

The Role of Vitamin K in Renal Osteodystrophy in Haemodialysis Patients

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Abstract: Background: Renal Osteodystrophy (ROD) is a collective term describing the mixture of pathophysiological conditions that affect the skeletal system of patients with chronic kidney disease (CKD). It is most evident in patients on hemodialysis (HD), but usually starts early in the course of CKD. **Aim of the work:** The current work was designed to clarify the role of vitamin k in renal osteodystrophy in hemodialysis patients with and without liver cirrhosis. **Patients and methods:** This study included 60 patients of chronic renal failure (CRF) on regular hemodialysis with renal osteodystrophy subdivided into two groups according to presence or absence of liver cirrhosis: Group 1: included thirty (30) patients with liver cirrhosis, group 2: included thirty (30) patients without liver cirrhosis. Both groups were selected from Nephrology Units in New Damietta hospital, Al-Azhar University, Kafr Saad and Elzarka General Hospitals, All patients subjected to the following: Full medical history, clinical examination and investigation includes: liver and renal function tests, s calcium, s phosphorus, PTH and s vitamin k, radiological examination include DEXA scan and Abdominal ultrasonography. **Results:** osteoporosis in group 1 were 21 patients (70%) and group 2 (19 patients (63.3%) there was statistically non-significant difference. osteopenia in group 1 (9 patients (30%) and group 2 (11 patients (36.7%) there was statistically non-significant difference. patients with osteoporosis increased in group 1 than group 2, PTH in group 1 77 ranged from (35 – 550) and group 2 (175 ranged from (40 – 620) there was statistically non-significant difference. PIVKA_II in group 1 (0.27 ranged from (0.10 –3.99) and in group 2 (0.14 ranged from (0.11 –2.99) there was statistically non-significant difference. **Conclusion:** Patients suffering from renal Osteodystrophy showing deficiency in vitamin K, as revealed by elevated PIVKA-II levels. Vitamin K deficiency is a risk factor for many consequences including osteoporosis, osteopenia and bone fracture so vitamin K status may be a modifiable risk factor. Vitamin K should be assessed in CKD patients to avoid complications.

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Abbreviations: HD: Hemodialysis, ABD: Adynamic Bone Disease, ROD: Renal Osteodystrophy, PIVKA-II: Proteins Induced by Vitamin K Absence

1. Introduction

Renal Osteodystrophy (ROD) is a collective term describing the mixture of pathophysiological conditions that affect the skeletal system of patients with chronic kidney disease (CKD). It is most evident in patients on hemodialysis (HD), but usually starts early in the course of CKD (1) Vitamin K is crucial in human being for the appropriate bone matrix proteins carboxylation (2).

The relationship between bone abnormalities and vitamin K deficiency was established during hemodialysis of patients. Low levels of serum vitamin K are associated with increased risk of fracture in chronic HD patients (3).

Renal Osteodystrophy classified according to bone turnover into: bone turnover is increased in

osteitis fibrosa cystica, due to secondary hyperparathyroidism. Bone turnover is low in addition to an increased volume of unmineralized bone in cases of osteomalacia. (Adynamic Bone Disease (ABD), in which bone turnover is low. This represents the major bone lesion in HD patients. Mixed osteodystrophy, in which elements of both high and low bone turnover may be observed. This is also characterized by marrow fibrosis and increased unmineralized osteoid. Signs appeared to these diseases usually in the form of bone pain and fractures.

2. Aim of the work

The current work was designed to clarify the role of vitamin k in renal osteodystrophy in hemodialysis patients with and without liver cirrhosis.

3. Patients and methods:

3.1. Study designs:

This study included 60 patients of chronic renal failure (CRF) on regular hemodialysis with renal osteodystrophy subdivided into two groups according to presence or absence of liver cirrhosis: Group 1: included thirty (30) patients with liver cirrhosis. Group 2: included thirty (30) patients without liver cirrhosis. Both groups were selected from Nephrology Units in New Damietta hospital, Al-Azhar University, Kafr Saad and Elzarka General Hospitals.

3.2. Ethical Aspects:

The knowledgeable agreement was obtained from all contributors. The research protocol did not interfere with any medical recommendations or prescriptions.

3.3. Inclusion criteria:

Patients with chronic kidney disease on regular hemodialysis and diagnosed as renal osteodystrophy and 30 patients with liver cirrhosis were included.

3.4. Exclusion criteria:

Patients with hepatocellular carcinoma and patients on oral anticoagulant.

3.5. Study protocol:

All Patients were submitted to full history taking, thorough clinical examination, laboratory investigations includes: Serum uric acid, Serum albumin, prothrombin time, Alkaline phosphatase, Serum calcium, Serum phosphorus, Parathyroid hormone measurement (PTH), Assessment of vitamin K by proteins induced by vitamin K absence (PIVKA-II) detected by Enzyme Linked Immuno Sorbant Assay (ELISA) by (PIVKA-II) ELISA Kit.

Radiological examination

Abdominal and pelvic ultrasound and Dual energy x-ray absorptiometry (DEXA) scan.

Measurement of bone mineral density:

Using DEXA LUNAR DPX apparatus at lumbar spine (L2-L4) and femoral neck, The BMD measurement compared with sex and age matched control as well as sex matched young healthy control (standard value of the apparatus). The values are then expressed as percentiles or standard deviation scores called Z and T scores Osteopenia T- score-1 to - 2.4 SD and Osteoporosis \geq -2.5 (4).

3.6. Statistical methodology:

The data were examined using the statistical package for social sciences (SPSS) 17.0 program. Quantitative variables were presented in the form of Mean and Stander Deviation (mean \pm SD), while Qualitative variables presented by relative frequency and percentage. Chi-square test was used to compare qualitative variables between groups. Unpaired t-test was used to compare quantitative variables, in parametric data. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy were calculated and significance level (P) value was expressed as follows: P >0.05 (Insignificant); P<0.05 (Significant); and P<0.01 (High significant).

4. Results:

The results revealed that, out of 30 patients, 13 cases (43.3%) were females and 17 cases (56.7%) were males in group 1. 16 (53.3%) were females and 14 cases out of 30 (46.7%) were males in group 2, there was a non-significant variation among groups 1 and 2 regarding sex distribution, age ranged from 45.0 to 60.0 years in group 1 and in group 2 range from 48.0 to 61.0 years. There was statistically non-significant decrease of age in group 1 (54.03 \pm 3.48) in comparison to age in group 2 (55.17 \pm 3.06).

With respect to systolic or diastolic blood pressure, a non-significant differences among groups 1 and 2 was observed. Also, the results revealed to a non-significant variation between groups 1 and 2 with respect to dialysis duration (years). Serum album was decreased significantly in group 1 compared with group 2. Also, there was a significant prolongation of PT in group 1 than group 2, and a non-significant variation in the levels of calcium and phosphorous and alkaline phosphatase between groups 1 and 2.

As regard to osteoporosis there was statistically non-significant difference in both groups (group 1 was 21 patients (70%) and group 2 19 patients 63.3%). And osteopenia was not significantly varied between the two groups. (9 patients (30%) in group 1, and 11 patients (36.7%) in group 2,.

PTH in group 1 was ranged from (35 – 550) and group 2 ranged from (40 – 620) there was statistically non-significant difference.

PIVKA II in group 1 (0.27) ranged from (0.10 –3.99) and in group 2 (0.14) ranged from (0.11 –2.99) there was statistically non-significant difference.

Table (1) comparison between studied groups as regard to different variable

VARIABLE		Mean	S. D	Minimum	maximum	t	P
Systolic (mmHg)	Group I	118	11.26	100	140	1.076	0.286 (NS)
	Group II	121.67	14.87	100	150		
Diastolic (mmHg)	Group I	76.33	9.28	60	90	1.499	0.139 (NS)
	Group II	80.33	11.29	60	100		
Dialysis duration years	Group I	4.12	1.13	2.5	7	1.413	0.163 (NS)
	Group II	4.63	1.65	2.5	10		
Albumin (mg/dl)	Group I	2.68	0.37	3.50	5.10	13.89	<0.001*
	Group II	3.97	0.35	3.40	5.30		
Prothrombin time (sec.)	Group I	14.93	1.26			11.27	<0.001*
	Group II	11.88	0.78				
Calcium (mg/dl)	Group I	9.02	1.61	8.70	10	0.705	0.483 (NS)
	Group II	8.71	1.72	8.30	10.10		
Phosphorous (mg/dl)	Group I	4.72	.97	8.30	10	0.863	0.392 (NS)
	Group II	4.94	1.03	8.20	10		
Alkaline phosphatase	Group I	322.70	164.82			0.482	0.632(NS)
	Group II	302.47	160.43				

Table (2): DEXA Statistical evaluation of groups 1 and 2.

DEXA	Group 1		Group 2		χ^2	P
	No	%	No	%		
osteoporosis	21	70%	19	63.3%	1.179	0.555
osteopenia	9	30%	11	36.7%		

Table 3. PTH and PIVKA II levels in groups 1 and 2.

	Group 1 (N=30)	Group 2 (N=30)	Z	P
PTH	77 (35 – 550)	175 (40 – 620)	1.251	0.211
PIVKA II	0.27 (0.10 – 3.99)	0.14 (0.11 – 2.99)	1.613	0.107

5. Discussion:

Serum level of PIVKA-II was increased non-significantly in group1 in comparison to group 2. Katarzyna et al., 2016 (5) reported that plasma PIVKA-II concentrations increased (>0.66 ng/mL) in 27.5 % of the HD patients, also they recorded PIVKA-II levels in HD patients and healthy subjects, and reported that PIVKA-II concentration in the serum of HD patients not significantly different than in healthy subject. Holden et al., 2010 (6) studied 172 subjects with CKD, stage 3–5, they found that the symptom for subclinical deficiency of vitamin K were found in 6 % of the subjects depending on assessment of circulating K1, by 60 % depending on OC carboxylation and by 97 % based on PIVKA-II levels. Lee et al., 2012 (7) carried an investigation on 24 HD subjects, they reported an elevation in PIVKA-II levels in 73 % of cases, whereas, Schlieper et al., 2011 (8) recorded an abnormal PIVKA-II levels in 64 % of HD subjects. Nerlander et al., 2009 (9) found that the insufficiency in vitamin K concentration depends on PIVKA-II level in 14.6 % of cases (where 60 % of

cases was treated with warfarin).

There was statistically significant increase of ALT in group 1 (RO with liver cirrhosis) (41.87+6.33) than group 2(RO without liver cirrhosis) (37.27+4.82), AST in group 1(RO with liver cirrhosis) (41.53+10.56) than in group 2(RO without liver cirrhosis) (35.70+5.66). This in agreement with Haber et al., 2009 (10) who reported that Patients with hepatic cirrhosis usually have normal or only somewhat increased in the concentration of ALT and AST in the serum.

As regard to serum bilirubin there was statistically significant increase in group1 (RO with liver cirrhosis) (2.07+0.70) than group2 (RO without liver cirrhosis) (0.97+0.09) which is in normal range, serum albumin statistically significant decrease in group1 (RO with liver cirrhosis) (2.68+0.37) than group2 (RO without liver cirrhosis) (3.97+0.35) but Prothrombin time increase in group 1(14.93+1.26) than group 2(11.88+0.78). Kujovich et al., 2005 (11) reported that the liver is the main the site of synthesis of all inhibitors and coagulation factors nearly, where

these factors plays an important role in blood coagulation. The hepatic reticuloendothelial system is moreover implicated in the clearance of activated coagulation factors as well as enzyme-inhibitor complexes. In addition to its role in the synthesis of coagulating factors. Usually, acute and chronic liver disease was associated with an abnormality in the coagulation processes.

Osteoporosis in group 1 was (RO with liver cirrhosis) (19 patients) (63.3%) and in group 2 (RO without liver cirrhosis) (18 patients) (60.0%). Osteopenia in group 1 (7 patients) (23.3%) and in group 2 (5 patients) (16.7%) normal DEXA scan in group 1 (4 patients) (13.3%) and in group 2 (7 patients) (23.3%). This is in agreement with a study published by Hart et al., 1985 (12) who reported that in osteoporotic patients who subjected for fractures had drop in vitamin K levels in 70% of patients than age-matched controls. This relationship has been frequently established with Booth et al., 2000 (13) which carried on 900 women and men, they found patients with lowest concentration of vitamin K in the serum had a 65% more risk of hip fracture in comparison with patients with high concentration of the nutrient. Cockayne et al. 2006 (14) reported that lower levels in circulating menaquinone and phylloquinone have been noticed in individuals with reduced BMD and supplements with vitamin K2 was efficient therapy for overcoming of osteoporosis, also, they carried an investigation randomly on controlled human along 6 months duration at least, they showed that vitamin K1 or K2 significantly reduced the frequency of fracture risk and decided that vitamin K decreased bone loss with K2 being more efficient, 60% dropping in the risk of vertebral fracture, 77% in the hip fracture and 81% in all non-vertebral fractures.

Patients with history of fracture in group 1 (RO with liver cirrhosis) were 15 patients (50 %) and in group 2 (RO without liver cirrhosis) 7 patients (23.3%)

Fusaro et al., 2011 (15) reported that osteoblasts secrete osteocalcin which being a vitamin K dependent protein and plays a main role in keeping proper bone turnover. Vitamin K deficiency may lead to a high in the probability of bone fracture risk and supplementation with vitamin K may avoid bone loss and diminish fracture risk. Fusaro et al., 2016 (16) reported that warfarin persuades a vitamin K scarce state by inhibiting the recycling of vitamin K, which leads to an inhibition of vitamin K-dependent proteins and showed that hemodialysis subjects treated with warfarin for more than 1 year had an increased risk of vertebral fractures in comparison with non-warfarin treated group.

Parathyroid hormone measured in group 1 (RO with liver cirrhosis) 77 ranged from (35-550) and in group 2 (RO without liver cirrhosis) 175 ranged from

(40-620).

Muntner et al., 2009 (17) reported that with osteitis fibrosa cystica there is an increase in parathyroid hormone (PTH) with GFR <70 ml/min/1.73m². While Ferreira et al., 2008 (18) reported that in a dynamic bone disease there is decreased bone turnover and collagen synthesis. This typically occurs later on in pre-dialysis CKD or end-stage renal disease (ESRD) often seen in diabetes and Mathew et al., 2007 (19) explained the mechanism that causes this syndrome due to over-suppression of PTH secondary to the use of calcium based phosphate binders and vitamin D analog supplementation. So In 2009, the KDIGO guidelines (20) suggested serum calcium, phosphate and PTH should all be checked at intervals based on the CKD stage. Hemoglobin level in group 1 (RO with liver cirrhosis) (10.44±1.33) and in group 2 (RO without liver cirrhosis) (9.44±2.19) these in agreement with (5). Serum calcium in group 1 (RO with liver cirrhosis) (9.02±1.61) and in group 2 (RO without liver cirrhosis) (8.71±1.72), phosphorous in group 1 (4.72±0.97) and in group 2 (4.94±1.03) (5).

6. Conclusion

Renal Osteodystrophy patients have vitamin K deficiency, as revealed by elevated concentrations of PIVKA-II. Vitamin K deficiency is a risk factor for many consequences including osteoporosis, osteopenia and bone fracture so vitamin K status may be a modifiable risk factor. Vitamin K should be assessed in CKD patients to avoid complications.

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