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Correlation of vitamin D deficiency and hyperparathyroidism with anemic in Female Iraqi

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Abstract: Vitamin D deficiency and anemia are common in the Middle East, and vitamin D deficiency and hyperparathyroidism have been study to be linked with an increased incidence of anemia. In this study, that vitamin D deficiency and hyperparathyroidism may be connected with anemia in female Iraqi population was tested.

Aim: To investigated correlation of hyperparathyroidism and vitamin D3 levels deficiency and insufficiency with anemia in female.

Materials and Methods: This study was conducted at Al-Hussein Medical City/ Al-Husain Teaching Hospital / Kerbala-Iraq. All samples 176 apparently are healthy female subjects as controls 80 and 96 female patients non- obese having iron deficiency anemia during the period from Nov. , 2015 to Sep., 2016with age ranged between (15- 50) years. The data of body mass index (BMI), Vitamin D3, serum iron levels, total iron binding capacity, creatinine ,complete blood count in blood were measured, alkaline phosphate, phosphorus and calcium .

Results: In females, the prevalence of anemia was significantly associated with vitamin D deficiency independent of parathyroid hormone levels (p=0.001). In females, the prevalence of anemia appeared to be significantly associated with hyperparathyroidism (odds ratio; 95% confidence interval; $P = 0.01$)

Conclusion: It was concluding that anemia female patients have significantly low levels of serum vitamin D3and high levels of serum parathyroid hormone than that in healthy. High prevalence rate of vitamin D deficiency was stronger in female population of Kerbala city in Iraq. Additional studies to determine whether vitamin D3 supplementation could be used to treat anemia are acceptable.

Key words: anemia, deficiency D, hyperparathyroid hormone.

Introduction

The occurrence of deficiency and insufficiency D has been reported to be high in numerous regions around the Middle East. Notwithstanding plenty sunshine throughout the year, meta-analysis of studies in the past decade suggesting that one-third of individuals living in Sub-Saharan Africa and the Middle East have serum vitamin 25(OH)D3 levels less then ,30 ng/mmoL.[1] In addition, to the well-documented role of vitamin D3 in the regulation of bone and mineral metabolism, vitamin D3 may have an effect on erythropoiesis including cellular proliferation and differentiation and induction of erythroid progenitors in bone marrow.[2] Vitamin D receptor in bone marrow.[3] Perhaps hyperparathyroidism has also been suggested to induce bone marrow fibrosis and suppress erythropoiesis – especially in subjects with secondary hyperparathyroidism, and vitamin D3 treatment of subjects with hyperparathyroidism has been shown to improve the response to erythropoietin therapy.[4,5,6] In addition, low 25(OH)D3 levels are reported to be associated with low hemoglobin concentrations in individuals with normal renal function.[7,8,9] Most published epidemiological studies and clinical trials have fixated on the possible protective effect of vitamin D3 against cancer[10,11] and risk of cardiovascular disease.[12,13] Evidence regarding the association of vitamin D3 deficiency and hyperparathyroidism with anemia is restricted especially in Middle Eastern populations. The Kerbala city in Iraq is sunny that presents an opportunity to investigate the risk factors associated with deficiency D. This study, the hypothesis that vitamin D insufficiency, deficiency, and hyperparathyroidism may be connected with anemic in females Iraqi was tested.

Materials and Methods

Location and Duration of the Study

This case-control study was conducted at Al-Hussein Medical City, Al-Hussein Teaching Hospital, Kerbala, Iraq, from November 2015 to September 2016.

Data collection

All subjects completed a questionnaire on age, gender, pregnancy, and history of any chronic diseases such as diabetes mellitus, hypertension, obesity, osteoporosis, osteomalacia, liver disease, renal disease, anemia, hypo or hyperparathyroidism, vitamin and mineral deficiency, and steroid therapy. They were also asked about medications that could interfere with vitamin D3 metabolism, vitamin therapy, and whether they were taking vitamin D3 and calcium supplements during a face-to-face interview. One-hundred and twenty-one were subsequently excluded because of obesity (>25 kg/m2), history of liver, renal, gestational, or , medications that influence bone metabolism and current vitamin D3 and calcium intake, and vitamin B12 deficiencies, aplastic anemia, hemolytic anemia, sickle cell anemia, and thalassemia. Therefore, 176 females (age between 15–50 years) were included in the final study.

Bio-markers Determined

Body mass index (BMI), complete blood count (CBC), serum 25(OH) D3, iron level, total iron binding capacity (T.I.B.C) , ceartinine, calcium(Ca), Phosphorus, Alkaline phosphatase (APL) and Parathyroid hormone (PTH) .

Serum 25(OH) D3 and parathyroid hormone (PTH) levels were measured using the new by ELISA assay kit which was designed for the determination in human serum or plasma samples (Eagle Biosciences Inc., MA, USA). BMI was determined by measuring weight (in kilograms) divided by the square of height (in meters); weight and height were measured by the same scale for all the sample subjects [BMI = weight (kg)/square height (m2)]. Serum iron level, total iron binding capacity, creatinine, phosphorus, alkaline phosphatase and calcium measured via spectrophotometry and complete blood count (Sysmex XP-300 Atomic Hematology Analyzer).

The mean ± SD of all parameters measured from patients iron deficiency anemia patients were determined and compared with the controls group.

The correlation coefficient *r* is used to describe the association between the different studied parameters; $P < 0.05$ was considered statistically significant

Statistical analysis

Student's *t*-test was used to compare the biochemical parameters between patients and controls. Analysis of variance and xi- square test were used to compare the hemoglobin and 25(OH)D3 insufficiency and deficiency of vitamin D3. Pearson's correlation coefficients were used to examine the correlation between serum total 25(OH) D3 and parathyroid hormone with other variables. All statistical inferences were made based on a two-sided significance level of P,0.05and P,0.01 were performed using IBM® SPSS® Statistics version 22.0 (IBM Corporation, Armonk, NY, USA).

Results

The distributions of biochemical and biometric parameters in patients and controls are shown in Table 1. Serum total 25(OH) D3 was significantly decreased in patients anemia than controls. Table 1 shows the results obtained for serum 25(OH) D3 in control group and the anemic female patients at $P < 0.0001$ and PTH was significantly higher in female patients' anemia than controls $P < 0.05$ as shown in Table1. The study group consist of one hundred seventy six (176) Vitamin D3 deficiency or insufficiency was present in 84.7% of the tested samples with low serum vitamin D3 levels < 30 ng/mmoL, in which 96 patients were had insufficient level with deficient level lower than that as shown in Table 3. The obtained data indicated that 25(OH) D3 was associated with inversely associated with PTH. In addition, it has positive correlation with Hb at $P < 0.001$, whereas was PTH positively associated with ALP and phsphorus in a high significant correlation $P < 0.05$ in patients as shown in Table 2. Statically Xi square test for multiple comparison analysis shows that among all the parameters, hemoglobin was significantly lower in females with vitamin D deficiency ($P < 0.001$) compared with those with optimal levels of hemoglobin normal as shown in Table 3. Further statistical analysis indicates that in females hemoglobin was significantly and positively correlated with total 25(OH) D3 ($r = 0.360$, $P = 0.001$) as shown in Table 2.

Table 1: Mean ± SD values of all parameters in anemia patients compared with controls group

Parameter	Anemic patients	Controls Group	P .value
25-(OH)D3 (ng/mmol)	11.20 ± 6.70	18.86 ± 9.91	<0.001
Hb (g/dl)	9.39 ± 1.53	13.04 ± 0.66	<0.001
PTH(pg/mmol)	81.16 ±51.37	61.38 ±35.91	<0.01
ALP(U/L)	98.02 ± 56.50	90.51 ± 51.00	NS
Serum Ca (mg/dl)	8.00 ±1.00	9.07 ±1.04	<0.001
Phosphorus (mg/dl)	3.55 ± 1.32	3.58 ±1.21	NS
Serum Iron level (µg/dl)	27.95 ± 51.64	62.84 ± 23.52	<0.001
T.I.B.C (µg/dl)	491.04 ± 445.69	282.06 ± 56.81	<0.01
BMI (kg/m2)	24.16 ± 2.58	23.35 ± 2.67	<0.04
Age (years)	31.54 ±10.99	29.6 ±10.51	NS
Creatinine (mg/dl)	0.64 ± 0.23	0.65 ± 0.13	NS

Hb: Hemoglobin; 25-(OH) D3: 25-hydroxyvitamin D3; T.I.B.C.: total iron binding capacity; BMI: body mass index; Ca: calcium; ALP: alkaline phosphatase: PTH :parathyroid hormone; NS: non-significant correlation at P > 0.05. High significant correlation at P < 0.001

Table 2. Correlation between 25(OH)D3, PTH and other parameters in anemic patients compared with controls group

Parameter		Hb	ALP	Ca	Phosphorus	PTH	
25(OH) D3	**Patients**	0.360**	-0.299 **	0.454**	0.046	-0.236**	
		0.001	0.001	0.001	NS	0.001	**P. value**
	Controls	0.052	-0.268**	0.379**	0.057	-0.186	
		NS	0.001	0.001	NS	NS	**P. value**
PTH	**Patients**	-0.066	0.351**	-0.413**	0.293**	----------	
		NS	0.001	0.001	0.001	----------	**P. value**
	Controls	0.067	0.230**	-0.410**	0.101	----------	
		NS	0.001	0.001	NS	----------	**P. value**

**High significant correlation at P < 0.001; NS: non-significant correlation at P > 0.05

Table3: Distribution of the values of serum 25 (OH) D3 level in anemia patients and controls

Parameter			D3			Total	P.Value
			Deficiency <10 (ng/mmol)	Insufficiency 10-30 (ng/mmol)	Normal >30 (ng/mmol)		
Hb	Hemoglobin (<12 g/dL)	Count	61	31	4	96	0.000
		%	32.7%	17.6 %	2.2 %	54.5 %	
	Normal Hemoglobin (>12 g/dL)	Count	12	45	23	80	
		%	6.8%	25.6 %	13.1%	45.5%	
Total		Count	73	76	27	176	
		%	41.5%	43.2%	15.3%	100.0%	

Discussion

This is the first population-based study to provide evidence that vitamin D3 deficiency is associated with anemia in female Iraqi. Table 3 highlighted clearly the significant association between the lower vitamin D levels found in anaemic patients compared to non-anaemic patients ($p<0.00$). A 52.3% of iron deficiency anaemia had vitamin D deficiency (34.7% less than <10ng/ml, 17.6% less than <30ng/ml) as compared to 32.4% of controls group (6.8% less than <10ng/ml, 25.6 less than <30 ng/ml). The correlation of vitamin D3 deficiency with an increased risk of anemia has been reported in this study in patients without chronic kidney disease.[12,13] The exact mechanism of association of vitamin D3 deficiency with anemia is still not known. This study suggested that vitamin D3 deficiency could lead to increased risk of reticulocytosis and anemia.[8] In bone marrow, there are enormous vitamin D3 receptors and vitamin D3 is reported to stimulate erythroid precursors. High local concentrations of 1,25 di hydroxyvitamin D3 in hematopoietic tissues is suggested to activate erythroid precursor cells in a paracrine fashion.[14,15] In

addition, high doses of calcitriol – the active form of vitamin D3 – has been widely used to increase hemoglobin levels and reticulocyte count in hematological disorders.[16,17] An inverse relationship between plasma 25(OH)D3 and PTH levels in females was also observed in this study. Through this relationship was statistically significant following multivariate regression analysis, it is consistent with this study in different populations and suggests that deficiency D3 could lead to secondary hyperparathyroidism, which is harmful to bone health. [18,19] It is now well established that vitamin D3 causes the suppression of PTH synthesis by increasing plasma calcium and by acting on parathyroid cells.[20,21] In addition, there was a positive correlation between 25(OH)D3 and hemoglobin and a negative correlation between hemoglobin and PTH. Moreover, stepwise multiple regression analysis showed that total 25(OH) D3 and PTH were the main and independent predictors of hemoglobin. In addition, although the results this study from logistic regression analysis shows that there was a significant association of vitamin D3 deficiency and hyperparathyroidism with anemia, this significant association of hyperparathyroidism with anemia disappeared when adjusted for 25(OH)D3. This study demonstrates that vitamin D-deficient females are prone to hyperparathyroidism and anemia. Secondary hyperparathyroidism is known to induce bone marrow fibrosis, impair erythropoiesis, and inhibit the endogenous production of erythropoietin. The prevalence of vitamin D3 deficiency is significantly higher in females in kerbala city in Iraqi the same reported in the Kingdom of Bahrain, Iran, Saudi Arabia's, Qatar and the United Arab Emirate. [22] The deficiency vitamin D3 status in females observed in the present study could be explained by females spending more time indoors and/or the type of clothing that females wear and sun protection and sun avoidance attitudes seen in city Kerbala female.[23] The association of vitamin D3 deficiency with anemia observed in this study is consistent with some recent studies in different populations.[12] Sim et al reported an increased prevalence of vitamin D3 deficiency associated with anemia in a cross-sectional study.[8] In addition, this study have the same observational studies have shown that African Americans have lower circulating levels of

25(OH)D3 and are more likely to be vitamin D deficient than other ethnic groups, and it is suggested that increased prevalence of anemia in non-Hispanic blacks is correlated with vitamin D3 deficiency.[24] Although this study demonstrates an association of vitamin D3 deficiency with anemia, a causal relationship cannot be established and further studies are warranted to investigate the relationship of vitamin D3 deficiency and hyperparathyroidism with causes of anemia in anemic patients in the Iraqi female.

Conclusion

The results of this study indicate that vitamin D3 deficiency is associated with anemia in healthy Kerbala city in Iraqi females. PTH is reported to be a resistance factor in recombinant human erythropoietin therapy. Ultimately, if these results can be replicated by others and extended, they could lead to randomized clinical trials to evaluate vitamin D3 supplementation as therapy for patients with anemia.

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