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THE RELATIONSHIP BETWEEN SERUM MAGNESIUM, CALCIUM, AND PARATHYROID HORMONE IN HYPERPARATHYROID PATIENTS: A CASE-CONTROL ANALYSIS

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THE RELATIONSHIP BETWEEN SERUM MAGNESIUM, CALCIUM, AND PARATHYROID HORMONE IN HYPERPARATHYROID PATIENTS: A CASE-CONTROL ANALYSIS

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ABSTRACT: *Hyperparathyroidism is an endocrine disorder characterized by elevated parathyroid hormone (PTH) levels. This study investigated the correlation between serum magnesium, calcium, and PTH levels in hyperparathyroid patients. Methods A case-control study was conducted with 81 hyperparathyroid patients and 81 healthy controls. Our current study was conducted at a tertiary care health center in Chennai, Tamil Nadu. Serum magnesium, calcium, and PTH levels were measured in both cases and controls. Statistical analysis was performed using SPSS version 23.0, including t-tests and Pearson's correlation. Results: Hyperparathyroid patients showed significantly lower serum magnesium levels (1.8±0.3 mg/dL) compared to controls (1.9±0.4 mg/dL, p=0.004). PTH levels were significantly higher in cases (278±311.8 pg/dL) than controls (42.2±11.1 pg/dL, p<0.001). No significant correlation was found between serum magnesium and PTH levels (r=-0.121, p=0.122). A weak positive correlation was observed between serum magnesium and calcium levels (r=0.120, p=0.876), while a negative correlation was found between serum calcium and PTH levels (r=-0.122, p=0.120). Conclusion: This study revealed a complex relationship between serum magnesium, calcium, and PTH in hyperparathyroidism. While PTH levels were elevated in hyperparathyroid patients, the relationship between serum magnesium and PTH was not directly correlated, suggesting that the relationship between these parameters appears complex and needs further investigation.*

KEYWORDS: *Cardiovascular Health, Renal Function, Bone Health, Endocrine Disorders, Biochemical Parameters, Parathyroid Hormone (PTH), Calcium Levels, Serum Magnesium, Hyperparathyroidism*

1. INTRODUCTION

Hyperparathyroidism (HPT) is an endocrine condition caused by aberrant calcium metabolism, leading to elevated levels of calcium and abnormal secretion of PTH [1]. It is generally found in postmenopausal women, characterized by high calcium levels and abnormal PTH levels. The condition originates from the overproduction and release of PTH by the parathyroid glands [2]. Due to parathyroid hyperplasia an excessive secretion of PTH takes place and often results in an abundance of calcium loss [3]. Therefore, inadequate diagnosis along with management of these patients may cause increased risk of renal, bone, and cardiovascular diseases, decreasing the standard of living, and eventually leading to overall elevation in severe complications [4]. Consequently, it was deduced that the rate of PHPT escalates with age, varying from 12-24 per 100,000 in individuals under 50 years of age, to 96-196 per 100,000 in those aged between 70 and 79 years [5]. HPT is diagnosed as an aberrant variation, which could

either be intrinsic, modifying the secretion of PTH (primary and tertiary HPT), or extrinsic, influencing calcium balance by promoting the synthesis of PTH (secondary HPT) [5].

The backbone of PTH is made up of an 84-amino acid which are aligned to form a polypeptide chain. It is efficiently secreted by the parathyroid gland, which is situated in posterior aspect of the thyroid gland. The initial structure of PTH is produced in pre-pro form, which consists of 115 amino acid polypeptide and on later state the pre-pro form is converted to pro form of PTH, and is made of 90 amino acids. Moreover, the structure is further divided at the amino-terminal, for the formation of active PTH which finally consists of 84 amino acids on its backbone structure [6]. This hormone is of considerable significance in managing the metabolism of serum calcium and phosphorus in the body. PTH is the key regulator of calcium, phosphate, magnesium, sodium, and potassium homeostasis [7]. Hence, it was claimed that PTH crucially acts in mineral metabolism. Moreover, constant monitoring is essential to prevent adverse mineral decompensation and avoid complications such as bone diseases and extra skeletal calcification, and reduce cardiac disease risk in ESRD patients. Moreover, reduced levels of calcium result in the stimulation of PTH secretion. On the other hand, high levels of calcium lead to the inhibition of hormonal secretion, which results in the degradation of parathyroid cells [8]. It is crucial that constant monitoring of fluctuations in calcium is essential, as any changes are instantly matched by an identical alteration in urinary calcium excretion. Possible evidence states that adequate secretion of PTH is significantly required for the minute-to-minute control of extracellular fluid calcium concentration [9]. Furthermore, a study suggested that the post-transcriptional impact of low serum phosphate levels in hypophosphatemic rats resulted in a notable decrease in PTH mRNA concentration [10]. An increase in the expression of SIc20a1, also known as PiT-1, was also observed. In addition, further examination was performed, which resulted in phosphorylation of IKKβ, degradation of IKBα, and high phosphorylation of p65, followed by nuclear entry. This results in the elevation of PTH transcription [11].

Magnesium, on the other hand, is one of the most underestimated elements in the biochemical perspective, where it is considered the second most common cellular cation within the body after Potassium [11]. Although the relationship between magnesium and the regulation of PTH may seem intricate, certain studies claim that it may not affect the levels of PTH. Hypomagnesemia may affect the function of PTH associated with other target organs. The correlation between magnesium and PTH is complicated as PTH improves magnesium absorption, while magnesium decreases PTH secretion in a slightly low calcium concentration

[12]. Therefore, hypomagnesemia, characterized by low magnesium levels, impedes the secretion of PTH and reduces the responsiveness of target organs to circulating PTH. This results in a biochemical profile equivalent to primary hyperparathyroidism. However, in the case of hypermagnesemia, stimulate the CaSR in the parathyroid gland. This results in the suppression of PTH secretion, although it does not have as much potency as calcium. As a result, serum magnesium tends to decrease PTH secretion, mainly during a slightly low calcium concentration and vice versa [13].

The existence of low levels of magnesium in HPT patients was observed; however, the cause of this is a prevalent endocrine disorder related to magnesium metabolism is unknown. There are limited studies with regard to the measure of magnesium levels and calcium levels in hyperparathyroidism. Hence, in our current study we planned to assess and figure the inter-relationship between the serum level of magnesium and calcium in accordance with PTH in hyperparathyroid patients.

2. MATERIALS & METHODS

Subjects

This study was performed at the Department of Biochemistry in Sri Ramachandra Institute of Higher Education and Research, Chennai-116. Leftover serum samples were obtained from the Central Laboratory, in the biochemistry department respectively.

Study Design

We planned to design our study as Case-Control centric fashion which comprises with a total of 162 participants included in it, who were later segregated into two study groups, where group 1 comprises of hyper parathyroid Cases (n=81) and group 2 as normal healthy control (n=81).

Criteria for Selection

Inclusion Criteria:

Cases: Patients aged 18-60 years diagnosed with hyperparathyroidism based on elevated PTH levels and clinical presentation.

Controls: Age-matched healthy individuals with normal biochemical parameters and PTH levels.

Exclusion Criteria:

Participants with other endocrine disorders, pregnancy, vitamin D deficiency, gastrointestinal disorders, or any hormonal disorder apart from hyperparathyroidism were excluded. Additionally, patients with renal dysfunction were excluded due to its potential impact on PTH levels.

Sample Collection and storage

Leftover blood samples of PTH analysed patient samples were obtained from the Clinical Biochemistry Central Laboratory and centrifuged at 3500 rpm for 15 minutes and stored at 2-8 °C. The serum was aliquoted and stored at -20 °C in the Department of Biochemistry, Sri Ramachandra Institute of Higher Education and Research. The samples were then processed on Biosystem semi autoanalyzer. AGAPPE serum Mg Kit was used to estimate Magnesium levels in given serum samples. The method was based on Xylidyl blue with the ATCS method where Xylidyl blue in alkaline medium forms a colored complex when reacting with Magnesium and is then measured by spectrophotometry. Normal biological reference values of magnesium in serum are 1.7-2.4 mg/dL (0.70-0.98 mmol/L).

Ethical Approval

The study was approved by the Institutional Ethics Committee of Sri Ramachandra Institute of Higher Education and Research, Chennai-600116, and was performed in accordance with its recommendations (REF: CSP/24/FEB/143/47).

Statistics

The software Statistical Package for the Social Sciences (SPSS) Version 23.0 was used for statistical analysis of data. The values were expressed as mean ±standard deviation. Followed to it parametric T-tests were performed for comparison between study groups. While correlation of Magnesium with PTH of the study was done by Pearson's correlation.

RESULTS:

The study included 162 participants (81 cases, 81 controls). In the case group, there were 37 (45.68%) males and 44 (54.32%) females, while the control group comprised 27 (33.33%) males and 54 (66.67%) females. The mean age was significantly higher in the case group (57.9±14.1 years) compared to the control group (53.7±12.2 years, p=0.039) (Table 1)

Table 1: Comparison of biochemical parameters between case and control groups

Parameter	Case (n=81) Mean ± SD	Control (n=81) Mean ± SD	t-value	p-value
Age (in years)	57.9±14.1	53.7±12.2	2.097	0.039*
Magnesium (mg/dl)	1.8±0.3	1.9±0.4	2.980	0.004*
PTH (pg/dl)	278±311.8	42.2±11.1	7.040	< 0.001**
Calcium (mg/dl)	9.0±0.8	9.0±0.6	-2.190	0.031*

Data were expressed in Mean ± SD, Student T test was used; p-Value of ≤ 0.05 was considered Statistically significant

* P Value indicates significance at single tail; ** P value indicates highly significant at double tail

Serum magnesium levels were significantly lower in cases compared to controls (p=0.004), with a medium effect size. PTH levels were significantly higher in cases (p<0.001), with a large effect size. A small but significant difference was observed in calcium levels (p=0.031).

The correlation among magnesium, PTH, and calcium levels is given in (Table 2), and observed that there was no significant correlation among the 3 parameters

Table 2: Pearson correlation coefficients among magnesium, calcium, and PTH levels

Parameters	**Magnesium**		**PTH**		**Calcium**	
	r-value	**p-value**	**r-value**	**p-value**	**r-value**	**p-value**
Magnesium	1	-	-0.121	0.122	0.120	0.876
PTH	-0.121	0.122	1	-	-0.122	0.120
Calcium	0.120	0.876	-0.122	0.120	1	-

No statistically significant correlations were observed among the parameters.

3. DISCUSSION

This study investigated the relationship between serum magnesium, calcium, and PTH levels in hyperparathyroid patients compared to healthy controls. Our findings reveal a complex interplay among these parameters, with some results aligning with previous research while others present new insights.

It has been established by many studies that low serum magnesium levels are due to high levels of PTH, which may be one of the causes of hyperparathyroidism. The condition generally affects women with a 3:1 - 4:1 prevalence and is mostly common within the 50-60year age group [14].

Our study demonstrated the relationship between gender, age, and PTH levels, claiming that there were more females (56.79%) than males (45.67%) who were affected by hyperparathyroidism (Table 1) and statistically significant (p=0.039). A recent study by Dadon, et al. observed similar results that more females were affected by hyperparathyroidism than males. The age-related increase in PTH levels and the associated risk of osteoporosis and cardiovascular disease necessitate a comprehensive approach to care that addresses both endocrine and systemic health issues.

In the present study, hypomagnesemia is associated with high levels of PTH in patients. The serum magnesium levels in the study showed a high significant difference (p=0.004) with mean ±SD of the case (1.8±0.3 mg/dL) and control (1.9±0.4 mg/dL) groups (Table 1). PTH stimulates the excretion of magnesium from renal excretion in HPT patients [15]. So, impaired magnesium absorption from the intestine may be another cause of hypomagnesemia [16].

The lack of significant correlations among magnesium, calcium, and PTH levels highlights the complexity of mineral homeostasis in hyperparathyroidism. It is also observed in our study that the correlation between magnesium and PTH is complicated as PTH improves magnesium absorption, while magnesium decreases PTH secretion in a state of slightly low calcium concentration because magnesium aids in regulating calcium balance in our body, specifically through the hormones such as 1, 25(OH)2D3 and PTH [13]. In our current study we do also observed a very weak positive correlation between the serum levels of magnesium and calcium (r= 0.120; p=0.876) (Table 1). This could also may be due to the inhibition of G-protein coupled receptors which causes elevation of PTH secretion [17]. Moreover, extreme hypomagnesemia could lead to the synthesis of defective cAMP in the parathyroid gland, resulting in the paradoxical block of PTH secretion.

Magnesium typically generates by influencing PTH secretion in a manner akin to calcium. High magnesium levels suppress PTH release and reduce the accumulation of cAMP stimulation by agonists in the parathyroid gland. Additionally, distinctions in the effect of calcium and magnesium on CaSR-mediated secretory responses may stem from their respective abilities to bind to the receptor and/or take part in the cellular signaling cascade activated by the CaSR [18]. Many researches has frequently indicated a relationship between serum magnesium and HPT, with serum magnesium concentrations typically being reduced as a result of hypomagnesemic states [19]. In addition, routine evaluation of serum magnesium may aid in the prediction of the clinical outcomes of PHPT [20].

Calcium levels in our studies were non-significant in both the groups that means the presence of normocalceima with high PTH. The cause of this condition is yet not known and it's challenging because multiple causes are associated with increased levels of PTH like in nephrolithiasis or a suspected metabolic bone [21]. Sometimes in hyperparathyroidism, Ca levels yet to respond before PTH levels increase rapidly.

4. CONCLUSION

This study concludes that while hyperparathyroid patients exhibit significant differences in serum magnesium, calcium, and PTH levels compared to healthy controls, the relationship between these parameters is complex and not directly linear. This study also revealed calcium as a non-significant negatively correlated variable with PTH, while it has a slight positive correlation with serum magnesium. The three parameters were also associated with both age and gender, where it was found that more females were diagnosed with hyperparathyroidism than males, with an age of and above 50 years.

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