Original Article

Study of Vitamin D and Interleukin 10 Levels in Uremic Peripheral Neuropathy in Children on Hemodialysis.

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ABSTRACT
Introduction: One of the frequent neurological complications of end stage kidney disease (ESKD) is uremic peripheral neuropathy (UPNP). A rapidly expanding literature on the relationship between 25(OH) vitamin D and UPNP shows a high link between them. Interleukin 10(IL-10) reduced level may contributes to UPNP. The aim was to assess the correlation between serum levels of vitamin D and IL-10 with the incidence of UPNP in children on regular hemodialysis.
Methods: A cross-sectional study included 71 children on regular hemodialysis, aged between 3 and 18 years. They were sub classified into two groups after assessment with nerve conduction studies (NCS) and neuropathy score; group I consisted of 24 patients with PNP and group II consisted of 47 patients without PNP. All patients were subjected to clinical examination, laboratory investigations and serum 25(OH) vitamin D and IL-10.
Results: Patients with PNP had significantly lower serum levels of IL-10 **(**P<0.001**) and 25(OH) vitamin D (P=0.003*) than those without PNP. 70% of patients with PNP had vitamin D deficiency with statistically significant difference (P < 0.001). The serum levels of 25(OH) vitamin D and IL-10 have a statistically significant negative correlation with severity of UPNP. There was a significant positive correlation between IL-10 and vitamin D levels (P= 0.022). Longer duration of dialysis with age more than 11 years, low vitamin D, and low IL-10 were independent variables for UPNP.
Conclusions: Low vitamin D and IL-10 levels increase the risk of PNP in children on hemodialysis
Keywords: End stage kidney disease, Uremic peripheral neuropathy, Interleukin-10

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INTRODUCTION

One of the frequent neurological side effects of chronic kidney disease (CKD) is peripheral neuropathy, sometimes referred to as uremic neuropathy of chronic kidney disease (UPNP). Up to 70% of patients at pre-dialysis and 90% of patients undergoing dialysis are affected by it [1]. The classical definition of peripheral neuropathy in CKD is distal symmetrical, mixed sensory neuropathy. Demyelination in addition to axonal degeneration can be seen in the nerves [2].

In children with CKD, peripheral neuropathy has a complicated etiology. It may be linked to uremic toxins buildup including myoinositol, parathyroid hormone, and others as well as nerve damage from reactive free radicals and aberrant electrolytes [3]. Particularly, hyperkalemia and hyperphosphatemia can disturb the normal ionic gradient and activate calcium-mediated mechanisms that result in axonal death, which in turn causes persistent depolarization of neurons [4].

In comparison to chronic conditions like type 1 diabetes, this comorbidity in juvenile CKD has gotten less attention [5, 6]. Peripheral neuropathy in children with CKD is likely underdiagnosed in absence of defined criteria and evaluation protocols, particularly in resource-constrained settings. Early detection of peripheral neuropathy and the variables contributing to its progression can aid in risk assessment and subject selection for focused therapies, reducing the likelihood of consequences such ulceration, infection risk, skin necrosis, and eventually limb loss [2].

More than 80% of CKD patients undergoing pre-dialysis suffer from a severe vitamin D deficit. Early on the course of the illness, vitamin D deficiency develops, and it tends to get worse as renal function is gradually lost [7]. In controlling the generation of inflammatory cytokines and proliferation of pro inflammatory cells prevention, vitamin D has been discovered to have a significant role in the modulation of the inflammatory and immune system [8]. This study aimed to assess the correlation of serum levels of 25(OH) vitamin D and IL10 with incidence of UPNP.

METHODS

Study group: In the Pediatric Nephrology and Neurology departments at Zagazig University Children's Hospital, we conducted this cross-sectional study during a 6-month period. Approval from Institutional Review Board (IRB) was obtained from our University (00-IRB #10182). We conducted the study on human volunteers in accordance with (Declaration of Heliniski), the world medical association's code of ethics. Before enrolment, parents' informed consent was obtained.

We examined 71 patients with ESKD who were receiving regular hemodialysis (2-4 weekly sessions of hemodialysis lasting 3–4 hours each). They ranged in age from 3 to 18 years. Children with co-occurring conditions that could affect the peripheral nerves, such as diabetes, connective tissue disorders, those with thyroid diseases, coeliac disease, or those taking medications that increase the risk of peripheral neuropathy, as well as those.

who have family history of peripheral neuropathy (inherited neuropathies), were excluded from the study. All study participants were subjected to a thorough

history taking and underwent both a general and nervous system checkup.

Laboratory investigations were done including CBC by "Sysmex XS 500i" supplied by Sysmex Japan. BD Vacutainer® Plus Plastic Serum Tubes were used to collect blood samples. Liver and kidney function tests measured using "Cobas 6000, e601 module, supplied by Roche Diagnostic (Germany)**,** C-Reactive protein (CRP) determined by Roche Cobas Integra 400, Iron indices (ferritin, iron) measured using Roche Cobas 6000 C 501, and Serum electrolytes which include sodium, potassium, serum calcium, phosphorus and magnesium determined by Roche Cobas 8000.

Serum 25(OH) vitamin D measurement: Levels of vitamin D were measured using a "Cobas 6000, e601 module" (Roche Diagnostics, Manniheim, Germany)

IL-10 measurement: Human IL-10 ELISA Kit (LifeSpan Biosciences, Inc., USA) [Catalog number: LS-F24131] was used to measure serum IL-10 levels. Prior to the assay, the serum was kept at 80°C; the usual range was 2–20 pg/mL. The ELISA techniques were carried out in accordance with the manufacturer's instructions. Both intra- and inter-assay CVs are 10%.

Intact Parathormone (I PTH) measurement: For the measurement of plasma intact PTH concentration, blood was collected into an EDTA-tube and immediately centrifuged owing to the short half-life of PTH and the plasma was frozen immediately and kept at -80°C until assayed by (Roche Cobas 6000 C501) **[9].**

Neuropathy score: Was done using the pediatric-modified Total Neuropathy Score (pedmTNS). This is a composite score of eight symptoms and indicators of neuropathy. A scripted interview was used to evaluate three different types of signs and symptoms: sensory (such as numbness, tingling, and pain), motor (such as trouble walking and handling stairs), and autonomic (such as dizziness and hot or cool hands or feet). A skilled clinician evaluated deep tendon reflexes, strength, and vibration sense using semi-objective assessment approaches. Each item is given a score between 0 and 4, and the sum of scores for all eight items range from 0 to 32. values more than or equal to 5 demonstrate the presence of PN as compared to healthy controls, and higher values represent more severe symptoms or a more proximal extension of neurological impairments **[10].**

Nerve conduction studies (NCS): Using the Micro Med equipment (Italy), (NCS) were performed in the neurology outpatient clinic. The median and sural nerves were chosen for the sensory nerve conduction studies, whereas the ulnar, median, common peroneal, and tibial nerves were chosen for the motor nerve conduction study. Surface disk electrodes were used for motor conduction tests, with the active electrode placed on the muscles and the associated nerves stimulated supramaximally.

STATISTICAL ANALYSIS

The data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 20, Chicago, USA). The normality of the data was first tested with a one-sample Kolmogorov–Smirnov test. The qualitative data were described as a number and a percent. The continuous variables were presented as mean ± SD (standard deviation). The association

between categorical variables was tested using a Chi-square test. The two groups were compared with the Mann–Whitney U test for nonparametric data. A logistic regression was used to identify independent predictors of immunological response to the hepatitis B vaccine among the samples studied. The tests were significant when $p \leq 0.05$.

RESULTS

Our study included 71children on regular hemodialysis, (35 males and 36 females), patients were sub classified into 2 groups: group I included 24 uremic patients with polyneuropathy and group II included 47 uremic patients, without polyneuropathy **Table 1**. Regarding age of our patients, there was statistically significant difference between both groups, being higher in patients with UPNP. But there was a non-significant difference between both groups in terms of height and BMI. A significant difference found regarding duration of dialysis, parathormone hormone, and alkaline phosphatase levels being higher in the neuropathy group ($p < 0.001$), while the other parameters showed no significant difference.

Patients with UPNP in the current study had significantly lower serum levels of IL-10 **(<0.001**)** and 25(OH) vitamin D **(0.003*)** than those without UPNP. Additionally, we found that, in comparison to patients without UPNP, 24.3% of patients with PNP had appropriate serum levels of vitamin D and 70% of them had vitamin D deficiency with statistically significant difference ($P < 0.001$) **Table 2.**

There is a statistically significant positive correlation between vitamin D and IL10 levels, moreover, age, duration of dialysis, parathormone, and alkaline phosphatase showed a statistically negative correlation with both vitamin D and IL-10 **Table 3**.

According to nerve score and neurophysiological studies, serum level of 25(OH) vitamin D and IL-10 has statistically significant negative correlation with severity of UPNP (peroneal motor nerve amplitude, tibial conduction velocity, median sensory nerve amplitude, ulnar motor latency, sural sensory nerve amplitude) as shown in **Table 4 - Figure 1**.

Validity of Vit D & Il-10 in evaluating risk of UPNP: In the current study, validity of IL-10 in prediction of peripheral neuropathy among studied groups at cut off level < 5.9 was 83.1% and validity of vitamin D at cut off level < 26 was 71.8% with significant validity **Table 5**.

Logistic regression of risk factors of peripheral neuropathy among pediatric CKD:

Potential variables were analyzed using regression analysis **Table 6**, older age [95% CI: 2.19(1.44-6.88), dialysis duration [95% CI: 3.77(1.82-10.26), P= 0.008], Low IL-10 [95% CI :3.38 (1.76-11.5]; P<0.001), Low Vitamin D [95% CI :2.66(1035-7.76); P= 0.005], were independent risk factors for peripheral neuropathy in uremic patients on hemodialysis.

Table 1: Demographic and laboratory data of the study populations

Variable	Peripheral neuropathy (n=24)	No peripheral neuropathy (n=47)	Test	p
Age (years)	13.63±3.23	9.87±2.7	**5.18**$^{\#}$	**<0.001****
Sex: Male N (%)	9(25.7%)	26(74.3%)	2.02$^{\$}$	0.16 NS
Female N (%)	15 (41.7%)	21 (58.3%)		
BMI: (Kg/m^2)	16.69±2.95	16.12±2.27	0.91$^{\#}$	0.37 NS
Duration of dialysis: (years)	8.5(3-13)	5(2-10)	**4.39**$^{\wedge}$	**<0.001****
TLC: (x10^3/mm^3)	7.25(3.7-12.9)	7(3.5-13)	0.96$^{\wedge}$	0.34 NS
PLT: (x10^3/mm^3)	237.5(120-487)	251(120-929)	0.48$^{\wedge}$	0.63 NS
Hb: (gm/dl)	9.68±0.93	9.78±0.98	0.43$^{\#}$	0.67 NS
Serum iron: (ng/ml)	63(33-167)	58(39-170)	1.12$^{\wedge}$	0.26 NS
Ferritin: (mcg/dl)	592(61.2-3600)	587(720-2293)	0.44$^{\wedge}$	0.66 NS
Parathormone: (pg/mL)	625(67-1600)	210(25-624.5)	**4.67**$^{\wedge}$	**<0.001****
Serum calcium: (mg/dL)	7.86±1.18	7.76±0.98	0.39$^{\#}$	0.70 NS
Serum phosphorus: (mg/dL)	5.42±1.71	5.15±1.14	0.82$^{\#}$	0.42 NS
Alkaline phosphatase: (U/L)	250(80-587)	135(132-145)	**3.93**$^{\wedge}$	**<0.001****
CRP: (mg/dl)	1.78(0.26-12)	1.6(0.3-12)	1.11$^{\wedge}$	0.27 NS

Data presented as mean ± Sd or median (range) or Number and percent $^{\#}$: independent t test $: Chi square test ($\chi^2$)
^: Mann Whitney test, NS: Non-significant (P>0.05) *: Significant (P<0.05) **: highly significant (P<0.001)

Table 2: IL-10 and 25 (OH) vitamin D levels in patients with and without peripheral neuropathy.

Variable	Peripheral neuropathy (n=24)	No peripheral neuropathy (n=47)	Test	P
IL-10 (pg/ml)	4.4(1-12)	11.1(4-15)	**5.1**$^{\wedge}$	**<0.001****
25(OH)Vitamin D (ng/ml)	19.5(5-45)	34(15-45)	**3.02**$^{\wedge}$	**0.003***
D level				
Deficient	14(70%)	6(30%)		
Insufficient	1(7.1%)	13(92.9%)	**17.64**$^{\$}$	**<0.001****
Sufficient	9(24.3%)	28 (75.7%)		

Data presented as median (range) or Number and percent $: Chi square test ($\chi^2$) ^: Mann Whitney test *: Significant (P<0.05)
**: highly significant (P<0.001) r: Spearman's correlation coefficient *: Significant (P<0.05) **: highly significant (P<0.001)

Table 3: Correlation between 25 (OH) vitamin D level & IL-10 with demographic & laboratory parameters.

Variable		IL-10 (pg/ml)	Vitamin D
25 (OH) vitamin	**R**	**0.272***	---
D(ng/ml)	**P**	**0.022**	---
Age "years"	**R**	**-0.380***	**-0.471****
	P	**0.001**	**<0.001**
BMI	**R**	-0.094	0.114
	P	0.434	0.345
Duration of dialysis	**R**	**-0.480****	**-0.256***
"years"	**P**	**<0.001**	**0.031**
Iron mcg/dl	**R**	0.224	0.050
	P	0.061	0.677
Ferritin ng/ml	**r**	-0.171	-0.085
	P	0.153	0.482
PTH pg/m	**r**	**-0.526****	**-0.427****
	P	**<0.001**	**<0.001**
Calcium	**r**	0.040	-0.100
8.8-10.8 mg/dl	**P**	0.738	0.409
Phosphorus	**r**	0.048	-0.173
3.3-5.6 mg/dl	**P**	0.692	0.149
Alkaline phosphatase	**r**	**-0.316***	**-0.266***
	P	**0.007**	**0.025**
CRP mg/l	**r**	-0.168	0.184
	P	0.162	0.125

r: Spearman's correlation coefficient *: Significant (P<0.05) **: highly significant (P<0.001)

Table 4: Correlation between 25 (OH) vitamin D level and IL-10 with nerve conduction studies of motor and sensory nerves.

Parameter		IL-10(pg/ml)	Vitamin D (ng/ml)
Peroneal motor Latency	**r**	**-0.295***	**-0.271**
	P	**0.013**	**0.022***
Peroneal motor amplitude	**r**	**-0.313****	**-0.249***
	P	**0.008**	**0.036**
Peroneal motor velocity	**r**	0.124	-0.001
	P	0.301	0.991
Tibial motor latency	**r**	0.122	0.165
	P	0.311	0.169
Tibial motor amplitude	**r**	0.004	-0.040
	P	0.973	0.743
Tibial motor velocity	**r**	**-0.315***	**-0.243***
	P	**0.007**	**0.041**
Median motor latency	**r**	0.039	-0.095
	P	0.750	0.429
Median motor amplitude	**r**	-0.013	0.140
	P	0.917	0.245
Median motor velocity	**r**	**-0.347****	**-0.410****
	P	**0.003**	**<0.001**
Ulnar motor latency	**r**	**-0.310****	**-0.254***
	P	**0.008**	**0.033**
Ulnar motor amplitude	**r**	-0.168	0.129
	P	0.161	0.283
Ulnar motor velocity	**r**	0.198	0.199
	P	0.098	0.097
Median sensory latency	**r**	0.064	0.120
	P	0.593	0.319
Median sensory amplitude	**r**	**-0.361***	**-0.313***
	P	**0.002**	**0.008**
Median sensory velocity	**r**	-0.042	-0.082
	P	0.730	0.498
Sural sensory latency	**r**	0.192	-0.148
	P	0.109	0.217
Sural sensory amplitude	**r**	**-0.312***	**0.234***
	P	**0.005**	**0.002**
Sural sensory velocity	**r**	0.019	-0.154
	P	0.876	0.201
Nerve score	**r**	**-0.492****	**-0.238***
	P	**<0.001**	**0.045**

r: Spearman's correlation coefficient *: Significant (P<0.05) **: highly significant (P<0.001)

Table 5: Validity of 25 (OH) Vitamin D & IL-10 in evaluating risk of UPNP.

Variable	Cut off	AUC (95% CI)	Sens	Spec	PPV	NPV	Accuracy	P
IL-10:	**<5.9**	**0.87 0.79-0.96**	**70.8**	**89.4**	**77.3**	**85.7**	**83.1**	**<0.001****
25(OH) Vitamin D	**<26**	**0.72 0.58-0.86**	**66.7**	**74.5**	**57.1**	**81.4**	**71.8**	**0.003 ***

AUC: Area under curve, CI: Confidence interval, Sens.: Sensitivity, Spec.: Specificity, PPV: Positive predicted value, NPV: Negative predicted value, *: Significant (P<0.05) **: Highly Significant (P<0.01)

Table 6: Logistic regression of risk factors of peripheral neuropathy among pediatric CKD.

Variable	B	CI	P
Age >11 y	1.12	2.19(1.44-6.88)	**0.01***
Dialysis duration >5y	1.52	3.77(1.82-10.26)	**0.008***
High Parathormone	0.19	1.82(0.15-4.4)	0.15 NS
High alkaline phosphatase	0.88	1.41(0.08-2.26)	0.08 NS
Low IL-10	1.22	3.38 (1.76-11.5)	**<0.001****
Low 25 (OH) Vitamin D	1.51	2.66(1.35-7.76)	**0.005***

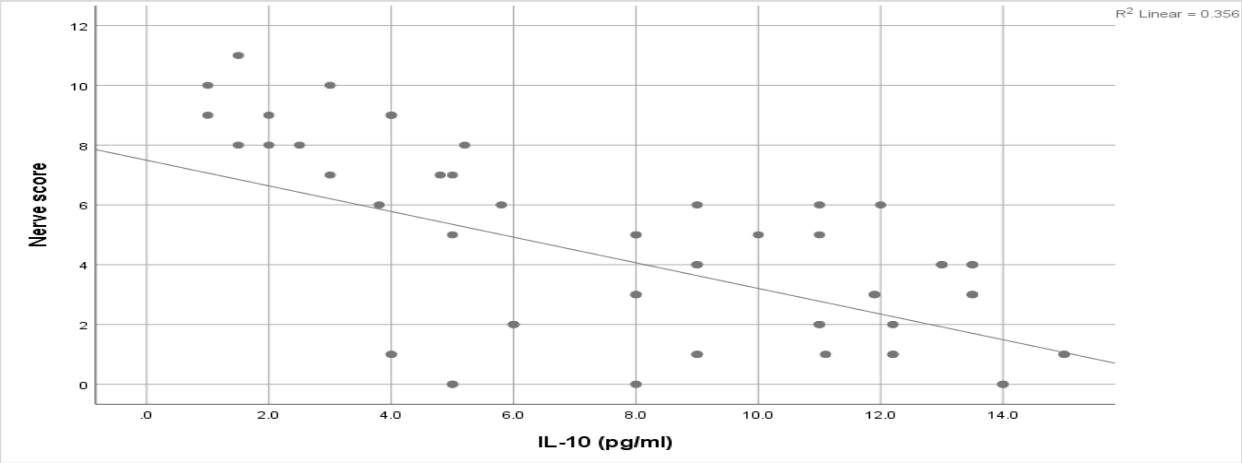

Figure 1. **Correlation between IL-10 with nerve score**

DISCUSSION

Neurological problems are very common in CKD, regardless of the reason. Injury can affect the nervous system at all levels, from the peripheral nervous system to the central nervous system, including conditions like autonomic and peripheral neuropathies, as well as conditions like cognitive dysfunction, and encephalopathy. The morbidity and mortality of patients are significantly impacted by the existence of these problems. Understanding the relevant physiological and pathological aberrations is therefore necessary for the clinical management of neurological problems in CKD [11].

Regarding vitamin D status in uremic children with peripheral neuropathy, mean 25(OH) vitamin D levels found to be significantly lower (0.003*) than patients without UPNP. This agreed with Thaier et al. who found highly significant decrease in the means of serum levels of vitamin D in patients with PN (p-0.005) [12], while Xiaohua et al. in their study aimed to determine the association between vitamin D deficiency and diabetic peripheral neuropathy (DPN), reported that there is insignificant difference regarding vitamin D deficiency prevalence (10–19.9 ng/mL) amongst patients with or without PN either painful or painless, however an increased frequency of severe deficiency of vitamin D levels in patients with painful DPN [13].

We found highly significant low levels of serum IL-10 in patients with UPNP
(4.4(1-12) pg /mL) in comparison to patients without UPNP (11.1(4-15) pg/mL). This result agreed with Zeng et al., who noted that TNFα, IL10, and HbA1c levels are significantly different in patients with and without DPN, which confirm inflammation role in neuropathy pathogenesis [14]. A previous study reported defective IL-10 synthesis in monocytes when exposed to a uremic environment [15].

In our study we found a significant positive correlation between vitamin D and IL-10 levels. Our results are in agreement with the highly significant correlation detected by Youssef et al., who studied the immune status of children on hemodialysis in relation to vitamin D [16]. The effect of vitamin D supplementation found to increase level of IL-10 and improve

neuropathy severity in patients with T2DM [17].

Vitamin D has a significant role in enhancing IL-10 release, which is suspected to be through a mechanism of CD4+ T-cell shift from an inflammatory type of T-helper (T- helper 17 and T-helper 1) to a protective regulatory T-cell and T-helper 2 [18]. Vitamin D protective effects against inflammation may be explained by its inhibitory actions on the production of multiple biochemical markers like tumor necrosis factor (TNF)-α, interleukin (IL)-2, IL-6, and interferon-γ (IFN-γ), in addition to stimulation of IL-10 release [19].

The association of PN with vitamin D deficiency in uremic patients seems to be multifactorial. Vitamin D deficiency is supposed to contribute to renal inflammation in CKD patients, through triggering the acute phase response, and eliciting oxidative stress that can induce neural ischemia and then PN development [20].

In the present study there is a significant negative correlation of vitamin D with neurophysiologic study and nerve score which support the hypothesis that vitamin D deficiency can cause UPNP. This result supported by previous studies that detected significant improvement of neuropathy scores in uremic children after vitamin D replacement either systemically or topical [21, 22].

He et al. found that diabetic patients with vitamin D deficiency had increased risk of polyneuropathy development [23]. In contrast to our results, Sonbhadra, et al. did not find association between vitamin D levels and UPN in their cohort [2].

IL-10 is a known anti- inflammatory cytokine. It is expressed in the peripheral nerves and DRG neurons. IL-10 reduced level had been implicated in the inflammatory process, contributing to PN [24], and this matches our findings regarding the significant negative correlations of IL-10 with nerve scores and neurophysiologic findings.

In the current study, validity of vitamin D in prediction of peripheral neuropathy among studied groups at cut-off level <26 had a sensitivity of 66.7% and specificity of 74.5%. Regarding IL-10, cut off level below<5.9 was of 70.8% sensitivity and 89.4% specificity. Abdelsadek et al. Demonstrated near results on their studies on diabetic patients (Vitamin D ≤ 28.3 ng/ml with sensitivity of 87.5%, specificity of 65%, and accuracy of 75 %.) [25].

On assessment of logistic regression UPNP risk factors, we found that older age (>11 years), longer dialysis duration (>7 years), Low Il-10 11.5], Low Vitamin D, were independent risk factors for PNP in uremic patients on dialysis. This is in agreement with what observed in prior studies [12]. While Gura et al failed to demonstrate a link between UPNP incidence and age [26].

Regarding duration of dialysis, our results agreed Ezzeldin et al [27] and Hussein et al [28]. In contrast Laaksonen et al. found no correlation between the dialysis duration and the presence of polyneuropathy [29].

Several studies carried before on type 2 diabetic patients and concluded that vitamin D level is an independent risk factor for peripheral neuropathy development [30]. Additionally, vitamin D's neuroprotective properties may help to restore neuronal damage and stop the development of DPN [31].

There was no association between high parathyroid hormone and polyneuropathy.

development, which disagreed with Hussein et al [28]. This may be due to different study design and sample size.

RECOMMENDATIONS

The early demonstration and screening of children with ESKD for uremic polyneuropathies are important. Measurement of serum levels of 25 (OH) vitamin D in all uremic children and vitamin D intake if there is vitamin D insufficiency is needed to decrease risk of uremic peripheral neuropathies.

LIMITATIONS

Being a single center study with small sample size, may exhibit some limitations to our study. Also, vitamin D levels may be affected by diet, seasonal variations or medications use.

CONCLUSIONS

The primary findings of this study confirm the substantial correlation between 25(OH) vitamin and IL-10 levels with PNP in uremic children on hemodialysis. This is primarily supported by the fact that children with UPNP had significantly lower mean levels of 25(OH) vitamin D and IL10. A strong favorable association between vitamin D and IL-10 was found.

ABBREVIATIONS

CKD	Chronic kidney disease
DNP	Diabetic peripheral neuropathy
ESKD	End stage kidney disease
IFN	Interferon
IL-10	Interleukin 10
IL-6	Interleukin 6
IL-2	Interleukin 2
NCS	Nerve conduction studies
PedmTNS	Pediatric-modified Total Neuropathy Score
UPNP	Uremic peripheral neuropathy
TNF	Tumor necrosis factor

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AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-author.
All authors have contributed to authorship, have read and approved the manuscript.
Conception and design of study: F A, M N A
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Analysis and/or interpretation of data: A E
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STATEMENTS

Ethics approval and consent to participate
This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Zagazig University (ZU-IRB #10182) and informed written consent was obtained in every case from their legal guardians.

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

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