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Original Article

Biochemistry Section

Status of Serum Calcium, Phosphorus, Magnesium and Copper in Hypothyroid Patients- A Case Control Study

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ABSTRACT

Introduction: Thyroid disorders are the most common endocrine abnormality in the world secondary to diabetes mellitus. Thyroid hormones are essential for growth, neuronal development, reproduction and regulation of energy metabolism. It influences the metabolism of all substrates including minerals. Many studies have shown that mineral metabolism is frequently disturbed in thyroid disorders.

Aim: To estimate the levels of serum calcium, phosphorus, magnesium and copper in hypothyroid cases and to correlate each of the parameter with serum Triiodothyronine (T3), Thyroxine (T4), Free T3 (FT3), Free T4 (FT4) and Thyroid-Stimulating Hormone (TSH), respectively.

Materials and Methods: The study was conducted on sixty newly confirmed hypothyroid cases based on the thyroid profile and sixty euthyroid cases were recruited as controls. Blood samples were collected from all the patients for the estimation of serum T3, T4, FT3, FT4, TSH, calcium, phosphorus and magnesium by autoanalyser method. Modified spectrophotometric micro-method was used to measure Serum copper using Bathocuprine Disulphonate Disodium Salt (BCDS) and Guanidine hydrochloride salt. The Statistical software namely SPSS 18.0, and R environment ver.3.2.2 were used for the analysis of the data.

Results: Study results shows that mean serum calcium, magnesium and copper levels were significantly ($p<0.001$) decreased while serum phosphorus levels were increased significantly ($p<0.001$) in hypothyroid cases as compared to euthyroid cases. A significant positive correlation was found between serum Ca vs T3, serum Ca vs T4, negative correlation with serum Ca vs TSH, serum Ca has no significant correlation with serum FT3 and FT4. Significant positive correlation was found between serum phosphorus and TSH while significant negative correlation of phosphorus in comparison with T3 and T4. No significant correlation was found between serum phosphorus with FT3 and FT4. Suggestive significant positive correlation was found between serum Mg with T3, T4 and significant negative correlation with serum TSH, Mg has no significant correlation with FT3 and FT4, there was no significant correlation of serum copper with serum T3, T4, TSH and FT4 but significant positive correlation with serum Cu with FT3 were observed.

Conclusion: The present study has shown that metabolism of minerals are altered in thyroid dysfunction cases. This study concluded that impaired metabolism of minerals like calcium, phosphorus, magnesium and copper can lead to various metabolic disorders. Preventive measures like supplementation of minerals or hormone replacement therapy can be initiated early to control these secondary disorders.

Keywords: Hypothyroidism, Mineral metabolism, Thyroid hormones

INTRODUCTION

The thyroid hormones play an important role in regulation of carbohydrate, fat, protein and mineral metabolism. They act to increase the basal metabolic rate, stimulate vitamin metabolism and help in regulating long bone growth. Hypothyroidism is a most common endocrine disorder in which the disease causes generalised slowing of metabolic processes [1]. It has been receiving more attention lately as it is an important cause of disturbance in mineral metabolism by their direct action on bone turnover and in long run causes secondary complications like osteoporosis [2]. There is a significant relation between thyroid hormones and minerals metabolism, although their changes may be slight, disturbances of these minerals like calcium and magnesium may lead to some defects like metabolic syndrome, hypertension and cardiovascular diseases. Potential mechanism is the basic role of these cations in metabolic pathways but the exact mechanism is not well understood [3]. As an index of bone resorption, phosphorous and serum calcium levels can be reasonably used. In hypothyroidism blood calcium levels are decreased as a result of impaired mobilisation of calcium into the bone due to depressed turnover.

It also increases production of calcitonin which can promote tubular reabsorption of phosphate and tubular excretion of calcium. Animal study done on rats has shown that FT3 elevates the renal phosphate reabsorption and elevates serum phosphorus levels. They also propose thyroid hormones as long term regulators for phosphate metabolism [4]. Thyroid hormones also alter magnesium metabolism. Serum magnesium influences thyroid hormone on glomerular filtration rate and thereby clearance of this mineral by filtration, so it usually decreases in hypothyroid cases [5].

In the metabolism of thyroid, copper plays an important role in hormone production and absorption. Further, copper is also essential in the synthesis of phospholipids, which are required to stimulate thyroid stimulating hormone (TSH). Studies on hypothyroid subject shows significant decrease of serum copper levels [6].

Studies on hypothyroid patients have shown contradictory results where the levels of serum calcium and phosphorus and magnesium levels were decreased [7] while others have observed low serum calcium and magnesium levels and an increase in serum phosphorus levels and even some studies have shown normal serum calcium and phosphorus levels [8]. Serum copper also showed no change while some studies showed decreased in hypothyroid patients [4]. The effect of thyroid hormones on mineral levels in plasma is still not clear as there are many studies done earlier have shown contradictory findings in hypothyroidism. The present study has been taken up to assess alterations of serum levels of calcium, phosphorus, magnesium and copper in hypothyroid cases and to compare with euthyroid controls.

MATERIALS AND METHODS

A case control study was done for the duration of one year (January 2017 to December 2017) on the confirmed patients of hypothyroid visiting Department of Biochemistry, Department of Medicine, Department of Endocrinology, at Vydehi Institute of Medical Sciences and Research Centre, Bangalore. Age, sex matched euthyroid healthy individuals visiting hospital for routine health checkups were taken as controls. Sixty clinically healthy volunteers with euthyroid status and sixty newly diagnosed and untreated cases of hypothyroidism patient among the age group of 25-60 years were taken for the study. Estimation of sample size was done by using sample size calculator Piface 1.72 and Power of the study was calculated more than 80%. 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.

Inclusion criteria: Biochemically, diagnosis of hypothyroidism was established based on decreased serum T3 (<0.5 ng/mL) and T4 (<4.6 µg/dL) levels associated with increased with TSH levels (>5.4 µIU/mL) and were included as cases in the study.

Exclusion criteria: Pregnant women, patient with history of hepatic disease, renal disease, alcoholism or critically ill patients or the patients who were on mineral supplementation, anti-thyroid drugs or any other medications that influence the calcium, magnesium, phosphorus and copper metabolism were excluded.

A 5 mL of venous blood samples was collected from median cubital vein by venipuncture avoiding haemolysis into an evacuated vacuum tube under aseptic precaution. Samples were centrifuged after 30 minutes at 3000 rpm for ten minutes. The sample was aliquoted and kept at -20°C as per standard protocol until analysis was done. All the analysis was carried on serum samples. Serum T3, T4 was measured by chemiluminescence immunoassay method, Serum TSH was measured by Two-site enzyme immunoassay 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 Bathocuprine disulphonate and Guanidine Hydrochloride disodium salt.

STATISTICAL ANALYSIS

Statistical analysis was done by SPSS 18.0, and R environment version.3.2.2 was used for the data analysis. Student paired t-test was used to compare the results of cases and controls. P-value of <0.05 was considered as significant. All the parameters were compared with T3, T4, TSH, FT3, FT4 levels and correlation between parameters was done by Pearson's correlation coefficient.

RESULTS

The study group consisted of 60 hypothyroid cases and 60 euthyroid controls. The cases and controls were age and sex matched. The mean age of hypothyroid cases was 42.28±9.92 years and in controls 41.56±10.53 years. There were (71.1%) of female participants form hypothyroid group and (74.8%) among control group with statistically no significance.

The mean concentration of serum T4 (6.49±3.01 µg/dL, was significantly less when compared with controls (8.75±1.69 µg/dL), serum FT3 (1.95±0.69 pg/mL) was significantly less when compared with controls (3.28±0.85 pg/mL) while serum TSH (30.18±31.20 µIU/mL was found to be significantly increased when compared with controls (3.38±1.12 µIU/mL) in hypothyroid cases [Table/Fig-1].

Variables	Results		Pairwise significance
	Case (n=60)	Control (n=60)	Case vs Control
T3 (ng/mL)	1.12±0.43	1.38±0.29	0.198
T4 (µg/dL)	6.49±3.01	8.75±1.69	0.002**
TSH (µIU/mL)	30.18±31.20	3.38±1.12	<0.001**
FT3 (pg/mL)	1.95±0.69	3.28±0.85	<0.001**
FT4 (ng/dL)	0.68±0.25	1.59±0.54	0.262

[Table/Fig-1]: Comparison of thyroid hormone parameters in the case vs control group by student paired t-test.
**Strongly significant (p-value: p<0.001)

The mean concentration of serum Ca in cases and controls were 8.96±0.36 mg/dL (p=0.002) and 9.71±0.40 mg/dL, respectively and were significantly decreased when compared with healthy controls (normal reference range: 9-11 mg/dL). The mean concentration of serum phosphorus in cases and controls were 5.46±0.45 mg/dL, (p<0.001) and 3.49±0.69 mg/dL, were significantly increased when compared with controls (normal reference range: 2.4-4.5 mg/dL). The mean concentration of serum Mg in cases and controls were 1.41±0.29 mg/dL, (p <0.001) and 2.39±0.29 mg/dL respectively, highly significant decreased levels were 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 were 64.94±5.9 µg/dL, (p <0.001) and 84.54±9.88 µg/dL respectively, significant decreased levels were observed when compared with controls (normal reference range: 70-140µg/dL) [Table/Fig-2].

Variables	Results		Pairwise significance
	Case (n=60)	Control (n=60)	Case vs Control
Ca (mg/dL)	8.96±0.36	9.71±0.40	0.002**
P (mg/dL)	5.46±0.45	3.49±0.69	<0.001**
Mg (mg/dL)	1.41±0.29	2.39±0.29	<0.001**
Cu (µg/dL)	64.94±5.9	84.54±9.88	<0.001**

[Table/Fig-2]: Comparison of minerals in the case vs control group by student paired t-test.
**Strongly significant (p-value: p<0.001)

Pearson correlation was applied to correlate the parameters with TSH, T3, T4, FT3, FT4. On analysing the values, a statistically significant negative correlation between serum Calcium with TSH (r value-0.891, p-value <0.001) and serum Mg with TSH (r value-0.858, p-value<0.001) was found. Serum phosphorus had significant negative correlation in comparison with T3 (r value -0.457, p-value 0.009) and also with T4 (r value-0.718, p <0.001). Positive significant correlation was observed between serum Phosphorus with TSH (r value 0.927, p-value <0.001). Also, statistically significant positive correlation between serum Calcium with T3 (r value 0.393, p-value 0.018) and T4 (r value 0.693, p-value <0.001), serum Mg with T3 (r value 0.328, p-value 0.051+), serum Mg with T4 (r value 0.674, p-value <0.001), serum Copper with FT3 (r value 0.446, p-value 0.006) was observed. No significant correlation was found between serum Calcium with FT3 and FT4. Serum Phosphorus also showed no significant correlation with FT3 and FT4. Correspondingly, no significant correlation between serum Mg with FT3, FT4 and Copper with T3, T4, TSH and FT4 was observed [Table/Fig-3].

DISCUSSION

The main aim of the study was to investigate alterations of minerals in hypothyroid cases. Thyroid hormones, they are essential in maintaining renal haemodynamics, glomerular filtration and electrolyte handling and has a direct effect on calcium and magnesium absorption [9]. The homeostasis of calcium, magnesium, phosphorous and copper was frequently disturbed in hypothyroidism. For the normal thyroid hormone functioning and metabolism, several minerals as well as trace elements are essential. The deficiencies of these trace elements can lead to

Pair	Case	
	r value	p-value
Ca vs T3	0.393	0.018*
Ca vs T4	0.693	<0.001**
Ca vs TSH	-0.891	<0.001**
Ca vs FT3	0.093	0.589
Ca vs FT4	-0.051	0.758
P vs T3	-0.457	0.009**
P vs T4	-0.718	<0.001**
P vs TSH	0.927	<0.001**
P vs FT3	-0.041	0.811
P vs FT4	0.176	0.304
Mg vs T3	0.328	0.051+
Mg vs T4	0.674	<0.001**
Mg vs TSH	-0.858	<0.001**
Mg vs FT3	0.118	0.493
Mg vs FT4	-0.080	0.642
Cu vs T3	-0.015	0.932
Cu vs T4	0.063	0.716
Cu vs TSH	-0.102	0.555
Cu vs FT3	0.446	0.006**
Cu vs FT4	-0.006	0.972

[Table/Fig-3]: Pearson correlation.
+Suggestive significance (p-value: 0.05 <p<0.10); *Moderately significant (p-value: 0.01<p<0.05); **Strongly significant (p-value: p<0.001)

impairment of thyroid function. Present study found a significant (p<0.001) decrease in levels of serum Ca in cases as compared to controls. The results of decrease serum calcium level were in agreement with the study done by Sridevi D et al., and Gohel MG et al., [1,3]. Abnormalities in calcium metabolism directly influence thyroid hormones as they play a major role in calcium homeostasis by their direct action on bone turnover. Thyroid hormones are required for maturation of the skeletal system and for normal growth. In hypothyroidism, thyroid calcitonin production is increased which promote tubular reabsorption of phosphate and favors tubular excretion of calcium. Blood calcium levels are normally regulated by releasing calcium from the cells, in hypothyroidism less thyroxine enters the cells as there is less thyroxine in the blood which ultimately leads to less release of calcium [10]. Significant positive correlation was found between serum calcium and serum T3 (r value 0.393, p=0.018). Similarly, significant positive correlation between serum calcium and serum T4 (r value 0.693, p<0.001) with strong significance. The present study also showed significant negative correlation between serum calcium with serum TSH (r value -0.891, p<0.001). These findings of present study are in agreement with the study done by Sridevi D et al., [1], Gohel MG et al., [3], Shivaleela MB et al., [7] Murgod R and Soans G [10]. The present study revealed, no correlation significant between serum calcium and serum FT4 (r value-0.051, p=0.758), in contrast to the study done by Mani V et al., where they have shown a positive correlation of serum calcium and FT4 with patient suffering from hypothyroidism [11].

Significant (p<0.001) increased levels of serum phosphorus was found in cases when compare with controls. This finding in present study is in accordance with the study conducted by Sridevi D et al., Gohel MG et al., Alcalde AI et al., and Schwarz C et al., [1,3,12,13]. In contrast to the present study, Gammage MD et al., [14] reported decreased serum phosphorous levels in hypothyroidism. Production of calcitonin is increased in hypothyroid patients who can promote tubular clearance of calcium and tubular reabsorption of phosphate which leads hypocalcaemia and hyperphosphatemia [1]. Serum T3, which is the active form of thyroid hormone is required for the stimulation of phosphorus reabsorption from renal tubules mediated through Na/P co-transporters, so elevation of serum phosphorus levels can be explained that renal mechanism mediated through T3 was the only process by which serum phosphorus levels was elevated which can be as a result of bone demineralisation [5]. In the present study, serum phosphorus had significant negative correlation with T3(r value -0.457, p=0.009) and T4 (r value -0.718, p<0.001). These findings are in disagreement with the study done by Modi A et al., where they have shown significant positive correlation between serum phosphorus with T3 and T4 [15]. Significant positive correlation between serum phosphorous and TSH (r value 0.927, p<0.001) was found in the present study which is in accordance to Gohel MG et al., [3]. In contrast no significant correlation between serum phosphorous and TSH among was observed by Sridevi D et al., [1].

The present study also showed, no significant correlation between serum phosphorus with serum FT3 (r value -0.041, p=0.811), which is accordance with the study done by Schwarz C et al., [13]. Similarly, no significant correlation between serum phosphorus with FT4 (r value 0.176, p=0.304). This finding is in disagreement with the study done by Mani V et al., where they revealed significant negative correlation between serum phosphorus and FT4 [11].

The present study showed that significant decreased (p<0.001) level of serum Mg when compared with control groups. Gohel MG et al., proved that, a total magnesium level in serum was found to be significantly lowered in hypothyroid patients [3]. In contradictory Sridevi D et al., observed statistically significant increase in serum magnesium in hypothyroidism compared to controls [1]. Serum magnesium level is reduced due to effect on PTH and calcitonin by influencing GFR which leads to increase in clearance. There is an increased renal blood flow leading to high clearance of magnesium from kidneys, so ultimately low level of serum magnesium will cause hypomagnesemia. In the present study, significant positive correlation was found between serum Mg and T3 (r value 0.328, p=0.051) which is accordance to the study done by Susanna TY et al.,. [2]. Serum Mg had positive significant correlation with T4 (r value 0.674, p<0.001) contradicts to the findings done by Susanna TY et al., where they revealed significant negative correlation between serum magnesium with T4, serum magnesium had significant negative correlation with serum TSH (r value -0.858, p<0.001) which is in agreement with the study done by Gohel MG et al., and Nisa FU et al., [2,3,16]. Present study also showed no significant correlation with serum Mg and FT3 (r value 0.118, p=0.493) which is in accordance to the study by Schwarz C et al., [13]. Present study found no significant correlation between serum magnesium with FT4 (r value -0.080, p=0.642), while Nisa FU et al., demonstrated a significant positive correlation between serum Mg and FT3 and FT4 which was in conflict with the present study [16].

In the present study, the levels of serum copper was significantly decreased (p<0.001) in comparison with control groups. In a study by Arora M et al., the level of copper in patients with hypothyroidism significantly decreased as compared with control groups. Tyrosine is a protein component of thyroglobulin for the synthesis of thyroid hormones and copper acts as a cofactor for tyrosinase enzyme for the biosynthesis of tyrosine [17]. Other than this, phospholipids which are synthesised by copper, 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. As there is alteration in serum copper levels correct treatment is necessary. In the present study, no significant correlation was found between serum copper with T3 (r value -0.015, p=0.932), T4 (r value 0.063, p=0.716) and TSH (r value -0.102, p=0.555). These findings are in agreement with the study done by Arora M et al., [17]. Present study revealed significant positive correlation between serum Cu and FT3 (r value 0.446, p=0.006), no significant correlation was found between

serum copper with FT4 (r value -0.006, p=0.972) these findings are in accordance to the study done by Kahatun S et al., [18]. 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 needs to be investigated further. The study can be extended by measuring other serum minerals and correlating it with duration and severity of hypothyroidism.

Limitation(s)

Dietary pattern of all the study participants should also have been monitored to avoid misinterpretations.

CONCLUSION(S)

The study showed that in hypothyroidism there was 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 hypothyroid 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 if necessary by supplementing minerals.

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REFERENCES

[1] Sridevi D, Dambal AA, Sidrah, Challa AS, Padaki SK. A study of serum magnesium, calcium and phosphorus in hypothyroidism. International journal of clinical Biochemistry and Research. 2016;3(2):236-39.
[2] Susanna TY, Sagayaraj A, Shashidhar KN, Gomathi M, Mahesh V. A correlative study of thyroid profile and mineral status in patients with hypothyroidism-A hospital based case control study. Asian Journal of Pharmaceutical and Clinical Research. 2016;9(3):292-94.
[3] Gohel MG, Shah AM, Shah AM, Makadia JS. A study of serum calcium, magnesium and phosphorus levels in hypothyroidism patinets. Int J Med Health Sci. 2014;3:308-12.
[4] Kavitha MM, Chandrashekharyya SH, Sunitha H, Neela BM, Ratna S. Alteration in levels of Serum calcium, phosphorous and magnesium in hypothyroidism patients. Int J Biol Med Res. 2014;5(4):4594-96.
[5] Suneel B, Nagendra DR, Aparna RR, Balakrishna D, Naidu JN. Mineral Status in Thyroid Disorder (Hypo & Hyper). Int J Appl Biol Pharm. 2011;2(4):423-29.
[6] Mohammed HI, Idrees OF, Ismail AM, Ahmed SA. Evaluation of copper and zinc among hyper and hypothyroidism patients. European Acad Res. 2015;3(5):5422-34.
[7] Shivaleela MB, Poornima RT, Jayaprakash Murthy DS. Serum calcium and phosphorus levels in thyroid dysfunction. Indian Journal of Fundamental and Applied Life Sciences. 2012;2(2):179-83.
[8] Sabuncu T, Aksoy N, Arikan E, Ugur B, Tasan E, Hatemi H. Early changes in parameters of bone and mineral metabolism during therapy for hyper-and hypothyroidism. Endocrine Research. 2001;27(1-2):203-13.
[9] Mamatha BV, Chandrakanth KH, Kashinath RT, Rakshitha MN. Assessment of mineral status in subclinical hypothyroidism patients- A case control study. International Journal of Clinical Biochemistry and Research. 2019;6(1):32-35.
[10] Murgod R, Soans G. Changes in electrolyte and lipid profile in hypothyroidism. International Journal of Life Science & Pharma Research. 2012;2(3):185-94.
[11] Mani V, Natarajan MS, Mohanakrishnan VV. Comparison of total and ionic calcium in hypothyroidism. J Clin Diagn Res. 2019;13(5):10-12.
[12] Alcalde AI, Sarasa M, Raldúa D, Aramayona J, Morales R, Biber J, et al. Role of thyroid hormone in regulation of renal phosphate transport in young and aged rats. Endocrinology. 1999;140(4):1544-51.
[13] Schwarz C, Leichtle AB, Arampatzis S, Fiedler GM, Zimmermann H, Exadaktylos AK, et al. Thyroid function and serum electrolytes: Does an association really exist? Swiss Medical weekly. 2012;142:01-07.
[14] Gammage MD, Parle JV, Holder RL, Roberts LM, Hobbs FD, Wilson S, et al. Association between serum free thyroxine concentration and atrial fibrillation. Arch Intern Med. 2007;167(9):928-34.
[15] Modi A, Sahi N. Effect of thyroid hormones on serum calcium and phosphorous. International Journal of Clinical Biochemistry and Research. 2018;5(4):570-73.
[16] Nisa FU, Mumtaz A, Ulla MI, Atif M, Sami W. Determination of serum zinc and magnesium levels in patients with hypothyroidism. Trace Elements and Electrolytes. 2014;31(04):43-47.
[17] Arora M, Mahat RK, Kumar S, Mustafa I, Sah SP. Study of trace elements in patients of hypothyroidism with special reference to zinc and copper. Biomed J Sci & Tech Res. 2018;6(2):5190-94.
[18] Kahatun S, Santhini GS, Malligai E, Kumar HV. Evaluation of Serum Zinc, Copper Level, and their Correlation with Cu/Zn Ratio and FT3/FT4 Ratio in Hypothyroidism. J Clinic Diagn Res. 2019;13(7):08-10.

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