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Relationship between Subjective Disease Severity and Vitamin D Deficiency in Iraqi Chronic Rhinos-Inusitis Patients with Nasal Polyps

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Abstract: ***Chronic rhinosinusitis (CRS) is a sinonasal mucosa inflammatory disease. It has traditionally been classified by phenotype, defined as the presence or absence of polyps. This retrospective analysis of collected data was performed in Al-Karama teaching hospital in Baghdad/Iraq on 100 subjects (49 males and 51 females), aged 18 to 71 years (mean±SD 43.9±12.4 years) to evaluate the serum vitamin D level in patients with chronic rhinosinusitis with nasal polyps and its relationship with the disease severity. Patients with chronic rhinosinusitis with or without nasal polyps who underwent endoscopic sinus surgery were recruited. Demographic information including age, gender, body mass index, smoke history, atopic status and asthma was collected. Disease severity was measured by the Lund-Mackay CT score and Iraqi-Nasal Outcome Test-22 score. Serum 25-hydroxyvitamin D3 was measured by enzyme-linked immunosorbent assay preoperatively. Serum 25-hydroxyvitamin D3 levels were significantly lower in patients with nasal polyps (CRSwNP, 33.8±10.5nmol/L; CRSsNP, 41.3±9.3nmol/L; control, 51.9±15.2nmol/L. p = 0.0005), and the levels were significantly associated with the preoperative Iraqi-Nasal Outcome Test-22 score (p=0.010), but not with the Lund-Mackay score (p=0.129). Furthermore, serum 25-hydroxyvitamin D3 levels were associated with the subjective improvement six months postoperatively (p<0.001). It can be concluded that Serum 25-hydroxyvitamin D3 levels are lower in Iraqi CRSwNP patients. These 25-hydroxyvitamin D3 levels are associated with SNOT-22 score. Preoperative 25-hydroxyvitamin D3 level may affect the symptom improvement after surgery.***

Keywords: Vitamin D Nasal Polyps Chronic Rhino sinusitis Vitamin D deficiency Disease severity

1. Introduction

Evidence suggests that chronic rhino sinusitis without nasal polyps (CRSsNP) and chronic rhino sinusitis with nasal polyps (CRSwNP) are unique disease entities associated with separate and distinct inflammatory milieu [1,2]. Furthermore, CRSwNP in Western is most closely associated with Th2 cytokine skewing; Iraqi patients with CRSwNP showed a Th1/Th17 cell pattern instead [3]. These observations indicate immunologic heterogeneity among different regions within the same disease phenotype.Vitamin D is a potent steroid hormone involved in theregulation of bone mineralization and calcium homeostasis; it is synthesized in the skin and then undergoes hydroxylation to produce biologically active 1α, 25-dihydroxyvitamin D3. The discovery that most tissues and cells have a vitamin D receptor has provided new insights into the function of this vitamin [4]. It is now recognized as a key regulator of the immune system due to the regulation of a variety of cell types, such as dendritic cells, monocytes, macrophages, and T cells [5,6]. Recent studies have evidenced theanti-inflammatory function of vitamin D for CRSwNP. It can reduce the proliferation of nasal polyp fibroblasts and its secretion of matrix metalloproteinase and cytokines [7–13]; it can augment innate immunity through the modulation of cathelicidin production by the sinonasal mucosa [14].In addition, vitamin D deficiency increases sinus mucosa dendritic cells in pediatricCRSwNP [15], and administration of vitamin D may relieve the symptoms and signs of CRS [16, 17]. The body vitamin D status is measured by serum 25-hydroxyvitamin D3 (25VD3) levels that is influenced by age, gender, and race [18]. To date, serum 25VD3 has been increasingly considered as an independent predictor of risk for many chronic illnesses [4].

Although several studies assessing CRS have shown an association with lower serum 25VD3 and this has specifically been linked to the presence of nasal polyps, there are still conflict results from patients with CRSwNP from different races [19–23]. To our knowledge, few studies have examined the vitamin D status in Iraqi patients with CRS. Therefore, we sought to determine whether serum vitamin D levels might be associated with CRS, and to explore its contribution to the disease severity and treatment results.

2. Materials and Methods

This study was conducted in Al-Karama teaching hospital in Baghdad/Iraq. A review was performed of prospective collected data of patients with CRS who underwent ESS (endoscopic sinus surgery). Diagnosis of CRSwNP (n=40) and CRSsNP (n=40) met the definition in 2012 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012) [1]. Patients with nasal septum deviation and free of radiographic and endoscopic evidence of inflammatory sinus disease at the time of surgery were used as a control group (n=20).

Exclusion criteria included use of daily vitamin D supplements, use of oral steroids or immunomodulatory agents within 30 days before admission, other systemic disorders that affect the absorbing and metabolism of vitamin D as well as and pregnancy.

Demographic information were collected, including age, gender, body mass index (BMI) and smoke history. Atopic status was determined by elevated serum specific immunoglobulin E (IgE) level. Asthma status was determined by

patient's history. Serum calcium and phosphate parameters were collected prior to surgery.

The objective disease severity was assessed by Lund-Mackay (LM) CT score. The SinoNasal Outcome Test-22 score (SNOT-22) was collected preoperatively and six months postoperatively. Subjective improvement was assessed using SNOT-22 delta score (score on the postoperative six months minus the baseline score). Serum 25VD3 level was measured by enzyme-linked immunosorbent assay (ELISA) prior to surgery. Insufficient vitamin D level was defined as<30ng/mL and deficient level was defined as<20ng/ mL according to the guidelines [24].

3. Statistical analysis

Data were analyzed using IBM SPSS Statistics version 21. Categorical parameters were assessed using chi-square analysis. Parametric data were analyzed using one-way (ANOVA). The Kruskal-Wallis test was used for nonparametric data. Correlations were examined using Pearson's analysis. $P < 0.05$ was considered significant.

4. Results

The study included 100 subjects (49 males and 51 females), aged (18-71) years(mean±SD 43.9±12.4years).Demographic data were summarized in table (1). There were no significant differences between the three groups regarding age, gender, BMI, smoke history and atopic status and asthma.

Table 1: Patient's characteristics in the three groups

	CRSwNP (40)	CRSsNP (40)	Control (20)	P value
Age (years)	46.5±11.7	42.6 ± 14.6	40.7±10.8	0.197
Male/female (n)	19/21	17/23	12/8	0.519
BMI (mean)	24.3±7.3	22.8±5.8	23.5±8.7	0.637
Asthma/non asthma	5/35	8/32	2/18	0.593
Atopy/non atopy	8/32	6/34	5/15	0.159
Smoke/non smoke	10/30	8/32	6/14	0.512
CRSwNP=CRS with nasal polyps; CRSsNP=CRS without nasal polyps; BMI=body mass index.				

Distribution of serum 25VD3 status in the three groups was detailed in table (2). Serum 25VD3 level in patients with CRSwNP was significantly lower than those in patients with CRSsNP or the controls (subjects with CRSwNP, 33.8 ± 10.5 nmol/L; subjects with CRSsNP, 41.3 ± 9.3 nmol/L; controls, 51.9 ± 15.2 nmol/L. P = 0.0005). However, the difference of serum VD3 levels between CRSsNP and the control group was not significant as shown in table (3) and Figure (1).

Table 2: Distribution of circulating VD3 status in the three groups

VD3 level	CRSwNP	CRSsNP	Control	P value
Normal (>30ng/mL)	0	1	2(10.0%)	0.0001
Insufficiency (20–30ng/mL)	3(7.5%)	10(25.0%)	11(55.0%)	
Deficiency (≤20ng/mL)	37(92.5%)	29(72.5%)	7(35.0%)	
VD3=25-hydroxyvitamin D3; CRSwNP=CRS with nasal polyps; CRSsNP=CRS without nasal polyps				

Table 3: Serum levels of VD3, calcium and phosphate in the three groups

	CRSwNP	CRSsNP	Control	P value
VD3 level (nmol/L)	33.8 ± 10.5	41.3 ± 9.3	51.9 ± 15.2	0.0005
Calcium level (mmol/L)	2.30 ± 0.11	2.27 ± 0.08	2.29 ± 0.12	0.411
Phosphate level(mmol/ L)	1.31±0.45	1.04±0.31	0.90 ±0.22	0.0005
VD3=25-hydroxyvitamin D3; CRSwNP=CRS with nasal polyps; CRSsNP=CRS without nasal polyps.				

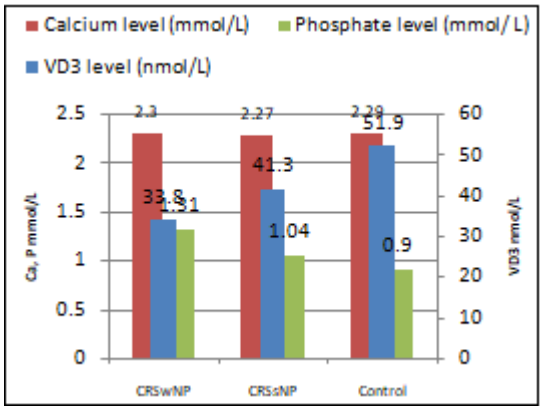

Figure 1: Serum levels of VD3, calcium and phosphate

The serum calcium levels in the three studied groups were 2.30±0.11 mmol/L in CRSwNP; 2.27±0.08 mmol/L inCRSsNP; and 2.29±0.12 mmol/L in the control group respectively. The differences between these three groups were not significant (P=0.411). In contrast, serum phosphate levels (in mmol/L) were found to be higher in the CRSwNP group (1.31±0.45) when compared with CRSsNP (1.04±0.31) and the control group (0.90 ±0.22) (p = 0.0005). On the other hand, there was no statistically significant difference in serum phosphate levels between CRSsNP and the control subjects (Table 3).

In patients with CRSwNP, serum 25VD3 level was not significantly associated with LM score (r=−0.237, p=0.129), but with preoperative SNOT-22 score (r=−0.389, p=0.010). Furthermore, improvement of SNOT-22 score postoperatively was significantly correlated with 25VD3 level (thirty-four patients had SNOT22 score available at six months postoperatively) (r=0.556, p < 0.001).

5. Discussion

The current study evaluated the circulating 25VD3 status in Iraqi patients with CRS. Our data showed that the serum 25VD3 level in patients with CRSwNP was significantly lower than those in patients with CRSsNP or the control group. The lower 25VD3 level in CRSwNP was inversely correlated with preoperative SNOT-22 score. Moreover, our study proved an influence of 25VD3 level on the symptom improvement after surgery in CRSwNP. Vitamin D is a potent immunomodulator that has been implicated in the development of respiratory health. Its deficiency is inversely correlated with upper respiratory tract infections [25].

Recent evidence supports that vitamin D may play an important role in CRS [7–13]. Furthermore, high therapeutic

dose of vitamin D may effectively reduce the nasal polyp size and restore the nasal mucosa near its normal state [17]. Previous studies have reported that 25VD3 deficiency/ inefficiency are more common in CRSwNP [19–21, 26], and this was confirmed by our data.

Our study also revealed lower serum 25VD3 level in CRSwNP cohort than CRSsNP or the control group in Iraqi patients. In our study, 25VD3 deficiency was present in 92.5% of CRSwNP group, 72.5% of CRSsNP group, and 35.0% of the control respectively; Meanwhile, 25VD3 insufficiency was present in 7.5% of CRSwNP, 25.0% of CRSsNP, and 55.0% of control respectively. In accordance with Wang et al., they also illustrated that patients with CRSwNP were identified as being VD3-insuffcient compared to CRSsNP in a study of 45 patients. However, the proportion of VD deficiency was 45.5% in their CRSwNP cohort, which was much lower than that of ours [26].

One possible explanation was that their patients lived in a southern city of Taiwan (lower latitude) with more intense sun exposure than us. Given race is a well-known contributing factor to 25VD3 deficiency [18], in some ways it is not surprising that there are some arguments concerning the systemic 25VD3 status in patients with CRSwNP from different races. Pinto et al. showed significantly lower serum VD3 levels in African Americans with CRS compared with race and sex-matched controls [20].

This observation was confirmed by Mostafa and Schlosser's reports who also found significantly lower VD3 levels in African American patients with CRSwNP compared to the race-matched control subjects [19,21]. On the contrary, two studies in Turkey showed the circulating levels of 25VD3 were equivalent between patients with CRSwNP and controls [22, 23].

Given the widespread effects of vitamin D on immune system [5,6], its potential role in mucus overproduction [27], and its antiangiogenic and antiproliferative properties [28], it is rational to hypothesize that vitamin D may have impact on the treatment result after ESS.

In this study, significant correlation was observed between circulating 25VD3 level and SNOT-22 score in CRSwNP, which was conflicted with Schlosser and Christensen's researches, who stated that the serum 25VD3 level was not associated with SNOT-22 score but with the local genes expression essential in vitamin D metabolism in CRSwNP [29,30]. However, the circulating level of 25VD3 was not correlated with LM score in our research, which was in line with the result reported by Wang et al. [26], but not with that of Schlosser's study [21].

It is possible that these discrepancies were due to CRS subgroups or the heterogeneity of CRS from different races being assessed in these studies. With respect to evidence from the published literature, the result presented here stresses the fact that systematic 25VD3, as a parameter for the disease severity of CRS, was to be determined. In our study, serum calcium levels were equivalent among the three subgroups, whereas the serum phosphate level significantly decreased in CRSwNP cohort. This is likely that vitamin D deficiency decreases intestinal calcium absorption, and consequently results in hyperparathyroidism. The secondary hyperparathyroidism can mobilize calcium from the bone to maintain the serum calcium level, accompanied with phosphaturia, which leads to an increasing of urinary phosphate loss and thus a low-normal or low serum phosphorus level [4].

Our data was in line with Mostafa's report who also found equal serum calcium levels in their cohort despite the lower concentration of serum VD3 level in patients with CRSwNP, who also had lower serum phosphate levels [19].

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