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A PHYSIOLOGICAL STUDY ON LEVELS OF VITAMIN D3 AND THEIR RELATIONSHIP WITH CALCIUM AND PHOSPHATE LEVELS IN HYPOTHYROID PATIENTS

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ABSTRACT

Patients affected with hypothyroidism are largely characterized by disruption of metabolism and mineral levels. Also known as cholecalciferol, vitamin D3 is an important regulator of calcium and phosphate homeostasis. The study aims to assess the connection between serum vitamin D3, calcium, and phosphate levels in hypothyroid female patients aged 45-85 years in Najaf province of Iraq. A case-control study was conducted at Al-Najaf Teaching Hospital on 80 females. The study population consisted of a total of 80 patients diagnosed with hypothyroidism and 40 cases suffering from the same conditions of similar age as the sufferer. We determined serum vitamin D3 levels by electrochemiluminescence immunoassay on the Cobas e411 analyser. We estimated serum calcium and inorganic phosphate levels spectrophotometrically. Statistical analysis was performed utilizing SPSS version 26.0 by utilizing the Independent Sample t test and Pearson Correlation. In the hypothyroid patients, serum levels of Vitamin D3 had a mean value of 13.40 ± 3.95 ng/ml whereas the control group had a mean value of 31.15 ± 4.80 ng/ml. The probability value was <0.001. Moreover, calcium in hypothyroid patients was found to be significantly lower reaching 8.05 ± 0.62 mg/dl while phosphate was found to be significantly higher at 4.68 ± 0.75 mg/dl ($p < 0.05$). There was a strong positive correlation between the Vitamin D3 and the calcium with coefficient value of 0.712 and probability value was below 0.01. A significant negative correlation between Vitamin D3 and phosphate with a correlation coefficient of −0.585 and probability value < 0.01 was observed. Based on the findings of the study, it was concluded that older women with hypothyroidism significantly increase the risk of mineral deficiency and deficiency of Vitamin D3. Low thyroid level might disrupt the Vitamin D–calcium–phosphate axis and cause hypocalcemia and hyperphosphatemia. For the clinical management of thyroid diseases and prevention of secondary bone disorders, monitoring these biochemical markers should be done routinely.

KEYWORDS: Hypothyroidism, Vitamin D3 deficiency, Calcium imbalance, Phosphate dysregulation, Female endocrinology, Mineral homeostasis

1. INTRODUCTION

The thyroid gland, which is part of the endocrine system produces thyroxine and triiodothyronine hormones also known as T4 and T3 respectively. Human metabolism is regulated with the help of hormones which will set the basal metabolic rate and also affect nearly all body's physiological process. This includes thermo genesis and macronutrient metabolism. (Mullur et al, 2014 and Holick, 2007).

When people have a deficiency of either of these hormones, which may be clinical or subclinical, metabolic activity slows down in a generalized manner. According to epidemiological studies, hypothyroidism is more prevalent in females and

strongly associated with autoimmune diseases and nutritional deficiencies (Vanderpump, 2011; Taylor et al., 2018).

Thyroid function and vitamin D3 (cholecalciferol) possibly represent one of the most significant and complex physiopathological relationships. Vitamin D3 is a steroid hormone that acts by means of the vitamin D receptor (VDR) which is very much expressed in immune cells and the thyroid (Mackawy et al., 2013; Bikle, 2014).

Under regular working conditions in the body, vitamin D3 is vital for calcium and phosphate balance by improving their absorption and reabsorption in the gut and kidney (Lips 2006; Nair & 2012).

Hypothyroid patients often show disordered metabolic homeostasis. Lower levels of thyroid hormone decrease the calcium-binding proteins expression in the cells of the intestine epithelium, and this decreases calcium absorption (Mosekilde et al. 1990; Bassett & Williams 2016).

Furthermore, a hypometabolic state can lead to inefficient metabolic activity required for the conversion of vitamin D3 to the active form of vitamin D3. Studies have shown that patients suffering from hypothyroidism usually have much lower serum vitamin D levels compared to health people (Chailurkit et al., 2013; Kim, 2016).Thyroid status also affects phosphate regulation. Changes in the levels of T3 and T4 affect phosphate handling through sodium-phosphate cotransporters in the renal tubular cells. These disturbances can cause secondary hyperparathyroidism or reduced mineralization because of Vitamin D deficiency (Duntas & Koch, 2019 and Williams et al. 2020).

In addition, through its effect on TSH levels, vitamin D may be linked to autoimmune processes. For example, polymorphisms in the VDR gene are associated with Hashimoto's thyroiditis (Wang et al. 2015; Tamer et al. 2011).

Both estrogen and vitamin D are important regulators of bone metabolism in the body. Most likely due to this entity, the effect is much more pronounced in females. According to clinical trials, vitamin D supplementation may diminish TSH level and increase quality of life of hypothyroid patients (Talaei et al., 2018).

The relationships between cholecalciferol and calcium and phosphate under specific physiological conditions need further investigation to better improve diagnostics and long-term management.

2. MATERIALS AND METHODS

2.1. Study Design and Ethical Considerations

A case-control study was conducted to evaluate the impact of vitamin D3 on calcium and phosphate levels in hypothyroid females. Approval for the study was obtained from the Scientific Committee of the Health Directorate of Najaf. The study objectives were explained to all participants and their written informed consent was obtained prior to the sample collection.

2.2. Setting and Study Population

The clinical part of this study was conducted at Al-Najaf Teaching Hospital, Najaf Governorate, Iraq. Between May 1 and October 1, 2024, sample collection was done on study population, 80 adult females in two groups.

The patient group included 40 females who were aged between 45-85 years and diagnosed with hypothyroidism based on clinical findings and thyroid function test showing elevated TSH and low free T4.The control group was composed of 40 apparently healthy females similar in age with no history of any endocrine disorders, chronic kidney disease and who were not on any drugs that would affect mineral metabolism.

2.3. Blood Sampling and Biochemical Preparation

Using a sterile syringe 5 ml of venous blood was collected from each subject for the study. The specimens were put in plain gel tubes and allowed to clot unassisted for 15-20 minutes at room temperature. Samples were then centrifuged at 3000 rpm for 10–15 minutes for serum separation (Rifai et al., 2018).The separated serum was taken in small quantities and preserved at −20°C until analysis to prevent biochemical activity (Brindle et al., 2010).

2.4. Laboratory Procedures

2.4.1. Determination of Serum Vitamin D3 (25-OH D)

Determination of serum vitamin D3 was done using electrochemiluminescence immunoassay (ECLIA) on a Cobas e411 analyzer(Roche Diagnostics, Germany). This is a widely accepted method for quantitative determination of 25-hydroxyvitamin D (Holick, 2009; Farrell et al., 2012) in clinical practice.

2.4.2. Analysis of Calcium and Phosphate Concentrations

Serum calcium and inorganic phosphate levels were estimated by colorimetric method using commercial kits (Biolabo, France). Calcium was measured through the o-cresolphthalein complexone method and phosphate was determined through ammonium molybdate method as describe (Endres & Rude, 2006; Burtis & Bruns, 2015).

2.5. Exclusion Criteria

Those that were excluded from the study were patients with malabsorption syndrome, chronic liver disease, chronic kidney disease, and those who used vitamin D or calcium supplements in the last three months.

2.6. Statistical Analysis

The process of examining the data was performed with the help of software SPSS. Results were expressed as mean ± standard deviation (SD).

Independent samples t-test used for comparison of groups. A study was conducted to evaluate the relationship between vitamin D3 levels and concentrations of calcium and phosphate using Pearson's correlation coefficient (r). When p-value is equal to or less than 0.05 then, it considered to be significant (Field, 2013).

3. RESULTS

3.1. Distribution of Study Groups by Age

The present investigation consisted of 80 female subjects aged between 45 to 85 years. The results of the statistical analysis indicate that the mean age of the hypothyroid patient group was 62.15 ± 10.45 years while that of the control group was 59.80 ± 9.12 years. The two groups were comparable in terms of age (P = 0.285), according to Table (3-1).

Table (3-1): Comparison between Age (Mean ± SD) between Patients and Control Groups.

Variable	Control Group (n=40)	Patient Group (n=40)	t-value	P-value
Age (Years)	59.80 ± 9.12	62.15 ± 10.45	1.076	0.285 (NS)

Data are expressed as Mean ± SD. NS: Non-Significant (P > 0.05).

3.2. Physiological Profile of Vitamin D3, Calcium, and Phosphate

The biochemical investigation indicated a unique physiological disturbance of the patient group. The level of serum Vitamin D3 (25-OH D) was significantly lower in females with hypothyroidism than in healthy controls (P < 0.001). In addition, the patient group was significantly different from the control group in terms of a significant decrease in serum total calcium but a significant increase in unorganised phosphate, as shown in table (3-2).

Table (3-2): Biochemical Parameters in Hypothyroid Patients and Control Groups.

Parameter	Control Group (n=40)	Patient Group (n=40)	P-value	Significance
Vitamin D3 (ng/ml)	31.15 ± 4.80	13.40 ± 3.95	0.000	Highly Sig.
Total Calcium (mg/dl)	9.38 ± 0.55	8.05 ± 0.62	0.001	Significant
Phosphate (mg/dl)	3.15 ± 0.38	4.68 ± 0.75	0.004	Significant

Values are Mean ± SD. Statistical significance is set at P ≤ 0.05.

3.3. Pearson Correlation Analysis

The study looked whether vitamin D3 levels have any effect on minerals concentration in the patient group through Correlation Analysis. There was a positive correlation of vitamin D3 and calcium (r = 0.712, P < 0.01) On the other hand, the serum Phosphate level was the most negatively correlated with Vitamin D3 (r = -0.585, P < 0.01). This shows that deficiency of Vitamin D3 is related to mineral imbalance case in hypothyroid.

Table (3-3): Correlation Coefficient (r) between Vitamin D3 and Mineral Markers in Patients.

Parameters Correlation	Correlation Coefficient (r)	P-value	Result
Vit D3 vs. Calcium	0.712	0.000	Positive Correlation
Vit D3 vs. Phosphate	-0.585	0.003	Negative Correlation

4. DISCUSSION

4.1. Interpretation of Vitamin D3 Deficiency in Hypothyroidism

The results of the present study revealed significantly reduced levels of serum vitamin D3 in hypothyroid females indicating a complex interaction between endocrine and metabolic pathways. Vitamin D3 (25-hydroxyvitamin D) is a precursor hormone which requires metabolic activation. In hypothyroid patients, the lowered basal metabolic rate may hinder the activity of renal 1-alpha-hydroxylase, which is the enzyme that converts 25-hydroxyvitamin D into 1,25-

dihydroxyvitamin D. Mackawy et al. (2013); Bikle (2014) Furthermore, physiological changes experienced with age, are important. In women aged between 45 and 85 years, cutaneous 7-dehydrocholesterol reduction significantly reduces scalar capacity to synthesize cholecalciferol. The hypometabolic state of hypothyroidism greatly decreases vitamin D production when coupled with this (Holick, 2007; Talaei et al., 2018).

Recent studies have suggested that high TSH levels may indirectly interfere with vitamin D metabolism via an immune mediated mechanism, rather than a more direct inhibitory one, especially in autoimmune thyroid disease (Chailurkit et al. 2013, Kim, 2016). Another key mechanism is reduced expression of vitamin D receptors (VDR) in hypothyroid states. A lack of thyroid hormones may result in downregulation of VDR expression causing it to be less responsive to vitamin D (Wang et al., 2015; Duntas & Koch, 2019).

4.2. Mechanisms of Calcium and Phosphate Dysregulation

The glycemia observed (Mean: 8.05 ± 0.62 mg/dL) might be due to combined intestinal and renal dysfunction. Vitamin D regulates the expression of calcium-binding proteins (such as calbindin), which allow the active uptake of calcium in the intestine. Vitamin D level deficiency and increased thyroid hormone level in hypothyroid patients reduces intestinal calcium transport which in turn decreases serum calcium level (Nair & Maseeh, 2012; Lips, 2006).

There is also a significant effect on renal handling of calcium. Thyroid hormones assist in the regulation of sodium-calcium exchangers (NCX1) of renal tubules. Their deficiency impairs renal responsiveness to parathyroid hormone (PTH) causing a rise in the excretion of calcium in urine (Bassett & Williams 2016).

Hypothyroidism is related to decreased cardiac output and glomerular filtration rate (GFR), which limits phosphate excretion; the mean phosphate level (4.68 ± 0.75 mg/dL) defines hyperphosphatemia (Mullur et al., 2014). Thyroid hormones also regulate sodium-phosphate cotransporters in the proximal tubules. Their deficiency causes impaired clearance of phosphate, leading to the phosphate accumulation in the blood (Duntas & Koch, 2019; Williams et al., 2020).

4.3. Correlation Analysis and Clinical Implications

There was a strong positive correlation of vitamin D3 with calcium level r = 0.712 P < 0.01. Vitamin D deficiency is an important contributor to calcium imbalance in hypothyroid patients. When vitamin D levels drop below 20 mg/mL, calcium regulation is altered leading to the risk of neuromuscular malfunctions and bone depletion (Kim, 2016).

On the contrary, there was a significant negative correlation observed between vitamin D3 and phosphate ($r = -0.585$; $P < 0.01$). This finding suggests disruption of the vitamin D-PTH-FGF23 axis. Under normal physiological conditions, active vitamin D lowers phosphate reabsorption. However, in the case of hypothyroid state the altered hormonal synergy alters this regulatory mechanism (Chailurkit et al., 2013; Wang et al., 2015).

In a clinical setting, assessment of thyroid function is inadequate. A complete assessment of levels of vitamin D, calcium and phosphate is necessary to avoid long-term complications such as osteoporosis and secondary hyperparathyroidism (Duntas & Koch, 2019).

5. CONCLUSIONS AND RECOMMENDATIONS

5.1.Conclusions

Research findings showed that hypothyroid females have low serum Vitamin D3 levels in comparison to healthy controls. Vitamin D3 deficiency causes thyroid dysfunction, indicating that there is a significant association. Consequently, Cholecalciferol may be useful for at-risk populations and plays an important role in physiology. The study discovered that the calcium level of hypothyroid patients was low and the phosphate level was high. The thyroid and failing vitamin D3 activity, which affects intestinal absorption and renal regulation, play a role in this.

RESULTS

also showed a strong positive relationship of vitamin d3 levels with calcium levels and negative with phosphate levels thus confirming the implication of vitamin d3 in biochemical equilibrium of minerals.The disturbances were more marked in females aged 45-85 years thus age does aggravate the severity of metabolic disturbances that may predispose them to long-term skeletal and vascular abnormalities. Results suggested a requirement of more clinical concerns for this population group.

The Thyroid Stimulating Hormone level would not help in the management of the patients – study. A broader clinical approach that could help improve diagnosis and reduce risk of long-term complications of hypothyroidism should include vitamin and mineral profile evaluations.

5.2. Recommendations

Serum levels of vitamin D3, calcium and phosphate must be included in the routine evaluation of

hypothyroid females, especially above 45 years of age, on a regular basis. Prompt identification of deficiencies and imbalances enables clinical intervention to improve outcomes.

If a deficiency occurs, vitamin D3 supplementation is recommended, and treatment is further followed according to laboratory reports for one's dose. At the same time, patients should be counselled to take calcium and vitamin D3 in the diet and safe sun exposure for endogenous vitamin D formation.

To minimize the complications of osteoporosis and vascular calcification, renal and bone function should also be assessed periodically.

Clinicians could use this technique to detect and prevent changes in health more effectively.

Vitamin D3 replacement therapy needs a proper evaluation to assess the effect of mineral balance and clinical outcome in large studies. This will assist in creating well-founded and data-driven therapeutic protocols.

In short, in Iraq, the healthcare professional has to be more aware regarding the necessity of assessment of mineral and vitamin profile in hypothyroid patient. By shifting focus from TSH measurements to high precision imaging, we can improve the long-term management of such patients and overall care.

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