



## Original Research Article

# Bone Mineral status in newly Diagnosed Hyperthyroid Patients

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## Abstract

*Hyperthyroidism is a common disorder affecting a large group of population and is a cause of the osteoporosis. Bone homeostasis abnormalities in patients with hyper thyroidism causes alteration in serum calcium and phosphorous levels. The aim of the present study is to evaluate the levels of bone minerals like calcium and phosphorous in newly diagnosed hyperthyroid subjects and controls. Total T3, T4, TSH, serum calcium and phosphorous levels were estimated. BMI was also measured for both controls and hyperthyroid patients. Total T3, T4, serum calcium and phosphorous levels have been found to be significantly higher where as TSH and BMI have been found to be significantly lower in hyper thyroid patients when compared to controls. Serum calcium and phosphorous levels elevated in hyperthyroidism patients. Elevated T3,T4 levels in hyperthyroidism causes the osteoclast formation by stimulating nuclear receptors leading to bone resorption, which results in high serum calcium levels by moving calcium from bone. Excessive tissue catabolism and decreased renal phosphate excretion causes increase in phosphorous levels.*

**Keywords:** Calcium, Hyperthyroidism, Phosphorous.

## Introduction

Hyperthyroidism is a fairly common endocrine disorder in clinical practice and it is the clinical syndrome caused by an excess of thyroxine (T4), triiodothyronine (T3) or both and decreased thyrotropin (TSH). The interdependence of this thyroid disorder with disorders of the mind and emotions, as well as with mental disorders, is not being given the required consideration in many clinical settings. Similarly, many clinical symptoms such as palpitations, angina, breathlessness, tremor, infertility, bone pains,

excessive sweating and insomnia suggesting thyrotoxicosis are sometimes overlooked. In addition, a lot of metabolic derangementssuch as hyperglycaemia, hypercalcemia, and hypocholeste-rolaemia can be secondary to thyrotoxicosis. Thyroid hormone (T3) is essential for normal bone growth and bone metabolism. T3 stimulates bone formation directly through T3 receptors in osteoblasts. It also stimulates bone resorption by osteoclasts probably secondarily through the osteoblasts<sup>[1]</sup>.

In thyrotoxic state, there is high turn-over of bone. It was reported that bone collagen breakdown is increased in thyrotoxicosis<sup>[2,3]</sup>. Hyperthyroid patients had decreased bone mineral density and increased risk of fracture<sup>[4]</sup>. Thyroid hormones induce high bone turnover, leading to a decreased structure integrity of the skeleton<sup>[5]</sup> with osteoporosis and an increased fracture risk as a direct effect of active thyroid hormones on bone cells<sup>(6,7)</sup> which alters the serum levels of calcium and phosphorus. In view of the above, the present study is aimed to evaluate total calcium and phosphorus levels in newly diagnosed hyperthyroidism patients.

### Materials and Methods

Eighty consecutive patients with newly diagnosed thyrotoxicosis attending to the department of endocrinology OPD, NRI General Hospital were enrolled. The eighty patients include sixty one women and nineteen men. Age of the patients is within the range of 25 to 40 years in both sexes. The inclusion criteria were: The diagnosis of thyroid disorders on the basis of clinical symptoms of hyperthyroidism; a suppressed serum thyroid-stimulating hormone (TSH  $<0.35\mu\text{IU/ml}$ ) and an elevated serum total T4 ( $>12.6\mu\text{g/dl}$ ) and total T3 ( $>1.8\text{ng/ml}$ ). All female patients and control subjects were pre-menopausal and patients with comorbidity (hypo- and hyperparathyroidism, vitamin D deficiency, Cushing's disease, inflammatory bowel disease, malabsorptive diseases or on medication (steroids, bisphosphonates, calcium, vitamin D, or hormonal replacement therapy) influencing bone turnover were excluded. Also pregnant and postmenopausal women were excluded. Patients had past history of using iodine containing drugs, hypothyroidism, hyperthyroidism, hepatic or renal disorders, alcoholism and thyroid cancer patients were also excluded.

The total number of 160 subjects were divided into two groups namely Group-I (controls) and Group-II (Hyperthyroid cases). Age and sex matched healthy subjects were taken as controls.

The selection criteria for hyperthyroid patients was on the basis of serum T3, T4 and TSH. All the selected patients were newly diagnosed hyperthyroid patients. Their serum T3, T4 levels were elevated and serum TSH levels were low.

Following details were collected from all the cases and controls with the help of a proforma.

Age, sex, occupation, physical activity and detailed clinical history of the patients were noted. Biochemical investigations like serum calcium, phosphorus total T3, total T4 and TSH were estimated. BMI (Body mass index) calculated both in controls and cases.

The blood sample was collected from cases and controls by venepuncture. Serum samples were used for the estimation of calcium, phosphorus, total T3, total T4 and TSH. The thyroid status of all subjects was estimated by ADVIA Centaur CP, an automated Hormone assay system using Siemens kits. Serum concentrations of calcium, and phosphorus were estimated by using automated clinical chemistry system of Randox Daytona using Randox kits. BMI has been calculated by individual's body weight in Kg divided by the square of height in meters.

### Statistical Analysis

Values for the variables are expressed as the Mean  $\pm$  Standard Deviation (SD). Comparison of hyperthyroid cases against the control group has been done using unpaired students t-test and at a level of  $p < 0.05$  is considered as statistically significant. SPSS 11.5 (SPSS Inc., United States) has been used for statistical analysis.

### Results

The mean age of the patients is  $33.08 \pm 3.98$  (mean  $\pm$  Standard Deviation) years while that of controls  $35.05 \pm 3.07$  years. 76% of the patients were female. The mean body mass index ( $\text{kg/m}^2$ ) was  $4.965 \pm 1.408$  ( $p$  value  $< 0.0001$ ), total T4  $24.97 \pm 3.56$  ( $p$  value  $< 0.0001$ ) are highly elevated and the mean body mass index ( $\text{kg/m}^2$ )  $16.87$  with a range of  $15.0$  to  $22.0 \text{ kg/m}^2$ . Patient and control group's

profiles, laboratory characteristics and statistical differences are shown in Table-1.

As expected, mean values of total T3 mean values of total T3  $4.965 \pm 1.408$  (p value  $< 0.0001$ ), total T4  $24.97 \pm 3.56$  (p value  $< 0.0001$ ) are highly elevated and TSH levels  $0.0176 \pm 0.0147$  (p value  $< 0.0001$ ) decreased in hyperthyroid subjects. Serum calcium levels elevated in hyperthyroid

patients  $11.69 \pm 0.939$  (p value  $< 0.0001$ ), which is highly significant when compared to control subjects. Serum phosphorus levels increased in hyperthyroid patients  $4.716 \pm 0.804$  (p value  $< 0.0001$ ), the difference is highly significant when compared to control subjects. BMI decreased in hyperthyroid patients  $18.04 \pm 1.958$  (p  $< 0.0001$ ) when compared to control subjects (Table-1).

**Table – 1:** Study Parameters with Mean, S.D. and p-Values of Controls and Cases

Parameters	Normal Range	Group-I Mean $\pm$ SD	Group- II Mean $\pm$ SD	p value
Age (years)	25 – 40	35.05 $\pm$ 3.57	35.08 $\pm$ 3.98	
Total T3( $\eta$ g/ml)	0.6 -1.8	0.988 $\pm$ 0.2579	4.965 $\pm$ 1.408	$< 0.0001$
Total T4( $\mu$ g/dl)	3.2 -2.6	8.386 $\pm$ 2.064	24.97 $\pm$ 3.56	$< 0.0001$
TSH( $\mu$ IU/ml)	0.35-5.5	2.851 $\pm$ 2.9011	0.0176 $\pm$ 0.0147	$< 0.0001$
Calcium (mg/dl)	8.1-10.4	9.274 $\pm$ 0.505	11.69 $\pm$ 0.939	$< 0.0001$
Phosphorus (mg/dl)	2.7 - 4.5	3.358 $\pm$ 0.6259	4.716 $\pm$ 0.804	$< 0.0001$
BMI (kg/m <sup>2</sup> )	18.5–24.9	21.06 $\pm$ 2.132	18.04 $\pm$ 1.958	$< 0.0001$

Group- I controls; Group-II Hyperthyroid patients; p $< 0.0001$  (highly significant);

## Discussion

Thyrotoxicosis, a clinical syndrome characterized by manifestations of excess thyroid hormone, is one of the commonly-recognized conditions of the thyroid gland. Thyrotoxicosis causes acceleration of bone remodelling and is one of the known risk factors for osteoporosis.<sup>[8,9]</sup>

Calcium is the most important mineral in the body. The total content of calcium in the adult man is about 1.5 Kg. As much as 99% of calcium present in bones and teeth and a small fraction (1%) of the calcium found outside the skeletal tissue, perform a wide variety of functions. Thyroid hormones (T3, T4) regulate the calcium homeostasis. Thyroid hormones maintain bone turn over by exerts its effect on osteoblasts via nuclear receptors to stimulate osteoclastic bone resorption<sup>[10,11]</sup>.

In hyperthyroidism thyroid hormone indirectly promotes osteoclast formation and activation by inducing the expression of cytokines, prostaglandins, and the receptor activator of nuclear factor NF $\kappa$ B ligand (RANKL). RANK ligand plays a major role in osteoclast formation. It binds to the RANK receptors on the surface of

the osteoblast precursors and signals the induction of osteoclast formation via nuclear factor kappa-B and jun N-terminal kinase (JNK) pathways. In hyperthyroidism T3,T4 levels are elevated that cause the osteoclast formation by stimulating nuclear receptors present on the osteoblasts which leads to bone resorption resulting in high serum calcium levels by moving calcium from bone<sup>[9,10,12-16]</sup>.

Thyroid hormone status influences calcium metabolism. To elucidate the mechanism of action of thyroid hormones on trans cellular transport, Ca<sup>2+</sup> influx and efflux studies were carried out in brush border membrane (BBM) vesicles and across the basolateral membrane (BLM) of enterocytes. Steady-state uptake of Ca<sup>2+</sup> into BBM vesicles as well as Ca<sup>2+</sup> efflux from the BLM enterocytes was increased in hyperthyroid patients. Increased Ca<sup>2+</sup> efflux across enterocytes was attributed to sodium-dependent Ca<sup>2+</sup> exchange activity which was high in hyperthyroid patients. cAMP, a potent activator of Na<sup>+</sup>/Ca<sup>2+</sup> exchanger, was found to be higher in intestinal mucosa of hyperthyroid patients. Ca<sup>2+</sup> influx across BBM is possibly modulated

with thyroid hormones by mediating changes in membrane fluidity. Thyroid hormones activated the  $\text{Na}^+/\text{Ca}^{2+}$  exchange in enterocytes possibly via cAMP mediated pathway. In hyperthyroidism intestinal calcium absorption increase leads to the increase of serum calcium levels in  $\text{ECF}^{[17-19]}$ .

Thyroid hormones (T3, T4) influence the renal absorption of 65% calcium from proximal convoluted tubule. In hyperthyroidism, the activity of increased 1- $\alpha$  hydroxylase which is located in the proximal tubular cells of the nephron which in turn activates the synthesis of 1,25(OH) $_2$ D $_3$ . Increased levels of 1,25 (OH) $_2$ D $_3$  enhances the calcium reabsorption in the DCT of the nephron<sup>[18,20]</sup>.

Phosphorus is a major intracellular constituent, both as the free anion and as a component of numerous organophosphate compounds. There are variable reports on serum phosphorus levels in patients with hyperthyroidism. Most of the studies indicate hyperphosphatemic state. Hyperphosphatemia in hyperthyroidism has been explained on the basis of an enhanced tissue catabolism leading to excess input of phosphorus to the plasma pool from bone and tissue and lower fractional clearance of phosphorus and increased renal tubular reabsorption of phosphorus<sup>[21]</sup>. Elevation of serum phosphate in hyperthyroidism is caused by increased bone resorption, enhanced renal tubular reabsorption of phosphate by direct action of the thyroid hormone<sup>[22,23]</sup>, and PTH suppression induced by hypercalcemia<sup>[24,25]</sup>. These effects lead to increase serum phosphorus levels in hyperthyroidism. In the present study serum calcium and phosphorus levels are significantly increased. The available data suggest that patients with hyperthyroidism show a significant impact on bone mineral homeostasis.

## Conclusions

It has been observed in the present study that serum calcium and phosphorus are increased in hyperthyroid patients. Depending on the results of this and previous studies, it can be concluded the bone metabolism is strongly affected by thyroid

hormone status such that increased thyroid hormones results alteration in serum calcium and phosphorus. It might be recommended to observe these levels in newly diagnosed hyper thyroid patients from the point of altered calcium and phosphorus status.

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