CALCIUM- PHOSPHORUS METABOLISM IN THYROID DYSFUNCTION

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Abstract

Key words: calcium-phosphorus metabolism, hypothyroidism, hyperthyroidism

Introduction

Thyroid hormones (TH) are central regulator of body hemodynamics, thermoregulation and metabolism. They influence the renal function, glomerular filtration and electrolyte handling and are essential for normal growth and maturation of skeleton. Thyroid dysfunction is frequently associated with disturbances of calcium and phosphorous homeostasis. Thyroid disorders are important cause of secondary osteoporosis. Previous studies done on serum calcium, phosphorus and parathyroid hormone (PTH) levels in thyroid disorders have conflicting results.

Osteomineral metabolism in hyperthyroidism

Hyperthyroidism is associated with impaired mineral metabolism. Hypercalcemia is known to be a complication of thyrotoxicosis with a multifactorial molecular mechanism of occurrence. Thyroid hormones affect bone turnover by direct stimulation of bone resorption thereby increasing serum calcium and phosphorus concentrations and also suppressing serum PTH and $1,25(OH)_2$vitamin D concentrations [1]. Renal calcium excretion is usually increased in hyperthyroidism and correlates positively with excess TH levels and cortical osteoclastic activity. The percentage of patients with hypercalcemia in thyrotoxic state varied between 8 and 27 % in different studies [2].

There are variable reports on serum phosphorus levels in patients with hyperthyroidism. Most of the studies reported hyperphosphatemia, while others show normal or low levels of serum phosphorus [3].

Some researchers have shown an increase in PTH while others have demonstrated unchanged PTH concentrations in hyperthyroidism [4, 5]. Most investigators have indicated counterregulation between PTH and TH [6, 7].

Osteomineral metabolism in hypothyroidism

Slight disturbances in some parameters of bone and mineral metabolism have been reported in hypothyroid patients. The suppressed bone turnover due to impaired mobilization of calcium into the bone leads to decreased blood calcium level, slightly elevated serum PTH and $1,25(OH)_2$ vitamin D, decreased alkaline phosphatase, urinary calcium excretion and glomerular filtration rate [8]. However, these changes are not statistically significant in hypothyroid patients compared with euthyroid controls, even during treatment [9].

In hypothyroidism, there is also an increased production of calcitonin which promotes the tubular reabsorption of phosphate and favors the tubular excretion of calcium which leadS to hypocalcemia and hyperphosphatemia [9].

The aim of present study was to assess the parameters of calcium-phosphorus metabolism in women with newly diagnosed thyroid dysfunction, not receiving specific treatment, and to compare them with those of the control group healthy women.

Materials and methods:

Study design and Subjects

The study was conducted in "St. George" University Hospital, Department of Endocrinology, in the period 2017-2019. 119 women with newly diagnosed thyroid dysfunction were included - 51 with onset of Graves' disease and 68 with autoimmune thyroiditis. 75 (63%) of them were premenopausal and 44 (37%) were postmenopausal, defined as having passed at least 12 months after the last menstrual period. A comparison was made with the data of 75 aged- and menopausal state- matched healthy women (Table 1).

Selection criteria

Inclusion criteria: women over 20 years of age with newly diagnosed thyroid dysfunction: Graves' disease and Autoimmune thyroiditis, signed written informed consent. Exclusion criteria: intake of levothyroxine and /or thyrostatics; taking oral contraceptives or hormone replacement therapy in the last 6 months, calcium-phosphorus preparations, vitamin D or medications that could affect calcium-phosphorus metabolism in the last 6 months; patients with concomitant diseases, affecting bone metabolism - severe systemic or other endocrine diseases, immunological or infectious diseases, malignant processes; women with current pregnancy and /or breast-feeding.

Analysis of Sample

TSH, FT4, FT3 were estimated by CLIA /chemiluminescent immunoassay/ using automated immunoassay analyzer Access 2®, Beckman Coulter Inc; Subjects with TSH values between 0.4 and 5.6 mIU/L were assumed to be euthyroid. TSH below 0.4 mIU/L was considered suppressed and TSH above 5.6 mIU/L was considered elevated. The reference range of FT4 was 7.86 – 14.41 pmol/L, FT3 - 3.8 – 6.0 pmol/L. PTH was measured by CLIA / chemiluminescent immuneassay / using immunological analyzer Immulite 2000, Siemens, with reference range 11- 67 pg/ml. Serum total and ionized calcium were determined by colorimetric method (with Arsenazo III), inorganic phosphate - by colorimetric method. Total serum calcium reference range was 2.12 - 2.62 mmol/l; Ionized calcium reference range - 1.06 -1.31 mmol/l; Inorganic phosphate reference range- 0.77 - 1.45 mmol/l.

Statistical analysis

Data were expressed as Mean ±SD. The normality of distribution was assessed by means of Kolmogorov –Smirnov test. The Student *t*-test was applied for comparison of normally distributed data. The Mann- Whitney U-test and the Kruskal-Wallis test were used for comparison of non-normally distributed variables. Correlation between parameters was studied by Pearson's correlation coefficient. *P*-values < 0.05 were considered as statistically significant. The data processing was done by using SPSS for Windows v.21 statistical software.

Results:

The characteristics of the studied subjects in both thyroid function groups and euthyroid control group are presented in Table 2.

The analysis found that the mean total serum calcium concentration in patients with hyperthyroidism was significantly higher than in the control group (2.42 ± 0.02 mmol/l compared to 2.37 ± 0.01 mmol/l, $p < 0.05$). There was no statistically significant difference in its concentration in hypothyroid women when compared to controls (2.39 ± 0.02 mmol/l versus 2.37 ± 0.01 mmol/l, $p > 0.05$). Ionized calcium was increased in hyperthyroid women (1.27 ± 0.02 mmol/l, $p < 0.01$). There was no significant difference in hypothyroid patients (1.19 ± 0.01 mmol/l, $p > 0.05$) as compared to controls (1.20 ± 0.01 mmol/l).

There was no statistically significant difference in serum phosphorus in cases compared to controls, hypothyroid (1.23 ± 0.04 mmol/l, $p > 0.05$) versus hyperthyroid (1.16 ± 0.033 mmol / l, $p > 0.05$) and controls (1.24 ± 0.05 mmol/l). No significant difference in PTH concentration was observed in hyperthyroid patients (28.39 ± 4.16 pg/ml, $p = 0.109$) compared to controls (36.15 ± 2.47 pg/ml) and markedly increased hormone levels in hypothyroid group were found (46.02 ± 4.20 pg / ml, $p <0.05$) (Table. 3).

Serum TSH, FT3, FT4 values of patients were studied in relation to serum total calcium, ionized calcium, phosphorus and PTH. On analyzing the results, a statistically significant positive correlation between ionized calcium, FT3 (r = 0.43; $p = 0.001$) and FT4 (r = 0.49; $p <0.05$) was observed and a negative correlation between serum PTH, FT3 (r = - 0.30; $p <0.05$) and FT4 (r = - 0.27; $p <0.05$) (Table 4).

Discussion:

Our study demonstrated significant higher total and ionized serum calcium in patients with hyperthyroidism compared to healthy controls. We observed positive correlation between ionized calcium, FT4 and FT3 levels. The results are consistent with most of the studies to date that analyze changes in calcium-phosphorus metabolism in thyrotoxicosis [10,7]. Manicort et al. [10] observed an increase in serum calcium in 50% of patients with hyperthyroidism. In contrast to our results, Dhanwal et al. [11] reported 26% hypocalcaemia in Indian patients. The associated vitamin D deficiency is a probable cause of decreased calcium in Indian patients with hyperthyroidism.

Hypercalcemia in hyperthyroidism may result from an abnormal calcium efflux from the skeleton, kidneys and gastrointestinal tract to the extracellular fluid. Previous studies have shown that hypercalcemia in thyrotoxicosis is mainly due to increased mineral bone mobilization. This is caused by a direct stimulation of bone cells by the high TH concentrations, with a consequent increase in bone resorption. T3 increased the mRNA expression of the RANKL in preosteoblastic cells, thus activating osteoclastogenesis and osteoclast activity [12]. The biochemical markers of bone formation and resorption, such as osteocalcin, alkaline phosphatase, bone-specific alkaline phosphatase, urinary pyridinoline and deoxypyridinoline, are increased in patients with hyperthyroidism, indicating enhanced bone remodeling activity. The increased mineral bone mobilization and consequent hypercalcemia, may lead to the suppression of PTH release in patients with thyrotoxicosis. It has also been reported that hyperphosphatemia, hypercalciuria and hyperphosphaturia frequently occur in these patients [1]. The calcium balance in patients with untreated hyperthyroidism is negative and the losses do not seem to be due to Vitamin D deficiency, since they are not reduced by Vitamin D supplementation. Some authors have also proposed that hypercalcemia in thyrotoxicosis may be due to increased adrenergic tonus. In support to this hypothesis there are studies showing that thyrotoxic patients with hypercalcemia

may become normocalcemic after therapy with propranolol alone [13]. Moreover, the serum levels of bone turnover markers (e.g., alkaline phosphatase and osteocalcin) are elevated in hyperthyroidism, and remain high for months during treatment, despite normalization of serum TH [14]. Hypercalcemia usually resolves with attainment of euthyroid state.

Hyperphosphatemia in hyperthyroidism has been explained based on increased bone resorption and tubular phosphate reabsorption; a direct action of TH on the renal N/Pi transporters and by PTH suppression induced by hypercalcemia. Hyperphosphatemia due to excess TH also seems to trigger compensatory mechanisms for the increase in phosphaturia. Recent studies reported that patients with Graves' disease exhibit high serum FGF-23 levels; however, this occurrence is exclusive for patients with hyperphosphatemia [15]. The increase in FGF-23 secretion appears to be a consequence of high phosphorus concentrations and not an event secondary to the direct action of TH. Antithyroid treatment normalizes serum phosphorus concentration. There was no significant difference in serum phosphorus in both patient groups in our study ($p > 0.05$).

We found a tendency of lower PTH concentrations in hyperthyroid patients without statistically significant difference compared to controls and significantly higher levels in hypothyroid group ($p<0.05$). In accordance with the results of most researchers, there was negative correlation between PTH, FT3 and FT4 among all studied groups and negative feedback with total serum calcium.

Serum parathyroid hormone concentrations are usually low or low-normal in thyrotoxic patients [3]. Boullion and De Moor first reported a decrease in serum PTH level in patients with hyperthyroidism [4]. Some researchers have found elevated PTH, while in others the concentrations are unchanged in hyperthyroidism [16]. Additionally, serum parathyroid hormone-related peptide (PTH-rP) levels increase in hyperthyroidism. In hyperthyroid patients, a significant elevation in PTH-rP levels was obtained when compared with healthy controls. After treatment, levels of PTH-rP declined. PTH-rP could be a factor in the pathogenesis of hypercalcemia in hyperthyroid patients [17].

We found a tendency of lower mean serum values of total serum and ionized calcium in hypothyroid patients in the absence of statistically significant difference compared to controls. There was no difference in serum phosphorus, significantly higher were PTH levels in this patient group.

These results coincide with some of the studies that examine the parameters of bone and mineral metabolism in hypothyroidism. Bone turnover is suppressed due to impaired mobilization of calcium from the bone, leading to decreased levels of serum calcium. The synthesis of calcitonin is increased, which stimulates tubular reabsorption of phosphate and promotes the excretion of calcium, which also leads to hypocalcemia and hyperphosphatemia. In overt hypothyroidism, elevated PTH is observed, which could be due to the development of resistance to PTH. This in turn leads to an increased $1,25(OH)_2$Vitamin D, causing a relative increase in calcium absorption [18]. However, some authors did not find statistically significant differences in serum calcium levels in hypothyroid patients compared with euthyroid controls even during treatment [9].

Suneel B et al. [19] studied mineral status in patients with thyroid disorders and found decreased calcium and increase phosphorous level in hypothyroidism, mainly due to influence of PTH and calcitonin which favour tubular excretion by inhibiting tubular reabsorption.

Roopa M et al. and Jaskiran K et al. [20, 21] studied changes in electrolyte profile in patients with hypothyroidism and reported significantly reduced calcium level and increased magnesium and phosphorous levels. It was also found that there was a significant positive correlation between serum TSH and magnesium and phosphorous levels. At same time, there was a significant negative correlation between TSH and calcium level. Schwarz C et al. [22] in their study of 9012 patients found that, there was a significant positive correlation between serum TSH and phosphate level. Phosphates levels were higher in cases with elevated TSH than in controls.

Shivaleela M B et al.[6] studied serum calcium and phosphorous level in thyroid dysfunction patients and found low calcium and phosphorous in hypothyroid patients.

Conclusion:

The observed changes in serum concentrations of total and ionized calcium in patients with newly diagnosed hyperthyroidism are consistent with the literature and reflect the accelerated bone metabolism in hyperthyroidism. In hypothyroidism, bone turnover is suppressed due to impaired mobilization of calcium from the bone, leading to decreased levels of serum calcium. Suppressed PTH in hyperthyroidism leads to hypercalciuria, which protects against hypercalcemia, but leads to a negative calcium balance. In hypothyroidism, elevated levels of PTH were observed, which could be due to the development of resistance to PTH. Both hyperthyroidism and thyroid insufficiency can lead to significant disturbances in the parameters of calcium-phosphorus metabolism, requiring periodic biochemical and hormonal control.

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Table1. Characteristics of the studied subjects.

	Patients		Controls	P
	N	%		
Subjects	**119**	**100**	**75**	
Age				
Mean±SE	**47.01 ± 1.1**		**44.59 ± 1.6**	**P>0.05**
Amplitude	**25-79**		**21-69**	
Menopause				
Premenopause	**95**	**60.4**	**43**	**P>0.05**
Postmenopause	**54**	**39.6**	**32**	
Thyroid dysfunction				
Hypothyroidism	**68**	**57.1**	**N/A**	**N/A**
Hyperthyroidism	**51**	**42.9**	**N/A**	**N/A**