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Prevalence of Relative Hypoparathyroidism among Hemodialysis Patients: Role of Vitamin D, Aluminium and Magnesium

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Abstract: *Factors of pathogenesis and prognosis of prevalence hypoparathyroidism among hemodialysis (HD) are largely unknown. Some studies have shown increasing risk of death among HD patients with low serum intact PTH (iPTH). This study was to evaluate the role of vitamin D, aluminium (Al) and magnesium (Mg) as risk factors of hypoparathyroidism prevalence among HD patients. This study included 63 HD patients and 22 healthy volunteers as normal control group. Any studied subject with history of previous parathyroidectomy was excluded. Patients with relative hypoparathyroidism had higher levels of aluminum, calcium and lower levels of urea reduction ratio (URR), alkaline phosphatase (ALP), magnesium and 25(OH)D than those with hyperparathyroidism, there were also significant negative correlations between iPTH and serum 25(OH)D, Mg & Al in relative hypoparathyroidism group. In HD groups, The levels of 25(OH)D and hemoglobulin were significantly lower, whereas the levels of serum Al, ferritin, phosphorous and ALP were significantly higher in comparison with those in the control group. In addition, in HD patients there were a significant negative correlation between serum Al and MCV. It was observed that there were significant relations between low iPTH and 25(OH)D, Mg, and Al levels in relative hypoparathyroidism patients.*
Key words: *Hemodialysis, Intact parathyroid hormone, Relative hypoparathyroidism, Serum aluminium, Vitamin D*

I. Introduction

Chronic kidney disease (CKD) is an international public health problem affecting 5–10% of the world population [1]. As kidney function declines, there is a progressive deterioration in mineral homeostasis and changes in circulating hormones. These changes include intact parathyroid hormone (iPTH; active form of PTH), 25-hydroxy vitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1,25(OH)2D], other vitamin D metabolites, fibroblast growth factor-23 (FGF-23) and growth hormone. In CKD, the conversion of 25(OH)D to 1,25(OH)2D is impaired, reducing intestinal calcium absorption and increasing iPTH [2]. In renal failure, the kidney fails to response adequately to PTH, which normally promotes calcium reabsorption and also to FGF-23, which enhances phosphate excretion [3]. Bone abnormalities are found in most patients with CKD requiring dialysis (stage 5D) and also in the majority of patients with CKD stages 3–5D. The prevalence of relative hypoparathyroidism may increase to 34.9% [4], 48.4% [5] or 64.4% [6] among HD patients with unknown pathogenesis and prognosis factors. The hypoparathyroidism is associated with adynamic bone diseases (ABD) characterized by low turnover [7]. The studies have shown increasing risk of death among dialysis patients with low serum iPTH [8, 9]. The measurement of serum iPTH is used to evaluate bone diseases [10]. In CKD, the vitamin D deficiency and aluminium toxicity are common [11-13]. 25(OH)D (the main circulating form of vitamin D with longer half-life time 2 – 3 weeks) is the better marker than other vitamin D metabolites to evaluate the levels of vitamin D [14]. Low vitamin D is associated with incident hypertension [15], insulin resistance [16], peripheral arterial disease cardiovascular disease [17, 18] and mortality [19]. High levels of aluminium associated with encephalopathy, microcytic anemia, arterial stiffness and osteomalacia [13].

In this study, we analyzed the relation between vitamin D, serum aluminium and serum magnesium with iPTH and their roles as risk factors of hypoparathyroidism prevalence among maintenance hemodialysis patients.

II. Material and Methods

This study included 85 subject; 63 patients were on regular maintenance HD with mean age 48.3 ± 13.01 year, and average duration of dialysis 2.0 ± 0.7 years, they were 32 (51.8%) males and 31 (49.2%) females recruited from attendants of hemodialysis unit at Mansoura university hospital, 22 healthy volunteers as

normal control group (14 males and 8 females), their mean age were (33.1 ±7.2 years). The study was performed in accordance with the principles of the local institutional ethics committee. Exclusion criteria include subjects with history of parathyroidectomy and any patient administered pulse intravenous high dose active vitamin D treatment. Participants underwent maintenance HD three times weekly using hollow-fiber dialyzers and bicarbonate dialysates containing calcium and magnesium at concentrations of 2.5 to 3.5 and 1.0 mEq/l, respectively.

The studied HD patients were divided according to iPTH level into three groups;

- Group I: includes 18 (28.6%) of HD patients with iPTH level lower than 150 pg/ml; 10 of them had absolute hypoparathyroidism (iPTH < 65 pg/ml) and 8 of them had relative hypoparathyroidism (iPTH from 65 to 150 pg/ ml).
- Group II: includes 14 (22.2%) of HD patients with iPTH level between 150-300 pg/ml.
- Group III: includes 31(49.2 %) patients with iPTH level more than 300 pg/ml (hyperparathyroidism); 18 of them had iPTH level between 300 and 600 pg/ml and 13 had iPTH level more than 600 pg/ml.

The studied subjects underwent full history including history of blood pressure, diabetes, duration of hemodialysis and drug intake e.g. calcium containing phosphate binders, and vitamin D analogues. All patients were on regular phosphate binder, calcium and erythropoietin supplements. Oral active vitamin D (alfacalcidol) was administered to 51 (80.9%) patients at dosages of 0.25 to1.0 µg/d.

Routine laboratory results of serum albumin, total bilirubin, AST, ALT, alkaline phosphatase (ALP), creatinine & urea pre- and post-dialysis, serum calcium, phosphorous, fasting blood sugar complete blood count and lipid profile; cholesterol, HDL-C, LDL-C and triglycerides were collected from medical records of cohort studies in dialysis unit at Mansoura university.

II.1 Blood sample collection and examination

A Pre-dialysis fasting blood sample (5 ml) were collected from all patients preoperatively and controls after informed consent by clean venipuncture using plastic disposable syringes then delivered into free plain tube with stopper. Blood were allowed to clot at 25°C for 30 minutes then centrifuged at approximately 3000 rpm for 5 minutes, the resulting sample was subjected for Biochemical, hormonal and metals assay. iPTH was measured using Electrochemilumenecence immunoassay (Elecsys 1010; Boehringer Mannheim, Germany), reference range, 10 to 65 pg/ml , 25(OH)D was measured using DRG 25-OH Vitamin D (total) ELISA Kit (reference range; 14 to 65 ng/mL), serum magnesium was measured by colorimetric method using Hitachi 902 automatic analyzer, Japan and serum aluminium was measured using Perkin Elmer (PinAAcle 900T) flame and Graphite furnace atomic absorption spectroscopy (GFAAS) at wave length 307.29 nm with heating program from 120 to 2450 ˚C using argon gas current for drying and pyrolysis. The serum 25(OH)D and aluminium concentrations of HD patients and control group was determined from the calibration curve of 25(OH)D standards (0, 4, 10, 25, 60 and 130 ng/ml) and the calibration curve of aluminium standards (25, 50, 100 pg/ml).

Urea reduction ratio (URR) calculated from formula: URR= (Upre – Upost)/Uper x 100%, to evaluate efficiency of hemodialysis; >65% considered efficient dialysis [20]. The corrected calcium calculated from formula: Calcium corrected = calcium total + 0.8 x (40 - albumin) [21]. In this study serum 25(OH) D levels below 12 ng/ml was considered vitamin D deficiency, 12 – 30 ng/ml ,vitamin D insufficiency and levels more than 30ng/ml, vitamin D sufficiency [22].

II.2 Statistical analysis

Data were analyzed using SPSS version 16. Data were presented using mean ± standard deviation (M ± SD) for all quantitative values, or number of cases, percentage for categorical variables. Independent t test was used for quantitative variables. The significance of correlations was determined using Pearson's correlation coefficient. Statistical significance was determined as p values ≤ 0.05.

III. Results

This study included 85 subject; 63 patients were on regular maintenance hemodialysis with mean age 48.3 ± 13.01 years, and average duration of dialysis 2.0 ± 0.7 years, they were 32 (51.8%) male and 31 (49.2%) female and 22 healthy volunteers as normal control group with mean age 33.1 ±7.2 years. 24 (38.0 %) of HD patients were diabetic and 46 (73%) were hypertensive with mean 24-hr systolic blood pressure (SBP) more than 150 mmHg and 24-hr diastolic blood pressure (DBP) more than 90 mmHg.

III.1 Demographic data

The demographic data of HD patients and control group are presented in Table (1). Patients with iPTH level 150 pg/ml or less (28.6%; relative hypoparathyroidism) were likely to have diabetes, older age and have longer duration of dialysis. Patients with iPTH level ≥ 300 pg/ml had lower Al, calcium and higher URR, ALP,

Mg and 25(OH)D levels than those of group I & II (Table 2). 22 (34.9%) of hemodialysis patients had vitamin D deficiency whereas 25 (39.7%) of them had vitamin D insufficiency and 16 (25.4 %) had vitamin D sufficiency. In group I (iPTH ≤ 150 pg/ml), 8 patients had vitamin D deficiency, 10 patients had vitamin D insufficiency and none of them had sufficient vitamin D levels. In group II (iPTH 150 - 300 pg/ml); 7 patients had vitamin D deficiency, 4 patients had vitamin D insufficiency and 3 patients had vitamin D sufficiency. In group III (iPTH > 300 pg/m); 5 patients had vitamin D deficiency, 8 patients had Vitamin D insufficiency and 18 of them had sufficient vitamin D levels (Fig. 1).

Table 1

Demographic and clinical data of studied subjects.

Variables		Group I (n= 18)	Group II (n=14)	Group III (n=31)	Controls (n=22)
Gender	Male	10 (55.5 %)	6	16 (51.6%)	14
	Female	8 (44.5%)	8	15(48.4%)	8
Age (mean ± SD)		52.1 ± 14.0	47.1 ± 11.1	46.1 ± 12.1	33.1 ± 7.5
Duration of HD (yr)		2.3 ± 0.3	2.2 ± 0.1	2.2 ± 0.2	--------
Diabetics %		9.0 (50.0 %)	5.0 (35.7 %)	9.0 (29.2 %)	0.0%
BMI(mean ± SD)		27.6 ± 3.8	26.7 ± 2.9	26.0 ± 2.7	32.0 ± 5.8
Mean of SBP (mmHg)/24hr		159.9 ± 13	157.5 ± 14.4	155.3 ± 11.0	121.4 ± 6.5
Mean of DBP (mmHg)/24hr		95.2 ± 5.1	93.5 ± 7.5	92.7 ± 8.4	79.1 ± 5.5

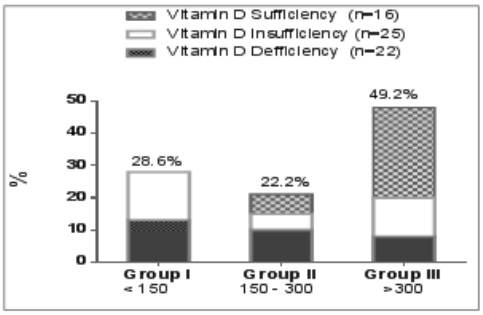


Figure 1: Distribution of iPTH and 25(OH)D levels among hemodialysis patients (n=63). There 22 patients had vitamin D deficiency. 25 patients had vitamin D insufficiency and 16 patients had vitamin D sufficiency .

III.2 Laboratory data

The laboratory characteristics of the three HD groups and control are presented in Table (2) together with significance levels for nonparametric statistical tests of hemodialysis patients versus control group and hemodialysis groups versus each others. Table (2) shows no significant differences between HD patients groups and control group for what concerns average of ALT, AST, cholesterol, LDL- C and triglycerides, while shows significant differences for what concerns average of iPTH, 25(OH)D, ferritin, serum Al, phosphate, albumin, creatinine, urea, blood urea nitrogen (BUN), fasting blood sugar (FBS), hemoglobulin, platelets and mean corpuscular volume (MCV). It shows also significant differences between control group and groups I & III for what concerns average of serum magnesium, corrected calcium and total bilirubin, in addition to significant differences between control with group II & III for what concerns average of alkaline phosphatase. Table (2) shows also significant differences between group I and group II for what concerns average of serum iPTH & albumin, and also between group I and group III for what concerns average of serum iPTH and 25(OH)D and shows significant differences between group II and group III for what concerns average of serum iPTH and 25(OH)D.

III.3 Analysis of correlation

In this study, as shown in Table (3), we found no statistically significant correlations in control group and group III. In group I, there was a statistically highly significant negative correlation between iPTH with 25(OH)D, Mg, and serum Al (r= -0.726; p=<0.001, r= -0.594; p= 0.009 and r= -0.700; p= <0.001 respectively), and also a highly significant positive correlation with MCV (r= 0.776; p= <0.001) (Fig. 2), whereas, on other hand, there were no significant correlations between iPTH with age, BMI, calcium, correlated calcium, ALP, phosphorous, albumin, bilirubin, ALT, AST, creatinine, urea, BUN, cholesterol, HDL-

C, LDL-C, triglycerides, FBS and hemoglobulin. And also in group I, there was a significant positive correlation between serum aluminium and 25(OH)D (r= 0.646; p= 0.004) and a significant negative correlation between serum Al and MCV (r= -0.828; p= <0.001) (Fig. 3). In group II, there was significant negative correlation between iPTH with 25(OH)D and (r = -0.854; p = <0.001). In all HD patients, there was only a significant negative correlation between serum Al and MCV (r= -0.781; p =<0.001) (Fig. 4).

Table 2

Biochemical Features of studied subjects. The mean of HD groups compared to each other and with the control. *p <0.05 controls versus group I, **p <0.05 controls versus group II, ***p <0.05 controls versus group III, #p <0.05 group I versus group II, # #p <0.05 group I versus group III, ¥p<0.05 group II versus group III

Variables	Controls	Group I	Group II	Group III
	M ± SD	M ± SD	M ± SD	M ± SD
iPTH(pg/ml)	40.4 ± 15.5***	64.1 ± 43.7#, # #	217.4 ± 43.7¥	816.2±727.7
25(OH)D (ng/ml)	48.0 ± 8.9*,**,***	12.9 ± 4.0# #	19.3 ± 15.0¥	31.0 ± 18.4
Ferritin (ng/ml)	159.0 ± 63.6**,***	372.4±434.1	438.0 ±463.8	433.8±378.0
Magnesium (mg/dl)	2.2 ± 0.2*,***	1.8 ± 0.5#,##	2.3 ± 0.66¥	2.9 ± 0.6
Aluminium (µg/l)	1.3 ± 0.9*,**,***	61.6 ± 15.2	54.4 ± 19.7	53.8 ± 16.0
ALP (Iu/l)	76.5 ± 17.2**,***	163.9±139.8# #	174.0 ± 99.7	248.0±193.0
Phosphorous (mg/dl)	3.7 ± 0.5*,**,***	6.4 ± 1.1	6.6 ± 1.1	6.3 ± 1.6
Calcium (mg/dl)	9.0 ± 0.7*,***	9.4 ± 0.7	8.8 ± 0.7	8.8 ± 0.7
Corr. Ca (mg/dl)	9.4 ± 0.67*,***	9.4 ± 0.7	8.9 ±0.78	9.0 ± 0.7
Albumin (g/dl)	4.4 ± 0.3*,**,***	3.6 ± 0.3#	3.9 ± 0.3	3.7 ± 0.5
T. Bilirubin (mg/dl)	0.8 ± 0.1*,***	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
ALT (Iu/l)	27.6 ± 8.4	30.3 ± 14.9	25.6 ± 5.0	30.0 ±14.2
AST (Iu/l)	30.8 ± 10.4	30.6 ± 14.3	27.6 ± 6.9	33.0 ± 17.1
Creatinine(mg/dl)	1.0 ± 0.1*,**,***	9.3 ± 1.9	9.3 ± 2.8	8.6 ± 2.2
Urea(mg/dl)	26.9 ± 4.88*,**,***	167.8 ± 58.1	141.9 ± 42.7	161.6 ± 22.2
BUN(mg/dl)	11.2 ± 2.0*,**,***	77.0 ± 14.3	56.9 ± 21.1	41.0 ± 22.3
URR	-----	60.4 ± 16.6	61.7 ± 9.2	74.1 ± 22.3
Hemoglobin(g/dl)	13.8 ± 1.3*,**,***	9.2 ± 1.6	9.7 ± 0.7	9.5 ±1.3
MCV (SI unit)	85 ± 7.4*,**,***	76.9 ± 4.9	80.8 ± 6.9	82.5 ± 4.2
Platelets x 10^9/L	265.0 ± 110.0*,**,***	188.9 ± 62.9	165.5 ± 44.7	192.0 ± 74.0
Cholesterol (mg/dl)	146.2 ± 24.3	169.4 ± 47.4	158.0 ± 42.5	154.3 ±38.7
HDL (mg/dl)	39.4 ± 4.4	37.7 ± 9.3	33.0 ± 7.6	38.4 ± 16.1
LDL (mg/dl)	83.4 ± 24.1	100.6±33.4	94.2 ± 37.4	92.8 ± 35
TG (mg/dl)	95.6 ± 13.5	155.6 ±92.3	154.0 ± 70.7	115.8 ± 63.1
FBS (mg/dl)	83.9 ± 1.3	183.3±68.3	180.9 ± 83.5	171.9 ± 53.0

IV. Discussion

Patients with renal failure often have signs and symptoms related to fluid, electrolyte and metabolic disturbances [23, 24], anemia, malnutrition, hypertension, bone disease, hormonal and gastrointestinal problems. In the end stages of renal diseases (ESRD), hypoparathyroidism is developed and increases in severity as the glomerular filtration rate deteriorates. The prevalence and pathogenesis of hypoparathyroidism are largely unknown. Some studies have shown increased risk of death among dialysis patients with low serum iPTH. In CKD patients, as the number of functioning nephrons decreases, the kidneys are unable to excrete aluminium, magnesium and phosphorus and there is a progressive increase in serum aluminium, magnesium and phosphorus. Increase of serum phosphorous level leads to continual over-stimulation of the parathyroid glands, tissue hyperplasia, and over-secretion of iPTH [25, 26]. Higher serum Al concentrations in hemodialysis patients are always an important risk factor for mortality in hemodialysis patients [13]. Increasing of serum aluminium with long-term hemodialysis leads to aluminium accumulation in parathyroid glands and reduces the parathyroid response to hypocalcaemia [27, 28]. Clinical consequences of increasing aluminum in ESRD patients include a neurologic syndrome (encephalopathy), aluminum-induced bone disease, and microcytic anemia [29]. Vitamin D insufficiency and deficiency are very prevalent in CKD patients across all its stages [30]. In renal diseases, the ability of kidney to convert 25(OH)D (calcidiol) to 1,25(OH)D (calcitriol; active form of vitamin D) decreases and the absorption of calcium form intestine as a consequence decreases; hypocalcaemia [31]. Decreasing serum calcium and increasing serum phosphorous stimulate the parathyroid gland to increase its secretion of PTH; hyperparathyroidism.

Biochemical patterns of mineral-related variables found in this study are very similar to those reported in the international literature, in spite of there were some differences among dialysis modalities. Hyperphosphatemia was less frequent whereas the hypermagnesaemia and hyperparathyroidism were more common in HD patients. Low iPTH probably associates with hyperglycemia [32]. Relatively hypoparathyroidism patients had higher levels serum Al (61.6 ± 15.2), lower serum Mg (1.8 ± 0.48) and lower 25(OH)D (12.9 ± 4.0) than other HD patients and control groups.

Table 3

Correlation between iPTH levels in HD patients and studied parameters.

$p > 0.05$; not significant (NS), $p < 0.05$; Significant, $p < 0.001$; highly significant.

Variables	iPTH					
	Group I		Group II		Group III	
	r	*p*	*r*	*p*	*r*	*p*
Age (years)	-0.177	NS	0.31 5	NS	-0.231	NS
Duration of HD	0.117	NS	-0.476	NS	-0.67	NS
BMI (kg/m^2)	0.054	NS	0.184	NS	0.139	NS
25(OH)D (ng/ml)	-0.726	<0.001	-0.845	<0.001	-0.41	NS
Ferritin (ng/ml)	0.631	NS	0.341	NS	0.288	NS
Magnesium (mg/dl)	-0.594	0.009	-0.291	NS	0.215	NS
Aluminium(µg/l)	-0.700	0.001	0.158	NS	-0.077	NS
ALP (Iu/l)	-0.382	NS	-0.212	NS	0.296	NS
Phosphorous (mg/dl)	0.194	NS	0.199	NS	0.186	NS
Calcium (mg/dl)	0.023	NS	-0.005	NS	0.183	NS
Corr.Ca (mg/dl)	0.121	NS	0.029	NS	0.234	NS
Albumin(g/dl)	0.236	NS	0.054	NS	-0.079	NS
T.Bilirubin (mg/dl)	-0.062	NS	-0.256	NS	0.231	NS
ALT (Iu/l)	-0.178	NS	0.022	NS	-0.179	NS
AST (Iu/l)	-0.201	NS	-0.373	NS	-0.163	NS
Creatinine (mg/dl)	0.053	NS	0.367	NS	0.020	NS
Urea (mg/dl)	-0.116	NS	-0.242	NS	-0.206	NS
BUN (mg/dl)	-0.116	NS	-0.241	NS	-0.206	NS
URR	-0.243	NS	0.054	NS	-0.073	NS
Hemoglobin(g/dl)	0.095	NS	0.046	NS	0.205	NS
MCV (SI unit)	0.776	<0.001	-0.223	NS	0.260	NS
Platelets x 10^9 /L	0.181	NS	0.227	NS	-0.224	NS
Cholesterol (mg/dl)	-0.183	NS	0.034	NS	0.182	NS
HDL-C (mg/dl)	0.268	NS	-0.464	NS	0.087	NS
LDL-C (mg/dl)	-0.217	NS	0.071	NS	0.170	NS
TG (mg/dl)	-0.215	NS	0.163	NS	-0.028	NS
FBS (mg/dl)	0.096	NS	0.165	NS	-0.035	NS

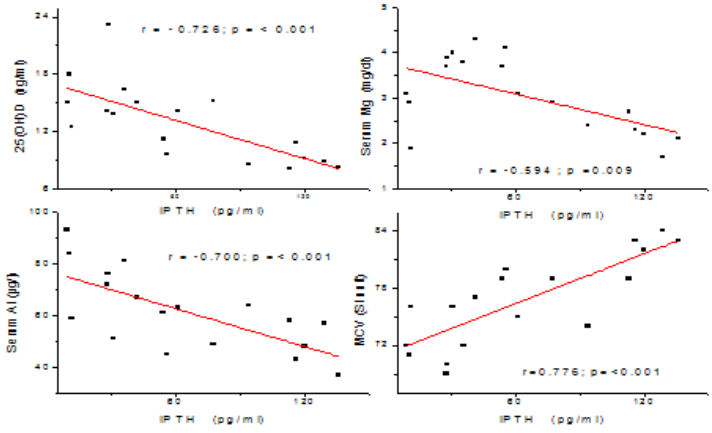
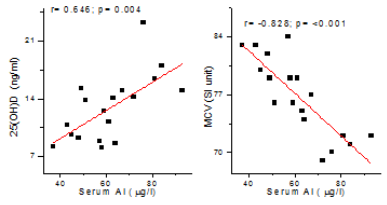


Figure 2: Correlation between iPTH with 25(OH)D, Mg, Al and MCV



with 25(OH)D and MCV

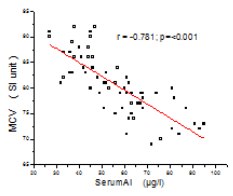


Figure 4: Correlation between serum Al with MCV in all HD patients

In hypoparathyroidism HD patients, we did not find any correlation between serum iPTH level and age, body mass index, systolic & diastolic blood pressure, ferritin, serum calcium, corrected calcium, phosphorous, ALP, albumin, ALT, AST, bilirubin, pre- and post-dialysis creatinine & urea, cholesterol, HDL-C, LDL-C, triglyceride, FBS, hemoglobulin, and platelets. We found no statistically significant correlations in control group and group III. We found that prevalence of hyperparathyroidism was 49.2% among HD patients, whereas the prevalence of hypoparathyroidism was 28.6%, a significant elevation in iPTH in all groups for what concerns the mean of iPTH. In group I, we observed a significant relation between serum iPTH with 25(OH)D, serum aluminium, magnesium and MCV in group I and also between iPTH and 25(OH)D in group II. The negative correlation between iPTH and all of the 25(OH)D, serum aluminium and magnesium reflects the degree of effects of high concentrations of serum 25(OH)D, aluminium and magnesium on decreasing the serum iPTH concentrations. The results were in agreements with [33-35]. The effect of aluminium on iPTH may occur by two assumptions: The first one is that the accumulation of the aluminium in the parathyroid glands can reduce the parathyroid response to hypocalcaemia [36]. The second one is that the calcium sensing receptor may also be sensitive to aluminium, which may act on the parathyroid gland and may exert a suppressor effect on PTH by inducing serum calcium elevation [37]. Prevalence of vitamin D deficiency among hemodialysis patients was 31.7%. In group I (iPTH <150 pg/ml), the vitamin D deficiency was 44.5%. In group II (iPTH 150-300 pg/ml), it was 50%. In group III (iPTH >300 pg/ml), it was 16.1%. There was highly significant negative correlation between 25(OH)D and iPTH in group I &II . The 25(OH)D deficiency may be due to urine loss of 25(OH)D through vitamin D binding protein [38]. In addition, renal megalin (Low density lipoprotein-related protein) decreases with CKD progression reducing 25(OH)D tubular reabsorption [39].

Finally, 11 of HD patients (17.4%) had hemoglobin levels 6 - 8 g/dl, 34(54%) had hemoglobin levels 8.1 – 10 g/dl, 15(23.8%) had hemoglobin levels 10.1 – 12 g/dl and 3(4.7%) had hemoglobin levels >12 g/dl. these results agree with [40]. There were significant differences between the all HD patients and control in compared with the means of hemoglobulin and MCV. There was a significant correlation between the MCV of hypoparathyroidism HD patients and iPTH. On other hand, linear regression analysis showed a highly significant negative correlation between serum aluminium and MCV in all HD patient (r=-0.781; p=<0.001). The HD hemoglobulin decreases may be due to erythropoietin deficiency [41].

V. Conclusion

Prevalence of hypoparathyroidism disease in patients with CKD increases with long-term hemodialysis. According to this study, we found that low serum 25(OH)D, low serum magnesium and high serum aluminium levels are associated with progression of hypoparathyroidism among HD patients suggesting that they may be used as prognosis for hypoparathyroidism and low turnover bone in hemodialysis patients .

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