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RESEARCH ARTICLE

EVALUATION OF CALCIUM AND PHOSPHOROUS IN THYROID DYSFUNCTION

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ABSTRACT

Background: Thyroid hormones influence almost all the tissues and systems in our body. Their excess or deficiency can lead to diverse consequences including development, maturity and also modeling and re modeling of the bone. The present study was conducted with a focus on effect of thyroid hormones on bone metabolism. **Objective:** To evaluate levels of two important minerals Calcium and Phosphorus in patients suffering from hypo and hyper thyroidism and to find a correlation between these two minerals and thyroid hormones. **Methods:** 50 patients (25 each of clinically proven Hypo and Hyperthyroidism) and 50 normal asymptomatic age and sex matched healthy controls were enrolled for the present study after taking informed consent. These individuals (both patients and controls) were investigated for Thyroid hormones, calcium and phosphorous. The data was analyzed using student's t test and $p<0.05$ was considered statistically significant. **Results:** Prevalence of thyroid dysfunction is more in female patients as compared to males. Levels of S. Calcium decreased significantly with increase in the levels of thyroid stimulating hormone in hypothyroid patients from 7.41 to 6.5mg/dl, whereas levels of phosphorous did not vary significantly. In hyperthyroid patients there was insignificant variation in the levels of S. calcium and phosphorous with increase in TSH from 0.01 to 0.38 µIU/ml. **Conclusions:** Hypothyroidism has effect on bone metabolism with significant change in levels of S. calcium and insignificant variation in levels of Phosphorous.

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INTRODUCTION

Out of all the hormones which are commonly specialized molecules able to influence other cells, tissues and systems, thyroid hormones are pleiotropic peptides whose primordial function is difficult to identify. The complex action of thyroid hormone can easily be witnessed by examining diverse consequences of excess and deficiency during development and after maturity. In particular, different manifestations in bone modeling and remodeling reflect the consequences of thyroid disturbances which are age dependent. While hyperthyroidism enhances bone mineralization and accelerates epiphyseal maturation in childhood and induces bone loss by activation of osteoclast activity in adults[1]. In the normal individuals, these hormones interact to maintain a dynamic equilibrium. TRH stimulates the pituitary to produce and release TSH which causes the thyroid gland to release T_3 and T_4.[2] Circulating levels of T_3 and T_4 exert feedback on pituitary, inhibiting the release of TSH, in this way, a metabolic equilibrium is maintained.[3]

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This balance can be upset, however, by abnormalities in any stage of negative feedback cycle with clinical manifestations resulting from over production (hyperthyroidism) or under production (hypothyroidism) of T_3 and T_4.[4] Thyroid hormones perform a wide array of metabolic functions including regulation of lipid, carbohydrates, protein and electrolytes and mineral metabolism.[5] It is a central regulator of body hemodynamics, thermoregulation and metabolism. Therefore, it has an influence on renal hemodynamics, glomerular filtration and electrolyte handling.[6] Mineral metabolism like calcium, magnesium and phosphorus is frequently disturbed in thyroid dysfunction. Thyroid hormones exert its effect on osteoblasts via nuclear receptors to stimulate osteoclastic bone resorption.[7] It probably stimulates bone resorption directly, thereby increasing serum calcium and phosphorus concentrations and also suppressing parathyroid hormone and 1, 25-dihydroxy Vitamin D_3 concentrations. The decrease in these bone resorbing hormones limits further increase in serum calcium concentration and also results in enhanced intestinal calcium absorption.[8] The serum calcium level is decreased significantly in patients with high TSH concentration in contrast with normal TSH.[9]

Untreated hypothyroidism in childhood leads to growth retardation or even growth arrest, disturbances of endochondral ossification, delayed bone age and persistent short stature.[10,11,12] Thyroid hormones exert its effects on osteoblasts via nuclear receptors to stimulate osteoclastic bone resorption.[13] Hyperthyroidism is thus one of the major causes of secondary osteoporosis.[14] Thyroid hormones stimulate bone resorption directly thereby increasing the serum calcium and phosphorus levels and suppressing PTH.[15] On the other hand opposite effects are seen in hypothyroidism disorder. In hypothyroidism increased production of thyroid calcitonin can promote the tubular reabsorption of phosphate and also favors tubular excretion of calcium. Whereas in hyperthyroidism decreased production of thyroid calcitonin promotes tubular excretion ofphosphate and tubular absorption ofcalcium.[16]

Recently, the disorders of thyroid function particularly hypothyroidism is receiving greater attention as an important cause of disturbance in mineral metabolism by their direct action on bone turnover,[7] and also as one of the causes for secondary osteoporosis. Calcium, phosphorus and magnesium are all divalent metal ions, which are necessary for metallo enzymes and various crucial metabolic pathways directly or indirectly regulated by thyroid hormones. Few studies show normal serum calcium and phosphorus levels while others show decreased levels in hypothyroidism. Even though the changes in the calcium and magnesium may be slight in thyroid disorders, these disturbances will be important for patient in the long run.[17] In hypothyroidism there is a depressed turnover due to impaired mobilization of calcium into the bone that leads to decrease in the blood calcium level. In hyperthyroidism there is a poor mobilization of calcium that leads to increase in the blood calcium level. Thus, keeping in view, the role of thyroid hormones in bone and mineral metabolism, the present study was planned to evaluate levels of two important minerals calcium and phosphorus in patients suffering from hypothyroidism and hyperthyroidism and to find a correlation between the levels of these minerals and thyroid hormones.

MATERIAL AND METHODS

The present hospital based observational and analytical study was conducted in Department of Biochemistry, Government Medical College, Amritsar in collaboration with Department ofMedicine, Guru Nanak Dev Hospital, Amritsar. The study comprised of100 subjects in which 25 were hypothyroid and 25 were hyperthyroid which were taken either from the emergency wards or admitted in the medicine wards ofGuru Nanak Dev Hospital, Amritsar. 50 healthy subjects were enrolled to serve as controls. The detailed history was taken and every case was thoroughly interviewed as per Performa and written informed consent was taken. The study was conducted after taking approval from institutional ethics committee, Government Medical College, Amritsar.

Collection and Processing of Blood Samples: Informed written consent was taken from all the patients. In patients under the age of18 years parents/guardian ofpatient gave the consent. 5 ml of venous blood was collected from the antecubital vein into plain vaccutainers under aseptic conditions. Then blood was allowed to clot for 30 minutes and was centrifuged at 2200-2500 rpm for 15 minutes for separation of serum. Serum was used for analysis of serum calcium, phosphorus and thyroid hormones both in patients and in controls.

Inclusion criteria: Hypothyroid and Hyperthyroid patients of age group of 15 to 55 years were included in the present study which consisted ofboth males and females.

Exclusion criteria Patients on calcium therapy, having history of diabetes mellitus, renal failure and pancreatitis were excluded from the present study.

- Serum T_3 (Triidothyronine) was estimated by the method describe by Agharanya JC (1990).[18]
- Serum Thyroxine T_4 was estimated by the method described by Frank JE (1990).[19]
- Serum Thyroid Stimulating hormone was estimated by the method described byBurger,H. G., Patel, Y.C (1997).[20]
- Serum calcium was done by OCPC method described by Gitelman (1967).[21]
- Serum Phosphorus was estimated by the method described by Gomorri G, (1925).[22]

The data thus generated was analyzed using student 't' test for calculating mean and standard deviation values of$p<0.05$ were considered to be statistically significant.

Observations

The patients were subdivided into different groups depending upon their age i.e. Group 1 of >15-25, Group 2 of >25-35, Group 3 of >35-45 and Group 4 of >45-55 years. It was observed that the maximum number ofindividuals belonged to age group of >45-55 years and controls belonged to the age group of>25-35 years.

Table 1: Classification of patients and controls according to various age groups

S.No.	Age Group(years)	Patients	Controls
1.	>15-25	6	11
2.	>25-35	17	20
3.	>35-45	8	12
4.	>45-55	19	7

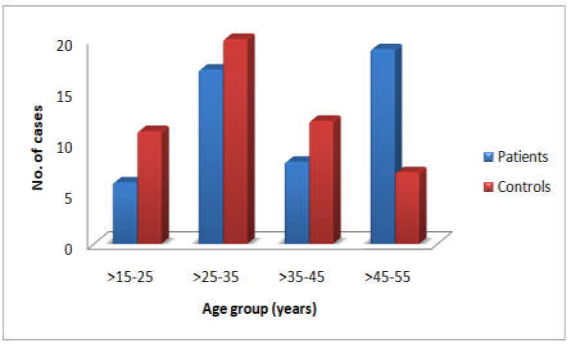

Fig 1. Classification of patients and controls according to gender

It was observed in the current study, there were 35 females as compared to 15 males, thus indicating the prevalence of thyroid dysfunction is more in females. It was observed that levels of T_3 and T_4 were increased significantly in patients with Hyperthyroidism, whereas in Hypothyroidism levels of

Table 2. Comparison of thyroid profile in patients and controls

S.No.	Groups	Triidothyronine (T_3) ng/ml (Mean±S.D)	Thyroxine(T_4) µg/dl (Mean±S.D)	Thyroid Stimulating Hormone(TSH) µIU/ml (Mean±S.D)
1.	Hyperthyroid Patients	6.3 ± 8.1*	8.5 ± 4.2*	0.19 ± 0.14*
2.	Hypothyroid Patients	1.04 ± 0.6	5.4 ± 2.9**	24.5 ± 12.34*
3.	Controls	1.05 ± 0.3	7.9 ± 1.7	2.4 ± 1.09

Table 3. Classification of patients depending upon the levels of TSH

S.No.	Group	Thyroid Stimulating Hormone (TSH) (µIU/ml) (Mean±S.D)	
		Males	Females
1.	Control	3.2 ± 0.8	2.3 ± 1.0
2.	Hyperthyroid	0.2 ± 0.1	0.2 ± 0.1
3.	Hypothyroid	20.7 ± 11.5	24.5 ± 12.3
4.	Subclinical Hypothyroid	----	9.5 ± 0.3

Table 4. Comparison of levels of serum Calcium in patients and controls

S.No.	Group	Serum Calcium (mg %) (Mean±S.D)
1.	Controls	9.4 ± 0.7
2.	Hyperthyroidism	9.2 ± 1.5
3.	Hypothyroidism	7.2 ± 0.7*

*p<0.05 When Hypothyroid Patients were compared to controls.

Table 5. Comparison of levels of Serum Phosphorus in Hypothyroid & Hyperthyroid patients

S.No.	Group	Serum . Phosphorus (mg/dl) (Mean ± S.D)
1.	Controls	3.5 ± 0.6*
2.	Hyperthyroid Patients	3.6 ± 0.9
3.	Hypothyroid Patients	5.3 ± 0.7*

*p<0.05 When Patients were compared with Controls.

Table 6. Levels of serum calcium and phosphorus in different quartiles of TSH in Hypothyroid patients

Groups	Quartile TSH	Thyroid Stimulating Hormone (TSH) (µIU/ml) (Mean)	Serum Calcium (mg/dl) (Mean)	Serum Phosphorus (mg/dl) (Mean)
Group I	9.31 – 12.7 (µIU/ml)	10.82	7.41	5.25
Group II	16.1 – 28.58 (µIU/ml)	20.09	6.8*	5.4*
Group III	33.3 - >40 (µIU/ml)	37.52	6.5*	5.6*

*p<0.001 when levels of Serum Calcium & Phosphorus were compared in different quartiles.

Table 7. Levels of serum calcium and phosphorus in different quartiles of TSH in Hyperthyroid patients

Group	Quartile of TSH	Thyroid Stimulating Hormone (TSH) (µIU/ml) Mean	Serum Calcium (mg/dl) Mean	Serum Phosphorus (mg/dl) Mean
Group I	0.01 – 0.2 (µIU/ml)	0.12	9.6	4.2
Group II	0.21 – 0.3 (µIU/ml)	0.25	9.1	3.2
Group III	0.31 – 0.38 (µIU/ml)	0.35	9.7	3.6

T_4 decreased significantly as compared to hyperthyroid patients and controls. All the patients were divided into three groups i.e. Hypothyroid, Hyperthyroid and sub clinical Hyperthyroid depending on levels of TSH to see the prevalence of subclinical hypothyroidism. In our study it was 8% and only females. Belonging to the age group of(>35-55 years). There was significantly decrease ($p<0.05$) in levels of calcium in patients of hypothyroidism as compared to controls. No significantly variation was observed in the levels of calcium in patients of hyperthyroidism as compared to controls. Levels of serum phosphorus were significantly increased ($p<0.05$) in patients with hypothyroidism as compared to controls and patients with hyperthyroidism. The patients of hypothyroidism were divided into various groups depending upon the quartiles of TSH i.e. Group I (9.31-12.7 µIU/ml), Group II (16.1-28.58 µIU/ml) and Group III (33.3->40 µIU/ml) and levels of serum calcium and phosphorus were observed in these groups.

Levels of serum calcium decreased significantly as the levels of TSH increased i.e. from quartile 1to 3 correspondingly significantly increased levels of serum phosphorus were observed in these quartiles. Similarly, patients of hyperthyroidism were divided depending upon the quartiles of TSH i.e. Group I (0.01-0.2 µIU/ml), Group II (0.21-0.3 µIU/ml) and Group III (0.31-0.38 µIU/ml). No significant variations in the levels of Serum calcium & phosphorus were observed in different quartiles of TSH in hyperthyroid patients.

DISCUSSION

Globally thyroid gland disease is one of the wide spread problem in the clinical practice. Almost 9% of women and 2% of men are affected by thyroid disorders worldwide. Classified as Hypothyroidism and Hyperthyroidism, the incidence of hypothyroidism is more as compared to hyperthyroidism and it increases with age.

The decreased thyroidal secretion can be due to decrease in TSH release from hypothalamus. Underlying clinical disorder known as subclinical hypothyroidism is prevalent in 3-8% of the population without known thyroid disease. This prevalence increases with age and is higher in women. Thyroid dysfunction lead to a number of related disorders like anovulatory cycles, sex hormones imbalance, abnormal sexual development, menstrual irregularity, Infertility on the other hand hyperthyroidism causes are Grave's disease, toxic multinodular goiter etc. The levels of T_3 and T_4 were statistically significantly increased in the females suffering from hyperthyroidism when compared with the controls as well as hypothyroid patients. The prevalence of thyroid disease in the women suggests that estrogen might be involved in the pathophysiology of thyroid dysfunction.[23]

The term Subclinical hypothyroidism has been generated where levels of TSH are <10µIU/ml In the present study two females were found to have Subclinical hypothyroidism based on the levels of TSH with signs and symptoms of overt hypothyroidism.[24] Hypothyroidism is an excessive concentration of thyroid hormones due to increased synthesis and release.[25] The clinical presentation of hyperthyroidism ranges from asymptomatic palpitations, heat intolerance, increased appetite, weakness of muscles and psychiatric symptoms[26] with decreased TSH levels and elevated T_3, T_4. Similar observation was made in the present study where the levels of TSH were 0.19µIU/ml. There was no difference of Mean TSH in hyperthyroid males and females. Even age variation did not show statically significant variation in the levels of TSH.

Levels of serum calcium were significantly reduced in patient of hypothyroidism as compared to controls. Thyroid hormones play an important role in homeostasis of calcium and phosphorus levels by their direct action on bone turnover. The metabolism of these 2 ions is frequently disturbed in thyroid dysfunction so much so negative calcium balance in hypothyroidism may lead to osteopenia.[27] This formed the basis of present study which was aimed to study levels of calcium and phosphorus in hypothyroid and hyperthyroid patients' similar results were also observed in the study done by Shivaleela MB in 2012. Hypothyroidism is known to affect the electrolyte levels. Thyroxine normally regulate blood calcium from the cells in hypothyroidism so there is less thyroxine in the blood stream thus less of this entering in the cells and less calcium is released. Thyroid hormones probably stimulate bone resorption directly thereby increasing serum calcium and phosphorus concentration and also suppressing PTH and 1,25 Dihydroxy D3 concentration. This observation is consistent with the present study where levels of calcium were significantly reduced in patients with hypothyroidism. The decrease in these bone resorbing hormones limits further increase in serum calcium and also results in enhanced intestinal calcium absorption. Although these changes are slight it is possible that these disturbances will be important for patient in long term. It has been suggested that some metabolic disorder, hypotension, cardiovascular disease is linked by defect in calcium and magnesium metabolism. Although the exact mechanism is not understood but the potential mechanism is the basic role of these cations in metabolic pathway.[28] In hypothyroidism there is depressed turnover due to impaired mobilization of calcium in to the bone that leads to decreased blood calcium levels.

In hyperthyroidism there is poor mobilization of calcium that leads to increased blood calcium levels. In hypothyroidism increased production of thyroid calcitonin can promote the tubular resorption of phosphate and also favors the tubular excretion of calcium. In hyperthyroid decreased production of thyroid calcitonin can promote tubular excretion of phosphate and also tubular absorption of calcium.[29] Similarly, in present study it was observed that the levels of calcium were significantly low in patients of hypothyroidism where as in patients with hyperthyroidism the values were within normal range. Thyroid hormones play an important role in linear development of Skeleton and are necessary for chief peak bone mass in adults. Hyperthyroidism leads to acceleration of bone turnover and loss of mineral density mainly in cortical bones.[30-32] In these patients cycles of bone remodeling and bone turnover is shortened almost by 50% and the proportion between bone formation and resorption are disturbed. Thus, Thyrotoxicosis leads to increased risk factors which may be modulated through elevated concentration of IL-6 as observed in patient with hyperthyroidism. IL-6 stimulates the production of osteoclast and may be mediator of parathyroid hormones on bone tissues.[33,34] In hyperthyroidism adverse changes in bone metabolism are connected with hypercalcemia and hyperuricemia but on the contrary in the present study the mean levels of serum calcium were within normal defined range of calcium i.e. 9-11mg/dl. This may be due supplementation of calcium given to these patients.

Levels of serum phosphorus were significantly increased in the patients of hypothyroidism (5.3 ± 0.7mg/dl) when compared to patients of hyperthyroidism (3.6 ± 0.9 mg/dl) as well as controls (3.5 ± 0.6 mg/dl). There are no studies based on alterations of calcium and phosphorus in hypothyroid and hyperthyroid patients according to age and gender further studies are required in this regard. The levels of mean serum calcium and phosphorus were within normal range i.e. 9-11 mg% and 2-4.5 mg% respectively. Patients of hypothyroidism were subdivided into 3 groups depending upon the quartiles of TSH i.e. Group I (9.31-12.7 µIU/ml), Group II (16.1-28.58 µIU/ml) and Group III (33.3->40 µIU/ml) . Similarly, patients of hyperthyroidism were divided depending upon the quartiles of TSH i.e. Group I (0.01-0.2 µIU/ml), Group II (0.21-0.3 µIU/ml) and Group III (0.31-0.38 µIU/ml). It was observed that the levels of serum calcium decreased significantly with a significant increase in the levels of serum phosphorus, thus indicating that as level of TSH increases, levels of serum calcium decrease with a corresponding increase in serum phosphorus levels. This clearly indicates the role of TSH in maintaining the calcium and phosphorus homeostasis.

Conclusion

Hypothyroidism has a more pronounced effect on bone metabolism as compared to hyperthyroidism. As stated in the present study as the levels of TSH increases the decrease in the levels of calcium are more pronounced than the changes in the levels of S phosphorous. Thus for the well being of the patient levels of S. calcium should be monitored especially in patients with hypothyroism.

Conflict of Interest: none

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Key points: Thyroid hormones

Metabolism
Calcium
Phosphorous

Abbreviations

Il-6- Interleukin 6
OCPC- O Cresoliphthalein complexone
PTH- para thyroid hormone
RPM- revolutions per minute
T_3 – Tri iodothyronine
T_4 – Tetra iodothyronine
TRH- Thyrotropin releasing hormone
TSH- Thyroid stimulating hormone

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