Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL 16, ISSUE 01, 2024

Original research article

Study of Serum Galectin-3, Novel Biomarker in Chronic Kidney Disease

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Abstract

Aim: The present study was conducted to estimate the Levels of Serum Galectin-3 in patients with CKD and to compare them with Healthy Normal Subjects.

Methodology: The study group consists of 40 Patients of known Chronic Kidney disease and 40 healthy patients as controls.

Results: In the Present study, 68.7% are male and 31.2% are female. Among cases 85% are male and 15% are female, among controls 52.5% are male and 47.5% are female. Among cases the mean serum creatinine is 10.78 ± 1.95 and among controls it is 1.16 ± 0.55. Among cases the mean urea is 249.17 ± 102.62 and among controls it is 27.92 ± 11.35. Among cases the mean glucose is 111.55 ± 40.27 and among controls it is 123.45 ± 37.29. Among cases the mean Galectin-3 level Is 524.92 ± 342.47and among controls it is 30.12 ± 35.24.The mean among 11-20 years age group is 397 ±0, among 21-30 years it is 505 ±0, among 31-40 years it is 594.30 ±0, among 41-50 years it is 470.41±339.92, among 51-60 years it is 418 ±196.68 among 71-80 years it is 474±0. No significant correlation observed between Serum creatinine levels and Galectin-3 level among CKD. No significant correlation observed between urea levels and Galectin-3 level among CKD. A significant Negative correlation observed between Blood sugar levels and Galectin-3 level among CKD.

Conclusion: The study concluded that a significant positive correlation observed between serum creatinine and Galectin-3 levels. This observation is statistically significant. A significant positive correlation observed between urea and Galectin-3 levels. This observation is statistically significant. A significant negative correlation observed between blood sugar and Galectin-3 levels. This observation is statistically significant.

Keywords: Galectin-3, serum creatinine, blood sugar, CKD, diabetes

Introduction

Inflammation occurs following tissue injury in order to promote healing and scar formation. However sustained inflammation can lead to formation of extensive scar tissue, causing complete organ failure. This is evident by the various studies which have demonstrated that macrophage activation and galectin-3 secretion are major mechanisms leading on to the accumulation of cardio-myo-fibroblast and their subsequent activation, finally causing cardiac fibrosis.Galectin-3 influences the extra-cellular matrix components of fibrosis and plays an essential role in the inflammatory response, which is an important cause in the process of cardiac remodeling. Drugs designed to antagonize galectin-3, may in future effectively reverse adverse cardiac remodelling.

The present study was conducted to estimate the Levels of Serum Galectin-3 in patients with CKD and To compare them with Healthy Normal Subjects.

Aim and Objectives of the Study

Aim

To estimate the Levels of Serum Galectin-3 in patients with CKD and to compare them with Healthy Normal Subjects.

Objectives of the study

1. To Estimate the Serum Level of Galectin-3 in patients with chronic kidney disease.
2. To evaluate the correlation between serum Galectin-3 Level and other risk factors such as Fasting Blood sugar, Blood urea and Serum Creatinine.

Materials and Methods

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The study group consists of 40 Patients of known Chronic Kidney disease and 40 healthy patients as controls

Inclusion Criteria
1. Patients with Chronic Kidney Disease.
2. Patient's older than 18 years.
3. Diabetic Patients.

Exclusion Criteria
1. Primary Tubular Diseases.
2. Recent or Concurrent Administration of Potentially Nephrotoxic Drugs.
3. Acute Kidney Injury.

Sample Collection
Informed consent was obtained from all patients prior to the study under aseptic precautions. 5ml of venous blood sample is collected after overnight fasting of 12 hours from all patients. After retraction of the clot, samples were centrifuged at 2000 RPM for 15 Minutes for separation of serum. An aliquot of the serum was taken from the estimation of serum was taken for the estimation of serum galectic and stored at -20 °C in the deep freezer. The remaining serum is used for estimation of Glucose, Urea and Creatinine.

Serumgalectin-3 Kit:
This ELISA kit uses the Sandwich-ELISA principle. The micro ELISA plate provided in this Kit has been precoated with an antibody specific to Human GAL3.
Standards are added to the micro ELISA plate wells and combined with the specific antibody. Then a biotinylated detection antibody specific for Human GAL3 and HRP conjugate are added successively to each micro plate well and incubated. Free components are washed away. The substrate solution is added to each well. Only those wells that contain Human GAL3, biotinylated detection antibody and Avidin-HRP conjugate will appear blue in colour. The enzyme-substrate reactions halted by adding of stop solution and it terns yellow in colour. Optical Density is measured at wavelength of 450nm.The OD value is directly proportional to Human GAL3.
The concentration of Human GAL3 in the samples by comparing the OD of the samples to the standard curve.

Kit Components & Storage
The Kit can be stored at 2-8 °C for 1 month. If the kit is not used within 1 month, store the components separately according to the conditions once the kit is received.
The concentration of Human GAL3 in the samples by comparing the OD of the samples to the standard curve.

Kit Components & Storage
The Kit can be stored at 2-8 °C for 1 month. If the kit is not used within 1 month, store the components separately according to the conditions once the kit is received.

Properties
Assay type Sandwich-ELISA
Format 96T/48T
Assaytime 3.5h
Detectionrange 0.16-10ng/ml
Sensitivity 0.10ng/ml

Results

Table 1: Age distribution

	Cases		Controls		Total	
	N	**%**	**N**	**%**	**N**	**%**
11-20	1	2.5%	0	0.0%	1	1.3%
21-30	1	2.5%	14	35.0%	15	18.8%
31-40	20	50.0%	17	42.5%	37	46.2%
41-50	12	30.0%	4	10.0%	16	20%
51-60	5	12.5%	4	10.0%	9	11.3%
61-70	0	0.0%	1	2.5%	1	1.3%
71-80	1	2.5%	0	0.0%	1	1.3%
Total	40	100.0%	40	100.0%	80	100%

Group, 20% belong to 41 to 50 years age group, 11.3% belong to 60 years age.

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Group, 1.3% belong to 61 to 70 years age group, 1.3% belong to 71 to 80 years age group.
Among cases 2.5% belong to 11 to 20 years age group 2.5% belong to 21 to 30.
Years age group 50% belong to 31 to 40 years age group 30% belong to 41 to 50.
Year's age group 12.5% belong to 51 to 60 years age group 2.5% belongs to 71 to 80 years age group.
Among controls 35% belong to 21 to 30 years age group, 42.5% belong to 31 to 40.
Years age group, 10% belong to 41 to 50 years age group, 10% belong to 51 to 60 years age group, 2.5% belong to 61 to70 years age group.

Table 2: Gender distribution

	Cases		Controls		Total	
	N	%	N	%	N	%
Male	34	85.0%	21	52.5%	55	68.7%
Female	6	15.0%	19	47.5%	25	31.2%
Total	40	100.0%	40	100.0%	80	100%

Table 2 shows distribution based on gender, 68.7% are male and 31.2% are female. Among cases 85% are male and 15% are female, among controls 52.5% are male and 47.5% are female.

Table 3: Serum creatinine

	Minimum	Maximum	Mean ± SD
Cases	4.7	13.8	10.78±1.95
Control	0.40	3.70	1.16±0.55

Table 4: Glucose

	Minimum	Maximum	Mean ± SD
Cases	58	212	111.55±40.27
Control	84	276	123.45±37.29

Table 4 shows distribution based on Glucose, among cases the mean glucose is 111.55±40.27 and among controls it is 123.45± 37.29.

Table 5: Galectin-3 level

	Minimum	Maximum	Mean ± SD
Cases	80	1595	524.92±342.47
Control	1.80	182	30.12±35.24

Table 5 shows distribution based on Galectin-3 level, among cases the mean Galectin-3 level is 524.92 ± 342.47 and among controls it is 30.12± 35.24

Table 6: Age distribution and Galectin-3 level

	Galectin-3 level (Mean ± SD)
11-20	397±0
21-30	505±0
31-40	594.30±0
41-50	470.41±339.92
51-60	418 ±196.68
61-70	-
71-80	474±0

Table 6 shows Age wise distribution of Galectin-3 level, the mean among 11-20 years age group is 397±0, among 21-30 years it is 505±0, among 31-40 years it is 594.30±0, among 41-50 years it is 470.41±339.92, among 51-60 years it is 418 ±196.68 among 71-80 years it is 474±0.

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Table 7: Gender distribution and Galectin-3 level

	Galectin-3 level (Mean ± SD)
Male	524.79±365.75
Female	525.66±178.76
T value=0.005, p=0.99, Not statistically significant	

Table 7 shows gender wise distribution based of Galectin-3 level, among male it is 524.79±365.75 and among female it is 525.66±178.76. This observation was not statistically significant.

Discussion

Age distribution

1.3% belong to 11 to 20 years age group, 18.8% belong to 21 to 30 years age group, 46.2% belong to 31 to 40 years age group, 20% belong to 41 to 50 years age group, 11.3% belong to 60 years age group, 1.3% belong to 61 to 70 years age group, 1.3% belong to 71 to 80 years age group. Among cases 2.5% belong to 11 to 20 years age group 2.5% belong to 21 to 30. Years age group 50% belong to 31 to 40 years age group 30% belong to 41 to 50. Years age group 12.5% belong to 51 to 60 years age group 2.5% belongs to 71 to 80 years age group. Among controls 35% belong to 21 to 30 years age group, 42.5% belong to 31 to 40. Years age group, 10% belong to 41 to 50 years age group, 10% belong to 51 to 60 years age group, 2.5% belong to 61 to 70 years age group.

Gender distribution

68.7% are male and 31.2% are female. Among cases 85% are male and 15% are female, among controls 52.5% are male and 47.5% are female.

Laboratory profile

Among cases the mean serum creatinine is 10.78 ± 1.95 and among controls it is 1.16±0.55. Among cases the mean urea is 249.17 ± 102.62 and among controls it is 27.92 ± 11.35. Among cases the mean glucose is 111.55 ± 40.27 and among controls it is 123.45± 37.29.

Galectin-3 level

Among cases the mean Galectin-3 level is 524.92 ± 342.47and among controls it is 30.12 ± 35.24.

The mean among 11-20 years age group is 397 ±0, among 21-30 years it is 505 ±0, among 31-40 years it is 594.30 ±0, among 41-50 years it is 470.41 ±339.92, among 51-60 years it is 418 ±196.68 among 71-80 years it is 474 ±0. No significant correlation observed between Serum creatinine levels and Galectin-3 level among CKD.

No significant correlation observed between urea levels and Galectin-3 level among CKD. A significant Negative correlation observed between Blood sugar levels and Galectin-3 level among CKD.

A significant positive correlation observed between serum creatinine and Galectin-3 levels. This observation is statistically significant a significant positive correlation observed between urea and Galectin-3 levels. This observation is statistically significant.

A significant negative e\correlation observed between blood sugar and Galectin-3 levels. This observation is statistically significant.

Galectin-3 in Kidney Development and Homeostasis

Gal-3, a specific kind of galectin, has undergone comprehensive testing across a variety of biological contexts to determine the precise nature of its involvement in maintaining a healthy inflammatory response [1-3]. Critical for embryogenesis, inflammation, and cancer metastasis, Gal-3 stimulates cell motility by altering cell-cell and cell-matrix adhesion [4].

Several epithelia throughout embryogenesis and in adult tissues have been shown to produce Gal-3; nevertheless, the expression patterns of gal-3 and its ligand are tissue-and time-dependent, indicating that their expression is tightly controlled [5].

Granulomas, tumour stroma, and intestinal epithelium all exhibit structural defects in Gal-3 knockout (KO) mice, indicating a crucial function for gal-3 in proper cell polarization/migration and cell/matrix interactions. Renal structure and function are intricately intertwined, thus it comes as no surprise that gal-3 is crucial to kidney health [6].

Multiple areas of the kidney have distinct functions, and these variances are reflected in conserved differences in gal-3 expression and gal-3 binding sites [7, 8].

Furthermore, in the adult kidneys of humans, rats, mice, and hamsters, gal-3 expression is restricted to the apical face of certain distal tubules. In contrast, gal-3 is either not expressed at all or is only minimally expressed at the glomerular/mesangial level [9, 10].

However, gal-3 is not limited to the glomeruli and may be detected in the interstitium under a variety of clinical circumstances in both humans and animal models. During experimental glomerulonephritis in rats, gal-3 nee-expression is seen both in the cytoplasm and on the basal face of distal tubules, including

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the macula (GN) Together, it implies that gal-3 is involved in tubular cell homeostasis in normal tissue, and that its expression may be triggered by a wide range of stimuli [11].

During normal kidney development and in kidney cystic disease, non polarized gal-3 expression was discovered in human tubular epithelia, indicating a crucial function for this gene in directing duct formation [7].

Gal-3 loss results in severe centrosomal abnormalities in the kidney in both vitro and *in vivo*, as this protein only transiently associates with centrosomes during epithelial polarization [12].

Exogenous gal- 3 decreased cyst development in suspension culture of cystic kidneys, indicating a function in epithelial stability, organisation, and maturation through ciliary signalling regulation, even if gal-3 is expressed in cyst epithelia. As a result, gal-3 upregulation in the ureteric bud and its derivative is essential for controlling the branching of the ureteric bud, so preventing the dilatation and distortion of the epithelia that line the ureter.

Renal problems were seen in gal-3 KO mice without any histological changes; these mice had 11% fewer glomeruli, an indicator of kidney hypertrophy. One year old gal-3 KO mice show no symptoms of chronic kidney disease, despite the fact that it is widely recognised that a hyperfiltration condition favours the evolution to renal failure in both human and animal kidneys via blood pressure rise and glomerular injury (CKD) [7].

In particular, it appears that resistance to the high-sodium diet stimulus is conferred by systemic gal-3 insufficiency. Indeed, gal-3 appears to be necessary for efficient para-cellular chloride reabsorption, since its lack results in an enhanced renal capacity to excrete chloride, chronically elevated plasma aldosterone levels, and a contraction of the extracellular fluid. 38 In addition to preventing hypercalciuric nephrolithiasis, Gal-3 may also help prevent kidney stones. Amplification of renal calcium reabsorption is achieved by gal-3-mediated Mucin-1 lattice formation, which inhibits endocytosis of the TRPVS renal calcium channel [13].

An ever-growing body of evidence indicates that gal-3 is critical for maintaining nephron shape and function both in health and illness. In example, it was observed that gal-3 secretion may have a role in the functional adaptation to metabolic acidosis [14].

lmmunofluorescence studies on adult mice reveal that gal-3 is expressed in the primary and intercalated cells of the collecting ducts, as well as in the thick ascending limbs of the loop of Henle. Unlike A-intercalated (acid-secreting) cells, which express gal-3 only in the cortex, B-intercalated (bicarbonate-secreting) cells express gal-3 in the inner stripe and inner medulla. The final differentiation of intercalated cells from B to A cell type is induced, however, by extracellular gal-3-hensin complex following gal-3 secretion.

Galectin-3 in renal fibrosis

There is a lot of evidence that suggests gal-3 contributes to systemic fibrosis in several organs [45]. From hepatic stellate cells to synovial fibroblasts, gal-3 increases collagen production in a wide variety of tissues. Since the cause of tissue fibrosis is unknown, gal-3 might be an excellent therapeutic target for treating the condition [15].

The importance of gal-3 in both autoimmune and non-autoimmune nephropathies has been shown by *in vitro* and animal model studies [16]. Chronic allograft damage and unilateral ureteral blockage both result in a dramatic upregulation of Gal-3, suggesting that it is ultimately essential for the development to renal fibrosis during chronic inflammatory responses.

Gal-3 expression does, in fact, remain focally in chronically changed tubules following experimental acute tubular necrosis, raising the possibility that these tubules are engaged in the residual interstitial fibrotic process. Several situations, such as hypertension and nephropathy, show that blocking gal-3 has a protective effect against renal fibrosis, indicating a unique treatment possibility for the prevention of CKD.

Renal fibrosis has long since been linked to transforming growth factor-beta (TGF-), however TGF-independent processes have been observed [17].

Enhanced proliferation and expression levels of-SMA and collagen following kidney injury are indicative of TGF-induced myofibroblast activation via increased gal-3 expression. Myofibroblast stimulation results in the secretion of gal-3, which has a direct pro-fibrotic impact by stimulating the proliferation and differentiation of fibroblasts, the expression of alpha-smooth muscle actin, and the production of collagen *in vitro*. Myofibroblasts, which are recruited by epithelial-mesenchymal transition and boost the inflammatory response at injury sites via cytokine production, are of particular interest.

These results collectively point to gal-3 as a critical modulator in kidney inflammation, maintaining the pro-fibrotic loop in an autocrine/paracrine way. However, it has been shown that the recruitment of myofibroblasts during tissue healing also decreases the degree of fibrosis.

Collectively, these findings support the idea that gal-3 promotes M alternative activation and may play a role in glomerulosclerosis, tubular atrophy, and interstitial fibrosis. The involvement of M in renal scarring is condition-specific because, due to their flexibility, M can play both a pro-fibrotic and reparative role at various periods, depending on the stage and degree of renal inflammation/injury. When

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the damage stimulus is long-lasting or intense, gal-3 may promote the shift from acute to chronic inflammation.

Gal-3 deficiency causes inflammation to spread more rapidly, become more severe, and become chronic. Experimental models of acute kidney damage, such as anti-Thy1.1 glomerulonephritis (GN), ischemia-reperfusion, and folic acid-induced renal injury, have shown that Gal-3 plays an important role in renal regeneration. In example, it has been demonstrated that gal-3 contributes to primary cilium biogenesis in regenerating renal epithelial cells by localising to the centromeres of cells lining the collecting ducts at sites of injury. Therefore, gal-3 KO animals failed In renal regeneration following subtotal nephrectomy, resulting in significant kidney hypertrophy and extensive tubular dilatations. In human proteinuric glomerulopathies, Gal-3 is produced only in glomeruli devoid of sclerotic characteristics, suggesting that it has anti-inflammatory properties. In this setting, it most likely aids in the survival of kidney cells [18].

As a result of renal/extra-renal immature cell growth, acute tubular necrosis caused by ischaemic-reperfusion damage can undergo a characteristic sequence of events that may lead to full structural and functional recovery. Already 12 hours after ischemia in a rat model, gal-3+, vimentin+, and CD44+ cells are detected in close proximity to the altered tubules and in the lumen of peritubular capillaries, progressively infiltrating the cortex and surrounding necrotic tubules. These cells lose expression of all three markers upon reepithelization, coinciding with the return of the brush boundary characteristic of mature cells, suggesting a potential involvement for gal-3 in the migration of immature renal cells. However, renal pedicle blockage causes less initial tubular necrosis and a more pronounced tubular regeneration in gal-3 KO mice. Therefore, during renal ischemia, gal-3 greatly promotes to inflammation and M infiltration by boosting monocyte chemoattractant protein-1, interleukin-6, interleukin-1 beta, and reactive oxygen species (ROS) generation. However, it is now generally accepted that M are crucial in orchestrating the sequential processes leading to proper wound healing and repair, and this is true across organ types. Gal-3 controls M-mediated actions. In fact, the fibrosis increase shown in mice following leukocyte pharmacological reduction may be suppressed by the adoptive transfer of M in the late stage of unilateral ureteral obstruction nephropathy. Increased expression of gal-3 was found in the kidneys of patients with unilateral ureteral obstruction, with the protein being expressed primarily in the tubules at first and then in the interstitial cells as the injury progressed, indicating that gal-3 may play a dynamic role in both acute and chronic renal responses.

Both glomeruli and renal tubules may be protected from long-term damage by the anti-apoptotic impact of endogenous gal-3. Although apoptosis is involved in GN resolution, it can also contribute to the loss of mesangial cells and, ultimately, glomerular sclerosis if it is allowed to continue unchecked.

The kidney-protective protein Gal-3 also blocks certain TGF- actions. For instance, fibroblasts' development into fibrogenic myofibroblasts is suppressed by gal-3 because it encourages the release of interleukin-1. Gal-3 can stimulate MMP expression whereas transforming growth factor beta (TGF-) suppresses it [19].

Galectin-3 in Glomerulonephritis

Gal-8 has recently been linked to lgA nephropathy because functional differences associated to lgA glycosylation diminish the binding of lgA to gal-8. Gal-3 loss during B cell development results in increased lgA expression and secretion in the serum and peritoneal fluid of mice, suggesting that gal-3 may play a role in the pathophysiology of lgA nephropathy.

Galectin-3 in Nephropathies Associated with Metabolic Disorders and Aging

There is mounting evidence that gal-3 plays a crucial role in the onset of metabolic diseases and their associated risk factors and consequences. Indeed, in the general population, elevated gal-3 serum levels are positively correlated with advanced age, excess body fat, diabetes, and high cholesterol [21]. The involvement of gal-3 in glucose metabolism, diabetes, and related problems has been the subject of varying reports. Resistance to beta cell apoptosis during pancreatic islet inflammation is a consequence of a lack of gal-3, which suggests that gal-3 may play a role in the pathophysiology of diabetes [21].

Gal-3 has been proposed as a novel biomarker for prediabetes and diabetes onset detection due to its role in the transition from prediabetes to diabetes. Serum gal-3 levels are inversely correlated with HbA1c and favourably correlated with insulin sensitivity in patients with type 2 diabetes. Furthermore, gal-3 is involved in adaptive responses and target organ damage due to diabetes, such as kidney.

Diabetic nephropathy is a serious condition, and there is mounting evidence that galectins play a crucial role in this condition. In individuals with type 2 diabetes, gal-9 serum levels were shown to be inversely linked with eGFR ($r = 0.188$, $p = 0.011$) [22].

The number of gal-3+ cells was significantly higher in glomeruli of humans with diabetic nephropathy compared to those with other nephropathies, and this increase was strongly correlated with the rate of decline in renal function ($r = 0.930$, P b 0.005) and with urinary protein excretion ($r = 0.688$, P b 0.05). 41 These results indicate that renal gal-3 expression may be a predictor of poor outcome in diabetic nephropathy. Diabetes has been shown in recent studies of glycol-code modulationunder varying conditions to alter galectin production and the pattern of protein glycosylation in the kidney.

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The renal inflammatory signature is altered qualitatively by diabetes in a gal-3- dependent manner. Albuminuria is significantly linked to leukocyte (blood cell) loss, especially B-cell loss, in diabetic nephropathy.

Conclusion

The study concluded that a significant positive correlation observed between serum creatinine and Galectin-3 levels. This observation is statistically significant. A significant positive correlation observed between urea and Galectin-3 levels. This observation is statistically significant. A significant negative correlation observed between blood sugar and Galectin-3 levels. This observation is statistically significant.

Conflict of Interest: None.

Funding Support: Nil.

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