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Relation of serum aluminum level to uremic pruritus in end-stage renal disease patients on maintenance hemodialysis

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ABSTRACT

Introduction: Uremic pruritus is a common discomfort in end-stage renal disease patients on long-term hemodialysis. It negatively affects patients' quality of life and is associated with increased mortality. The pathogenesis of uremic pruritus is complex. Aluminum is a toxic metal and common human allergen that causes an immune reaction in patients on hemodialysis. Aluminum is hypothesized to play a vital role in the pathogenesis of uremic pruritus. Controlling serum aluminum levels is still critical for patients on long-term hemodialysis.

Objectives: To determine the prevalence of hyperaluminemia and assess its correlation with uremic pruritus in patients on long-term hemodialysis.

Patients and Methods: We conducted a case-control study on 90 patients on long-term hemodialysis at the dialysis units of Ain Shams university hospitals. We used the 5-D itch scale numerical rating system to determine the presence and severity of pruritus in our study participants. We collected blood samples to estimate blood urea nitrogen levels pre- and post-dialysis, as well as the measured urea reduction ratio, serum creatinine, hemoglobin level, intact parathyroid hormone, ionized calcium, serum phosphate levels, iron study and serum aluminum levels.

Results: Our study showed no statistically significant differences between the pruritic and non-pruritic study groups (median values 9.78 [6.48–11.72] and 9.13 [6.3–10.4] for the pruritic and non-pruritic groups, respectively; $P = 0.32$).

Conclusion: The serum aluminum levels of our study participants were higher than the normal levels in humans. Patients in the pruritic group had higher levels than those in the non-pruritic group. However, aluminum levels were not significantly associated with either the presence or severity of pruritus in patients on long-term hemodialysis.

Implication for health policy/practice/research/medical education:
Elevated serum aluminum levels have deleterious effects on the human body, especially on patients on long-term dialysis. These effects include uremic pruritus, which affects patients' quality of life and is associated with increased mortality. Controlling serum aluminum levels attenuates these deleterious effects and improves patients' quality of life.

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Original Article

Introduction

Uremic pruritus is a pervasive discomfort with complex pathogenesis in patients with end-stage renal disease on long-term hemodialysis.

Aluminum, one of the toxic metals, is a common human allergen that provokes a variety of immune reactions, especially in dialysis patients.

Aluminum removal from dialysis water by reverse osmosis and deionization, as well as the use of widely available non-aluminum-containing phosphate binders, have significantly decreased the prevalence of severe aluminum toxicity in patients with end-stage renal disease on long-term hemodialysis. Nevertheless, controlling serum aluminum levels remains a fundamental requirement for patients on long-term hemodialysis (1).

The accumulation of aluminum in patients on long-term hemodialysis is caused primarily by the inefficient removal of the metal during dialysis and drug prescriptions, which could either be oral (aluminum-containing phosphate binders and antacids) or other medications that are commonly used during dialysis sessions (calcitriol, vitamin B complex, iron and erythropoietin) (1).

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Uremic pruritus is a common and obnoxious condition in patients with end-stage renal disease, affecting the quality of life and contributing to increased mortality (2). The prevalence of this condition ranges from 42% to 90% (2).

The pathogenesis of uremic pruritus is multifactorial and poorly understood. The main hypotheses for uremic pruritus pathogenesis include the loss of normal skin function, inflammation, dysregulation of the endogenous opioidergic system, and central/peripheral neural dysfunction. Other factors that may be involved in the pathogenesis of the condition include xerosis, increased parathyroid hormone levels, the presence of calcium phosphate-containing precipitates, iron deficiency anemia, and hepatitis virus infections (3).

Aluminum removal from the blood occurs only by glomerular filtration. Therefore, aluminum accumulates in patients with renal failure and increases susceptibility to aluminum toxicity. This metal accumulates primarily in the skeleton and the brain, resulting in clinical manifestations such as osteomalacia (resistance to vitamin D therapy), bone and muscle pain, iron-resistant microcytic anemia, and neurologic abnormalities, including speech disorders, encephalopathy, and dementia (4).

The main aluminum source in patients on maintenance hemodialysis is the water used for dialysate solutions and aluminum-containing phosphate binders. Aluminum concentrations in dialysate solutions have been significantly reduced as a result of reverse osmosis and deionization pretreatment of tap water. The widespread use of non-aluminum-containing phosphate binders has also decreased the risk of aluminum toxicity. Controlling serum aluminum levels, on the contrary, remains a fundamental requirement for patients on long-term hemodialysis, as aluminum removal by dialysis is not efficient (5).

Friga et al demonstrated a positive correlation between serum aluminum levels and uremic pruritus in 94 patients on long-term hemodialysis (6). Nonetheless, few studies have investigated the association between serum aluminum levels and uremic pruritus after the study by Friga et al. The association between serum aluminum levels and uremic pruritus among patients on maintenance hemodialysis remains undetermined (6).

Objectives

To determine the prevalence of high serum aluminum levels and assess its relationship with uremic pruritus in patients on long-term hemodialysis.

Patients and Methods

Study design

We included patients with end-stage renal disease undergoing dialysis at the dialysis units of Ain Shams university hospital.

Study population

This is a case-control study conducted on 90 patients aged >18 years on adequate hemodialysis for more than six months who had normal phosphorous levels, intact parathyroid hormone(iPTH) level of less than 600 pg/mL, and transferrin saturation levels of >20%. All our study participants had no history of viral (hepatitis B virus or hepatitis C virus) or autoimmune hepatitis, no malignancy, no chronic infection, no occupational or residential exposure to heavy metals, and no clinical evidence of jaundice or chronic skin diseases. Additionally, none of our female participants were pregnant during the study period.

Study procedure

We collected relevant demographic data (age, gender, profession and residence) of the study participants, reviewed their medical history (hemodialysis vintage, history of diabetes mellitus, hypertension, and other relevant co-morbidities), and reviewed their detailed drug history.

We considered patients to have uremic pruritus if pruritus occurred after hemodialysis with or without antipruritics as observed by trained dermatologists or nephrologists.

Pruritus could be constant or intermittent and accompanied by xerosis. The arms, head, abdomen, and back were the most commonly affected areas by pruritus. We used the 5-D itch scale numerical rating system to determine the presence and severity of pruritus in our study patients.

We collected blood samples from all study participants to conduct the following tests; blood urea nitrogen pre- and post-dialysis, measuring the urea reduction ratio, serum creatinine, hemoglobin, serum intact parathyroid hormone, ionized calcium, serum phosphate levels and performing iron studies. Moreover, serum aluminum levels were determined (by graphite furnace atomic absorption spectrometry).

Specimen collection

The serum was allowed to clot for 10-20 minutes at room temperature.

Assay principle

Prior to the procedures, blood samples were centrifuged, and all samples were deproteinized using trichloroacetic acid and microwave irradiation. All steps of sample preparation were conducted under a laminar flow hood. Using a Perkin-Elmer 3100 atomic absorption

spectrometer with Zeeman background correction and an L'vov platform equipped with a graphite furnace, aluminum levels were measured by a graphite furnace and an auto-sampler. Distilled and deionized water was conducted during all procedures. The working standard solutions were prepared using an aluminum standard solution containing 1000 mg/L of aluminum. Nitric acid (HNO_3, 65% m/m, 1.17 g/mL) was further purified by sub-boiling distillation. In order to avoid contamination, only plastic materials were used. All laboratory wares (e.g., pipette tips and volumetric flasks) were immersed for at least 48 hours in a 10% (v/v) HNO_3/ethanol solution and washed with purified water shortly before use. All sample and reagent preparation steps were performed on a clean bench to avoid contamination from the air.

Statistical analysis

All study data were reviewed for completeness and consistency. Statistical analysis was performed using SPSS (statistical package for the social sciences, version 20.0, SPSS Inc, Chicago, Ill, USA). Categorical variables were represented as numbers and percentages, while continuous variables were presented as the mean ± standard deviation for normally distributed data and the median and interquartile range for skewed data. The independent-samples *t* test was conducted for between-group comparisons. The chi-square test or Fisher's exact test, where appropriate, was conducted to determine associations between categorical variables. Pearson's correlation test was applied to determine correlations between serum aluminum levels, uremic pruritus, and its severity with other study parameters. Two-sided *P* values of <0.05 were considered statistically significant.

Results

By screening all patients with end-stage renal disease undergoing long-term hemodialysis at the dialysis units of Ain Shams university hospitals, there were unit records of 219 patients in total, of whom only 90 were eligible to participate in our study. Our study included 41 males (45.5%) and 49 females (54.5%).

Based on the participants' clinical history, physical examination findings, and 5-D itch scale scores, we divided the study population into two groups: the pruritic group (with itching as classified by the 5-D itch scale) and the non-pruritic group (No itching with 5-D itch scale scores of 0).

The pruritic group was made up of 45 patients, 19 males (42.2%) and 26 females (57.8%), with a mean age of 51.6 ± 14.98 years, while the non-pruritic group included 45 patients, 22 males (48.9%) and 23 females (51.1%), with a mean age of 47.53 ± 16.92 years.

There were no statistically significant differences in the two study groups' primary demographic data, as shown in Table 1.

In terms of medications administered on a regular basis during hemodialysis sessions, there was no statistically significant difference between the two groups (such as erythropoiesis stimulating agents [ESA], vitamin B complex, and carnitine).

In this study, 77.8%, 93.3%, and 84.4% of the pruritic group of participants were receiving ESA, vitamin B complex, and carnitine, respectively. While 86.7%, 91.1%, and 80% of the non-pruritic participants received ESA, vitamin B complex, and carnitine, respectively.

In our study, 31 (34%) participants had serum aluminum levels that exceeded the normal threshold level of 10 µg/L.

There were no statistically significant differences in the other laboratory data between the two groups, as depicted in Table 2. There was no statistically significant difference in the median serum aluminum levels of the participants in the two groups (9.78 [6.48–11.72] for the pruritic group and 9.13 [6.3–10.4] in the non-pruritic group, $P = 0.32$) (Figure 1).

There was also no statistically significant difference in the median serum ferritin levels of the participants in the two groups (685 [279.5–1077 ng/mL] for the pruritic

Table 1. Demographic characteristics of the study participants

		Pruritic patients (m = 45)		Non-pruritic patients (m = 45)		Student's *t* test	*P* value
		Mean	SD	Mean	SD		
Age (y)		51.60	14.98	47.53	16.92	1.21	0.23
HD vintage (mon)		76.47	60.93	75.78	62.52	0.05	0.96
		N	%	N	%	χ2	*P* value
Gender	Male	19	42.2	22	48.9	0.40	0.53
	Female	26	57.8	23	51.1		
Diabetes mellitus	Yes	17	37.8	9	20.0	3.46	0.06
	No	28	62.2	36	80.0		
Hypertension	Yes	34	75.6	33	73.3	0.06	0.81
	No	11	24.4	12	26.7		
Cardiovascular diseases	Yes	14	31.1	13	28.9	0.05	0.82
	No	31	68.9	32	71.1		

Table 2. Laboratory data and their correlations between both groups

	Pruritic patients (n = 45)		Non-pruritic patients (n = 45)		t-value*	*P* value
	Mean	SD	Mean	SD		
Calcium (mg/dL)	8.80	0.91	8.64	0.86	0.88	0.38
PO4 (mg/dL)	3.39	0.93	3.42	0.83	0.14	0.89
Albumin (g/dL)	3.71	0.65	3.83	0.34	1.04	0.31
HB (g/dL)	10.01	1.35	9.82	1.60	0.61	0.54
Iron (mcg/dL)	64.93	22.76	65.22	27.77	0.06	0.96
PTH (pg/mL)	301.67	191.89	299.53	170.84	0.06	0.96
TIBC (mcg/dL)	225.35	48.84	225.19	51.53	0.02	0.99
TSAT (%)	29.58	12.00	29.61	12.83	0.01	0.99
Urea 1 (mg/dL)	60.48	14.94	61.46	13.65	0.78	0.438
Urea 2 (mg/dL)	11.42	4.51	10.32	5.41	0.35	0.438
URR (%)	80.69	6.37	82.96	7.76	1.15	0.254
Aluminum (µg/L)	9.78	6.48–11.72	9.13	6.30–10.40	0.99**	0.32
Ferritin (ng/mL)	685.00	279.50–1077.00	794.80	262.50–1160.00	0.50**	0.62

PO4, Phosphorus; Hb, Hemoglobin; PTH, Parathyroid hormone; TIBC, Total iron-binding capacity; TSAT, Transferrin saturation; URR, Urea reduction ratio.
*Student's t-test; **Mann Whitney U test (median and interquartile range).

group and 794.8 [262.5–1160 ng/mL] in the non-pruritic group, *P*=0.62), as shown in Table 2.

The pruritic group's 5-D itch scale scores ranged from 6 to 25, with a mean value of 13.18±4.99. When correlating the itching measured by the 5-D itch scale with various factors, we found no significant correlation between the 5-D itch scale scores and hemodialysis vintage (*P* = 0.09).

Furthermore, diabetes mellitus, hypertension, and cardiovascular diseases had no significant correlations with 5-D itch scale scores (*P* = 0.99, 0.59, and 0.53, respectively), as displayed in Table 3. According to Table 3, both ESA and carnitine levels were not significantly correlated with 5-D itch scale scores (*P* = 0.58 and 0.25, respectively), while intravenous vitamin B demonstrated a negative correlation with higher 5-D itch scale scores, with the mean 5-D itch scale score being significantly higher in vitamin B complex non-receivers (18.67 ± 2.08) than receivers (12.79 ± 4.92), with a *P* value of 0.05 (Figure 2).

A highly significant positive correlation was detected between serum calcium levels and 5-D itch scale scores (*P* = 0.009). Likewise, there was a highly significant positive correlation between serum albumin levels and 5-D itch scale scores (*P* = 0.013). As depicted in Table 4, both hemoglobin and post-dialysis urea levels manifested significant positive correlations with 5-D itch scale scores (*P* = 0.044 and 0.050, respectively). All other laboratory data demonstrated no significant correlations with 5-D itch scale scores.

Discussion

Uremic pruritus is a common, troubling, and sometimes debilitating problem for chronic kidney disease and end-

Table 3. Correlation between 5-D itch scale scores and medical history and medications

		5D Itch Scale scores		Student's *t* test	*P* value
		Mean	SD		
Diabetes mellitus	Yes	13.18	6.11	0.001	0.999
	No	13.18	4.30		
Hypertension	Yes	13.41	5.18	0.55	0.59
	No	12.45	4.52		
Cardiovascular diseases	Yes	13.07	4.53	0.10	0.93
	No	13.23	5.26		
Intravenous vitamin B	Yes	12.79	4.92	2.04	0.05
	No	18.67	2.08		
Intravenous carnitine	Yes	13.00	4.93	0.55	0.58
	No	14.14	5.64		
Erythropoiesis stimulating agent	Yes	12.71	4.93	1.17	0.25
	No	14.80	5.14		

Table 4. Correlations between 5-D itch scale scores and laboratory data

	5-D itch scale scores	
	Pearson's correlation	***P* value**
Calcium (mg/dL)	0.385	0.009
PO4 (mg/dL)	0.202	0.183
Albumin (g/dL)	0.367	0.013
Hb (g/dL)	0.301	0.044
Iron (mcg/dL)	0.051	0.738
PTH (pg/ml)	–0.111	0.467
TIBC (mcg/dL)	0.199	0.191
TSAT (%)	–0.051	0.738
Urea 1 (mg/dL)	0.010	0.948
Urea 2 (mg/dL)	0.294	0.050
URR (%)	–0.266	0.077
Aluminum (µg/L)	–0.016*	0.916
Ferritin (ng/mL)	–0.082*	0.591

PO4, Phosphorus; Hb, Hemoglobin; PTH, Parathyroid hormone; TIBC, Total iron-binding capacity; TSAT, Transferrin saturation; URR, Urea reduction ratio.
*Spearman's rho correlation.

stage renal disease patients with poor psychosocial and medical outcomes. This condition is often under-reported by patients and overlooked by healthcare providers (7).

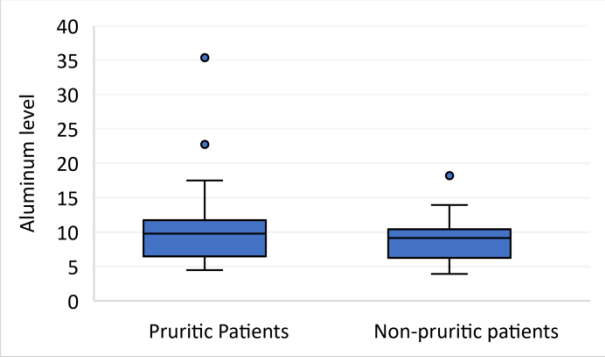

Figure 1. Box plot of the distribution of values (median, interquartile range, and outliers identified as dots) for aluminum levels between the two study groups.

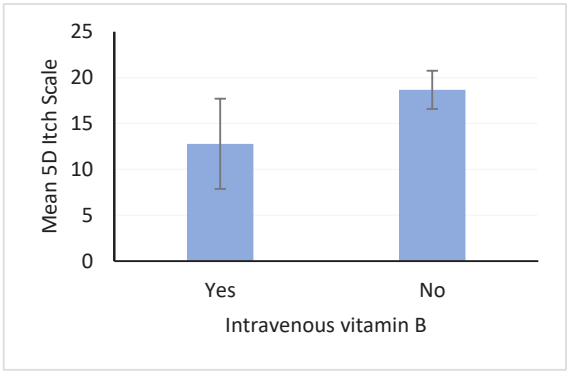

Figure 2. Error bars showing the correlation between intravenous vitamin B levels and 5-D itch scale scores in the pruritic group.

Uremic pruritus is a common troublesome condition in patients with advanced kidney disease, particularly individuals on chronic maintenance dialysis. It does not present with a distinguished dermatomal pattern and can vary from localized to generalized pruritus (8).

The etiology of uremic pruritus varies widely. Different data demonstrate that uremic pruritus prevalence ranges from 20% to 90%. Different settings significantly affect the way the prevalence of uremic pruritus varies. However, the prevalence of the condition declined significantly with the availability of better dialysis facilities, different dialysis modalities, and the easy access and adequacy of these dialysis facilities. The condition's prevalence also depends on the mode of dialysis, i.e., hemodialysis or peritoneal dialysis (9).

The pathogenesis of uremic pruritus is still ambiguous, while several potential etiologies are present, but none of which is fully proven.

These etiologies include inflammation and the release of specific cytokines during hemodialysis, mast cell proliferation, and increased deposition of the calcium phosphate complex in the skin due to secondary hyperparathyroidism. Other factors contributing to uremic pruritus pathogenesis include xerosis, environmental air pollution, inadequate dialysis, precipitated calcium phosphate crystals, iron deficiency anemia, neuropathy, and hepatitis virus infection (3).

One proposed etiology for uremic pruritus is a high serum aluminum level; however, few studies have investigated this possibility (6).

Aluminum is a commonly present metal in the environment, and its human exposure is through multiple sources, including (but not limited to) oral intake, drugs, and occupational exposure (10).

Our study investigated the association between serum aluminum levels and uremic pruritus in patients on hemodialysis. We attempted to identify what factors might affect the presence and severity of uremic pruritus.

According to our findings, the pruritic group consisted of 52 (57.8 %) females, and 38 (42.2 %) males, which is compatible with the findings of Dar and Akhter et al (11). Consistent with our findings, Ersoy and Akyar also had more females in their study populations of patients with uremic pruritus (8).

However, in contrast to our findings, some studies reported more males in the uremic pruritus population, such as those by Pisoni et al and Wikström (12,13). In other studies, the participants were equitably distributed between the two genders. Such studies include those by Mathur et al and Hu et al (14,15).

All the previous studies showed no significant correlation between gender distribution and uremic pruritus (8,11-15).

Our data revealed that the prevalence of hyperaluminemia was 34% in our study population, which is inconsistent with those of Jaffe et al, who reported that only 2.1% of their participants had hyperaluminemia (5).

Accordingly, Tsai et al reported low serum aluminum levels among patients on dialysis, with a median of 5.9[3.7–8.6] µg/L (1). Sharma et al demonstrated that 93.7% of their study participants had serum aluminum levels in the non-toxic range (4).

We found higher serum aluminum levels in the pruritic group than in the non-pruritic group; nevertheless, there was no significant correlation between serum aluminum levels and the severity of pruritus, as determined by the 5-D itch scale. This finding aligns with Hsu et al and Asghar et al (16,17).

In addition, Friga et al found a significant positive relation between serum aluminum levels and uremic pruritus in patients on hemodialysis, which is in disagreement with our data. They reported that reducing the serum aluminum level would reduce the severity of pruritus (6).

Another critical factor in uremic pruritus is the associated co-morbidities, such as diabetes mellitus and hypertension.

Our data ruled out any association between both diabetes mellitus and hypertension and pruritus severity as the 5-D itch scale scores of diabetic patients did not differ significantly from those of non-diabetic patients, which was confirmed by the studies of Zhao et al and Hsu et al who concluded that diabetes mellitus and hypertension do not affect the severity of pruritus (16,18). Similarly, Narita et al found no association between both diabetes mellitus and hypertension and the severity of pruritus (19).

Despite the non-significance of the association, our data showed that most of the patients in the pruritic group were non-diabetic and hypertensive, which is in line with the findings of Sarhan et al and Asghar et al (17, 20). However, in contrast with our findings, Afsar and Elsurer Afsar and Hsu et al reported that diabetes mellitus is significantly associated with uremic pruritus and its severity. They even reported that glycated hemoglobin is directly involved in the pathogenesis of uremic pruritus (16, 21).

Our study also investigated several factors that were hypothesized to play a contributory role in the pathogenesis of uremic pruritus and their association with the presence and severity of uremic pruritus.

Our results revealed that hemodialysis vintage has no effect on the presence or severity of uremic pruritus. On the contrary, Shirazian et al concluded that shorter dialysis vintage is associated with pruritus. Dialysis vintage of less than or equal to three months was associated with moderate-to-severe pruritus, and those on dialysis for over ten years were less likely to have pruritus. Similar findings were reported by Narita et al and Pisoni et al (12,19,22).

According to the study by Mathur et al, dialysis vintage has no effect on the severity or presence of pruritus, which aligns with our study's findings (14).

Variations in the association between uremic pruritus and hemodialysis vintage may be due to the different modalities of dialysis, different dialyzer membranes, different surface areas, and other factors that may be overlooked but affect the efficacy of dialysis (14). Accordingly, standardizing dialysis before further studies is indispensable.

One of the potential sources of aluminum in patients on dialysis is the use of intravenous medications such as vitamin B, iron, carnitine, and ESA supplementation.

We found that both ESA and carnitine did not affect both the presence and severity of uremic pruritus, with no documented changes in the severity of pruritus occurring using both medications. Nonetheless, Arzhan et al concluded that erythropoietin therapy could result in significant improvements in the prevalence and severity of pruritus (23).

We found that vitamin B supplementation induced a decrease in the severity of pruritus among the members of the pruritic group. Unfortunately, there is a paucity of data on the association between intravenous vitamin B use during dialysis sessions and uremic pruritus. However, Aramwit and Supasyndh stated that oral vitamin B might reduce itching in patients with uremic pruritus, while Simonsen et al reported no benefit of oral vitamin B over placebo in reducing the severity of uremic pruritus (24, 25).

Hence, it is essential to conduct further larger-scale, in-depth studies to evaluate the effects of intravenous vitamin B complex on uremic pruritus and its severity in patients on dialysis.

In our study, we assessed the relation between pruritus and some primary laboratory data. Our results showed that iPTH, serum iron, serum TIBC, transferrin saturation, and phosphate were not associated with the occurrence of uremic pruritus, or its severity as measured with the 5-D itch scale. Moreover, pre-dialysis urea and the urea reduction ratio demonstrated no association with uremic pruritus. Our data revealed that hyperalbuminemia, hypercalcemia, hyperhemoglobinemia, and elevated post-dialysis urea were positively correlated with the severity of itching in uremic pruritus measured 5-D itch scale (Figure 3).

Hsu et al concluded that elevated serum albumin levels increase the severity of itching in patients with uremic pruritus on dialysis, while Ozen et al and Ghassan et al reported no correlation between albuminemia and uremic pruritus (16,26, 27). Ghassan et al and Zhao et al also reported that calcium and phosphate show no association

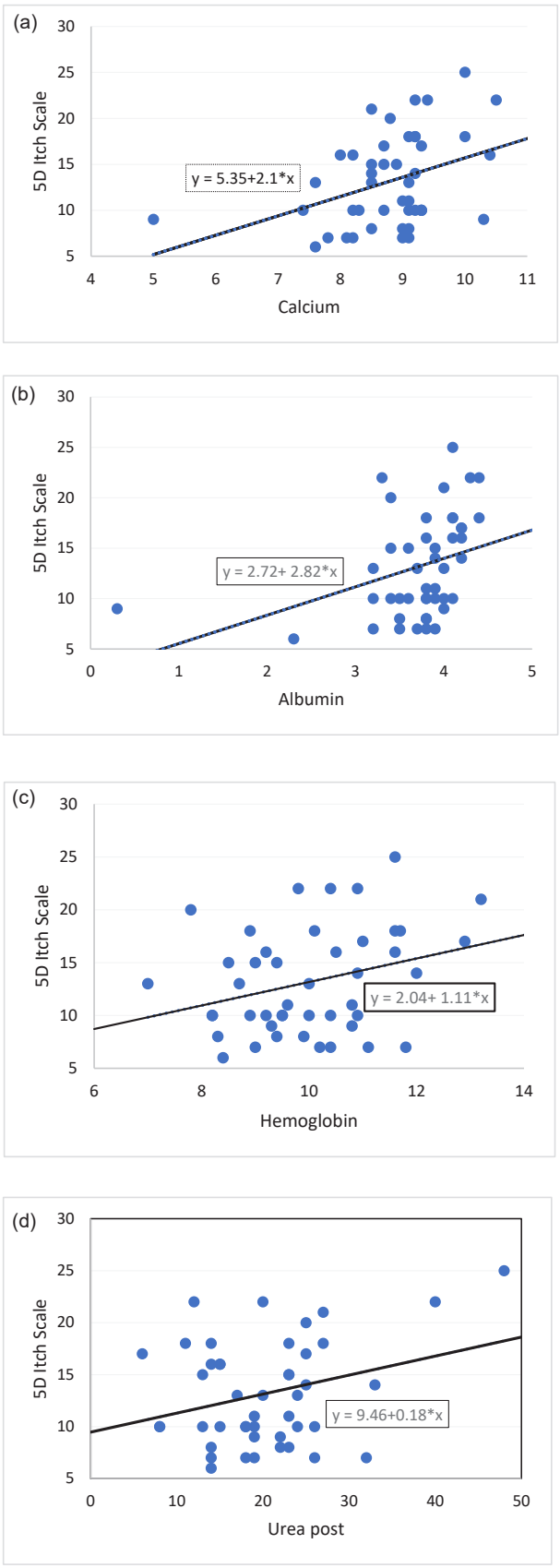

Figure 3. Scatter plot showing the positive correlation between 5-D itch scale scores and (a) serum calcium levels, (b) serum albumin levels, (c) hemoglobin levels and (d) urea post in the pruritic group.

with any change in the severity of pruritus in patients with uremic pruritus on dialysis. Moreover, Ozen et al also reported similar regarding calcium levels (18,26,27).

Furthermore, Zhao et al reported an association between elevated hemoglobin levels and increased uremic pruritus severity. In contrast, Ozen et al reported that hemoglobin levels demonstrated no correlation with any change in the severity of pruritus in patients with uremic pruritus on dialysis, with similar results reported by Ghassan et al (18,26,27).

We found that post-dialysis urea has a positive correlation with the severity of itching in patients with uremic pruritus on dialysis. Prior studies, including the study by Dar et al, reported correlations between elevated urea levels and itching severity in patients with uremic pruritus on dialysis (11).

However, there is a paucity of available data on the association between post-dialysis urea and the severity of uremic pruritus. Consequently, there is a need for further larger-scale, in-depth studies to investigate this association.

Finally, various factors contribute to pruritus and its severity in patients on hemodialysis, and there is still a paucity of studies on this subject. Hence, there is a need for further studies to assess these factors and their effects.

The serum aluminum level and its association with uremic pruritus are still ambiguous, and thus further larger-scale studies are indispensable for more clarification on this subject.

Conclusion

In conclusion, despite exceeding normal levels in humans and being higher in the pruritic group, the serum aluminum levels of our study participants were not significantly correlated with the presence or severity of pruritus.

Limitations of the study

The current study has some limitations. First, our inclusion criteria were strict regarding any minor laboratory disarrangement that could cause pruritus rather than the investigated cause. Secondly, age eligibility of older than 18 years further limited the population eligible for our study.

Authors' contribution

The study's principal investigators were IIS, AMT, and MNA. IIS, TWE, HSH, AMT, and MNA conceived and designed the study. IIS, AMT, and MNA revised the manuscript and critically reviewed the intellectual contents. All authors contributed to preparing the final draft of the manuscript, revised the manuscript, and critically reviewed the intellectual contents. In addition,

they all have read and approved the final manuscript and are responsible for its accuracy and integrity.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical issues

The study was carried out in accordance with the principles of the Declaration of Helsinki. The ethics committee of the faculty of medicine of Ain Shams university approved this study (reference number; FWA 000017585). Additionally, the institutional ethical committee at the faculty of medicine of Ain Shams university also approved all study protocols. Prior to intervention, written informed consent was obtained from all study participants. Besides, The authors have completely observed ethical issues (including plagiarism, data fabrication, and double publication).

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