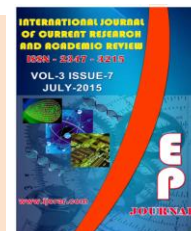




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The comparison of blood vitamin A level between patients under hemodialysis with and without cutaneous manifestations

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A B S T R A C T

Skin problems are common in patients with chronic renal diseases and in those with a long history of hemodialysis. Although some speculations have been suggested, the exact underlying mechanism (s) of these cutaneous problems is yet to be defined. It is an old finding that the level of plasma vitamin A increases in renal diseases. Interestingly, skin manifestations seen in vitamin A hypervitaminosis and dialytic patients are similar. This study aimed to investigate the presence of a possible connection between the level of serum vitamin A and the development of skin problems in patients receiving long-term hemodialysis. A total of 91 chronic dialytic patients (45 cases with and 46 cases without skin problems) were recruited from three educational centers. The levels of serum vitamin A, retinol-binding protein (RBP), Ca, P, Na, K, Fe, ferritin, uric acid, creatinine, iPTH, alkaline phosphatase (ALP), triglyceride, cholesterol, hemoglobin, hematocrit, fasting sugar and platelet count were compared between the two groups. The case group was significantly older than the control group (52.40 years vs. 48.48 years, $p=0.05$). They were, however, comparable for sex (29 males and 16 females in the case group vs. 28 males and 18 females in the control group, $p=0.73$). Both the mean levels of serum vitamin A ($0.45 \mu\text{mol/L}$ in the case group vs. $0.48 \mu\text{mol/L}$ in the control group) and RBP ($62 \mu\text{g/mL}$ in the case group vs. $68 \mu\text{g/mL}$ in the control group) did not differ significantly between the cases and controls ($p=0.68$ and 0.57 , respectively). The rate of patients with hypo- (40% in cases, 34.8% in controls) or hyper-vitamin A (15.6% in cases, 13% in controls) was not different significantly between the two groups ($p=0.76$). The only independently different parameter in comparison between the two groups was the mean level of serum Ca, which was significantly higher in the case group (8.92 mg/dL vs. 8.51 mg/dL ; $p=0.02$, Exp (B)=0.50). The optimal cut-off point was set at $\geq 8.85 \text{ mg/dL}$ (sensitivity=64.4%, specificity=63%). It is not likely that the level of serum vitamin A is associated with skin problems in patients with a history of chronic hemodialysis. Instead, an increased serum level of Ca may play a pivotal and independent role in this regard.

Introduction

Chronic renal failure is defined as progressive loss of renal function over a period of months or years. It is subdivided to five separate stages in which the disease worsens stage by stage by progressive loss of glomerular filtration and is defined by the creatinine measurement. The final stage of the disease which is stage five renal failure may end up in uremic syndrome in which some kind of renal replacement like hemodialysis or peritoneal dialysis is mandatory in order to keep the water and electrolyte balance of the body and failing to do so may end up in demise (1).

The number of hemodialysis patients is increasing about 15% annually in Iran and had summed up to a number about 14000 patients in 2007 (2). A complex phenomenon like chronic renal failure causes many different complications in the patients and could have sundry detrimental effect on different body organs; one of those different effects are different cutaneous manifestations in these patients like change of skin color, itching, skin dryness, contact dermatitis, pseudo Kaposi sarcoma, bullous dermatitis, calciphylaxis, nail changes and acquired perforating dermatoses (3, 4).

On the other hand the common cutaneous manifestations of vitamin A deficiency syndrome are so much similar to those ones in patients under hemodialysis like follicular hyperkeratosis, keratotic plaques with follicular papules, skin dryness and brittle hair (5). It has been inferred from some studies that we have got higher levels of serum vitamin A in end stage renal failure patients due to lack of transformation of the retinol to retinoic acid in ESRD patients kidneys (6-10). This is contrary to the results of other studies which have reported a lack of serum vitamin A in CKD patients (11).

Considering various cutaneous complications occurring in ESRD patients under dialysis and the fact that these manifestations are one of most bothersome complications to the patients their study seems to be mandatory. On the other hand many studies have pointed to the higher serum levels of vitamin A in patients under hemodialysis and have advocated limitation of the vitamin A supplementation besides other dietary limitations in these patients which could end up in exacerbation of the cutaneous complications.

It is very interesting to know that most of patients enrolled in the aforementioned studies have been under multiple vitamin containing supplementation treatments which included vitamin A causing higher serum vitamin A level in these patients (6-10) and so far there has been no clinical trial to study the real relationship of the level of serum vitamin A with the cutaneous manifestations; so the goal of this study is to perform a survey for finding the relationship of the level of the serum vitamin A and the cutaneous complications in the patients under hemodialysis.

Materials and Methods

In a peer reviewed descriptive-analytical study our chronic hemodialysis patients were divided to two case and control group based on the presence of the cutaneous lesions. Our sampling was based on enrolling all eligible patients under hemodialysis during years 2013 & 2014 in Tabriz Sina, Shahid Madani and Imam Reza hospitals by consecutive sampling and counting matches.

The sample size was based on the Aguilera et al (2002) study. In this study an average serum vitamin A level of 1.36 ± 0.77 was reported in their hemodialysis patients (11).

With considering the $\alpha=0.05$ and a 80% potency and a 10% deviation from mean, 45 patients got enrolled in this study for each case and control groups and the final sample size sunned up to 90.

Lastly 45 patients were considered for the case group with cutaneous lesions and 46 for the control group without lesions. Our inclusion criteria allowed every patient in the 18-60 year old age range having been under chronic hemodialysis for more than 6 months and having a PTH under 800 and patients with other systemic disorders with cutaneous lesions or patients having any other distinctive cutaneous maladies were excluded from the study.

This study was endorsed by the ethics committee of the tabriz university of medical sciences. In 45 patients with confirmed cutaneous lesions by a dermatologist serum vitamin A and retinol binding protein (RBP) levels were measured and the same survey was done for the 46 patients of the control group with no skin lesions. For serum vitamin A level measurement HPLC method was utilised and the serum retinol binding protein (RBP) level was measured by the ELISA. A serum vitamin A level of 0.3-0.8 $\mu\text{mol/Lit}$ was considered normal, the final levels were compared between two groups.

Statistical Analysis

Data are depicted as standard deviation \pm mean or mean standard error; abundance or percent depending on the quality of the obtained quantitative data. We used SPSS ver. 16 for the analysis of the data. The normal distribution of the obtained quantitative data was confirmed by Kolmogorov-Smirnov test. The quantitative comparison of the obtained data between two groups was performed by the T-test for

independent samples and the comparison of the qualitative data was performed by squared Chi and Fisher`s exact test. The logistic regression test was utilized as our multivariate model. For the exact determination of the cut point the ROC curve was Utilised; $p\leq 0.05$ was considered significant.

Results and Discussion

The basic information of the case and control groups are depicted in table 1. As it is depicted the mean age of the case group was significantly higher. Cutaneous manifestations and their abundance is summerized in Table 2. The average serum variables of the case and control groups are depicted and compared in Table 3. As seen only average serum hemoglobin and calcium of the case group was significantly higher than the control group.

Mean serum vitamin A level of the all enrolled cases occurred to be 0.46[0.04] $\mu\text{mol/Lit}$ (0.1 to 2.12); we found a low serum vitamin A level in 34 (37.4%) of cases, 44 (48.4%) had normal levels of serum vitamin A and 13 (14.3%) had increased levels; this measurements were consecutively seen in 18 (40%), 20 (44.4%), 7 (15.6%) of the patients in case group and 16 (34.8%), 24 (52.2%), 6 (13%) of the patients in the control arm; so there was no statistically significant difference between the two groups ($p=0.76$).

Considering the fact that skin dryness was the most prevalent cutaneous manifestation, this variable was measured and compared between the three groups of the patients with high, normal and low serum calcium levels and it consecutively occurred to be 17 (50%), 19 (43%) and 7 (53.8%) in the three groups and based on Chi-square analysis there was no significant difference ($p=0.73$).

Results of the multivariate analyses comparing the case and control groups are depicted in table 4. Only the serum calcium level showed a significant independent difference between the two groups; in other words higher levels of serum calcium was purportedly correlated with the occurrence of the cutaneous lesion in patients under hemodialysis.

The ROC curve depicted in graph 1 shows the predictive value of the serum calcium level for the prevalence of the cutaneous lesions (area under curve=0.66, p=0.01). The best cut point has been 8.85 mgr/dl of calcium level (specificity:63% & sensitivity: 64.4%).

Table.1 Basic Information of the Patients in case and control groups with and without cutaneous lesions

Variable		Cases (45 patients)	Controls (46)	P
Gender	Male	29 (64.4)	28 (60.9)	0.73
	Female	16 (35.6)	18 (39.1)	
Age		52.40±8.29 (60-25)	48.48±10.36	0.05
Smoking History		5 (11.1%)	3 (6.5%)	0.49
Cause Of Renal Failure	Glomerulonephritis	3 (6.7)	6 (13)	-
	Diabetes	18 (40)	13 (28.3)	
	Hypertension	11 (24.4)	13 (28.3)	
	Obstructive	3 (6.7)	4 (8.7)	
	NOS	10 (22.2)	10 (21.7)	
Duration In Dialysis (Months)		75.58 (8.42)	66.20 (9.63)	0.47
Number of Dialysis Sessions Per Week		2.64±0.57 (3-1)	2.52±0.55	0.30
Medications	Calcium Carbonate	37 (82.2)	42 (91.3)	0.20
	Rocaltrol	36 (80)	41 (89.1)	0.23
	Folic acid	33 (73.3)	40 (87)	0.10
	B-Complex	32 (71.1)	39 (84.8)	0.12
	Anti Hypertensive	17 (37.8)	13 (28.3)	0.33
	Eprex	2 (26.7)	17 (37)	0.29
	Renagel	6 (13.3)	12 (26.1)	0.13
	Venofor	10 (22.2)	13 (28.3)	0.51

All data are depicted as (minimum-maximum)/standard deviation±mean or the standard error from the mean value; 0.05 is considered significant ≤p-value. (*)

Table.2 Skin manifestations and their prevalence in the patients under dialysis

Cutaneous Manifestations	Prevalence	percent
Keratotic Plaque	1	2.2
Dryness Of Skin	15	33.3
Keratotic plaque & Dryness of skin	2	4.4
Dryness of skin & itch	20	44.4
Dryness of skin & hair loss	2	4.4
Dryness of skin & scaling	2	4.4
Itch & follicular papule	1	2.2
Dryness of skin, itch & hair loss	1	2.2
Dryness of skin, itch & hair loss	1	2.2

Table.3 Different measured variables in two case and control groups of the patients under dialysis

	Control Group (45 patients)	Case Group (46 patients)	p-value
FBS (mg/dL)	109. 14±41. 58 (57-222)	113. 78±65. 81 (62-368)	0. 69
Hemoglobin (mg/dL)	11. 63±2. 15 (8. 10-19. 20)	10. 67±2. 21 (5-15. 40)	0. 04
Hematocrit (%)	36. 92±6. 47 (26. 90-57. 40)	34. 43±5. 88 (16. 40-48)	0. 06
Platelet Count (109/L)	177. 53±58. 88 (60-320)	164. 76±54. 96 (78-311)	0. 29
BUN (mg/dL)	64. 86[5. 55] (11. 60-181)	66. 15[6. 14] (21-232)	0. 88
Creatinine (mg/dL)	8. 18 ±26 (3. 60-12)	8. 74±2. 24 (4. 50-13. 90)	0. 24
Triglyceride (mg/dL)	171. 98±92. 98 (54-410)	181. 47[22. 73] (28-916)	0. 72
Cholestrol (mg/dL)	152. 42±46. 48 (86-366)	158. 07 ±38. 90 (97-252)	0. 54
Alk Phosphatase (IU/L)	390. 83 [48. 35] (4. 30-1617)	410. 96 [43. 13] (8. 60-1313)	0. 76
Uric Acid (mg/dL)	6. 77±1. 38 (3-10)	7. 12±1. 66 (3. 60-13)	0. 29
Serum Iron (microg/dL)	69. 28±25. 80 (14-140)	69. 47±31. 54 (13. 160)	0. 98
TIBC (microg/dL)	336. 6±91. 00 (194-772)	328. 16±63. 12 (195-483)	0. 63
Ferritin (ng/mL)	352. 14 [37. 91] (6. 30-875)	438. 86[46. 86] (11-1000)	0. 15
Sodium (mEq/L)	139. 24±2. 63 (135-145)	138. 91±3. 10 (132-146)	0. 59
Potassium (mEq/L)	4. 97±0. 53 (4. 10-6. 50)	5. 07±0. 57 (4. 20-7)	0. 38
Phosphorus (mg/dL)	4. 69±1. 13 (3-8. 20)	4. 87±1. 21 (2. 80-8. 50)	0. 49
Calcium (mg/dL)	8. 92±0. 77 (6. 50-10)	8. 51±0. 83 (6. 40-10. 10)	0. 02
Ipth (pg/mL)	34. 32[3. 34] (2. 70-80)	31. 97[3. 25] (4. 10-76. 0)	0. 62
Vitamin A (micromol/L)	0. 45[0. 05] (0. 10-1. 78)	0. 48[0. 06] (0. 11-2. 12)	0. 68
RBP (microgram/mL)	62. 00[8. 00] (19-213)	68. 00[7. 00] (20. 00-204. 00)	0. 57
RBP/Vitamin A	0. 92[0. 10] (0. 18-2. 95)	2. 56[1. 44] (0. 14-66. 50)	0. 26

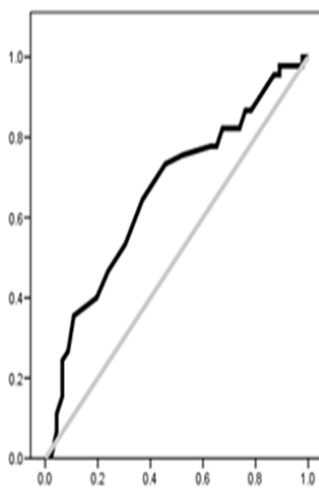
All data are depicted as (minimum-maximum)/standard deviation±mean or the standard error from the mean value
 0. 05 is considered significant≤p-value .(*)

BUN: blood urea nitrogen, **FBS:** fasting blood glucose, **TIBC:** total iron binding capacity, **iPTH:** intact parathyroid hormone, **RBP:** retinol-binding protein

Table.4 Results of multivariate analyses for the comparison of the two groups with/without skin lesion

Variable	Exp (B)	p-value	df	Wald	SE	B
Age	0. 96	0. 09	1	2. 91	0. 03	-0. 04
Serum Hemoglobin	0. 81	0. 06	1	3. 58	0. 11	-0. 21
Serum Calcium	0. 50	*0. 02	1	5. 60	0. 29	-0. 69

0. 05 is considered significant≤p-value .(*)



Graph.1 ROC curve showing the predictive value of the serum calcium level for the prevalence of cutaneous lesions in patients under hemodialysis

APPENDIX. Severity scoring of key symptoms				
SCORE	ERYTHEMA	INDURATION/ PAPULATION	EXCORIATIONS	LICHENIFICATION
0 = None	No evidence of erythema	No perceptible elevation	No evidence of excoriations	No evidence of skin thickening
1 = Mild	Very light pink, faintly detectable erythema	Barely perceptible elevation	Scant evidence of excoriations with no sign of deeper skin damage (i.e., erosion, crust)	Slight thickening of the skin, discernible only by touch and with markings minimally exaggerated
2 = Moderate	Dull red, clearly distinguishable erythema	Clearly perceptible, but not extensive, elevation	Several linear marks of skin, with some showing evidence of deeper skin injury (i.e., erosion, crust)	Definite thickening of the skin, with skin markings exaggerated so that they form a visible crisscross pattern
3 = Severe	Deep, dark red	Marked and extensive elevation	Many erosive or crusty lesions	Thickened indurated skin with skin markings visibly portraying an exaggerated crisscross pattern

Graph.2 Itching scale for determination of the patients with significant cutaneous lesions

Cutaneous lesions are prevalent between patients under chronic hemodialysis. We encounter different lesions in these patients including skin color change, itching, dryness of skin, contact dermatoses, pseudo kaposi sarcoma, bullous dermatitis, calciphylaxis, nail changes and acquired perforating dermatosis; skin dryness and itching have been reported to be the most prevalent lesions in these patients (12).

On the other hand its been shown for years in different occasions that the serum vitamin A level of these patients is significantly higher than the normal population; this higher serum level may cause manifestations of hypervitaminosis in which their cutaneous forms are so similar to the lesions found in chronic hemodialysis patients (6-10).

So, its possible for these patients to have higher levels of vitamin A causing cutaneous lesions. By performing this study we tried to analyse this possibility by measuring the serum vitamin A and retinol binding protein level in two groups of the patients under hemodialysis and comparing the results between two groups; the results of our study showed that the mean serum

level of these two variables had no significant difference between the two studied groups.

As far as we know there has been only one similar study so far; In a study by Delacoux et al 50 chronic hemodialysis patients were selected and divided to 4 groups; patients with normal skin, dry skin, dry skin with keratosis and mere keratosis; Thirty healthy individuals were chosen to be enrolled as normal controls; Serum levels of RBP, retinol and retinoic acid were measured and compared in these five groups; Similar to our findings there was no significant difference in all variables between these groups; but the serum level of RBP and retinol of the patients were significantly higher than the normal controls (13). In another study by Vannucchi et al it was shown that in chronic dialysis patients vitamin A hypervitaminosis caused no clinical manifestations including cutaneous lesions (14). In spite of all these, in a study performed by Vahlquist et al, it was suggested that there may be a possibility of the vitamin A accumulation in the skin of the chronic hemodialysis patients caused by its transportation by RBP causing various cutaneous manifestations (15). Some

researchers believe that increasing levels of vitamin A in chronic renal failure patients is indicative of rising plasma RBP levels and as long as proportional level of vitamin A to RBP is normal or low there will be no clinical implication (16). In order to clarify this matter we compared the proportional value of the serum vitamin A to RBP in these two group and found no significant difference justifying the aforementioned hypothesis. However it seems that the paucity of studies about the relationship of serum vitamin A level and cutaneous manifestations in chronic hemodialysis patients makes it mandatory to have more firm peer reviewed clinical trials to reach more established results. This is noteworthy that the vitamin A level measurements which have been made in such old and scarce studies may not have had the required sensitivity due to technical limitations at the time and the traditional routines of vitamin A supplementation in these patients may have caused these differences between new and old studies. An interesting finding of this study was the significant difference of the serum calcium level between the two case and control groups and the serum calcium level of the patients with skin lesions was significantly and independently higher than those control cases with no cutaneous lesions (8.92 mgr/dl compared to 8.51 mgr/dl) $p=0.02$.

It has been shown in previous studies that the severity of the uremic pruritus of chronic dialysis patients may be proportional to serum calcium, phosphate, magnesium and PTH levels; but it should be beared in mind that in all these studies there has been no specific relationship of this special kind of pruritus with all of these variables simultaneously (17-21). Even though we had significant higher serum levels of calcium in the case group, the serum levels of phosphate and i-PTH showed no

significant difference in these two groups. In a study performed by Lin and colleagues it was shown that reduction in serum level of calcium could cause amelioration of the skin itching (22). The role of serum calcium level has been implicated in causing acquired perforating dermatosis in chronic dialysis patients (23); these findings can justify the role of calcium level in such cutaneous findings. In this study we showed that when serum calcium level increased beyond 8.85 mgr/dl there is an increased occurrence of cutaneous complications. Wikstrom reported this cut point of serum calcium level in predicting of the itching of the chronic dialysis patients to be 10.2 mgr/dl (21); this reported cut point has been indexed based on serum albumin level. It seems that most of these studies have been emphasizing the role of the serum calcium level in causing skin itching and our study in finding a relationship between serum calcium and other kinds of cutaneous manifestations is a first in its kind. The real mechanism of the relationship of the calcium to skin itching has not been completely elucidated yet but it may be due to precipitation of calcium in skin or subcutaneous capillary plexus (21); future studies for elucidation of its pathophysiological basis seems to be crucial.

Conclusion

It is not likely that the level of serum vitamin A is associated with skin problems in patients with a history of chronic hemodialysis. Instead, an increased serum level of Ca may play a pivotal and independent role in this regard.

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