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CALCIUM-PHOSPHORUS METABOLISM IN FEMALES WITH AUTOIMMUNE THYROIDITIS AND HYPOTHYROIDISM

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Abstract

Thyroid dysfunction is frequently associated with disturbances of calcium and phosphorus homeostasis. Previous studies on bone and mineral metabolism in women with autoimmune thyroiditis (AIT) and hypothyroidism have conflicting results. The aim of the present work was to study the parameters of calcium-phosphorus metabolism in women with newly diagnosed autoimmune hypothyroidism and to compare them with those of the control group of healthy women. The study included 64 women with newly diagnosed autoimmune hypothyroidism. A comparison was made with the data of 75 age-, BMI- and menopausal state-matched healthy women. FT3, FT4, TSH, TPO-Ab, TG-Ab, total and ionized serum calcium, inorganic phosphate, magnesium, parathyroid hormone (PTH) and 25(OH) vitamin D were studied. Total and ionized calcium were lower in hypothyroid women in the absence of statistically significant difference compared to the controls. Intergroup analysis revealed no differences in serum phosphorus and 25(OH)D levels. Serum magnesium and PTH were significantly higher in hypothyroid 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 serum calcium levels and ele-

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vated PTH. We found a significant effect of thyroid hormones on magnesium homeostasis. The study did not find differences in vitamin D status between the groups. The observed inverse correlation between 25(OH)D and TgAb supports the concept of pathogenic relationship between vitamin D and the development of AIT.

Key words: calcium-phosphorus metabolism, autoimmune thyroiditis, hypothyroidism

Introduction. Thyroid dysfunction is frequently associated with disturbances of calcium and phosphorus homeostasis. Thyroid disorders are important cause of secondary osteoporosis. Although hypothyroidism increases the duration of the bone remodelling cycle resulting in decreased bone turnover and accelerated mineralization [1], population-based studies have shown that patients with hypothyroidism are at increased risk of fractures [2, 3]. Previous studies done on serum calcium, phosphorus, magnesium, 25(OH) vitamin D and parathyroid hormone (PTH) levels in women with autoimmune thyroiditis (AIT) and hypothyroidism provide conflicting results.

Osteomineral metabolism in hypothyroidism. Dysturbances 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, mildly elevated serum PTH and $1{,}25(OH)_2$vitamin D, decreased alkaline phosphatase, urinary calcium excretion and glomerular filtration rate [4]. However, these changes are not statistically significant in hypothyroid patients compared to the euthyroid controls, even during treatment [5].

In hypothyroidism, there is also an increased production of calcitonin which promotes the tubular reabsorption of phosphate and favours the tubular excretion of calcium which leads to hypocalcemia and hyperphosphatemia [5].

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

Patients and methods. ***Study design and subjects.*** The study was conducted in "St. George" University Hospital – Plovdiv, Bulgaria, Department of Endocrinology. A total of 64 women with newly diagnosed autoimmune hypothyroidism were included in the study. Of them 63% ($n = 40$) were premenopausal and 37% ($n = 14$) were postmenopausal. A comparison was made with the data of 75 age-, BMI- and menopausal state-matched healthy women (Table 1).

Selection criteria. Inclusion criteria: women over 20 years of age with newly diagnosed autoimmune thyroiditis and hypothyroidism, signed written informed consent. Exclusion criteria: treatment with levothyroxine and/or antithyroid drugs; use of oral contraceptives or hormone replacement therapy in the last 6 months, calcium-phosphorus preparations, vitamin D or medications that could

Table 1

Characteristics of the studied subjects

	Patients		Controls	P
	N	%		
Subjects	64	100	75	
Age (mean ± SE)	46.61 ± 1.1		44.59 ± 1.6	$P > 0.05$
Menopause				
Premenopause	40	63	43	$P > 0.05$
Postmenopause	14	37	32	

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; pregnant and breast-feeding women.

Analysis of sample. TSH, FT4, FT3, TPO-Ab, TG-Ab, 25(OH)vitamin D were measured by CLIA (chemiluminescent immunoassay) using automated immunoassay analyzer Access 2®, Beckman Coulter Inc; TSH values above 5.6 mIU/L were considered elevated. The reference range of FT4 was 7.86–14.41 pmol/L, FT3 – 3.8–6.0 pmol/L. TPO-Ab was in the reference range: $\leq$ 9 IU/mL, TG-Ab $<$ 4.0 IU/mL. Vitamin D values were presented in ng/ml. Factor to convert individual values of 25(OH)D from ng/ml to nmol/l is 2.5. Blood was collected between October and March to avoid seasonal variations.

PTH was measured by CLIA (chemiluminescent immunoassay) using immunological analyzer Immulite 2000, Siemens, with reference range 11–67 pg/ml. Serum total and ionized calcium were determined by colourimetric method (with Arsenazo III), inorganic phosphate and magnesium by colourimetric 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. Magnesium reference range was 0.77–1.03 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 assessed by Pearson's correlation coefficient. P-values < 0.05 were considered statistically significant. The data processing was done by using SPSS for Windows v.21 statistical software.

Results. The characteristics of the studied subjects in the hypothyroid and control groups are presented in Table 2.

The analysis found that there was no statistically significant difference in the mean total serum calcium concentration in patients with hypothyroidism compared to the controls (2.39 ± 0.02 mmol/l versus 2.37 ± 0.01 mmol/l, $p > 0.05$).

Table 2

Characteristics of the studied groups – hypothyroid and healthy controls

Parameters	Hypothyroid ($n = 64$) mean ± SEM	p	Controls ($n = 75$) mean ± SEM
TSH (mIU/L)	46.16 ± 6.36	0.000	2.04 ± 0.13
FT4 (pmol/L)	6.68 ± 0.47	0.000	11.31 ± 0.29
FT3 (pmol/L)	4.41 ± 0.16	0.000	5.05 ± 0.12
TPOAb(IU/mL)	590.82 ± 58.27	0.000	3.38 ± 1.40
TGAb(IU/mL)	471.52 ± 115.14	0.000	0.58 ± 0.12

There was no significant difference in ionized calcium in hypothyroid women (1.19 ± 0.01 mmol/l, $p > 0.05$) as compared to the controls (1.20 ± 0.01 mmol/l).

There was no statistically significant difference in serum phosphorus in hypothyroid (1.23 ± 0.04 mmol/l, $p > 0.05$) versus controls (1.24 ± 0.05 mmol/l). Markedly increased PTH concentration levels were found in hypothyroid group (46.02 ± 4.20 pg/ml, $p < 0.05$) compared to the controls (36.15 ± 2.47 pg/ml) (Table 3).

Table 3

Parameters of calcium-phosphorus metabolism in patients with hypothyroidism and healthy controls (*$p < 0.05$)

Parameters	Hypothyroid ($n = 64$) mean ± SEM	p	Controls ($n = 75$) mean ± SEM
Ca (mmol/l)	2.39 ± 0.018	0.375	2.37 ± 0.01
iCa (mmol/l)	1.19 ± 0.019	0.566	1.20 ± 0.01
P (mmol/l)	1.23 ± 0.045	0.849	1.24 ± 0.05
Mg (mmol/l)	0.90 ± 0.015	0.027*	0.86 ± 0.01
PTH (pg/ml)	46.02 ± 4.20	0.033*	36.15 ± 2.47
25(OH) vitamin D (ng/ml)	16.83 ± 1.01	0.159	19.74 ± 1.41

The mean value of serum magnesium was significantly higher in hypothyroid women (0.90 ± 0.015 mmol/l, $p < 0.05$) compared to the control group (0.86 ± 0.01 mmol/l).

There was no statistically significant difference in the levels of 25(OH)D between the two groups. The mean 25(OH)D concentration in hypothyroid individuals was 16.83 ± 1.01 ng/ml, in the controls was 19.74 ± 1.41 ng/ml.

Serum TSH, FT3, FT4, TPO-Ab, TG-Ab of patients were studied in relation to serum total calcium, ionized calcium, phosphorus, magnesium, PTH

Table 4

Correlation between serum calcium, phosphorus, PTH and FT3, FT4

	TSH	FT3	FT4
Ca	NS	NS	NS
iCa	NS	$r = 0.43^*$	$r = 0.49^*$
P	NS	NS	NS
PTH	NS	$r = -0.30^*$	$r = -0.27^*$

and 25(OH)D. Positive correlation was observed between ionized calcium, FT3 ($r = 0.43$; $p = 0.001$) and FT4 ($r = 0.49$; $p < 0.05$), between magnesium and TSH ($r = 0.32$; $p = 0.001$), TPO-Ab ($r = 0.24$; $p < 0.05$), PTH ($r = 0.27$; $p < 0.05$), total calcium ($r = 0.27$; $p < 0.05$), phosphorus ($r = 0.25$; $p < 0.05$). A negative correlation was found between serum PTH, FT3 ($r = -0.30$; $p < 0.05$), FT4 ($r = -0.27$; $p < 0.05$) and phosphorus ($r = -0.35$; $p = 0.001$) (Table 4). There was a positive correlation between 25(OH)D and FT3 ($r = 0.267$, $p < 0.05$) and a negative one with TG-Ab ($r = -0.265$, $p < 0.05$).

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

These results are in accordance 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 serum calcium levels. The synthesis of calcitonin is increased, which stimulates tubular phosphate reabsorption and promotes calcium excretion, 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 [6]. However, some authors did not find statistically significant differences in serum calcium levels in hypothyroid patients compared to the euthyroid controls even during treatment [5].

Suneel et al. [7] studied mineral status in patients with thyroid disorders and found decreased calcium and increased phosphorus level in hypothyroidism, mainly due to influence of PTH and calcitonin which favour tubular excretion by inhibiting tubular reabsorption.

Murgot and Soans [8] and Kaur et al. [9] studied changes in electrolyte profile in patients with hypothyroidism and reported significantly reduced calcium level and increased magnesium and phosphorus levels. It was also found that there was a significant positive correlation between serum TSH, magnesium and phosphorus levels and a negative correlation between TSH and calcium level.

Our patients with hypothyroidism had higher magnesium levels than the controls ($p < 0.05$). We observed a positive correlation between magnesium and TSH ($p = 0.001$) and negative between magnesium, FT3 and FT4 ($p < 0.001$).

Similar results found Frizel et al. [10]. In their study total and ionized plasma magnesium were elevated in hypothyroidism. McCaffrey and Quamme [11] studied the renal excretion of calcium and magnesium in rats with a deficiency or excess of thyroid hormones. They found 15–30% increased kidney magnesium reabsorbtion in hypothyroid rats. Due to the direct effect of thyroid hormones on the renal tubule, their chronic absence leads to retention of magnesium in the kidney [11].

Schwarz et al. [12] found that there was a positive correlation between serum TSH and phosphate level. Phosphates levels were higher in cases with elevated TSH than in the controls. Gohel et al. [13] found decreased levels of calcium and magnesium in hypothyroid patients.

Shivaleela et al. [14] studied serum calcium and phosphorus level in thyroid dysfunction patients and found low calcium and phosphorus in hypothyroid patients.

Serum levels of 25(OH)D, $1,25(OH)_2D$ and other metabolites of vitamin D in thyroid dysfunction have been extensively analyzed. Bouillon et al. [6] found no difference in vitamin D levels in hypo- and hyperthyroid patients and healthy individuals. No changes in circulating vitamin D levels were reported by Jastrup et al. [15] and Macfarlane et al. [16]. Accordingly our results do not show difference in serum levels of 25(OH)D among patients with hypothyroidism compared to the healthy controls.

There are several limitations at this phase of the study with the small number of the subjects included being the most significant. Data obtained from the patients follow up after restoration of euthyroidism will provide valuable information on the causal relationship between thyroid hormones and the parameters of calcium and phosphorus metabolism.

The results of the present and other similar studies will provide further knowledge on the problem with potential clinical implications in the differential diagnosis and treatment of bone and mineral metabolism disorders in patients with thyroid dysfunction.

Conclusion. The results of the present study revealed significant elevation of PTH in women with newly diagnosed autoimmune hypothyroidism compared to the healthy controls. However, no differences in the concentration of Ca, ionized Ca, P and 25(OH)D were found. Higher magnesium levels were detected in hypothyroid group probably due to increased kidney magnesium reabsorbtion. The observed inverse correlation between 25(OH)D and TgAb supports the concept of pathogenic relationship between vitamin D and the development of AIT. The results are in accordance with other studies and reflect the changes in bone

metabolism in patients with thyroid hormones deficiency. The reported correlation of 25(OH)D with FT3 requires further investigation.

REFERENCES

[1] Mosekilde L., E. F. Eriksen, P. Charles (1990) Effects of thyroid hormones on bone and mineral metabolism, Endocrinol. Metab. Clin. North Am., **19**(1), 35–63.

[2] Vestergaard P., L. Rejnmark, J. Weeke, L. Mosekilde (2000) Fracture risk in patients treated for hyperthyroidism, Thyroid., **10**(4), 341–348.

[3] Vestergaard P., J. Weeke, H. C. Hoeck et al. (2000) Fractures in patients with primary idiopathic hypothyroidism, Thyroid., **10**(4), 335–340.

[4] Eriksen E. F. (1986) Normal and pathological remodeling of human trabecular bone: three dimensional reconstruction of the remodeling sequence in normals and in metabolic bone disease, Endocr. Rev., **7**(4), 379–408.

[5] Sabuncu T., N. Aksoy, E. Arikan et al. (2001) Early changes in parameters of bone and mineral metabolism during therapy for hyper- and hypothyroidism, Endocr. Res., **27**(1–2), 203–213.

[6] Bouillon R., E. Muls, P. De Moor (1980) Influence of thyroid function on the serum concentration of 1,25-dihydroxyvitamin D3, J. Clin. Endocrinol. Metab., **51**(4), 793–797.

[7] Suneel B., D. R. Nagendra, R. R. Aparna et al. (2011) Mineral status in thyroid disorders (Hypo&Hyper), IJABPT, **2**(4), 423–429.

[8] Murgot R., G. Soans (2012) Changes in electrolyte and lipid profile in hypothyroidism, Int. J. Life Sci. Pharm. Res., **2**(3), 185–194.

[9] Kaur J., N. Ahmad, A. Gupta (2014) Changes in the electrolyte profile of patients having hypothyroidism, JMSCR, **2**(4), 633–637.

[10] Frizel D., A. Malleson, V. Marks (1967) Plasma levels of ionised calcium and magnesium in thyroid disease, Lancet, **1**(7504), 1360–1361.

[11] McCaffrey C., G. A. Quamme (1984) Effects of thyroid status on renal calcium and magnesium handling, Can. J. Comp. Med., **48**(1), 51–57.

[12] Schwarz C., A. B. Leichtle, S. Arampatzis et al. (2012) Thyroid function and serum electrolytes: does an association really exist?, Swiss Med. Wkly, **42**(3738), w13669, https://doi.org/10.4414/smw.2012.13669.

[13] Gohel M. G., A. M. Shah, A. M. Shah, J. S. Makadia (2014) A study of serum calcium, magnesium and phosphorous level in hypothyroidism patients, Int. J. Med. Health Sci., **3**(4), 308–312.

[14] Shivaleela M. B., R. T. Poornima, D. S. Jayaprakash Murthy (2012) Serum calcium and phosphorous levels in thyroid dysfunction, Ind. J. Fund. Appl. Life Sci., **2**(2), 179–183.

[15] Jastrup B., L. Mosekilde, F. Melsen et al. (1982) Serum levels of vitamin D metabolites and bone remodelling in hyperthyroidism, Metabolism, **31**(2), 126–132.

[16] Macfarlane I. A., E. B. Mawer, J. Berry, J. Hann (1982) Vitamin D metabolism in hyperthyroidism, Clin. Endocrin., **17**(1), 51–59.

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