

Impact of Disease Duration on ADMA and Vitamin D Levels in Children with Nephrotic Syndrome

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ABSTRACT

Aim: To investigate the relationship between disease duration, ADMA levels, and vitamin D deficiency in children with nephrotic syndrome compared to healthy controls.

Background: Nephrotic syndrome (NS) is a pediatric kidney disorder characterized by proteinuria, hypoalbuminemia, hyperlipidemia, and edema, often leading to cardiovascular and metabolic complications. ADMA, a marker of endothelial dysfunction, and vitamin D deficiency are significant concerns in NS management.

Methods: This study included 25 children with NS and 25 healthy controls matched for age and sex. Serum ADMA and vitamin D levels were measured using enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed to evaluate the relationship between disease duration and the biomarkers.

Results: Children with NS showed significantly higher ADMA levels and lower vitamin D levels compared to controls. Disease duration was positively correlated with ADMA and negatively correlated with vitamin D levels.

Conclusion: Prolonged NS is associated with increased endothelial dysfunction and vitamin D deficiency, highlighting the need for comprehensive monitoring and targeted interventions to reduce cardiovascular and metabolic risks in affected children.

Keywords: Nephrotic syndrome vitamin D Endothelial Dysfunction Disease duration cardiovascular risks.

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INTRODUCTION

Nephrotic syndrome (NS) is characterized as having edema, proteinuria greater than 40 mg/m²/h or a urine protein-to-creatinine ratio greater than 2.0, and hypoalbuminemia less than 2.5 g/dl¹. Nephrotic Syndrome is classified as primary or secondary, or by age of onset (congenital, infantile, or late-onset NS), and histopathologically as minimal change disease (MCD), mesangial hypercellularity, focal segmental glomerulosclerosis (FSGS), and membranoproliferative. The most practical classification is based on steroid response (steroid sensitive or resistant, with steroid sensitive illness further classified as frequent relapses and steroid dependent NS)². Steroid dependent nephrotic syndrome (SDNS) is described as patients who have steroid sensitive NS and have a relapse during weaning of the dose of steroids, or within 2 weeks of ceasing steroid treatment. Frequent relapsing nephrotic syndrome (FRNS) is defined as two or more relapses of nephrotic syndrome within six months of initiating steroids, or four or more relapses in any twelve-month period^{1,3}.

Nephrotic syndrome (NS) leads to homeostatic failure due to protein loss through damaged filtration membranes in the renal glomeruli and is often associated

with dyslipidemia.^{4,5} The precise mechanisms connecting dyslipidemia and NS are unclear but are thought to involve common metabolic pathways. Dyslipidemia disrupts glomerular structures, including the endothelium, mesangium, and podocytes, which have receptors for lipoproteins⁶.

In NS, uncontrolled lipoprotein accumulation in these cells leads to their proliferation and subsequent oxidative modification, forming oxLDL that stimulates antibody production. These oxLDL antibodies are processed by macrophages, transforming them into foam cells that promote inflammation and collagen synthesis, eventually leading to podocyte apoptosis, glomerular dysfunction, and chronic kidney disease^{7,8}. Dyslipidemia is also a key contributor to atherosclerosis, though specific markers of endothelial dysfunction are not yet well-established in clinical practice

One of the most prominent biomarkers associated with NS is asymmetric dimethylarginine (ADMA), an endogenous nitric oxide (NO) synthase inhibitor that limits NO synthesis and contributes to the pathophysiology of many human disorders.⁹ ADMA is a naturally occurring amino acid.¹⁰ ADMA has attracted a lot of attention in

Table 1: Comparison of baseline data between cases and control

	Nephrotic syndrome (N=25)	Control (N=25)	p-value
Age (years)			
Mean ±SD	11.8 ±3.4	11.7±3.1	0.96
(Range)	8:18	8:18	
Sex			
Male	17(68%)	13(52%)	0.24
Female	8(32%)	12(48%)	
Type of Nephrotic syndrome			
Steroid-Dependent	14(56%)	-----	
Steroid-Resistant	11(44%)	-----	
Height (cm)			
Mean ±SD	132.9±10.6	136.8±11.4	0.21
(Range)	(115-158)	(115-165)	
Weight (kg)			
Mean ±SD	35.6±8.3	43.1±11.4	0.01*
(Range)	(24-55.5)	(26-65)	
BMI			
Mean ±SD	20±3.3	23.4±7	0.03*
(Range)	14.4-30.3	11.1-39	
Systolic blood pressure (mm\Hg)			
Mean ±SD	117.8±13.9	116±9.8	0.60
(Range)	100:150	100:130	
Diastolic blood pressure (mm\Hg)			
Mean ±SD	76.4±12.2	76±8	0.89
(Range)	60:100	60:85	
Duration of the disease (months)			
Mean ±SD	58.9±45.8	----	
(Range)	4-168		

* significant at p value <0.05%

recent decades because it is an endogenous inhibitor of nitric oxide (NO) synthesis^{11,12,13}. ADMA is involved in the development of a variety of human disorders¹⁰.

According to existing research, ADMA is a biomarker that predicts increased mortality in chronic kidney disease (CKD)¹⁴ and faster progression of renal injury¹⁵. However, significantly less research has been conducted on ADMA in the pediatric population.

Our aim of the study is to assess the relationship between disease duration and endothelial dysfunction in patients with nephrotic syndrome, focusing on the evaluation of ADMA levels as potential markers of endothelial damage and cardiovascular risk

PATIENTS AND METHOD

This is a case-controlled study that included 50 children in the age group (8-18) years; they were divided as follows:

Group 1 (cases): included 25 children already diagnosed with steroid-dependent and steroid-resistant nephrotic syndrome

Group 2 (control): included 30 children healthy, with age and sex-matched with the previous groups.

Sample Size

For sample size calculation, the power analysis was performed using G power software using a t-test. Assuming type 1 error of 0.05, total power of 95%, and an effect size of 1.09 depending on the difference in ADMA

between nephrotic cases and control, the total sample size after adding 10% to adjust of follow-up loss was estimated at 50 cases divided into 25 nephrotic cases and 25 control.

Ethical Consideration

The study was approved by the “Faculty of Medicine, local Research Ethical Committee (FMREC), Minia University”. Written consents were signed by all the study population to the use of their data. All study populations were evaluated at pediatric nephrology outpatient clinics of El-Minia University hospitals, Minia University, Egypt, between January 2022 and May 2022. The study adhered to the tenets of the Helsinki Declaration.

Inclusion Criteria

- All children with steroid-dependent and steroid-resistant nephrotic syndrome.
- Children in the age group (8-18) years.

Exclusion Criteria

- Any cause for CKD other than nephrotic syndrome

Pediatric Evaluation

The cases were selected from the pediatric nephrology outpatient clinic. They were either steroid-dependent or steroid-resistant nephrotic syndrome. The controls were enrolled from children visiting the general pediatric outpatient clinic. All cases and controls were subjected to thorough history taking and general examination to ensure that they were devoid of systemic diseases and fulfilled the criteria for enrollment to our study.

Laboratory Investigation

Serum vitamin D

It was measured by enzyme-linked immunosorbent assay using an available commercial kit (Pelobiotech GmbH, Planegg, Germany)

ADMA

Kits supplied by BT LAB bioassay technology, assessment by EIA using Humareader 451572, Germany

Statistical Analysis Methodology

The analysis of the data was carried out using the IBM SPSS 27.0 statistical package software (IBM; Armonk, New York, USA). Graphs were performed using GraphPad Prism version 9.3.1 (GraphPad, San Diego, CA). Data were expressed as mean±SD, minimum and maximum range for quantitative parametric measures, or median, interquartile range (IQR) for non-parametric data, in addition to both number and percentage for categorized data. The student t-test for parametric data or Mann-Whitney U test for non-parametric data were used to compare two independent groups. Analysis of variance (ANOVA) was used for comparison between independent groups for parametric data followed by the Bonferroni post hoc test to assess intergroup differences. In contrast, the Kruskal-Wallis (KW) statistical test followed by Dunn's post-hoc test was used for non -non-parametric data. The Chi-square test or Fisher's exact test was used to compare categorical variables. Correlations between the parameters were analyzed by Pearson correlation analysis. A p-value of less than 0.05 was considered statistically significant.

Table 2: Comparison of lab data between cases and control

	Nephrotic cases (N=25)	Control (N=25)	p value
Serum vit D (ng\dl)	15.4±7.3	24.3±6.2	<0.001
Mean ±SD (Range)	(3-26.6)	(10-35)	*
Vit. D level			
Deficiency	7 (28%)	4 (16%)	<0.001
Insufficiency	18 (72%)	6 (24%)	*
Sufficiency	0(0%)	15 (60%)	
ADMA (ng\dl)			
Mean ±SD (Range)	664.2±183.4 (250-950)	183.8±57.5 (105-294)	<0.001 *

* significant at p value <0.05%

Table 3: Correlation between the duration of the disease and different markers among NS cases

	Duration of disease	
	R	P
Serum vit D (ng\dl)	-0.81	<0.001*
Serum ADMA	0.57	0.003*

* significant at p value <0.05%

RESULTS

The baseline comparison between the nephrotic syndrome (NS) group and the control group reveals the following:

- Age and Sex Distribution:** Both groups are similar in age (11.8 ± 3.4 years for NS and 11.7 ± 3.1 years for controls) with no significant difference (p = 0.96). The sex distribution shows more males in the NS group (68%) compared to the control (52%), though this difference is not statistically significant (p = 0.24. (Table 1)
- Anthropometric Measures:** Height was slightly lower in the NS group (132.9 ± 10.6 cm) compared to controls (136.8 ± 11.4 cm), but the difference was not significant (p = 0.21). However, weight and BMI were significantly lower in the NS group (p = 0.01 and p = 0.03, respectively), suggesting that patients with NS may have nutritional or growth impacts associated with the disease. (Table 1)
- Blood Pressure:** No significant differences were observed in systolic and diastolic blood pressure between the groups (p = 0.60 and p = 0.89, respectively), indicating that hypertension may not be a distinguishing factor at baseline between these groups. (Table 1)
- The laboratory data highlights significant metabolic and biochemical differences between NS patients and controls:
- Vitamin D Levels:** NS patients had significantly lower serum vitamin D levels (15.4 ± 7.3 ng/dl) compared to controls (24.3 ± 6.2 ng/dl), with a p-value of <0.001. A high percentage of NS patients were deficient or insufficient in vitamin D, contrasting with the control group where the majority had sufficient levels (60% sufficiency). (Table 2)
- Asymmetric Dimethylarginine (ADMA):** Levels of ADMA, a marker of endothelial dysfunction, were significantly higher in NS patients (664.2 ± 183.4 ng/dl) compared to controls (183.8 ± 57.5 ng/dl), indicating a potential increased risk of cardiovascular complications in NS patients (p < 0.001). (Table 2)

Correlation Between Disease Duration and Biomarkers in Nephrotic Syndrome Cases

The study further explored correlations between the duration of nephrotic syndrome and various biomarkers:

- Negative Correlation with Vitamin D:** There was a strong negative correlation between disease duration and serum vitamin D levels (r = -0.81, p < 0.001), suggesting that prolonged disease duration may worsen vitamin D deficiency in these patients. (Table 3)
- ADMA Correlation:** A moderate positive correlation was found between disease duration and ADMA levels (r = 0.57, p = 0.003), supporting the idea that prolonged disease may exacerbate endothelial dysfunction. (Table3).

DISCUSSION

This study examines the clinical and biochemical differences between patients with nephrotic syndrome (NS) and healthy controls, with a focus on anthropometric

measures, highlighting the significant impact of NS on growth and nutritional status.

Our study observed lower weight and BMI in NS patients compared to controls reflecting the common complications of the disease, such as protein loss, steroid therapy, and chronic inflammation and this agreed with a recent prospective cohort study that found that children with nephrotic syndrome are at higher risk of obesity and altered growth patterns due to chronic illness and the side effects of prolonged corticosteroid use¹⁶. Furthermore, the NEPTUNE study highlighted significant growth deficits in children with NS, with findings indicating that steroid-dependent courses are particularly detrimental to normal growth patterns¹⁷.

Similar findings were reported in a case-control study conducted at a tertiary health facility, demonstrating significant differences in nutritional status between children with NS and their healthy peers, with the NS group showing poorer growth outcomes. This study emphasizes the importance of regular nutritional assessments and interventions to mitigate growth retardation in these patients.¹⁸

This study assessed blood pressure measurements in patients with nephrotic syndrome (NS) compared to healthy controls, finding no significant differences in both systolic and diastolic blood pressure between the groups. These findings contrast with some prior studies that have reported elevated blood pressure in NS patients, particularly during active disease or frequent relapses. For instance, Sarkar et al. (2017) utilized ambulatory blood pressure monitoring and found that frequently relapsing NS patients exhibited increased blood pressure variability and elevated systolic and diastolic readings compared to healthy peers.¹⁹ This study suggests that the relapsing nature of NS, coupled with corticosteroid therapy, may contribute to hypertension, highlighting the importance of continuous blood pressure monitoring in these patients.

Additionally, Carboni et al. (2024) conducted a longitudinal analysis of blood pressure and lipid profiles in childhood NS and reported a significant association between NS and elevated blood pressure over time, particularly in steroid-dependent patients.²⁰

However, some studies have reported normal blood pressure levels in children with NS, aligning with the results of our study.

The American Journal of Nephrology published findings from Küster et al. (1990), which indicated that while some NS patients exhibit elevated blood pressure, many maintain normal levels, especially during remission periods²¹.

Moreover, a review article on hypertension in childhood nephrotic syndrome highlighted that not all children with NS develop hypertension; those without a history of frequent relapses or with well-controlled disease tend to maintain blood pressure within the normal range.²²

This study highlights the significant prevalence of vitamin D deficiency in children with nephrotic syndrome (NS) compared to healthy controls. The findings are consistent with several studies that have documented a high prevalence of vitamin D deficiency among children

with NS, similar to our findings. A study by Maji et al. (2022) from a tertiary care center in Northern India found that children with NS had significantly lower levels of serum 25-hydroxyvitamin D compared to healthy controls. This deficiency was more pronounced in patients with frequent relapses, underscoring the impact of disease severity on vitamin D status.²³

Yousefichaijan et al. (2018) also reported that children with NS exhibited lower serum vitamin D levels compared to healthy controls. The study highlighted that the urinary loss of vitamin D binding protein contributes significantly to this deficiency, particularly during active disease phases. They noted that frequent relapsers and those on prolonged corticosteroid therapy had the lowest vitamin D levels, suggesting a compounded effect of disease activity and medication on vitamin D status.²⁴

Similarly, Marzouk et al. (2019) investigated factors influencing vitamin D levels in children with NS and found that frequent relapsers had the most severe deficiencies.²⁵

In contrast to the above findings, some studies suggest that not all NS patients suffer from severe vitamin D deficiency. A study by Sharma et al. (2018) examined vitamin D levels in pediatric steroid-resistant nephrotic syndrome and found that while there was a notable deficiency, the levels were not significantly lower than those in the control group. This difference was attributed to proactive supplementation and better overall management of the disease in their study population.²⁶

Subandiyah et al. also reported varied levels of vitamin D deficiency among NS patients, noting that those with well-controlled disease and regular supplementation had similar levels of vitamin D compared to healthy controls. This suggests that with appropriate management, the extent of deficiency can be mitigated, contrasting with studies reporting severe deficiencies.²⁷

Our study found elevated ADMA levels in children with NS, particularly in those with more severe or relapsing forms of the disease. These findings align with several studies showing that ADMA, a known marker of endothelial dysfunction, is elevated in pediatric renal diseases, including nephrotic syndrome. Hsu and Tain (2021) discussed the role of ADMA as both a pathophysiological marker and a clinical biomarker in pediatric renal diseases, highlighting its elevated levels in NS patients compared to healthy controls. They emphasized that ADMA's role in promoting vascular damage could link NS to increased cardiovascular risk.⁹

Similarly, Aksu et al. (2019) reported higher serum ADMA levels in children with NS, linking these elevations to cardiovascular risk factors such as hypertension and dyslipidemia. Their findings support our results that ADMA levels are not just elevated but are associated with broader cardiovascular risk profiles in children with NS.²⁸

Contrary to these findings, Skrzypczyk et al. (2019) concluded that ADMA is not a significant marker of arterial damage in children with glomerular kidney diseases, including NS. This discrepancy suggests that while ADMA is elevated, it may not directly correlate

with structural arterial changes in all pediatric renal conditions. The variability in findings across studies underscores the complexity of ADMA's role and indicates that its impact may depend on disease severity and other individual factors²⁹.

Our results demonstrated a significant correlation between the duration of nephrotic syndrome and ADMA levels, suggesting that prolonged disease may exacerbate endothelial dysfunction. This observation is supported by findings from Jezierska and Stefanowicz (2022), who noted that longer disease duration is associated with sustained elevations in ADMA, potentially due to ongoing inflammation and oxidative stress in chronic renal conditions³⁰. Also, Hsu and Tain (2021) emphasized that ADMA plays a crucial role in pediatric renal diseases as a marker of endothelial dysfunction and cardiovascular risk. They noted that longer disease duration in chronic kidney conditions, including NS, is associated with sustained elevations in ADMA, which can contribute to long-term cardiovascular complications.³¹

However, Hyla-Klekt et al. (2015) found that while ADMA levels are elevated during NS relapse, they did not significantly correlate with disease progression markers such as proteinuria or GFR which disagreed with our findings. They suggested that elevated ADMA could be influenced by metabolic disturbances such as hypercholesterolemia rather than being directly linked to disease duration⁶.

Also, Aksu et al. (2019) examined the relationship between serum ADMA levels and cardiovascular risk factors in children with NS. The study found no significant difference in serum ADMA levels between children with NS and healthy controls, nor was there a significant correlation between ADMA levels and markers of disease progression, such as carotid intima-media thickness (CIMT) and blood pressure.²⁸ This finding contrasts with our results, where prolonged disease duration was associated with higher ADMA levels, suggesting that ADMA may not be a consistent marker for endothelial dysfunction in all pediatric NS patients.

Our findings also demonstrated a significant negative correlation between disease duration and vitamin D levels, highlighting the persistent risk of vitamin D deficiency in chronic NS. This is in line with the study by Maji et al. (2022), which reported that children with prolonged NS had significantly lower vitamin D levels compared to those with shorter disease durations, especially in frequent relapsers²³.

Conclusion

The observed correlations between disease duration, ADMA, and vitamin D levels in children with nephrotic syndrome emphasize the complex interplay of metabolic and cardiovascular risks associated with prolonged disease. These findings highlight the necessity for comprehensive monitoring and tailored interventions to address these risks effectively, improving long-term outcomes for pediatric NS patients.

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