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Research Article

ALTERATIONS OF SERUM CALCIUM, PHOSPHORUS, MAGNESIUM, AND COPPER IN HYPERTHYROIDISM PATIENTS: A CASE–CONTROL STUDY

DIANA ATHOKPHAM, SHRABANI MOHANTY, VENKATA BHARATKUMAR PINNELLI

Department of Biochemistry, Vydehi Institute of Medical Sciences and Research Centre, Nallurhalli, Whitefield, Bengaluru, Karnataka, India. Email: pvbharatkumar@yahoo.co.in

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ABSTRACT

Objective: The objective of the study was to estimate the levels of serum calcium, phosphorus, magnesium, and copper in hyperthyroid cases and to correlate each of the parameter with serum T3, T4, TSH, FT3, and FT4, respectively.

Methods: The study was conducted on 60 newly confirmed hyperthyroid cases based on the thyroid profile and 60 euthyroid cases were recruited as controls. Blood samples were collected from all these subjects and estimation of serum T3, T4, TSH, FT3, FT4, calcium, phosphorus, and magnesium was done by autoanalyzer method. Serum copper was measured by modified spectrophotometric micro-method using guanidine hydrochloride and bathocuproine disulfonate disodium salt. The statistical analysis was done by paired test and Pearson's correlation.

Results: Study results in hyperthyroid cases show mean serum calcium and copper levels were significantly ($p<0.001$) increased, serum phosphorus levels were significantly ($p<0.001$) decreased when compared to euthyroid. However, there was no significant change in magnesium when compared with euthyroid controls ($p=0.556$). We also found a significant positive correlation among serum Ca versus T3, T4, FT3, and FT4. A negative correlation with serum Ca versus TSH as observed. We also found significant positive correlation between serum phosphorus with TSH and significant negative correlation of phosphorus with T3, T4, FT3, and FT4. No suggestive significant correlation was found between serum Mg with T3, T4, TSH, FT3, and FT4 and serum copper with serum T3, T4, TSH, FT3, and FT4.

Conclusion: The present study has shown that metabolism of minerals is altered in hyperthyroid cases. Impaired metabolism of calcium, phosphorus, magnesium, and copper can lead to various metabolic disorders. Estimation of serum calcium, phosphorus, magnesium, and copper may be helpful in better management to prevent further complication and can be used as diagnostic or prognostic aid in patients with hyperthyroidism along with other biochemical parameters.

Keywords: Hyperthyroidism, Mineral metabolism, Thyroid hormones.

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INTRODUCTION

The thyroid hormones play a pivotal role in regulation of various metabolisms such as carbohydrate, fat, protein, vitamin, and minerals, influence the basal metabolic rate, and regulate bone growth. Hyperthyroidism is a condition in which the thyroid gland produces excess thyroid hormone and Graves' disease is the most common cause of hyperthyroidism. The symptoms of an overactive thyroid gland include unintentional weight loss, anxiety, sweating, frequent bowel movements, difficulty sleeping, and muscle weakness [1]. There is a significant relation between thyroid hormones and minerals metabolism, although their changes may be slight, disturbances of these minerals such as calcium, phosphorus, and magnesium may lead to some defects such as metabolic syndrome, hypertension, and cardiovascular diseases. Although the exact mechanism is not well understood, there is a potential role of these minerals in metabolic pathways. In addition to genetic and environmental factors, trace elements like copper may also play key roles in thyroid physiology and pathology [2] and known to influence hormones action, secretion, activity, and binding to target tissue. In vice versa, hormones influence trace metals metabolism at several levels of action, including excretion and transport of trace elements.

It has been reported that thyroid gland is the organ with the highest levels of trace elements [3]. These elements have potential links with thyroid hormone metabolism, and any deficiency or excess can affect thyroid hormones homeostasis [4-6]. Copper (Cu) has been reported to be essential cofactors of antioxidant and anti-inflammation system [7,8], which are involved in the production of thyroid hormone [9,10]. Therefore, the trace elements in the body should be present in appropriate concentrations, and abnormal levels of trace metals can develop when the oxidation-antioxidation system fails [11,12].

Hence, minerals and trace elements assay in biological fluids can be used as diagnostic or prognostic help in patients with different hormonal disturbances along with other biochemical parameters.

The previous studies investigating serum calcium, phosphorous, magnesium, and copper in hyperthyroidism have revealed conflicting results. The effect of thyroid hormones on mineral levels in plasma is still not clear. The present study has been taken up to assess alterations of serum levels of calcium, phosphorus, magnesium, and copper in hyperthyroid cases and to compare with euthyroid controls.

METHODS

A case–control study of duration 1 year (January 2017–December 2017) was conducted on patients confirmed of hyperthyroid visiting Department of Biochemistry, Department of Medicine, Department of Endocrinology at Vydehi Institute of Medical Sciences and Research Centre, Bengaluru. Age- and sex-matched euthyroid healthy individuals visiting hospital for routine health checkups were taken as controls. Sixty clinically healthy volunteers with euthyroid status and 60 newly diagnosed and untreated cases of hyperthyroidism patient among the age group of 25–60 years were taken for the study. Sample size was estimated using sample size calculator Piface 1.72. The study was approved by the ethical committee of the institution (EC Reg No: ECR/747/Inst/KA/2015 Dated 10/10/2016). Informed consent was taken from all the participants.

Biochemically, diagnosis of hyperthyroidism was established based on increased serum T3 (>1.9 ng/ml) and T4 (>12.0 μg/dl) levels associated with decreased with TSH levels (<0.5 μIU/ml) and was included in the study. Pregnant women, patient with a history of hepatic disease, renal disease, alcoholism, or critically ill patients or those who were on mineral supplementation, antithyroid drugs, or any other medications known to affect the calcium, magnesium, phosphorus, and copper metabolism were excluded from the study.

Five milliliters of venous blood samples were collected from median cubital vein by venipuncture avoiding hemolysis into an evacuated vacuum tube under aseptic precaution. Samples were centrifuged after 30 min at 3000 rpm for 10 min. The sample was aliquoted and kept at −20°C as per standard protocol until analysis was done. All the analyses were carried on serum samples. Serum T3 and T4 were measured by chemiluminescence immunoassay method, serum TSH was measured by two sites immunoenzymatic method, serum FT3 was measured by competitive immunoassay binding method, and serum FT4 was measured by two-step enzyme immunoassay method by Beckman Coulter Unicel DXI 600 Synchron Clinical System. Serum calcium was measured by ISE electrolyte reference kit and ISE electrolyte buffer reagent method, serum phosphorus was measured by phosphorus molybdate method, and serum magnesium was measured by calmagite method by Beckman Coulter Unicel DXC 800i Synchron Clinical System. Serum copper was measured by modified spectrophotometric micro-method with the use of bathocuproine disulfonate and guanidine hydrochloride disodium salt.

Statistical analysis

The statistical software, namely, SPSS 18.0, and R environment ver.3.2.2 were used for the analysis of the data. The results of cases and controls were compared by student "t" test. $p<0.05$ was considered statistically significant and $p<0.01$ was considered highly significant. All the parameters were compared with T3, T4, TSH, FT3, and FT4 levels and correlation between parameters was studied by Pearson's correlation coefficient.

RESULTS

The study group consisted of 60 hyperthyroid cases and 60 euthyroid controls. The cases and controls were age and sex matched. The mean age of hyperthyroid cases was 41.25±10.26 years and in controls 41.56±10.53 years. There were 72.2% of female participants form hyperthyroid group and 74.8% among control group with statistically no significant.

The mean concentration of serum T3 3.48±0.76 ng/ml was significantly increased when compared with controls 1.38±0.29 ng/dl ($p<0.001$**), serum T4 13.80±2.95 μg/dl was significantly increased when compared with controls 8.75±1.69 μg/dl ($p<0.001$**), serum FT3 6.98±1.92 pg/ml was significantly increased when compared with controls 3.28±0.85 pg/ml ($p<0.001$**), serum FT4 5.98±4.21 ng/dl was significantly increased when compared with controls 1.59±0.54 ng/dl ($p<0.001$**), while serum TSH (0.13±0.11 μIU/ml) was found to be significantly decreased when compared with controls 3.38±1.12 μIU/ml ($p<0.001$**) in patients with or without orbitopathy in Northeast hyperthyroid cases (Table 1).

The mean concentration of serum Ca in cases and controls was 11.64±0.79 mg/dl and 9.71±0.40 mg/dl ($p<0.001$**), respectively, and was significantly increased when compared with healthy controls (normal reference range: 9–11 mg/dl). The mean concentration of serum phosphorus in cases and controls was 2.38±0.74 mg/dl and 3.49±0.69 mg/dl ($p<0.001$**), was significantly decreased when compared with controls (normal reference range: 2.4–4.5 mg/dl). The mean concentration of serum Mg in cases and controls was 2.43±0.73 mg/dl and 2.39±0.29 mg/dl ($p=0.559$), respectively, no significant change was observed when compared with controls (normal reference range: 1.7–2.2 mg/dl). The mean concentration of serum Cu levels in cases and controls was 134.03±19.53 μg/dl and 84.54±9.88 μg/dl ($p<0.001$**), respectively, statistically significant increase was observed when compared with controls (normal reference range: 70–140 μg/dl) (Table 2).

Pearson's correlation was applied to correlate the parameters with T3, T4, TSH, FT3, and FT4. On analyzing the values, a statistically significant positive correlation between serum calcium with T3 ($r=0.890$, $p<0.001$**), T4 ($r=0.736$, $p<0.001$**), FT3 ($r=0.786$, $p<0.001$**), and FT4 ($r=0.516$, $p<0.001$**) was observed, whereas a significantly negative correlation was observed with TSH ($r=0.637$, $p<0.001$**). A statistically significant negative correlation between serum phosphorus with T3 ($r=-0.680$, $p<0.001$**), T4 ($r=-0.814$, $p<0.001$**), FT3 ($r=-0.616$, $p<0.001$**), and FT4 ($r=-0.655$, $p<0.001$**) was observed, whereas a significantly positive correlation was observed with TSH ($r=0.803$, $p<0.001$**). No significant correlation was found between serum magnesium and copper, respectively, with T3, T4, TSH, FT3, and FT4 (Table 3).

DISCUSSION

Thyroid hormones act as key regulators of body hemodynamics, thermoregulation, and metabolism. Therefore, it has an influence on renal hemodynamics, glomerular filtration, and electrolyte handling [13]. The homeostasis of calcium, magnesium, phosphorous, and copper was frequently disturbed in thyroid dysfunctions. Minerals are essential for normal thyroid hormone metabolism and their deficiencies can impair thyroid function [14]. Hyperthyroid-related disorders can lead patients to a variety of clinical situations including electrolyte and mineral disturbances, congestive heart failure, and coma. India being highly prevalent to thyroid diseases has a major health concern. The main aim of the study was to investigate alterations of minerals in hyperthyroid cases. This study was designed to estimate serum levels of calcium, phosphorus, magnesium, and copper in patients of hyperthyroid and compare it with euthyroid controls and to find the correlation of serum calcium, phosphorus, magnesium, and copper levels with serum TSH, T3, T4, FT3, and FT4 in hyperthyroidism.

Our present study has shown significant increase ($p<0.001$**) levels of serum calcium (11.64±0.79 mg/dl) as compared with controls (9.71±0.40 mg/dl) in hyperthyroid cases. A study done by Suneel *et al.* [15], Shivaleela *et al.* [16] also found similar high serum calcium levels when compared with control groups. An abnormality in calcium

Table 1: Comparison of thyroid hormone parameters in the hyperthyroid patient's versus control group

Variables	Results		Pairwise significance
	Hyperthyroid (n=60)	Control (n=60)	Hyperthyroid versus control
T3 (ng/ml)	3.48±0.76	1.38±0.29	<0.001**
T4 (μg/dl)	13.80±2.95	8.75±1.69	<0.001**
TSH (μIU/ml)	0.13±0.11	3.38±1.12	<0.001**
FT3 (pg/ml)	6.98±1.92	3.28±0.85	<0.001**
FT4 (ng/dl)	5.98±4.21	1.59±0.54	<0.001**

**Strongly significant ($p<0.001$)

Table 2: Comparison of minerals in the hyperthyroid patient's versus control group

Variables	Results		Pairwise significance
	Hyperthyroid (n=60)	Control (n=60)	Hyperthyroid versus control
Ca (mg/dl)	11.64±0.79	9.71±0.40	<0.001**
P (mg/dl)	2.38±0.74	3.49±0.69	<0.001**
Mg (mg/dl)	2.43±0.73	2.39±0.29	0.556
Cu (μg/dl)	134.03±19.53	84.54±9.88	<0.001**

**Strongly significant ($p<0.001$)

Table 3: Pearson's correlation

Pair	Hyperthyroid	
	r value	p value
Ca versus T3	0.890	<0.001**
Ca versus T4	0.736	<0.001**
Ca versus TSH	−0.637	<0.001**
Ca versus FT3	0.786	<0.001**
Ca versus FT4	0.516	<0.001**
Phos versus T3	−0.680	<0.001**
Phos versus T4	−0.814	<0.001**
Phos versus TSH	0.803	<0.001**
Phos versus FT3	−0.616	<0.001**
Phos versus FT4	−0.655	<0.001**
Mg versus T3	−0.068	0.694
Mg versus T4	0.024	0.887
Mg versus TSH	−0.149	0.387
Mg versus FT3	−0.061	0.724
Mg versus FT4	−0.047	0.787
Cu versus T3	0.132	0.153
Cu versus T4	0.201	0.098
Cu versus TSH	−0.220	0.089
Cu versus FT3	0.319	0.210
Cu versus FT4	0.204	0.182

+Suggestive significance (p value: 0.05<p<0.10), *moderately significant (p value: 0.01 < p<0.05), **strongly significant (p<0.001)

metabolism directly influences thyroid hormones as they play a major role in calcium homeostasis by their direct action on bone turnover. Thyroid hormones are most essential for normal growth and maturation of the skeletal system. In hyperthyroidism, there is accelerated bone turnover which leads to direct stimulation of bone cells causing high thyroid hormone concentration. These patients usually had decreased production of thyroid calcitonin and due to this tubular excretion of phosphate is enhanced and favours tubular absorption of calcium [15]. The mean serum calcium concentrations of hyperthyroid patients are higher than those of control subjects could be due to an abnormal calcium efflux from the skeleton, kidneys, and gastrointestinal tract to the extracellular fluid [17,18].

In our study, among hyperthyroid cases, highly significant positive correlation was found between serum calcium and T3 (r=0.890, p<0.001). Similarly, significant positive correlation between serum calcium and T4 (r=0.736, p<0.001) was seen. These findings among hyperthyroid cases are in agreement with the study done by Modi *et al.* [19] where they have shown strong significant positive correlation between serum calcium with serum T3 and T4 levels. Our study also found that serum calcium has significant negative correlation with TSH (r=−0.637, p<0.001) in hyperthyroidism, this is in agreement with a study done by Modi *et al.*[19] where strong significant negative correlation of serum calcium with TSH was shown. However, our findings are in disagreement to the study done by Bharti *et al.* [20]. We also found a significant positive correlation between serum calcium and FT3 (r=0.786, p<0.001) and FT4 (r=0.516, p<0.001) which is accordance with the study done by Chrishtoph Schwarz *et al.* [21].

In our study among hyperthyroid cases, we found significant (p<0.001) decreased levels of serum phosphorus (2.38±0.74 mg/dl) levels as compared with controls (3.49±0.69 mg/dl). These findings in our study of hyperthyroid cases are in accordance with the study conducted by Abbas *et al.* [22], Alcalde *et al.* [23], Schwarz *et al.* [21], and Gohel *et al.* [24]. However, our findings are in disagreement with the study by Gammage *et al.* [25].

In our study, we found significant negative correlation between serum phosphorus and T3 (r=−0.680, p<0.001) and between serum phosphorus and T4 (r=−0.814, p<0.001) in hyperthyroid cases. The present study also showed a significant positive correlation with serum phosphorus and TSH (r=0.803, p<0.001) among hyperthyroid cases. These findings are in disagreement with the study done by Modi *et al.* [19].

Similarly, in hyperthyroidism, our present study, we found significant negative correlation between serum phosphorus and FT3 (r=−0.616, p<0.001) and FT4 (r=−0.655, p<0.001), which is in contrast to the study done by Schwarz *et al.* [21] in hyperthyroid cases. Our study also revealed in hyperthyroidism no significant change in serum Mg (2.43±0.73 mg/dl) as compared with controls (2.32±0.29 mg/dl) (p=0.556). A study done by Mane *et al.* [26] who have shown no changes in serum magnesium levels in hyperthyroid patients as compared to controls, which is in accordance with the present study where possible reason could be attributed to poor dietary magnesium intake by hyperthyroid patients. However, the present finding is contradictory to the earlier reports; a study done by Suneel *et al.* [15] who has shown significant increase in serum magnesium levels as compared with control groups.

In the present study, no significant correlation was found between serum magnesium and T3 (r=−0.068, p=0.694) and T4 (r=0.024, p=0.887) which is in disagreement with the study done by Shibutani *et al.* [27] and also found no statistically significant correlation between magnesium and FT3 (r=−0.149, p=0.387) and FT4 (r=−0.047, p 0.787) which is contradictory to the findings done by Shibutani *et al.* [27], they revealed significant negative correlation with FT4, and however, our findings are similar to Bharathi *et al.* [20], Jaskin *et al.* [28], Schwarza *et al.* [21], and Frizel *et al.* [29].

Our study also revealed in hyperthyroid patients, statistically significant change of serum copper (134.03±19.53 μg/dl) levels as compared to controls (84.25±9.08 μg/dl) (p<0.001**). Copper is an essential element, acts as a cofactor for tyrosinase which is essential for the biosynthesis of tyrosine, which is a protein component of thyroglobulin needed for the synthesis of thyroid hormones. Other than this, copper is also required for the synthesis of phospholipids, which are found in the myelin sheaths that regulate nerves to protect them. As phospholipids are required for the stimulation of TSH, correct level is needed to prevent thyroid diseases.

Our study also found significant changes in serum copper level in hyperthyroid patients which is in accordance with the other findings where most of the studies show significant increase in serum copper level. Vaghela *et al.* [30] revealed significant increase serum copper level in hyperthyroid patients, in which the author has explained that most of the plasma copper is bound to ceruloplasmin and only small fraction bound to plasma albumin. Ceruloplasmin is one of the acute-phase reactants that the level increases in response to inflammation.

Our present study also found among hyperthyroid cases, no significant correlation between serum copper with T3, similarly, no significant correlation between serum copper with T4. Our study also showed no significant correlation with serum copper and TSH, which is in accordance with the study done by Gungor AKCAY *et al.* [31] and also no correlation between serum copper and FT3, which is similar to the study done by Yongping Liu *et al.* [32] in which the author revealed significant positive correlation with FT4 levels.

The above findings show that altered metabolism of serum calcium, phosphorus, magnesium, and copper has association with thyroid hormones. Many contradictory findings are observed in various studies and need to be investigated further. The study can be extended by measuring other serum minerals and correlating it with duration and severity of hyperthyroidism.

CONCLUSION

The study shows that in hyperthyroidism, there is imbalance in the levels of serum calcium, phosphorus, magnesium, and serum copper in comparison to controls. These changes may play an important role in assessing the complications of hyperthyroid cases. The impaired

metabolism of these minerals may have a contributory role in the progression of thyroid disease and later development of complications. Estimation of serum calcium, phosphorus, magnesium, and copper may be helpful for better management to prevent further complication and can be used as diagnostic or prognostic aid in patients with hyperthyroidism along with other biochemical parameters.

Limitations

Further studies are required to validate the present findings; dietary pattern of the all study participants should also be monitored to avoid misinterpretations.

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AUTHORS' CONTRIBUTIONS

All authors contributed to data collection and analysis, drafting, and revising of the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

DECLARATION OF CONFLICTING INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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