, and that blocking its expression in cells derived from the transplanted bone marrow improved the cardiac phenotype. The results of this research point to Gal-3 as a possible mediator of type 3 cardio-renal syndrome inter-organ communication [61]. Although the exact function of Gal-3 in cardiorenal syndrome is still unclear, some preclinical investigations are attempting to pin down its involvement in the kidneys in this setting [80].

4. Gal-3 as a Biomarker

4.1. Kidney Function

While Gal-3 was originally investigated for its potential as a biomarker of cardiac injury [81], it has since been the subject of multiple investigations on its potential as a biomarker of acute kidney injury.

The baseline Gal-3 level was assessed by Drechsler et al. from two studies: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study (2579 patients with coronary angiograms) and the German Diabetes mellitus Dialysis (4D) study (1168 dialysis patients with type 2 diabetes mellitus). As renal function became more severe, the Gal-3 level rose steadily, going from 12.8 ± 4.0 ng/mL in individuals with an estimated glomerular filtration rate (eGFR) of 90 mL/min per 1.73 m2 to 54.1 ± 19.6 ng/mL in the 4D study's dialysis patients [82].

In their study of 1498 patients undergoing cardiac surgery, Von Ballmos et al. examined the plasma Gal-3 value for the purpose of predicting AKI. They found that the highest tercile of Gal-3 was linked to severe AKI (OR of 2.95; $p < 0.001$) [83].

Tan et al. showed that Gal-3 was linked to a doubling of serum creatinine (HR 1.19 CI95%[1.14,1.24, $p< 0.001$) in a long-term follow-up study of 1320 patients with type 2 diabetes and an estimated glomerular filtration rate (eGFR) of 30 mL.min−1 1.73 m−2, even after accounting for chronic renal risk factors, baseline eGFR, and albuminuria status [84].

Patients with acute kidney injury (AKI) had higher median serum and urine Gal-3 levels at admission compared to non-AKI patients in another translational study that included patients admitted to the intensive care unit with severe sepsis. The comparison was statistically significant ($p < 0.001$ for AKI serum and 13.27 ng/mL for non-AKI urine; AUC for serum Gal-3 was 0.88 and for urine Gal-3 was 0.87). Urinary Gal-3 was linked to an increased risk of mortality after adjusting for a renal damage biomarker (urinary NGAL) in a sample of 132 heart failure patients studied by Tariq Ahmed et al. [84].

After adjusting for severity biomarkers and non-renal recovery confounding factors (such as gender, age, CKD, vasopressor treatment, SAPSII, Charlson score, Screat at admission, and lactate value at admission), we found that plasma Gal-3 level at ICU admission was associated with AKI with an OR of 1.12 CI95%[1.04, 1.2]. This association persisted even after adjusting for heterogeneous diagnoses. For patients without AKI, the plasma Gal-3 level increased at a rate of 16.6 (12.7-34.2) ng/mL, and for KDIGO 1 and KDIGO 3, it ranged from 23.6 (18.2-34.2) ng/mL to 38 (24.5-57.1) ng/mL, respectively, according to the research [85].

Plasma and urine Gal-3 may be useful biomarkers of AKI severity in a diverse population, independent of the cause of renal failure, according to these investigations.

4.2. Proteinuria

In renal biopsies of 37 individuals with glomerulonephritis (GN), Kikuchi et al. found an association ($r = 0.616$, $p < 0.001$) between proteinuria and glomerular infiltrating Gal-3 positive monocytes. The number 86. Additionally, in 81.8% (72/88) of patients with lupus GN, Kang et al. discovered a strong expression of Gal-3 in the glomeruli in conjunction with renal inflammatory cells. Histologic activity indices, anti-dsDNA titers, and complement 3 and 4 levels were found to be linked with this overexpression of Gal-3 [87]. A study conducted by Ostalska-Nowicka et al. in children investigated different GNs, including minimal change disease (MCD), mesangial proliferation (DMP), and focal segmental glomerulosclerosis (FSGS). The researchers found that there were a significant number of Gal-3 positive cells in both the cortex and the medullary areas of the kidneys that did not react to steroid treatment ($p < 0.001$). The number 88.

The blood Gal-3 levels of 75 patients with Mediterranean fever (FMF) and GN were greater than those of the control group. Moreover, there was a significant connection of 0.785 ($p < 0.001$) between proteinuria and creatinine in these patients. An area under the curve (AUC) of 0.88 was achieved by serum Gal-3 in predicting proteinuria [89].

With a prediction performance of 0.776 (CI95%[0.677, 0.875]; $p \leq 0.0001$), the Gal-3 plasma level was noticeably higher in individuals with poor kidney function (Stage IV-V CKD) and in macroalbuminuria ($p \leq 0.05$). [90].

According to these research, patients with glomerular injury are more likely to have immune cells infiltration expressing Gal-3, which is linked to increased production of Gal-3 in the kidneys and plasma.

Kidney Disease and Its Prognosis 4.3

In two longitudinal cohorts, the Clinical Phenotyping and Resource Biobank (C-PROBE) study and the Seattle Kidney Study (SKS), Alam et al. found high plasma levels of Gal-3 in patients with severe comorbidities (heart failure, CKD). These levels were associated with chronic renal

disease (HR = 1.35, CI95%[1.01-1.80]) [91]. Gal-3 plasma levels were assessed in 9148 participants who did not have chronic renal disease or chronic heart failure in a prospectively analyzed research from Atherosclerosis Risk in Communities (ARIC). Low estimated glomerular filtration rate and urine albumin-to-creatinine ratio were found to be associated with higher levels of Gal-3. Additionally, CKD was associated with Gal-3 at an odds ratio of 2.22 (95% CI 1.89 to 2.60). The number 92.

Elevated serum creatinine and urine protein/creatinine ratio were independently linked to Gal-3 plasma levels, which in turn were associated with the course of chronic kidney disease (CKD) in another cohort of patients [93].

In a sample of 2076 patients hospitalized to the intensive care unit, our research investigated renal prognostics using MAK criteria. An odds ratio (OR) of 1.37 (CI95%[1.27,1.49]) was related with MAKE when we looked at the Gal-3 dosage at admission. With a 95% CI of 0.74 to 0.78, Gal-3 had good predictive performance for MAKE [85].

In a study involving 249 individuals who had kidney biopsies, Ou et al. found that plasma Gal-3 levels were higher in patients with CKD than in those without the disease. Interstitial fibrosis, tubular atrophy, and vascular intimal fibrosis were all linked to elevated Gal-3 levels, and RNA-sequencing research revealed that Gal-3 was upregulated in fibrotic kidney biopsy samples [94].

Results from these investigations show that Gal-3 is associated with a worse renal prognosis and the progression from acute to chronic renal impairment.

4.4. Transplantation

Because it can enable modifications in therapeutic strategy, a reliable biomarker is critically important in kidney transplantation. The median Gal-3 level at baseline was 21.1 (IQR [Q1:17.0, Q2:27.2] ng/mL) in the 561 patients studied by Sotomayor et al. Specifically for patients with hypertension (HR, 2.29; CI95%[1.80, 2.92]; $p < 0.001$) or a smoking history (HR, 2.56, CI95%[1.95, 3.37]; $p < 0.001$), Gal-3 was linked to an elevated risk of graft failure (hazard ratios (HR) per 1 SD change, 2.12; CI95%[1.63, 2.75]; $p < 0.001$). [95]

4.5. Coronavascular Disease and Death

Lastly, mortality rates are typically greater in people with renal disorders. High levels of Gal-3 in plasma were linked to an increased risk of death from any cause, including cardiovascular disease, in the 4D and LURIC populations with renal impairment compared to those without renal disease [82]. Mortality was independently predicted by a level of Gal-3 > 23.73 ng/mL in patients on hemodialysis, as validated by Hogas et al. (HR: 2.60; CI95%[1.09, 6.18]) [96].

Following this, Zhang et al. confirmed the association between Gal-3 and an increased risk of all-cause mortality and cardiovascular (CV) events in CKD patients in a large meta-analysis involving 5226 patients (HR:1.379, [1.090, 1.744]). They also found that Gal-3 was associated

with an increased risk of CV events in CKD patients (HR = 1.054, CI95%[1.007, 1.102]).The number 97.

As a result, Gal-3 is a reliable indicator of a poor cardiovascular prognosis, especially in AKI patients [98]. These findings emphasize the significance of Gal-3 in cardio-renal syndrome, which is linked to a bad prognosis for both the kidneys and the heart. The role of Gal-3 in type 3 cardio-renal syndrome has begun to emerge in preclinical investigations [61]. In this setting, the process is still intricate, but it does include the immune system and the expression of Gal-3 in tissues.

Lastly, in a recent study including the intensive care unit (ICU) population, we found that Gal-3 levels at admission were greater in patients who did not survive. These levels were also linked to all-cause death at 30 days (OR CI 1.25, CI95%[1.17, 1.34]), and they had a predictive performance of 0.69 (CI95%(0.67-0.72) [85].

Therefore, it seems that Gal-3 is linked to cardiovascular outcomes and mortality following renal illnesses and injuries.

Figure 4 displays all clinical study outcomes associated with galectin-3.

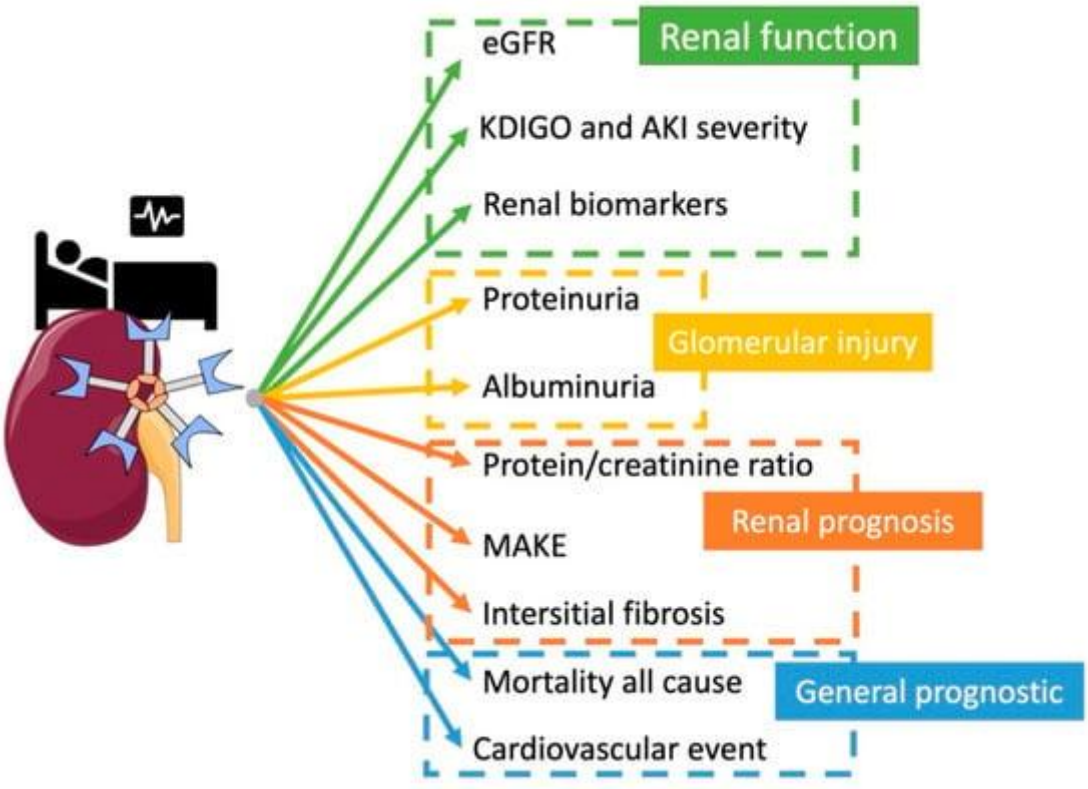

Figure 4. Kidney galectin-3 association with outcome in clinical studies.

5. Gal-3 as a Therapeutic Target and Perspective

The effects and potential therapeutic implications of Gal-3 inhibitors have only been the subject of a small number of clinical trials. The Gal-3 inhibitor GCS100 (NCT01843790) is now part of a phase IIa blinded, multi-center, randomized clinical trial that includes 121 patients enrolled with stage 3b or 4 CKD. The purpose of this research was to compare the pre- and post-8-week eGFR changes between the GCS-100 group and the placebo group [99]. A pharmacological Gal-3 inhibitor considerably improved the glomerular filtration rate, uric acid, and blood urea nitrogen (BUN) levels of 121 patients with chronic kidney disease from baseline to end of treatment, relative to placebo, according to a press-release from the authors. At 1.5 mg/m2, the authors noted no serious side effects [100].

In a randomized controlled trial, Lau et al. examined the efficacy of MCP in treating hypertensive cardiac complications. They discovered that blocking Gal-3 had no effect on the expression of fibrosis cardiac biomarkers, but was slightly linked to lower plasmatic creatinine levels and higher estimated glomerular filtration rate (eGFR) in patients treated with MCP. Although there is a lack of data to draw firm conclusions, this does raise the possibility that Gal-3 inhibitors could be useful for patients suffering from renal damage [101].

The potential of Gal-3 to alleviate pulmonary fibrosis has also been investigated. Using an inhaled Gal-3 inhibitor, Hirani et al. treated 36 healthy individuals and 24 pulmonary fibrosis patients; the former group showed high tolerance, while the latter group saw a reduction in plasmatic markers linked to pulmonary fibrosis [102]. Although some trials have employed Gal-3 inhibitors in cancer treatment, these studies have not collected enough data to provide any therapeutic recommendations based on drug resistance and survival endpoints [103]. However, there is a lack of clinical evidence that could help determine the effect of inhibition in clinical treatment, especially with regard to enhancing renal outcome. Although there is encouraging preclinical evidence, the exact pathophysiology of renal protection is not yet known. From a clinical perspective, further research is required to recommend this treatment.

There are a number of angles from which to view further research into Gal-3 or similar pathways. To begin, the ability to track and direct targeted treatment plans for individuals with renal disease has been greatly improved by the introduction of Gal-3 as a biomarker. Additionally, Gal-3 can assist in the stratification of individuals suffering from renal impairment, even though its precise therapeutic application is still unproven. To validate Gal-3 inhibition as a possible therapeutic target to reduce renal damage, additional preclinical investigations are required.

6. Conclusions

From animal models to human clinical trials, Gal-3 has been investigated in the context of kidney disease. Inhibiting renal Gal-3 has been suggested as a possible therapeutic target based on the partial pathophysiology of its involvement in particular renal damage that has been partially discovered by basic science. Research in the clinic has shown that Gal-3 can be used as a

biomarker for kidney illness to help with treatment planning and monitoring. Further mechanistic investigations are required to validate the possible advantages of Gal-3 inhibition.

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