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ORIGINAL RESEARCH ARTICLE

Proteinuria Level and Associated Changes in Glomerular Podocytes and Renal Tubular Epithelium

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Abstract

The correlation between glomerular podocytes and renal tubular cells involved in handling of leaked proteins and the level of proteinuria was evaluated. Retrospective 22 cases of clinical proteinuria in patients with various glomerulopathies were retrieved and analyzed. Glomerulopathies in the concerned patients were pathologically diagnosed through light and electron microscopic examination of the submitted renal biopsies. Three cases with protein levels in urine within the acceptable normal range were additionally analyzed as controls. Electron microscopic examination of the glomerular podocytes and immunofluorescence of the renal tubular epithelium in the relevant cases constituted the base for the present study. Among the studied cases, it was found that the greater the number of glomerular podocytes with reabsorbed intracytoplasmic proteins and the higher score of tubular protein immunofluorescence, the lower the level of proteinuria. Comparatively, cases with fewer number of podocytes with reabsorbed proteins and lower score of tubular protein immunofluorescence had higher levels of proteinuria.

The present study aims to pay the attention to the correlation between morphologically recognizable glomerular podocytes and renal tubular epithelium with reabsorbed proteins and the level of proteinuria in patients with various glomerulopathies. The current study may serve as a base for the future research work concerned with the structural changes of glomerular podocytes and renal tubular epithelium as a compensative mechanism in cases of proteinuria.

Keywords

Podocytes, Tubular epithelium, Reabsorbed proteins, Proteinuria

Introduction

Podocytes (glomerular visceral epithelial cells) are highly specialized cells constituting a crucial component of the three-layered glomerular filtration barrier of the kidney [1,2]. Failure of podocyte function is involved in the progression of chronic glomerular disease [3]. Renal tubular cells are actively engaged in reabsorption of proteins that may leak into urine due to disruption of the glomerular filtration barrier [1-7].

Proteinuria is the condition characterized by the presence of greater than normal amounts of proteins in the urine [4-6,8-11]. There are 3 main causes of proteinuria, namely; glomerular diseases, increased quantity of proteins in serum (overflow proteinuria), and low reabsorption of the renal proximal tubules [7,12,13]. In case of glomerular diseases, the glomerular filtration barrier is damaged permitting proteins such as albumin to leak from the blood into the urine. Proteinuria can be classified on the basis of protein amount (nephrotic or non-nephrotic), on the type of protein (albuminuria or low molecular weight proteinuria), or on the underlying pathological changes (glomerular vs. non-glomerular) [14-16]. Low protein reabsorption of the renal proximal tubules is one of the three main causes of proteinuria [7,12]. Renal tubular dysfunction is accordingly classified as a non-glomerular contributing factor in the development of proteinuria. The aim of the present retrospective study is to evaluate the correlation between the glomerular podocytes and renal tubular epithelium containing reabsorbed proteins, as recognizable by transmission electron

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microscopy and immunofluorescence, and the level of proteinuria in patients with various glomerulopathies.

Materials and Methods

Patients

The study was conducted in Anatomic Pathology Section, Department of Pathology and Laboratory Medicine, College of Medicine, King Saud University, over a period extending from January, 2013 to December, 2015. Twenty-two patients with clinical proteinuria were enrolled in the study with the involvement of additional three patients with protein levels in urine within the acceptable normal range as controls. At the time of sample collection, none of the concerned patients received any treatment that may influence the results of urine samples analysis.

Histopathology

Renal biopsies obtained from all patients were processed for light microscopic examination and all staining protocols, including the routine and immunofluorescence staining, were carried out.

Electron microscopy

Transmission electron microscopic examination of the renal biopsies was performed to examine the glomerular podocytes at the ultrastructural level. Briefly, renal tissues were primarily fixed in 2.5% buffered glutaraldehyde (phosohate buffer, pH 7.2) and post-fixed in 1% osmium tetroxide (OsO4). Tissues were then dehydrated in ascending series of ethyl alcohol and subsequently embedded in epoxy resin (Epon: Araldite mixture). Semi-thin tissue sections (0.5 µm thickness) were made and accordingly ultra-thin sections (70-85 nm thickness) were prepared and double stained with uranyl acetate and lead citrate. Ultra-thin tissue sections were examined and photographed under a transmission electron microscope (TEM) (JEM-1400 TEM, JEOL Co., Tokyo, Japan) operating at 100 kV.

Counting of glomerular podocytes

The appropriate methods, including Weibel and Gomez point counting method, described in previous studies [9,17,18] to measure the proportion of glomerular cell types were employed. Accordingly, the glomerular podocytes were counted and the average number of podocytes/glomerulus in each of the examined cases was calculated. The average number of podocytes containing reabsorbed intracytoplasmic proteins/glomerulus was also estimated.

Immunofluorescence

Reabsorbed proteins (albumin) in renal tubular cells were the target immunofluorescence (IF) staining. Serial frozen sections were prepared from the unfixed renal tissues and treated with a fluorescein-labelled antibody specific for albumin. The intensity of IF staining in renal tubular cells was expressed semi-quantitatively as: negative, no reabsorption proteins; mild, less than 25% of the tubules show reabsorption proteins; moderate, 26% to 50% of the tubules show reabsorption proteins; and severe, more than 50% of the tubules show reabsorption proteins. The corresponding reabsorbed albumin scores as observed by light microscopy in renal tubular cells were: 0, no significant hyaline cytoplasmic reabsorption droplet change; 1+, Minimal hyaline reabsorption droplet change; 2+, Mild hyaline reabsorption droplet change; 3+, Moderate hyaline reabsorption droplet change.

Statistical analysis

Data on counting of glomerular podocytes with reabsorbed proteins, immunofluorescence scoring of reabsorbed proteins and albumin scores in the renal tubular cells, and proteinuria levels were recorded and presented as mean and standard deviation. Statistical analysis of the data was done using Wilcoxon Mann-Whitney U test (p-value = 0.035).

Results

Immunofluorescence (IF), electron microscopic findings, and the pathological diagnosis for each of the studied 25 cases was summarized in (Table 1A and Table 1B). Because of the existing variations of disease etiology, the studied cases were divided into 2 groups; the first group (Table 1A) encompassed those cases with immunocomplex deposition-related glomerulonephritis, and the second one involved those with non-immunocomplex-related glomerulopathies.

In (Table 2), demonstrate the level of proteinuria, average number of podocytes/glomerulus, and average number of podocytes with reabsorbed intracytoplasmic proteins/glomerulus in 25 patients with various glomerulopathies. The average number of podocytes/glomerulus was variable among the studied disease entities and ranged from 20-26. The average number of podocytes with reabsorbed intracytoplasmic proteins/glomerulus ranged from 0-5. The highest average number of podocytes with distinct reabsorbed proteins/glomerulus (3-5 cells/glomerulus) were found in cases with low proteinuria levels (0.49-2.32 gm/day). Cases with the average number of only one podocyte with reabsorbed proteins/glomerulus revealed the highest level of proteinuria ranging from 4+ to 28.97 gm/day.

Contents of (Table 3) clearly indicated that cases in high number group (three-five podocytes with reabsorbed proteins/glomerulus) manifested the lowest level of proteinuria, while the highest level of proteinuria was encountered in cases of low number group (one podocyte/glomerulus).

Levels of proteinuria, tubular immunofluorescence and albumin scores of reabsorbed proteins in the renal tubular epithelium as well as tubular cell injury in each case were shown in (Table 4).

Table 1A: Immunoflourescence, electron microscopic findings, and pathological diagnosis in 25 patients with various glomerulopathies.

A. Immunocomplex deposition-related glomerulonephritis.

	Case #	Age	Sex M:male F:female	Immunoflourescence Immunoglobulin and complement Effacement of the epithelial cell foot processes	Electron Microscopic Findings Electron dense immune deposits and other findings	Pathological Diagnosis
1	33	F	Diffuse mesangial and focal capillary positivity IgG (2+) and IgM (1+). finely granular diffuse capillary and focal mesangial positivity for C3 (2+), C1q (2+), Kappa (1+) and lambda (2+)	Diffuse	Subepithelial, intramembranous, subendothelial and mesangial deposits	Lupus nephritis
3	50	M	Focal mesangial and capillary deposition of IgA (1+) & Lambda (1+) and focal mesangial deposition of C3 (1+) in the glomeruli.	Extensive patchy	Electron dense deposits in the mesangium and Focal double contouring	Consistent with IgA nephropathy
4	34	F	Diffuse linear capillary positivity for IgA (1+), IgG (3+), C3 (3+), C1q (3+), kappa (2+) and lambda (2+). There is focal capillary and mesangial positivity for IgM	Extensive patchy	Subendothelial electron dense deposits	Immune complex mediated disease with membrano-proliferative pattern of injury
5	17	F	IgA and IgM: moderate (3+), IgG, C1q and C3: severe (4+), Kappa and Lambda: severe (4+) diffuse mesangial and diffuse capillary positivity	Extensive patchy	Mesangial, paramesangial and subendothelial areas	Lupus nephritis
8	67	M	IgA: Mild (2+) extensive mesangial positivity	Diffuse	Mesangium and paramesangium	IgA nephropathy
9	25	F	IgA, IgG and IgM: 2+diffuse mesangial positivity. C3 and C1q: 3+ diffuse granular capillary and mesangial	Extensive diffuse	Subendothelial, sub epithelial, mesangial and paramesangia	Lupus nephritis.
10	20	F	IgA and IgG: Negative. IgM: 1+ focal mesangial and capillary positivity. C3: 2+ diffuse capillary and focal mesangial positivity. Focal vascular positivity	Diffuse	Glomerular basement membrane, mesangial and paramesangial areas and ribbons of marked electron dense deposits	Crescentic glomerulonephritis secondary to Dense Deposit Disease (C3 Glomerulopathy).
12	48	M	IgA and IgM: Negative. IgG: 2+ diffuse coarse granular capillary positivity. C3 and C1q: Negative. Kappa: 2+ diffuse capillary positivity Lambda: 2+ focal capillary positivity	Diffuse	Intramembranous	Membranous glomerulonephritis
13	48	M	IgA, IgM, C3: Moderate extensive mesangial positivity IgG: Negative. Kappa: Mild (2+) focal mesangial positivity. Lambda: Moderate (3+) extensive mesangial positivity	Extensive diffuse	Mesangial and paramesangial areas	IgA nephropathy.

14	25	F	IgM: Moderate (3+) extensive mesangial positivity C3: Severe (4+) extensive mesangial positivity. IgA and IgG negative	Focal	Mesangial and paramesangial areas and sub-endothelial deposits with double contour formation	C3 glomerulonephritis with a mesangioproliferative pattern.
16	16	M	IgM: 2+ diffuse mesangial IgA, IgG, C3 and C1q: Negative. Kappa and Lambda: Negative	Diffuse	Mesangium and paramesangium with Microvillous degeneration	IgM nephropathy
17	6	M	IgA, IgG, C3 and C1q: Negative. IgM: 2+ extensive mesangial	Focal	Mesangial and paramesangial areas	IgM nephropathy
18	36	F	IgA: 1+ diffuse capillary IgG: 3+ diffuse granular capillary IgM: 1+ focal capillary C3: 1+ diffuse capillary and Focal arteriolar positivity C1q: 1+ diffuse capillary Kappa and Lambda: 2+ diffuse capillary	Diffuse	Subepithelial and intramembranous electron	Membranous nephropathy
19	16	M	IgA, IgG, IgM, C3 and C1q: moderate(3+) diffuse mesangial and focal capillary Kappa and Lambda: moderate (3+) diffuse mesangial	Diffuse	Subendothelial, mesangial and paramesangial areas	Lupus nephritis
20	50	F	IgA and IGM: Trivial (1+) focal mesangial IgG, C3 and C1q: Mild (2+) focal mesangial	Little focal	Large subendothelial deposit and a few mesangium and paramesangium	Lupus nephritis.
21	2	F	IgA and IgG: Trivial (+/-) focal mesangial positivity IgM: Moderate (3+) diffuse mesangial positivity in all glomeruli. C3 and C1q: Negative. Kappa and Lambda: Trivial (1+) focal mesangial positivity.	Diffuse	Mesangial and paramesangial areas	IgM Nephropathy
22	49	F	IgA : 2+ IgG, IgM, C3 and C1q: Negative	Extensive diffuse	Mesangial and paramesangial areas.	IgA nephropathy
23	46	M	IgA : 3+ IgG, IgM, C3 and C1q: Negative Kappa: 1+ Lambda: 2+	Focal	Mesangial and paramesangial areas.	IgA nephropathy
24	30	F	IgA and IgM: 1+ finely granular focal capillary positivity. IgG: 3+ finely granular diffuse capillary positivity. C3: Negative. C1q: 1+ diffuse capillary Kappa: 2+ diffuse capillary Lambda: 1+ diffuse capillary	Diffuse	Intramembranous and subepithelial	Lupus nephritis
25	23	F	IgA, IgG, IgM and C3: 2+ focal capillary and mesangial Kappa and Lambda: 2+ focal capillary and mesangial	Focal	Subendothelial, mesangial and paramesangial areas	Lupus nephritis

Table 1B: Immunoflourescence, electron microscopic findings, and pathological diagnosis in 25 patients with various glomerulopathies.

B. Non-immunocomplex-related glomerulopathies.

	Case #	Age	Sex M:male F:female	Immunoflourescence Immunoglobulin and complement	Electron Microscopic Findings	Pathological Diagnosis
				Effacement of the epithelial cell foot processes	Electron dense immune deposits and other findings	
2	39	M	Focal mesangial deposition of IgA (H) and C3 (1+) in the glomeruli	Focal	Subendothelial space widening by electron lucent material	Focal and segmental glomerulosclerosis secondary to functional and structural adaptations
6	41	F	IgA, IgG, IgM: Negative. C3: Trivial (1+) focal mesangial positivity. C3: Trivial (1+) focal mesangial positivity.	Global sclerosis of only one glomerulus present	Global sclerosis of only one glomerulus present	Focal and segmental glomerulosclerosis
7	24	M	IgM: Mild (2+) diffuse mesangial positivity	Diffuse	microvillus formation	Advance focal and segmental glomerulosclerosis,
11	53	M	IgA, IgG and IgM: C3 : 1+ focal mesangial positivity. C1 : Negative.	Focal	-	Focal and segmental glomerulosclerosis
15	56	M	IgA, IgG, IgM and C3: Negative. Kappa: Negative in the glomeruli. Casts are positive. Lambda: Negative in the glomeruli. Casts are negative. Fibrinogen: Non-specific interstitial staining.	Focal	-	Myeloma cast nephropathy with associated acute tubular injury

Table 2: Level of proteinuria, average number of podocytes/glomerulus, and average number of podocytes with reabsorbed intracytoplasmic proteins/glomerulus in 25 patients with various glomerulopathies.

Case	Age	Sex Male,M; Female,F	Proteinuria (gm/day) (Normal range = 0.01-0.15 gm/day)	Average number of Podocytes/glomerulus	Average number of podocytes with reabsorbed proteins/glomerulus
1 *	33	F	2.32	26	3
2**	39	M	1.02	21	3
3*	50	M	2.27	23	3
4* control	34	F	0.16	22	0
5*	17	F	0.89	25	3
6**	41	F	1.11	23	3
7**	24	M	3+	24	2
8*	67	M	13.83	26	1
9*	25	F	3.46	23	2
10*	20	F	28.97	20	1
11** control	53	M	0.14	22	0

12*	48	M	1.71	21	3
13*	48	M	1.54	25	5
14*	25	F	2+	21	4
15**	56	M	4.24	20	2
16*	16	M	6.14	23	1
17* control	6	M	0.01 trace	21	0
18*	36	F	0.60	24	3
19*	16	M	3.69	26	2
20*	50	F	0.49	25	3
21*	2	F	4+	21	1
22*	49	F	1.35	23	3
23*	46	M	2.60	22	2
24*	30	F	0.58	23	3
25*	23	F	1.78	20	3

*Immunocomplex deposition-related glomerulonephritis; **Non-immunocomplex-related glomerulopathies.

Table 3: Groups of cases with various numbers of glomerular podocytes with reabsorbed intracytoplasmic proteins/glomerulus; Three to five podocytes (high), Two podocytes (moderate), One podocyte (low), and the average level of proteinuria in each group.

Group	Cases	Average level of proteinuria (gm / day)
3-5 podocytes (high)	1, 2, 3, 5, 6, 12, 13, 14, 18, 20, 22, 24, 25	1.36
2 podocytes (moderate)	7, 9, 15, 19, 23	3.40
1 podocyte (low)	8, 10, 16, 21	13.24

Table 4: Albumin and immunofluorescence scores of tubular reabsorbed proteins, tubular cell injury and level of proteinuria in patients with various glomerulopathies.

Case #	Reabsorbed Albumin Scores*	Immunoflourescence scores**	Tubular Cell Injury***	Level of Proteinuria (gm/day) (Normal = 0.01-0.15 gm/day)
1	1+	Mild	+	2.32
2	3+	Moderate	++	1.02
3	3+	Moderate	++	2.27
4	0	Negative	0	0.16
5	3+	Severe	++	0.89
6	3+	Moderate	+	1.11
7	0	Negative	0	3+
8	0	Negative	0	13.83
9	0	Negative	0	3.46
10	0	Negative	+	28.97
11	0	Negative	+	0.14
12	3+	Moderate	++	1.71
13	3+	Moderate	++	1.54
14	3+	Moderate	++	2+
15	0	Negative	0	4.24
16	0	Negative	+	6.14
17	0	Negative	0	0.01 trace
18	3+	Moderate	++	0.60
19	0	Negative	0	3.69
20	3+	Moderate	++	0.49
21	0	Negative	0	4+
22	3+	Moderate	++	1.35

23	3+	Moderate	++	2.60
24	3+	Moderate	++	0.58
25	3+	Moderate	++	1.78

*Reabsorbed albumin scores as observed by light microscopy in renal tubular cells:

0: No significant hyaline reabsorption droplet change in tubular cells cytoplasm; 1+: Minimal hyaline reabsorption droplet change in tubular cells cytoplasm; 2+: Mild hyaline reabsorption droplet change in tubular cells cytoplasm; 3+: Moderate hyaline reabsorption droplet change in tubular cells cytoplasm

**Immunofluorescence scores:

Negative, no reabsorption proteins; Mild, less than 25% of the tubules show reabsorption proteins; Moderate, 26% to 50% of the tubules show reabsorption proteins; Severe, more than 50% of the tubules show reabsorption proteins.

***Tubular cell injury:

0: No significant tubular cell changes; +Mild tubular cell injury in the form of cytoplasmic vacuolar change; ++Moderate tubular cell injury in the form of cytoplasmic vacuolation, apical blebbings, partial loss of brush border.

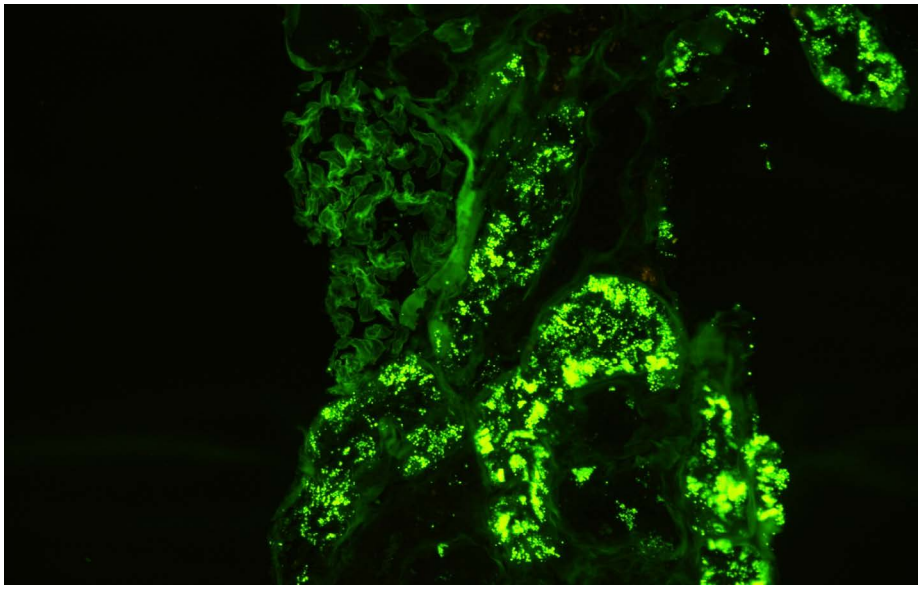

Figure 1: Immunofluorescence micrograph of a renal tissue showing severe IF staining, more than 50% of the tubules show positivity for reabsorbed albumin in their lining epithelium.

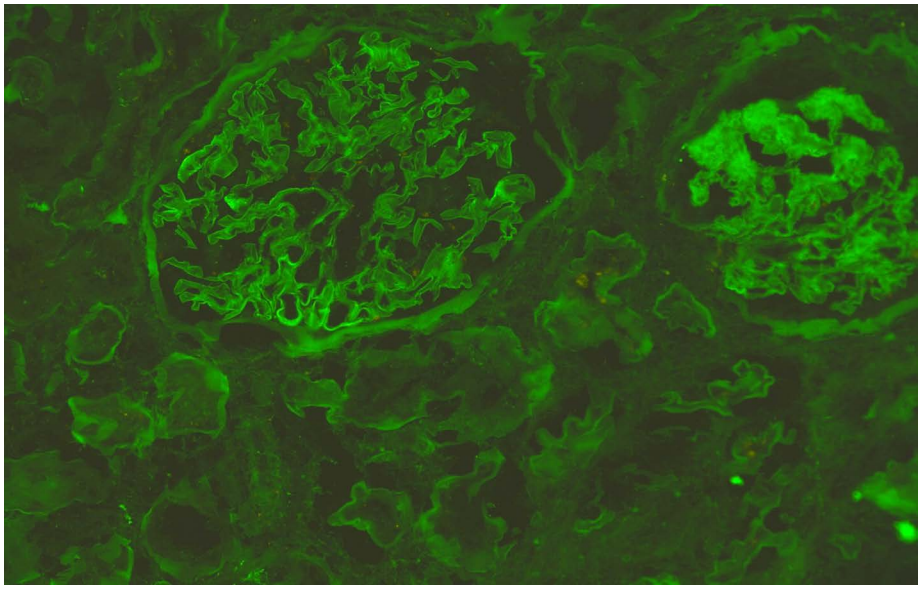

Figure 2: Immunofluorescence micrograph of a renal tissue show negative tubular IF staining for reabsorbed albumin.

Figure 1 and Figure 2 show the immunofluorescence (IF) staining in two different cases; a case with mild IF, less than 25% of the tubules showing reabsorption proteins (Figure 1), and another case with severe IF, more than 50% of the tubules show reabsorption proteins (Figure 2).

Transmission electron microscopy revealed the presence of glomerular podocytes with low and high-reabsorbed intracytoplasmic protein droplets in the examined cases (Figure 3 and Figure 4 respectively). The reabsorbed proteins were recognized as highly electron dense amorphous structures. Prevalence of the reabsorbed proteins in podocytes varied among

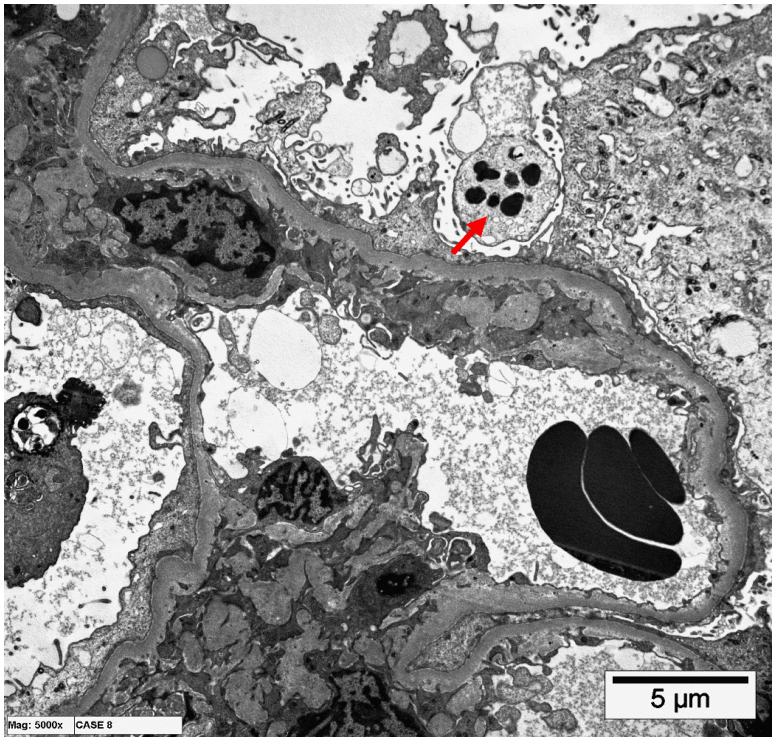

Figure 3: Transmission electron micrographs showing glomerular podocytes with low reabsorbed intracytoplasmic proteins (arrows). (uranyl acetate, lead citrate, x6000).

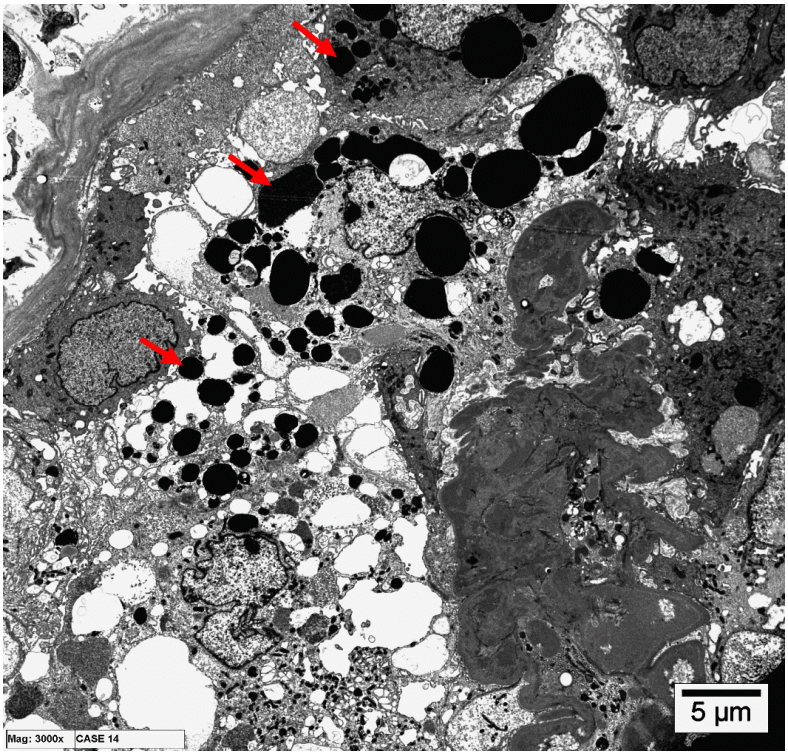

Figure 4: Transmission electron micrographs showing glomerular podocytes with high reabsorbed intracytoplasmic proteins (arrows). (uranyl acetate, lead citrate, x6000).

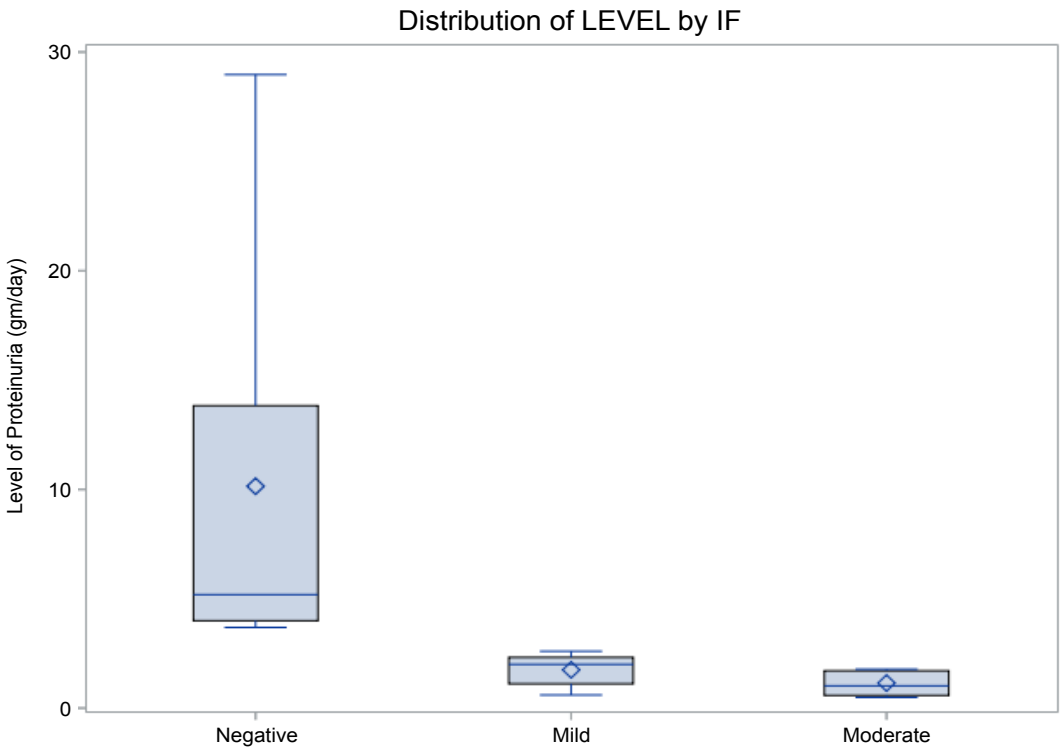

Figure 5: Statistical boxplot showing negative correlation between IF score and various levels of proteinuria.

Table 5: Statistical analysis of data relevant to the count of podocytes with reabsorbed intracytoplasmic proteins in the different groups of cases in relation to the level of proteinuria in each group.

Group	N	Mean of proteinuria level	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Low-Moderate*	9	5.8533**	8.16011	2.35562	0.6686	11.0380	0.01	28.97
High*	13	1.3585**	0.63460	0.17601	0.9750	1.7419	0.49	2.32
Total	22	3.5160	5.99780	1.19956	1.0402	5.9918	0.01	28.97

*Low-moderate and high groups of cases with one-two, three-five podocytes with reabsorbed proteins, respectively; **Significant difference at p-value < 0.05.

the different cases and also varied from area to another within the same glomerulus. Podocytes containing cytoplasmic reabsorbed protein droplets were enlarged and disclosed disrupted cytoplasmic organelles and deteriorated surface microvilli.

Table 5 summarizes the statistical analysis of the obtained glomerular data. Low and moderate groups indicated in Table 3 were merged in one group to be statistically analyzed against the high group. The analysis approved significant differences between the studied groups. No significant differences were detected among cases of different sex and age.

Statistical analysis of the renal tubular data is shown in a boxplot (Figure 5). A significant negative correlation between the Immunofluorescence tubular scores and level of proteinuria was detected by the statistical analysis.

Discussion

Presently, the correlation between the morphologically abnormal podocytes and renal tubular epithelium containing reabsorbed intracytoplasmic proteins and the level of proteinuria was evaluated.

Normal urinary protein excretion is < 150 mg/24 hour, and daily albumin excretion in a normal person is < 30 mg. 11 Loss of proteins in urine is the hallmark of tubular and glomerular diseases, and may arise from structural and/or functional alterations involving different cell types [19-21]. Various proteinuric diseases may share similar renal pathological changes and may have a common progression of renal injury [6,22-25]. Albuminuria is strongly associated with the progression of renal disease [26-28].

Proteinuria of the presently studied cases was most likely of glomerular origin, i.e., at the glomerular level, based upon the encountered glomerular structural changes. Beside the well-known protein endocytosis at the renal proximal tubular cells, there is an increasing evidence of glomerular protein handling by podocytes [22,29-31]. It has been concluded that identifying the

mechanisms involved in albumin handling in podocytes is essential to understand the pathogenesis of various glomerulopathies [19]. Such mechanisms in human podocytes are committed to internalizing albumin (albumin endocytosis) through a receptor-mediated mechanism [29].

The structural integrity of podocytes is crucial to guard against leakage of proteins in urine. In this regard, podocytopathies are the most common group of glomerular disorders leading to proteinuria [1,19]. The final clinical scoring of proteinuria is largely related to the podocytes integrity and activity in reabsorbing leaked proteins.

The present results clearly indicate that cases of glomerulopathies with the higher average number of podocytes containing reabsorbed cytoplasmic protein droplets had the lower levels of proteinuria. Subsequently, it can be concluded that the larger the number of morphologically recognizable podocytes containing reabsorbed proteins, the lower the level of the expected clinical proteinuria.

Hyper-filtration of proteins is known to be followed by increased reabsorption in the renal proximal tubules [12]. The basic defects leading to tubular proteinuria arise from proximal tubules, with the result of excretion of proteins that are normally reabsorbed efficiently by the proximal tubular cells through a receptor-mediated endocytosis [6].

The reabsorbed proteins can be cytotoxic to proximal tubular epithelium and extensive reabsorption of large quantity of abnormally filtered proteins may provoke tubular damage [17,24].

Similar to glomerular Podocytes, active reabsorption of filtered proteins by proximal tubular cells is done by endocytosis by the crucial aid of endocytic surface receptors, such as megalin and cubilin as a form of receptor-mediated process [1,5,12]. Changes in the expression and/or subcellular distribution of these two endocytic receptors are expected to be associated with proteinuria due to receptor dysfunction [32,33].

The present data, regardless the type of the underlying glomerulopathies, showed that the greatest average number of podocytes with distinct reabsorbed proteins and the highest immunofluorescence tubular score were detected in cases with lower proteinuria levels. In contrast, cases with the highest proteinuria level had the fewer number of podocytes containing reabsorbed proteins and the lowest IF tubular score. Subsequently, the level of proteinuria and the progression of a proteinuric disease can be predicted through estimation of these parameters.

These findings might indicate a parallel and synergic glomerular and tubular roles to handle, retain and preserve proteins and thus hindering protein leakage into urine and reabsorb proteins that may leak into the glomerular filtrate.

The present work was concentrated objectively on the correlation between the morphologically recognizable reabsorbed proteins in glomerular podocytes and renal tubular epithelium, and the level of clinical proteinuria in patients with glomerulopathies. The current study may hopefully constitute a base for the next investigations concerned with the structural changes of glomerular podocytes and renal tubular epithelium as a compensative mechanism in cases of proteinuria.

However, further investigations on a larger scale of patients with clinical proteinuria are needed to strongly establish the currently evaluated correlation.

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Declaration of Interest with Statement

I have no relevant interests to disclose. This research is not funded by any agency.

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