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Original article

Role of Urinary Hemopexin in the Pathogenesis and Diagnosis of Proteinuria in Children with Idiopathic Nephrotic Syndrome

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Abstract

Background: Nephrotic syndrome (NS) is one of the most prevalent chronic renal diseases in kids. It is distinguished by selective proteinuria, hypoalbuminemia, hyperlipidemia, and edema. Majority of cases of nephrotic syndrome are referred to as idiopathic nephrotic syndrome (INS) because they do not have an underlying etiology. The study aimed to measure urinary hemopexin level and its role in INS pathogenesis, activity and response to treatment. **Methods:** Urinary samples were obtained from group 1 (35 patients with INS), which was subdivided into a newly diagnosed group consisting of 13 children, and a group of old patients in relapse including twenty-two kids. A second division has been made with regard to the applied therapy, a group involving twenty-three patients treated with glucocorticoids (GCS) only and a group including twelve patients treated with glucocorticoids and corticosteroid-sparing agents. Group 2 included 25 healthy children. Levels of urinary hemopexin (uhpx) and urinary protein creatinine ratio, serum creatinine, albumin, CRP and total cholesterol and blood hemoglobin were estimated and investigated for associations between them. **Results:** There were significant rises in urinary hemopexin in INS both in the active and remission states compared to the controls. According to treatment applied during relapse, uHpx was significantly greater and then in remission it was significantly less in kids received only GCS than those received glucocorticoids with sparing agent. **Conclusion**: Urinary hemopexin level can be considered as a pathogenic factor in children with INS and may be useful as a predictor of disease activity.

Key words: proteinuria; hemopexin; idiopathic nephrotic syndrome.

Introduction

The most prevalent form of podocytopathy in kids is idiopathic nephrotic syndrome. Among children aged one to ten years, it is responsible for more than ninety percent of cases, whereas among children aged ten and older, it accounts for approximately fifty percent of cases. The prevalence has been evaluated to be approximately sixteen cases per hundred thousand in the pediatric population and two to seven new cases per hundred thousand kids under the age of fifteen. The diagnostic criteria are massive proteinuria over fifty milligram/kg/day, hypoalbuminemia (less than 2.5gram\liter) and edema [1]. Hyperlipidemia is present in conjunction with these symptoms. Minimal change disease (MCD) is the most prevalent morphologic feature of this syndrome (approximately eighty five percent of patients), followed by mesangial proliferative glomerulonephritis (MPGN) and focal segmental glomerulosclerosis (FSGS). Both the effacement of podocyte foot processes and the structural disorder of the glomerular filtration barrier (GFB) are present in each of these forms of the disease. Although the majority of cases (eighty to ninety percent) respond well to gluco-corticosteroids (GCS), steroid resistance has been reported in around ten percent, mainly in focal segmental glomerulosclerosis, with a poorer prognosis for renal survival [2].

As indicated by the emergence of new hypotheses, the pathophysiology of nephrotic proteinuria in cases with MCD is a complicated process that has not yet been completely explained [3]. The earliest research, which dates back to the 1970s, proposed that the development of proteinuria in minimal change disease has been caused by circulating protein permeability factors that have been released by dysfunctional T lymphocytes. [4]. Interleukin 10 (IL-10), transforming growth factor-β (TGF-β) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) molecule are typically involved in the recovery of podocyte stimulation by T-regulatory cells (T-regs). [5] The "two-hit" theory, which is the most current, is based on the assumption that the process of podocyte destruction is more intricate and partially incorporates the earlier hypotheses. The most current initial impact is the stimulation of podocytes by T-linked cytokines, bacterial or viral fragments, allergens, or other factors, which leads to a rise in the expression of CD80 (also known as B7.1). The induction of CD80 results in podocyte destruction and a rise in protein permeability. The second hit is the earliest one which was explained by regulatory T-cell dysfunction, permanent up regulation of CD80, leading to INS [6].

One of the β-1 glycoproteins that circulate in plasma is called hemopexin (Hpx). The molecular weight of hemopexin is fifty-kilodaltons (kDa). It is encoded by a gene that is situated on chromosome eleven, the Hpx gene (pp. 15.4–15.5) [7]. Hepatocytes were the primary cells responsible for its synthesis as a single polypeptide chain. It is composed of a disulfide bond in addition to a heme moiety. Iron homeostasis is affected by the presence of hemopexin. The heme molecule in serum is bound to hemopexin, which then transports it to the liver for catalysis [8]. The urinary hemopexin concentration is two milligrams per liter physiologically, and it increases in diabetes mellitus when

glomerular proteinuria develops [9]. Urinary hemopexin levels are elevated in other conditions, such as inflammatory psychiatric disorders, neuromuscular diseases, and malignancy [10]. Its serine protease activity is responsible for the anti- and pro-inflammatory effects of hemopexin, as well as its capability to inhibit cell adhesion and granulocyte necrosis [11]. In last years, Hpx has been discovered to affect glomerular filtration barrier permeability and then progress of proteinuria [7].

Consequently, the current study has been performed to estimate the pathogenicity of urinary hemopexin concentration in kids with idiopathic nephrotic syndrome and to ascertain its utility as a predictor of disease activity.

Patients and methods

The current study is a randomized prospective comparative study. It has been performed in the Nephrology Unite of the Department of Pediatrics at Benha University Hospitals between September 2023 and September 2024. The ethical committee of the Faculty of Medicine, Benha University Hospitals granted approval for this study. The ethical approval code number is {M.S.8.7.2023}. Parents provided informed written consents.

The study has been performed on sixty kids categorized into 2 groups:

Group (1) involved thirty-five patients suffering from idiopathic nephrotic syndrome, (twelve girls and twenty-three boys), aged one to fourteen years. The diagnosis of INS has been established with regard to the International Study of Kidney Disease in Children (ISKDC) criteria. Steroid sensitivity was defined as the attainment of remission within the 1st four weeks of glucocorticoid therapy, while steroid dependence was described as an incidence of at least 2 relapses within two weeks following stopping glucocorticoids or during the period of steroid-dose decrease. Remission has been defined as the absence of protein in urine for a minimum of three consecutive days.

The group of patients with idiopathic nephrotic syndrome has been further separated into subgroups: the newly diagnosed group comprised 13 children with first incidence of INS, and the group old patients in relapse consisted of twenty-two kids. A second division has been performed based on the applied therapy, with the first group consisting of twenty-three kids who were treated exclusively with glucocorticoids and the second group consisting of twelve kids who have been treated with glucocorticoids and corticosteroid-sparing agents.

Group (2) the control group, consisted of 25 healthy children.

Exclusion criteria: Patients with the following criteria were excluded from this study.

1. Nephrotic syndrome with impaired kidney function
2. End-Stage Renal Disease (ESRD) on dialysis
3. Organ transplantation.
4. Extreme urinary pH values.
5. Parents of children who refused to share in the study

Methods

All the children have been subjected to the following:

a) Complete history taking: including complaint, and personal, past, perinatal, present, dietetic developmental, vaccination and family history.
b) Full clinical examination: both general and local examination of the abdomen by inspection, palpation, percussion, and auscultation.
c) Biochemical assessment: All the laboratory tests were assessed once on hospital admission, according to the routine lists of our university laboratory tests. They included complete blood count, serum albumin, protein, creatinine, CRP (C-reactive protein) and total cholesterol as well as urine creatinine. They were estimated in all the kids. Proteinuria was evaluated in all the children who participated by determining the urinary protein creatinine ratio (uPCR) from a 1st morning urine sample. In nephrotic syndrome, an uPCR value of two mg/mg or higher in the urine was considered a marker of proteinuria [12].
d) Specific investigations: The concentrations of hemopexin in urine were measured by ELISA utilizing commercial assessments in accordance with the manufacturer's instructions (AssayPro, St. Charles, MO, States; kit catalog number for urine analyses: EH2001-1). Hemopexin values were expressed in nanograms per milliliter.

Within the control group, urine has been collected once, but within the kids suffering from idiopathic nephrotic syndrome, it has been collected twice, once at the beginning of the disease and once immediately following remission. Urine has been collected utilizing a sterile tube, centrifuged at a speed of 2000-3000 revolutions per minute for twenty minutes, and the supernatant has been collected without any sediment.

Statistical Analysis

Data have been coded and analyzed utilizing the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, state). Data have been summarized utilizing median and interquartile range for quantitative data and utilizing frequency (count) and relative frequency (percentage) for categorical data. Both the non-parametric Kruskal-Wallis test and the Mann-Whitney test have been utilized in order to analyze the differences and similarities between the quantitative variables. The non-parametric Wilcoxon signed rank test has been utilized since it allowed for the comparison of serial measures within each case. Association among quantitative variables has been performed utilizing Spearman correlation coefficient.

ROC curves have been created with area under curve analysis to determine the best cutoff value of urinary hemopexin for identifying patients. A logistic regression analysis has been conducted to determine whether urinary hemopexin functions as an independent predictor of INS. Statistically significant P-values were defined as those that were lower than 0.05.

Results

The present study was a randomized, prospective and comparative investigation

including thirty-five kids from the pediatric nephrology unit at Benha University Hospital. They were divided into 2 groups. Group **1 (Study Group)**: This group included 35 patients with idiopathic nephrotic syndrome. It was subdivided into a newly diagnosed group consisting of thirteen kids with the first occurrence of idiopathic nephrotic syndrome, and a group with subsequent relapses involving twenty-three kids. A second division has been performed with regard to the applied therapy, a group involving twenty-three kids, treated only with glucocorticoids, and a group involving twelve kids treated with glucocorticoids and corticosteroid-sparing agents. **Group 2 (Control Group)**: included 25 healthy children with matching age and sex.

In the current study, the median level of urinary hemopexin in the active disease was 942 ng/ml (IQR: 834.70 - 1064.90 nanogram per milliliter) while the median level of urinary hemopexin in the patients during remission was 551.20 ng/ml (IQR: 340 – 701 ng/ml)**.** The level in active disease was significantly higher than in remission and both groups showed a significantly greater level than the control group (median level 280 ng/ml, IQR: 210_382 ng/ml) (p=0.001) **(Table 1).** There was statistically significant elevation in uHpx value in newly diagnosed cases compared to the value after their remission (p<0.001) **(Table 2).** In the recent study, there was a statistically insignificant variance in the urinary hemopexin in newly diagnosed and subsequent relapse sates. Urinary hemopexin level in kids with the first onset of the disease immediately following achieving remission was significantly less than those with subsequent remission (p<0.001**) (Figure 1A), (Table 3).**

In the present study, there was a statistically significant variance in the urinary hemopexin concentration between patients received glucocorticoids only and those received glucocorticoids with sparing agent. During relapse, urinary hemopexin was significantly higher (p>0.007), then in remission, it was significantly lower in children treated with glucocorticoids only (p0<0.01) **(Figure 1 B,C).**

In the current study, the best cut off level of urinary hemopexin in active disease was 540.4 ng/ml and the area under the curve (AUC) was 0.987 with sensitivity hundred percent and specificity ninety-six percent. The best cut off level of urinary hemopexin in remission was 509.2 ng/ml with AUC 0.809, sensitivity 62.9 and specificity ninety-six percent **(Table 4).**

The current study shows that univariate linear regression analysis revealed that urinary protein to creatinine ratio, serum albumin, total cholesterol and urinary hemopxin all were significant predictors for the disease **(Table 5).**

The area under the curve analysis has been conducted to construct a ROC curve that would reveal the optimal cut-off value for urinary hemopexin in order to detect and identify patients **(Figure 2).**

Table 1: uHpx in patients and controls

INS state	uHpx in Patients (ng/ml)			uHpx in Controls (ng/ml)			P value
	Median	First quartile	Third quartile	Median	First quartile	Third quartile	
Activity	942.00	834.70	1064.90	280.00	210.00	382.00	< **0.001**
Remission	551.20	340.00	701.00	280.00	210.00	382.00	< **0.001**

Table 2: uHpx in newly diagnosed patients during activity and remission

INS state	uHpx (ng/ml)			P value
	Median	1st quartile	3rd quartile	
Newly diagnosed activity	1019.00	951.90	1073.80	**0.001**
Remission	305.50	268.60	360.70	

Table 3: uHpx in newly diagnosed/relapse in old cases during disease activity and remission

INS state	uHpx (ng/ml)						
	Newly diagnosed			Relapse			P value
	Median	First quartile	Third quartile	Median	First quartile	Third quartile	
Newly diagnosed/relapse	1019.00	951.90	1073.80	895.55	834.00	992.60	0.062
Remission	305.50	268.60	360.70	648.40	551.20	707.00	<**0.001**

Table 4: Sensitivity and specificity of uHpx level in disease activity and remission

INS state	Area under the curve	P value	95% Confidence Interval		Cut off	Sensitivity %	Specificity %
			Lower Bound	Upper Bound			
Newly diagnosed / Relapse	0.987	< **0.001**	0.962	1.013	540.4	100	96
Remission	0.809	< **0.001**	0.696	0.922	509.2	62.9	96

Table 5: Univariate logistic regression for prediction of INS cases

Variables	P value	OR	95% confident interval	
			Lower	Upper
Serum albumin (g/dl)	**0.003**	0.018	0.001	0.245
Total cholesterol (mg/dl)	**<0.001**	1.030	1.014	1.047
mg urinary protein /mg creatinine ratio	**0.004**	10629994.277	176.905	638743387099.434
uHpx Remission (ng/ml)	**<0.001**	1.007	1.003	1.011

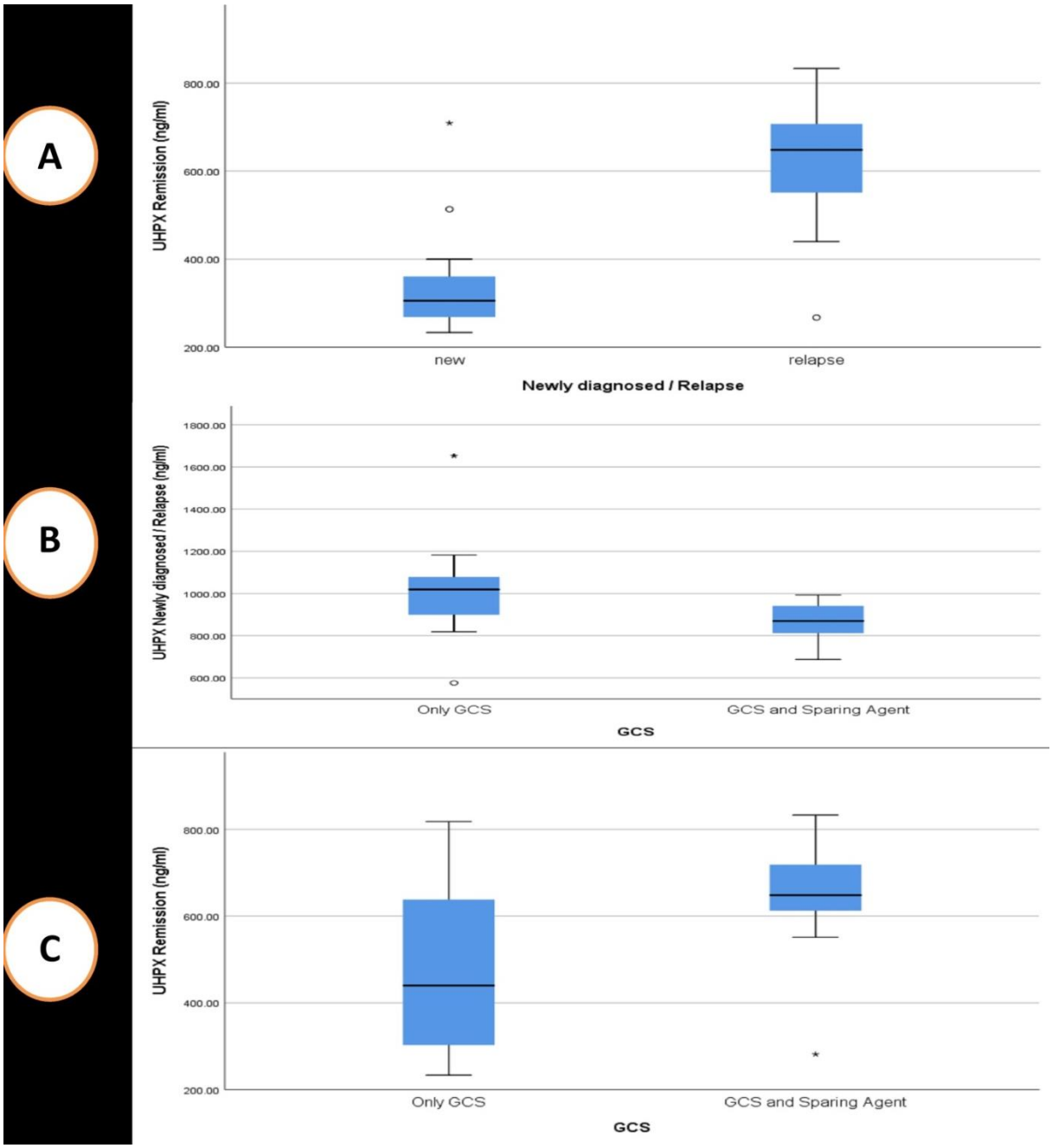

Figure 1: Box blot uHpx level in:

A. Remission of newly diagnosed patients and patients with subsequent remission.
B. Relapse of patients receiving only GCS and those receiving GCS with a sparing agent.
C. Remission of all cases receiving only GCS and those receiving GCS with a sparing agent.

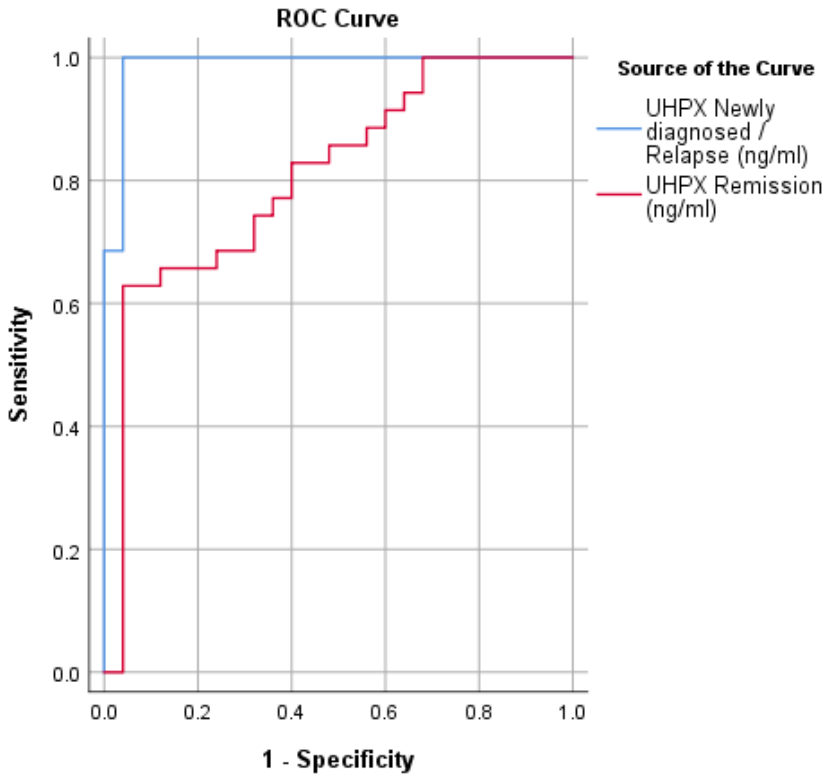

Figure 2: ROC curve for the performance of uHpx in detection of acute phase and remission of INS

Discussion

Nephrotic syndrome is a prevalent kidney condition in kids that is caused by the dysfunction of the glomeruli, leading to the leakage of protein from the circulation into urine [13]. There are numerous underlying etiologies that can lead to NS, including glomerular diseases, genetic mutations, toxins, vasculitis, and cancer. However, the majority of cases are due to unexplained causes [14].

Hemopexin (Hpx) is a glycoprotein that has a molecular weight of sixty kilodaltons and is mostly expressed by the liver. It is a member of the acute phase protein family and exhibits a high affinity for heme [15]. Circulating hemopexin is inactive under normal circumstances. However, it can be activated as a serine protease under specific circumstances [16]. It has been observed that Hpx interacts with nephron at the slit diaphragm, causing changes to the cytoskeleton of the podocytes and raising the permeability of albumin in vitro [17].

There is evidence suggesting that the active isoform of hemopexin may have a role in the development of minimal change nephrotic syndrome. The infusion of human plasma hemopexin to rats results in the initiation of reversible proteinuria, which is accompanied by the elimination of podocyte foot processes and the loss of the negative charge of the glomerular basement membrane (GBM). [18].

However, there is lack of the human studies about the role of hemopexin in nephrotic syndrome (NS). So, the current study has been carried out to estimate the urinary hemopexin level in kids suffering from idiopathic nephrotic syndrome as a pathogenic factor and to estimate its usefulness as a predictor of disease activity.

In our study, the median level of urinary hemopexin in the active disease was 942 ng/ml (IQR: 834.70 - 1064.90 nanogram/milliliter) while its level during remission was 551.20 ng/ml (IQR: 340 – 701 ng/ml). The level in active disease was significantly greater than in remission and both groups demonstrated a significantly greater level than the control group (median level 280 ng/ml, IQR: 210_382 nanogram/milliliter).

Our findings came in accordance with [7] who investigated fifty-one kids suffering from idiopathic nephrotic syndrome and eighteen age-matched controls. The overall idiopathic nephrotic syndrome group had higher serum and urine hemopexin values in relapse than those of the controls (p-value 0.000). The levels declined while in remission, but they remained greater than in the control group (p-value 0.000), which may indicate a hemopexin's impact on the onset of proteinuria. A ROC curve has been created utilizing area under the curve analysis to determine the ideal urine hemopexin cut off value for case detection [7].

The current results also agreed with other studies which aimed to evaluate the role of urine Hpx in the prediction of active lupus nephritis (LN), connect its level with disease activity, and predict the responsiveness to initiating the management in Egyptian SLE cases suffer from nephritis. There were twenty-two control subjects and forty-four patients (two men and forty-two women). They have been categorized into 3 groups. Patients in group I had active lupus nephritis; cases in group II had SLE without lupus nephritis; and group III was a healthy control group. Urinary hemopexin has been demonstrated to be statistically greater in patient with lupus nephritis (11.85 IU/L) than in healthy persons' (3.63 IU/L) and in SLE without nephritis (4.84 IU/L) [19].

Additionally, investigates examined more than one thousand distinct proteins in the urine of individuals with active lupus nephritis and identified several proteins that were greater in active lupus nephritis than in active SLE. Activated leukocyte cell adhesion molecule, platelet factor-4, hemopexin, calpastatin, properdin, tissue factor pathway inhibitor, and vascular cell adhesion protein-1 were the urinary proteins that demonstrated the highest sensitivity and specificity in association with renal disease activity [20].

The function of Hpx in minimal change disease was first proposed in the late 1990s. Hemopexin was discovered in a portion of human plasma. When injected in rat kidneys in vivo and ex vivo, it resulted in proteinuria and a reduction in anionic charges. In kids suffering from minimal change nephrotic syndrome, activated hemopexin is elevated [21].

It has been shown that **Hpx** seems to be more “active”, depending on elevated proteinase activity, during relapse compared to remission. when studied the effect of active Hpx on human podocytes and glommerular endothelial cells , Withen thirty minute of manrgement with Hpx, cytoskeletal rearrangement in podocytes in a nephron-dependent

manner, this effect reserved within four hours and have been inhibited by preincubation with normal human plasma. This shows that factors in normal plasma act to protect podocytes [17].

In minimal change nephrotic syndrome, plasma may contain fewer of these factors, which can expose podocytes to the impact of activated hemopexin. It is possible that these plasma factors are exerting their effect directly on podocytes in order to regulate the development of receptors or to ensure that the slit diaphragm complex remains intact. There is also the possibility that these factors are acting as direct inhibitors of active hemopexin in a manner that is analogous to that of other circulating proteases that have circulating inhibitors [17].

An explanation for our findings is that immediately following achieving remission, hemopexin levels did not reach our normal control level, despite being lower than in relapse, suggesting that the pathological processes have not been fully silenced. This is a premise for the ongoing course of therapy. It has been shown that hemopexin can be partially produced into circulation from glomerular mesangial cells. The local release of Hpx by these cells acts directly on the glomerular barrier with podocytes. These cells are responsible for the production of Hpx into the circulation [22].

In contrast, an investigation conducted in collaboration with[23] examined the presence or activity of hemopexin in plasma and urine samples from patients with minimal change disease who were either in relapse (number = eighteen) or in remission (number = twenty-three) following therapy with prednisolone. Also, the study included plasma and urine from proteinuria patients suffering from focal and segmental glomerulosclerosis (number=eleven), membranoproliferative glomerulonephritis (MPGN) (number = nine), IgA nephropathy (number = five), and healthy control donors (number = ten) for comparison. The findings indicated that the mean titer of plasma hemopexin was lower in minimal change nephrotic syndrome relapse than in minimal change nephrotic syndrome in remission (0.21±0.14 milligrams per milliliter vs 0.44±0.06 mg/ml; p-value less than 0.01). This suggests that the protease activity has been enhanced in subjects in relapse in comparison to subjects in remission, subjects with other forms of primary glomerulopathy, or healthy control individuals. Rather than an absolute reduction in the plasma level of hemopexin, the reduction in hemopexin titer detected in this study may be indicative of an altered molecular configuration of hemopexin.

In contrast to urine samples from other proteinuria subjects with focal and segmental glomerulosclerosis, membranoproliferative glomerulonephritis, or IgA nephropathy, the eighty kilodalton hemopexin band in blots of urine from minimal change disease relapse was either virtually absent or has a decreased stability. The authors discovered that hemopexin may be present in a changed isoform in minimal change disease relapse subjects. Additionally, the control group of ten participants comprised of adults up to thirty-five years of age, serves as a reminder that serum hemopexin level varies with age (in neonates, twenty percent and in kids eighty percent compared to adults). The authors only reported that the values

of urinary hemopexin in patients during relapse were greater than those during remission, which is consistent with our findings. However, the values were less than those of the controls [23].

In a study, there was a statistically insignificant variance in urinary hemopexin levels between newly diagnosed and subsequent relapse patients. However, immediately following achieving remission in kids who experienced the first onset of the disease, the urinary hemopexin level was significantly less than that of those who experienced subsequent remission. They were the first to detect this, positing that there is expected association with shortened intervals between relapses, which is insufficient to suppress the disorganization of the glomerular filtration barrier [7].

In this investigation, there was a statistically significant variance in the urinary hemopexin levels between patient received glucocorticoids only and those who received glucocorticoids with a sparing agent. During relapse, urinary hemopexin was significantly greater compared to those in remission, and significantly lower in kids treated with glucocorticoids only. This was in accordance with who involved fifty-one kids with idiopathic nephrotic syndrome. The cases have been separated into subgroups based on the number of relapses (group IA—the initial episode of idiopathic nephrotic syndrome group IB—with relapses) and the method of therapy (group IIA treated with glucocorticosteroids, group IIB managed with glucocorticosteroids and other immunosuppressants). In comparison to group IIB, urinary hemopexin excretion was greater in relapse p-value less than 0.026 and reduced in remission p-value less than 0.0017 in group IIA [7].

The explanation was that as opposed to the group who were solely treated with glucocorticoids, in the group received glucocorticoids and other sparing agents during relapse, the levels of cytokines involved in the pathogenesis of minimal change disease were reduced as a result of higher suppression of immunocompetent cells. The increased urinary hemopexin level in remission in children with combination therapy, compared with the decreased level in cases with glucocorticoids only therapy is determined by the persistence of elevated local levels of these cytokines in kids who are receiving combination treatments. Consistent with the higher urinary interleukin-13 levels in this group during remission, the values are significantly reduced during relapse [7].

In the present study, the optimal cut-off level of urinary hemopexin in active disease was 540.4 nanograms per milliliter, with an area under the curve (AUC) of 0.987, sensitivity of hundred percent, and specificity of ninety-six percent. The optimal cut-off level for urinary hemopexin of patients in remission was 509.2 nanograms per milliliter, with an area under the curve of 0.809, sensitivity of 62.9, and specificity of ninety-six percent. Our results demonstrate that the univariate linear regression analysis reveals that total cholesterol, urinary protein/creatinine ratio, urinary hemopxin and serum albumin, all were significant predictors for the disease.

In partial agreement with us, it was showed a significant difference in serum albumin, and total cholesterol between the relapse-free group (65 cases) and the

relapse group (55 cases). Also, urinary creatinine differed insignificantly between the two groups [24].

Similarly, a study done previously aiming to build a nomogram that could predict the probability of progression over time for individuals suffering from primary membranous nephropathy who presented with nephrotic syndrome. They showed a significant correlation between serum albumin and proteinuria. However, they did not find any correlation between serum creatinine and proteinuria [25].

Conclusion

Our results exhibited that urinary hemopexin concentration can be considered as a pathogenic factor in kids suffering from idiopathic nephrotic syndrome. Also, since the newly diagnosed/relapsed INS children showed higher levels of hemopexin compared to the remission patients, urinary hemopexin concentration may be useful as a predictor of disease response to treatment. We recommend more studies with large sample sizes and correlation with serum samples.

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