Original Article

Study of the Value of Urinary Vitamin D-Binding Protein as a Prognostic Biomarker in Cases of Childhood Idiopathic Nephrotic Syndrome and its Relation to Calcium /Phosphorus Metabolism

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Abstract

Introduction: Nephrotic syndrome (NS) is a common chronic kidney disease in childhood and it is mostly idiopathic.

Aim of the Study: To determine if uVDBP measurements can be used as a non-invasive prognostic biomarker in cases of childhood idiopathic NS and its relation to Ca/P metabolism.

Methods: This prospective study was carried out on children who were newly diagnosed with idiopathic nephrotic syndrome presented to the pediatric nephrology unit, Ain Shams University hospitals during the period from November 2019 till May 2020.

Results: The present study showed that levels of uVDBP were significantly higher in cases than in healthy control children.

Conclusion: We can conclude that uVDBP measurements represent a non-invasive prognostic biomarker in cases of childhood idiopathic NS**.**

Keywords: Childhood idiopathic nephrotic syndrome, Ca /P metabolism, urinary vitamin D-binding protein.

Running title: Study of the Value of Urinary Vitamin D-Binding Protein as a Prognostic Biomarker in Cases of Childhood Idiopathic Nephrotic Syndrome and its Relation to Calcium / Phosphorus Metabolism.

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Introduction

Nephrotic syndrome (NS) is a common pediatric kidney disease, that is classically defined by nephrotic-range proteinuria (≥40 mg/ m^2/hour or urine protein/creatinine ratio ≥ 2 mg/mg or 3 + protein on urine dipstick), hypoalbuminemia (<2.5 g/L), generalized edema and hyperlipidemia [1].

NS subtypes have markedly different disease courses and outcomes. Invasive biopsy remains the only method for giving an impression about the prognosis and course of the disease, and the 2 most frequent histopathological findings are minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) [2].

Children with MCD most commonly display a steroid sensitive course, whereas those with FSGS are often steroid resistant. The prognosis of children with NS depends on the underlying histopathology and the response to steroid treatment [3].

Diagnosis of steroid-sensitive NS (SSNS) is made when remission of NS was obtained within the period of 4 weeks of adequate treatment with prednisolone 60 mg/m2/day, maximum 80 mg/day. Diagnosis of steroid-resistant NS (SRNS) is established when there is continuous proteinuria despite 4 weeks of adequate treatment with prednisolone 60 mg/m2/day [4].

Both SSNS and SRNS are associated with a deficiency in vitamin D, attributed largely to the loss of its carrier, vitamin D-binding protein (VDBP), in the urine. It was found that the urinary vitamin D is unconjugated and likely excreted along with VDBP, which has a molecular weight (VDBP – 58 kDa versus albumin 66 kDa) and isoelectric point (VDBP – variants range from pI 4.8–5.2 vrsus albumin – pI 4.8) similar to albumin. They also found that urinary VDBP (uVDBP) excretion is positively correlated with albumin excretion. Also, vitamin D deficiency is associated to a greater degree with SRNS than SSNS. [5].

Urinary VDBP excretion has recently been demonstrated to be a potential marker of renal interstitial damage and fibrosis. Urinary VDBP is increased in subjects with microalbuminuria as well as in patients with chronic kidney disease (CKD) from diverse etiologies with overt proteinuria [3].

Our current study aims to determine if uVDBP measurements can be used as a non-invasive prognostic biomarker in cases of childhood idiopathic NS and its relation to Ca/P metabolism.

Methods

This prospective case control study was conducted in the pediatric department-Ain Shams University hospitals, over a period of 6 months from November 2019 to May 2020.

The study included newly diagnosed nephrotic syndrome patients with ages: 2-8 years old, 22males and 8 females. All patients were studied before they started corticosteroid therapy.

While patients with ages less than 2 years old or above 8 years old and those who started corticosteroid therapy were excluded from the study.

All children included in this study were divided into two groups: Group I (patients group) which included 30 children (22 males and 8 females) who

were newly diagnosed with idiopathic nephrotic syndrome recruited from the pediatric nephrology unit. Group II (control group): The group included 30 healthy age and gender matched children (15 males and 15 females) attending the pediatric outpatient clinic for follow up of anthropometric measures.

All studied patients were subjected to the following:

A) Detailed history taking: including age at onset of the disease, preceding infection and complications e.g (infections and thromboembolic manifestations).

B) Careful clinical examination: General examination: edema (its level and distribution). Vital data: blood pressure, heart rate and respiratory rate. Scoring system for diagnosis of hypertension: Normal systolic blood pressure (SBP) or diastolic blood pressure (DBP) defined as: < 90^{th}, prehypertension SBP or DBP defined as: 90^{th} to < 95^{th} or if BP exceeds 120/80 mmHg, Stage 1 hypertension defined as: 95^{th} percentile to the 99^{th} percentile plus 5 mmHg, stage 2 hypertension defined as: > 99^{th} percentile plus 5 mmHg [6]. Measurements: weight and height.

C) All cases were followed clinically after 3 months of initial diagnosis to determine who became diagnosed as SSNS and who became diagnosed as SRNS, in addition to follow up of complications e.g. hypertension, DM, infections and thromboembolism. Steroid-sensitive NS (SSNS) diagnosis is made when remission of NS was obtained within the period of 4 weeks of adequate treatment with prednisolone 60 mg/m^2/day, maximum 80 mg/day. Steroid-resistant NS (SRNS) diagnosis is made when the patient has persistant proteinuria despite 4 weeks of adequate treatment with prednisolone 60 mg/m^2/day [4].

D) Laboratory investigations included serum albumin, serum creatinine, urea, electrolytes (Na, K, Ca, P) and alkaline phosphatase, complete blood count with differential count, CRP and ESR, urine analysis, protein/ creatinine ratio in urine (random sample) or 24h urinary proteins, lipid profile e.g. fasting serum cholesterol, triglycerides, HDL and LDL.

Levels of vitamin D binding protein in urine (uVDBP) were measured using enzyme linked immunosorbent assay (ELISA). All cases were sampled once at initial diagnosis of the disease and before starting corticosteroid therapy to test for the level of uVDBP.

Sampling: random urine samples (5ml) were collected in sterile containers. Samples were centrifuged at 4000 rpm for 10 minutes and stored at -80°C till usage.

Measurement of uVDBP:

I) UVDBP was measured using enzyme-Linked Immunosorbent Assay (Biossay Technology Laboratory, China), According to manufacture's instructions.

II) Steps of the assay: Samples were diluted 4x before used. VDBP standards and samples were added to the wells pre-coated with a monoclonal antibody. Then biotin-conjugated antigens were added to the wells. The antigens in the standards or samples compete with the biotin-conjugated antigen to bind to the capture antibody and incubate. Unbound antigen was washed away during a washing step. An avidin-HRP was then added and incubated. Unbound avidin-HRP was washed away during a washing step.

TMB Substrate was then added and color developed. The reaction was stopped by addition of acidic stop solution and color changed into yellow that could be measured at 450 nm. The intensity of the color developed was inversely proportional to the concentration of DBP in the sample.

Statistical Analysis

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 20 for windows). Data cleaning and checking for quality of data and data entry was performed. Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

Results

Table 1 showed that 73.3% of cases were males and 26.7% were females. Mean age of cases was 4.6±2.0years. Regarding controls: 50% were males and 50% were females, Mean age of controls was 5.0±1.6years. **Table 2** showed a non-significant correlation between cases and controls regarding age and gender. **Table 3** showed that twenty two cases (73.3%) had genital edema. sixteen cases (53.3%) had fever. Eleven cases (36.7%) had chest infection (4 cases (36.36%) of them had pneumonia and 7 cases (63.64%) had bronchitis). One case (3.3%) had acute cerebral sinus venous thrombosis (Rt transverse and sigmoid sinuses thrombosis).

Table 4 showed the laboratory results of cases at initial presentation revealing that: mean serum Ca was 8.2± 0.7mg/dl ranging between 6.5 and 9.9mg/dl, mean serum phosphorus was 4.9± 0.7mg/dl ranging between 3.5 and 6.3mg/dl, mean serum alkaline phosphatase was 284.9± 124.1 U/L ranging between 140.03.5 and 687.7 U/L, mean 24hrs urinary proteins was 6200.9± 3912.8 mg/24h ranging between 958.4 and 18840.0 mg/24h, mean serum albumin was 1.7±0.4g/dl ranging between 0.9 and 2.5 g/dl. Data at follow up of cases after 3months of initial presentation **(Table 5)** showed that: regarding steroid responsiveness: sixteen cases (53.3%) were steroid sensitive and fourteen cases (46.7%) were steroid resistant. Regarding blood pressure centiles: five cases (16.7%) were normotensive, four cases (13.3%) were prehypertensive and twenty one (70%) were hypertensive. No cases presented with diabetes mellitus. This table revealed that one case (3.3%) developed deep venous thrombosis (DVT) and one case (3.3%) who had acute cerebral sinus venous thrombosis at initial presentation developed new acute on top of chronic sinus thrombosis. Eleven cases (36.7%) had chest infection. (2 cases (18.18%) of them had pneumonia and 9 cases (81.81%) had bronchitis).

Table 6 showed that 75% of our SSNS children were hypertensive while 64.30% of our SRNS children were hypertensive with no significant statistical difference between the two groups (P-value is 0.821). **Table 7** showed that: the mean of uVDBP level of cases was 433.3± 200.3, while the mean of uVDBP level of controls was 49.2± 18.0. Levels of uVDBP were significantly higher in cases than in

healthy control children (P-value is 0.0000).

Table 8 showed that: cutoff value of uVDBP was 420 ng/ml which gave sensitivity 0.90 (90%) and specificity 1.0 (100%). Figure (1) showed ROC curve analysis. If the level of uVDBP is less than this cutoff value (420 ng/ml), we can anticipate the case will be steroid responsive but if the level of uVDBP. **Table 9** showed a non-significant correlation between serum levels of (Ca, phosphorus, alkaline Phosphatase) on one hand and uVDBP levels on the other hand (P> 0.05).

Table 10 showed that there was a non-significant correlation between values of 24h urinary protein and uVDBP levels(P> 0.05). Also, there was a non significant correlation between serum albumin and uVDBP levels. **Table 11** showed a non-significant correlation between incidence of hypertension and uVDBP levels (P> 0.05).

Table 1: Descriptive data of cases and controls: age and gender

		Case Group		Control group	
		N.	Percent (%)	N.	Percent (%)
Gender	Male	22	73.3	15	50.0%
	Female	8	26.7	15	50.0%
Age: years		4.6±2.0		5.0± 1.6	

Table 2: Comparison between cases and controls regarding gender and age.

			Study group		X^2/ t	P value	Significance
			Cases	Controls			
Gender	**Male**	**N.**	22	15	2.574	0.109	NS
		%	73.3%	50.0%			
	Female	**N.**	8	15			
		%	26.7%	50.0%			
Age: years	**Cases**		4.6 ± 2.0		-0.692	0.492	NS
	Controls		5.0 ± 1.6				

Table 3: Descriptive data of cases regarding complications (genital edema, fever, chest infection and thrombosis) at initial presentation.

Complications		N.	Percent (%)
Genital edema	+ve	22	73.3
	-ve	8	26.7
Fever	+ve	16	53.3
	-ve	14	46.7
Chest Infection	+ve	11	36.7
	-ve	19	63.3
Thrombosis	-ve	29	96.7
	DVT	0	0.0
	CNS embolism	1	3.3

DVT: deep venous thrombosis. CNS embolism: central nervous system embolism.

Table 4: Descriptive data of cases regarding laboratory results at initial presentation:

	Mean ± SD	Minimum – Maximum
Serum albumin: g/dl	1.7 ± 0.4	0.9 - 2.5
Calcium: mg/dl	8.2 ± 0.7	6.5 - 9.9
Phosphorus: mg/dl	4.9 ± 0.7	3.5 - 6.3
Alkaline phosphatase: U/L	284.9 ± 124.1	140.0 - 687.7
24hrs urinary protein: mg/24h.	6200.9 ± 3912.8	958.4 - 18840.0
UVDBP level: ng/ml	433.3 ± 200.3	200.0 - 840.0

UVDBP: Urinary Vitamin D binding protein.

Table 5: Descriptive follow up data of cases after 3 months including:

		N.	Percent (%)
Steroid responsiveness	steroid sensitive	16	53.3
	steroid resistant	14	46.7
Systolic blood pressure centiles	5th- 90th p(normotensive	5	16.7
	>90th-95th p(prehypertensiv	4	13.3
	>95th- < 99thp or 130/80-	21	70.0
Diastolic blood pressure centiles	5th- 90th p(normotensive	5	16.7
	>90th-95th p(prehypertensiv	4	13.3
	>95th- < 99thp or 130/80-	21	70.0
Diabetes Mellitus	-ve	30	100.0
Thrombosis	-ve	28	93.3
	DVT	1	3.3
	CNS	1	3.3
Chest Infection	+ve	11	36.7
	-ve	19	63.3

Table 6: Relation between steroid responsiveness and hypertension among studied cases

			Steroid responsiveness		X^2	P value	Sig.
			steroid sensitive (N=16)	steroid resistance (N=14)			
Systolic blood pressure / diastolic blood pressure	**5th- 90th p (normotensive)**	**N.**	3	2	0.285	0.821	NS
		%	18.75%	14.30%			
	>90th-95th p (pre-hypertensive)	**N.**	1	3			
		%	6.25%	21.40%			
	>95th- < 99thp or 130/80+	**N.**	12	9			
		%	75.00%	64.30%			

Table 7: Comparison between cases and controls regarding results of uVDBP**:**

	Study group	Mean	SD	t	p value	Sig.
UVDBP level: ng/ml	**Cases**	433.3	200.3	9.750	0.000	HS
	Controls	49.2	18.0			

P-value > 0.05: non-significant; P-value <0.05: significant.
UVDBP: Urinary Vitamin D binding protein.

Table 8: Cutoff value of uVDBP at which we can anticipate when the case will be steroid responsive or resistant during the course:

Area Under the Curve	Std. Error(a)	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
			Upper Bound	Lower Bound
0.983	0.022	0.000	0.941	1.026

Positive if UVDBP Greater Than or Equal To (a)	Sensitivity	Specificity
199.00	1.000	0.000
216.00	1.000	0.083
236.00	1.000	0.167
250.00	1.000	0.417
270.00	1.000	0.500
300.00	1.000	0.583
340.00	1.000	0.750
380.00	0.900	0.917
420.00	0.900	1.000
460.00	0.800	1.000
520.00	0.600	1.000
640.00	0.500	1.000
740.00	0.200	1.000
800.00	0.100	1.000
841.00	0.000	1.000

Table 9: Correlation between Ca, P, alkaline phosphatase and results of uVDBP:

		UVDBP level: ng/ml
Calcium: mg/dl	Pearson Correlation	0.178
	P value	0.428
	Sig.	NS
Phosphorus: mg/dl	Pearson Correlation	-0.113
	P value	0.618
	Sig.	NS
Alkaline phosphatase: U/L	Pearson Correlation	0.162
	P value	0.471
	Sig.	NS

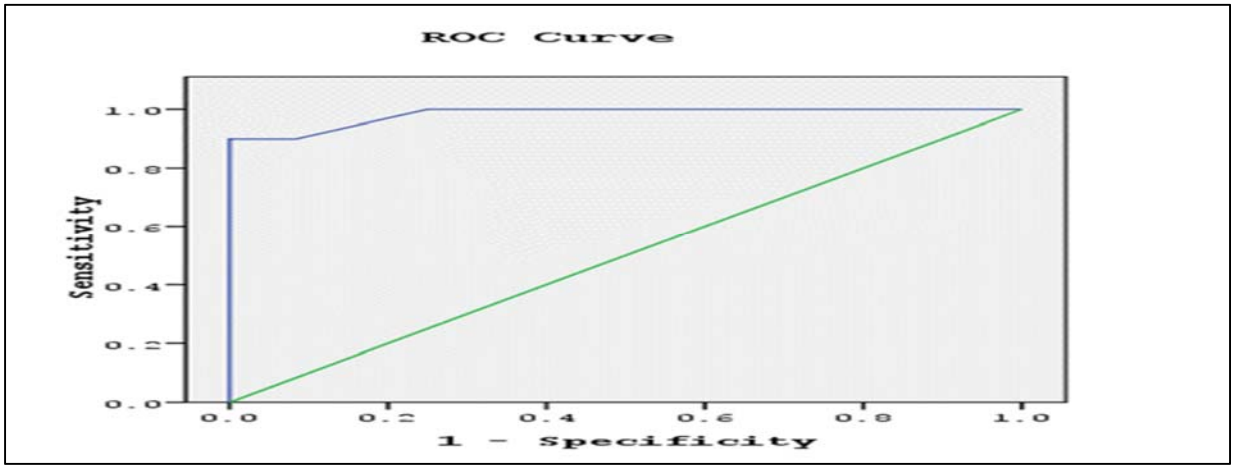

Figure 1: ROC curve analysis of uVDBP cutoff value.

Table 10: Correlation between proteinuria and uVDBP:

		UVDBP level: ng/ml
24hrs urinary protein: mg/24h.	Pearson Correlation	-0.137
	P value	0.544
	Sig.	NS
Serum albumin: g/dl	Pearson Correlation	0.203
	P value	0.366
	Sig.	NS

Table 11: Correlation between uVDBP levels and incidence of hypertension at initial presentation

		Mean UVDBP level: ng/ml	SD	P value	Sig.
Hypertension	**5th- 90th p (normotensive)**	456.0	197.2	0.859	NS
	>90th-95th p (prehypertensive)	360.0	169.7		
	>95th- < 99th p or 130/80-	435.5	214.6		
	-ve	427.2	203.2		

Discussion

VDBP is a circulating plasma protein in the alpha globulin region mainly produced in the liver. Its production is relatively stable in children and adults, though some physiological changes such as pregnancy can increase its levels. Vitamin D deficiency is seen commonly in all types of NS, which is mainly due to the excretion of a high amount of VDBP in urine [7].

VDBP has similar molecular weight and isoelectric point to that of albumin and excreted in patients with NS [8].

The aim of this study was to determine if uVDBP measurement can be used as a non-invasive prognostic biomarker in cases of childhood idiopathic NS and its relation to Ca/P metabolism.

This was a prospective study that was conducted on children who were newly diagnosed with idiopathic nephrotic syndrome presented to the Pediatric Nephrology unit - Ain Shams University hospitals during the period from November 2019 till May 2020.

The present study showed that 73.3% of cases were males and 26.7% were females with their mean age 4.6± 2.0 years, while regarding the controls: 50% were males and 50% were females with their mean age 5.0± 1.6 years. From the above results, male predominance among nephrotic patients is clear. Also, this study showed a non-significant correlation between cases and controls regarding age and gender. This was in accordance with Marzouk et al. [5] who reported that the mean age of nephrotic children was 5.30 ± 2.45 years.

Regarding the associated symptoms and signs during the initial presentation of our cases, 73.3% had genital edema. 53.3% of cases had fever, 36.7% of our cases had chest infection (36.36% of them had pneumonia and 63.64% had bronchitis). 3.3% had acute cerebral sinus venous thrombosis (Rt transverse and sigmoid sinuses thrombosis). Sahana [9] reported that all patients presented with puffiness of face and lower limb edema. In variance with our results, genital edema in 31% of their cases was reported.

In contrast to our results, Lebel et al. [10] reported that pneumonia was diagnosed in 5% of patients and bacteremia /sepsis in 3% in patients with nephrotic syndrome at initial presentation.

Regarding data of laboratory results of cases at initial presentation in the present study, mean serum Ca was 8.2±0.7mg/dl ranging between 6.5 and 9.9mg/dl. Mean serum phosphorus was 4.9±0.7mg/dl ranging between 3.5 and 6.3mg/dl. Mean serum alkaline phosphatase was 284.9± 124.1 U/L ranging between 140.03.5 and 687.7 U/L.

Our results were different from Marzouk et al. [5] who reported that mean serum calcium of NS children was 9.31±0.86 mg/dl ranged between 7.41 and 11.7 mg/dl. The higher mean serum calcium of their cases in comparison to that of our cases can be explained by lower mean serum albumin of our cases. Aggarwal et al. [11] reported that mean serum Ca was 8.77 ± 1.06 mg/dl ranging between 6.07 and 11.08 mg/dl among NS adult patients. Mean serum phosphorus was 3.72 ± 0.86 mg/dl ranging between 2.04 and 5.71 mg/dl among NS patients.

Regarding data of laboratory results of cases at initial presentation in the present study, mean 24hrs urinary proteins was 6200.9± 3912.8 mg/24h ranging between 958.4 and 18840.0 mg/24h. Mean serum albumin was 1.7±0.4g/dl ranging between 0.9 and 2.5 g/dl. In contrast to our results, Marzouk et al. [5] stated that the mean 24hrs urinary proteins of NS children was 1270±1860 mg/24h ranged between 20and 8500 mg/24h. Moneim et al. [12] reported that mean 24h proteinuria was 2880±1120 mg/24h in SRNS and 2520±800 mg/24h in SSNS. Aggarwal et al. [11] reported that mean 24h proteinuria was 5510 ± 3240 mg/24h in nephrotic syndrome adult patients, ranging between 1700 and 19000 mg/24h.

In the present study, regarding the data at follow up of cases after 3 months. Our study showed that 53.3% of cases were steroid sensitive (SSNS) and 46.7% of cases were steroid resistant (SRNS). This is in agreement with Bennett et al. [3] who reported that 46% of patients had SRNS, 54% of patients were SSNS.

In the present study regarding the data at follow up of cases after 3 months: four cases (13.3%) were prehypertensive and twenty one (70%) were hypertensive. Also, the current study showed that 75% of our SSNS children were hypertensive while 64.30% of our SRNS children were hypertensive with no significant statistical difference between the two groups (P-value is 0.821). Regarding hypertension among SRNS children, this can be explained by the chronic state of nephrosis, corticosteroid toxicity and side effects of other immunosuppressive e.g cyclosporine A. But regarding hypertension among SSNS children, our explanation is that these children might suffer from sequaly of corticosteroid toxicity used at initial presentation combined with bad dietetic habits (high salt intake). Also, it has been reported that 10-15% of children with idiopathic NS show hypertension at initial presentation. No cases presented with diabetes mellitus.

Choudhary et al. [13] reported that 21% of SSNS children were hypertensive while 35% of SRNS children were hypertensive with no significant statistical difference between the 2 groups. Bennett et al. [3] reported that incidence of hypertension was 56.5% in SRNS versus 21.4% in SSNS ($P < 0.01$).

In the present study regarding the data at follow up of cases after 3 months, one

case (3.3%) developed deep venous thrombosis. One case (3.3%) who had acute cerebral sinus venous thrombosis at initial presentation developed new acute on top of chronic sinus thrombosis. Two cases (18.18%) had pneumonia. Kayali et al. [14] reported that (0.5%) of patients with nephrotic syndrome had pulmonary embolism, (1.5%) had deep venous thrombosis, and fewer than (0.5%) had renal vein thrombosis.

Variation in the incidence of venous thromboembolism (VTE) among nephrotic syndrome children depends on several factors e.g. underlying inherited thrombophilia, abuse of diuretics and coinciding infections like gastroenteritis.

In the present study, the mean uVDBP level of cases was 433.3± 200.3 ng/ml while the mean uVDBP level of controls was 49.2± 18.0 ng/ml. It was clear that levels of uVDBP were significantly higher in cases than in healthy control children (p=0.000). Our results were in agreement with the results of Bennett et al. [3] who found that uVDBP concentrations were markedly increased in patients than in controls. They also reported higher urinary VDBP level in SRNS versus SSNS patients. Regarding the cutoff value of uVDBP in the present study, it was 420 ng/ml which gave sensitivity 0.90 (90%) and specificity 1.0 (100%). If the level of uVDBP is less than this cutoff value (420 ng/ml), we can anticipate that the case will be steroid responsive but if the level of uVDBP is higher than this cutoff value (420ng/ml) we can anticipate that this case will be steroid resistant.

Choudhary et al. [13] reported ROC curve analysis to evaluate the ability of different urinary markers to predict steroid responsiveness in children with idiopathic NS. According to their results, uVDBP showed an area under the curve (AUC) of 0.897 indicating that uVDBP had a significant predicting power with cutoff value of 303.8ng/ml. They concluded that uVDBP can be used to predict the steroid responsiveness accurately in NS children.

In the present study, we aimed to study the possible relation between Ca profile and uVDBP levels in nephrotic children. Our goal was to assess if the results of Ca profile can reflect vitamin D and uVDBP status in this group of patients.

The present study showed no significant correlation between serum levels of (Ca, phosphorus, alkaline phosphatase) on one hand and uVDBP levels on the other hand (P> 0.05). Unfortunally, it was difficult for us to find studies discussing this correlation in this group of patient.

In the present study, there was no significant correlation between values of 24h urinary proteins and uVDBP levels (P> 0.05). Also, there was a non-significant correlation between serum albumin and uVDBP levels.

In contrast to the results of the present study, Grymonprez et al. [15] and Doorenbos et al. [16] investigated VDBP in NS children and showed strong correlations between uVDBP and proteinuria. In addition, Bennett et al. [3] reported positive correlation between uVDBP excretion and proteinuria ($r = 0.66$, $P < 0.001$).

When we studied the correlation between uVDBP levels on one hand and incidence of each of (hypertension, fever & chest infections) on the other hand, the results were non-significant.

A limitation of our study is the lack of measurement of vitamin D level for our cases to correlate it with uVDBP levels.

This was a financial limitation.

We can conclude that uVDBP measurements represent a non-invasive prognostic biomarker in cases of childhood idiopathic NS**.**

List of abbreviations

CKD	Chronic kidney disease
DVT	Deep venous thrombosis
DBP	Diastolic blood pressure
FSGS	Focal segmental glomerulosclerosis
MCD	Minimal change disease
NS	Nephrotic syndrome
SBP	Systolic blood pressure
SRNS	Steroid-resistant NS
SSNS	Steroid-sensitive NS
uVDBP	Urinary Vitamin D binding protein
VDBP	Vitamin D-binding protein
VTE	Venous thromboembolism

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Statements

Ethics approval and consent to participate

The local ethical committee permitted the study under the Helsinki declaration of Bioethics and its later amendments. Informed consent (written form) was obtained from all participants or their caregivers.

Consent for publication

The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

Availability of data and material

"Not applicable",

The author has indicated that the data and material are factual and genuine.

Conflict of interest

The authors declare no conflict of interest.

Funding

The authors declare that this research work didn't receive any fund, Cairo, Egypt.

Acknowledgements

None

Submitted : 13/06/2021
Accepted : 14/07/2021
Published online : 28/07/2021