STUDY OF THE CHANGES IN BONE MASS AND BONE METABOLISM MARKERS IN THYROTOXIC OSTEOPOROSIS. THERAPEUTIC IMPLICATIONS.

Scientific coordinator:
Prof.Univ.Dr. MARIAN BISTRICEANU

PhD candidate:
VASILE IONUȚ SILVIU

CRAIOVA
2011
CONTENTS:

INTRODUCTION

GENERAL PART

Chapter I. PHYSIOLOGICAL EFFECTS OF THE THYROID HORMONES
1.1. THYROID HORMONES BYOSYNTHESIS
   1.1.1. THYROID HORMONES SYNTHESIS
   1.1.2. THYROID HORMONES TRANSPORT
   1.1.3. SECRETION ADJUSTMENT OF THE THYROID HORMONES.
1.2. EFFECTS OF THE THYROID HORMONES
   1.1.4. MECHANISMS OF ACTION OF THE THYROID HORMONES
   1.1.5. BIOLOGICAL ACTIONS OF THE THYROID HORMONES
   1.1.6. THYROID HORMONES’ INFLUENCES ON BONE

Chapter II. ETIOPATHOGENESIS AND DIAGNOSIS OF OSTEOPOROSIS
2.1. DEFINITION AND IMPACT
2.2. ETIOPATHOGENESIS OF OSTEOPOROSIS
   2.2.1. BONE REMODELLING
   2.2.2. MARKERS OF THE BONE TURN-OVER
      2.2.2.1. MARKERS OF BONE FORMATION
      2.2.2.2 BONE RESORPTION MARKERS
   2.2.3. RISK FACTORS
2.2.4. OSTEOPOROSIS DIAGNOSIS
   2.4.1. POSITIVE DIAGNOSIS
      2.4.1.1. THE ROLE OF THE CLINICAL DIAGNOSIS IN BONE DENSITY MEASUREMENT
   2.4.2. DIFFERENTIAL DIAGNOSIS
   2.4.3. GENERAL PRINCIPLES OF SCREENING

Chapter III DIFFERENTIAL THERAPEUTIC ATTITUDES IN THYROTOXIC OSTEOPOROSIS
3.1. OSTEOPOROSIS PROPHYLAXIS
3.2. CURATIVE TREATMENT OF THYROTOXIC OSTEOPOROSIS
   3.2.1. THERAPEUTIC PRINCIPLES AND MEANS OF THYROTOXICOSIS
   3.2.2. MEDICAL TREATMENT OF OSTEOPOROSIS
      3.2.2.1. ANTIOSTEOPOROTIC MEDICINES CLASSIFICATION
SPECIAL PART

Chapter I. SCOPE, OBJECTIVES AND MOTIVATION OF THE RESEARCH

Chapter II. MATERIAL AND METHOD
2.1. CLINICAL EXAMINATION
2.2. LABORATORY INVESTIGATIONS
2.3. OVERVIEW OF THE STUDIED PATIENTS
2.4. WORKING PROTOCOL
2.4.1. CLINICAL CRITERIA FOR INCLUSION IN THE STUDY
   2.4.1.1. THYROXIC OSTEOPOROSIS
          Graves Basedow Graves disease
          Autonomous thyroid nodule (toxic Node Plummer)
          Multinodular toxic goiter
   2.4.1.2. POSTMENOPAUSAL OSTEOPOROSIS

Chapter III. RESULTS
3.1. METABOLIC INVESTIGATIONS
   3.1.1. INVESTIGATION OF THE CARBOHYRATE, LIPIDS AND CALCIUM
          METABOLISMS OF THE STUDIED POPULATION.
   3.1.2. BIOCHEMICAL MARKERS OF BONE TURNOVER
3.2. HORMONAL INVESTIGATIONS
   3.2.1. THYROXIC OSTEOPOROSIS
   3.2.2. POSTMENOPAUSAL OSTEOPOROSIS
3.3. IMAGING METHODS
   3.3.1. WHOLE BODY DUAL X-RAY ABSORPTIOMETRY (DEXA)
          3.3.1.1. DEXA WHOLE BODY DETERMINATION OF BONE MINERAL
          DENSITY
          3.3.1.2. DEXA WHOLE BODY DETERMINATION OF FAT AND LEAN
          MASS

Chapter IV. DISCUSSION AND INTERPRETATION OF RESULTS

Chapter V. CONCLUSIONS

REFERENCES

Keywords: thyrotoxic osteoporosis, thyroid hormones, DEXA, thyrotoxicosis, bone turnover
INTRODUCTION

Thyrotoxic osteoporosis has been neglected in terms of research, the overwhelming majority of studies focusing on postmenopausal osteoporosis. The purpose of this paper is to study the metabolic and hormonal changes in thyrotoxic osteoporosis, a consequence of thyrotoxicosis. Osteoporosis, defined as a decrease in bone mass, is a relatively common disease, a painless, 'silent disease'. If bone pain is present, there may be other underlying conditions such as osteoarthritis or small fractures that are responsible for the pain. We should mention that, because both impaired thyroid disease and osteoporosis are relatively common, especially in women, there are many patients who develop both a thyroid disease and osteoporosis. This does not always imply a causal relationship between the two conditions. The thyroid hormones are known to stimulate osteoblasts, favoring osteoid formation. Excessive secretion of thyroid hormones stimulates osteoclastic activity, resulting in increased bone resorption.

Osteoporosis and osteopenia are relatively frequently encountered in hyperthyroidism, significantly more than in the euthyroidian population. Causal factors are considered to be: an increased stimulation of osteoblasts compared to osteoclasts and the alteration of bone remodeling by the thyroid hormones.

THE SPECIFIC OBJECTIVES that we intend to accomplish through this research are:

1. Objective and subjective clinical criteria of the studied patients;
2. The evaluation of bone mineral density in patients with thyrotoxic osteoporosis induced by different clinical forms of thyrotoxicosis (Basedow Graves disease, autonomous thyroid nodule, toxic multinodular goiter);
3. Metabolic and hormonal assessment of the studied patients;
4. Assessing the influence of absolute fat and lean mass on bone mineral density;
5. Study of the influence of body composition changes due to thyrotoxicosis on bone mass;
6. The evaluation of the results of differentiated therapeutic attitudes: anti-thyroid agents, radiotherapy, surgery, in combination with antiosteoporotic medication on bone mineral density.
MATERIAL AND METHOD

Cases were selected from the Ambulatory of Endocrinology and from the patients hospitalized in the Clinic of Endocrinology, Emergency County Hospital of Craiova in 2005 - 2010.

The casuistry is represented by 64 patients:
- A group of 26 patients with thyrotoxic osteoporosis and aged 40 to 60 years.
- A group of 38 patients with postmenopausal osteoporosis and in euthyroidism aged 45 to 65 years.

Patients were selected based on objective criteria, allowing hyperthyroidism documentation and eliminating possible interferences with other predisposing factors or previous therapies. In addition to routine laboratory investigations (haematological and biochemical), the PhD candidate pays special attention to biochemical markers of bone turnover (osteocalcin and CrossLaps) hormone investigations (TSH, FT3, FT4, TRAb, LH, FSH, PRL, oestradiol, progesterone), bone mineral density assessment by Dual X-Ray Absorptiometry (DEXA). The author uses the DEXA Whole Body technique, that allows an evaluation of the bone mineral density and body composition taking into consideration bone, fat and lean masses.

Biochemical markers of bone turnover were evaluated in the biochemistry laboratory of the County Emergency Hospital Craiova, on sera taken from patients hospitalized in the Endocrinology Clinic with a diagnosis of hyperthyroidism and those with osteoporosis who have benefited from the National Osteoporosis Program.

RESULTS AND DISCUSSION

The study of biochemical markers of bone turnover showed elevated values both for osteocalcin and for CrossLaps. Osteocalcin is a protein synthesized exclusively by osteoblasts, odontoblasts and hypertrophic chondrocytes and is regarded as a specific marker of the osteoblasts’ function. It was shown that serum levels of immunoreactive osteocalcin correlate well with the bone formation rate, as assessed by histomorphometry.
Normal values of serum osteocalcin are:
- in premenopausal women: 17.9 ± 6.5 ng / ml,
- in post-menopausal women: 28.4 ± 9.5 ng / ml.

The values we found in patients with thyrotoxic osteoporosis were 27.92 ± 19.47 ng / ml (an increase of 60% compared to normal premenopausal values). This shows a significant stimulation of bone formation by the excess of thyroid hormones. In patients with postmenopausal osteoporosis we found values of 17.29 ± 9.12 were ng / ml (normal postmenopausal values close to 18.4 ± 9.5 ng / ml). Variations were correlated with the number of years since menopause occurred. In the postmenopausal period estrogen deficiency consecutive increases bone remodeling. This fact, already known for some time, is reflected in our study, the average value for bone formation and resorption markers being significantly higher in thyrotoxic osteoporosis than in premenopausal osteoporosis (52.8).

CrossLaps (carboxy-terminal telopeptides of collagen type I) normal values, interpreted as biochemical markers of bone resorption are:
- in premenopausal women: 0.31 ± 0.155 ng / ml,
- in postmenopausal women: 0.506 ± 0.255 ng / ml,
CrossLaps values determined by us for patients with thyrotoxic osteoporosis were: 0.304 ± 0.887 ng / ml (approximately 80% higher than normal levels of premenopausal)

For patients with postmenopausal osteoporosis the values were: ±0.277 0.842 ng / ml (close to the normal values of the postmenopausal period: 0.251 ± 0.761 ng / ml). Analyzing the results that we obtained for subjects with thyroxic osteoporosis we can notice that an excess of thyroid hormones leads to an acceleration of both bone formation and resorption but especially regarding increased bone resorption.

In clinical practice, monitoring of both bone formation and resorption by following their biochemical markers can be used in monitoring the antiosteoporotic therapy.

TSH values showed that in 50% of the cases it was very suppressed, being below the detection limit of the device. Regarding FT4, 12% of patients had values above the
calculation limit of the device: 46% between 23-30 pmol / L, 19% between 30-40 pmol / L and 23% with very high values of 40 -70 pmol / L. FT3 had high values (73%) and very high (27%). The high levels of thyroid hormones that were found without exception in the entire studied group, correlated with low TSH values confirmed the diagnosis of thyrotoxicosis for the group of subjects diagnosed with thyrotoxic osteoporosis. Similarly, dosing the ovarian hormones in the group with postmenopausal osteoporosis confirmed menopause.

For multivariate analysis we used linear regression, the stepwise method, quantifying the contribution of each clinical variables, expressed by the non-standardized beta coefficient, to explain BMD. Statistical significance was defined as a p value of <0.05. Statistical analysis was performed using SPSS 16 software for Windows. For bivariate statistical analysis of sizes continue to use Pearson's correlation coefficient and Student test. Fat and lean tissue masses were expressed as a percentage of body weight, as absolute values (kg) and as relative values for each segment separately. Other clinical variables taken into account for the initial bivariate analysis were: height, weight, TSH, FT3, FT4, T-score.

We found a first correlation between serum FT4 level and the weight of subjects with thyrotoxic osteoporosis. Sig (p) = 0.024 shows a significant correlation (the first significance level reached at 0.05, p <0.05) and *r = - 0.442* shows that there is an inverse correlation: if FT4 increases, the weight will drop. The explanation for this correlation lies in the biological effects exerted by thyroid hormones that increase oxygen consumption and energy metabolism of all tissues and organs, except only the brain, spleen, lungs, gonads and retina. Thus basal metabolism may increase by 60-100% above normal values whenever there is an excessive thyroid secretion.

The second correlation identified the cause in FT4- levels and the effect in the T-score of upper limbs. Sig (p) = 0.031 and *r = - 0.424* show that there is a significant inverse correlation (taking into account the second significance level of 0.05). Thus there is a significant inverse correlation between FT4 levels and T-score of upper limbs on our lot for 26 patients with thyrotoxic osteoporosis, showing that an excess on FT4 leads to a T-score decreases in the arms.

The last significant correlation was established for FT4 and the fat mass of the
pelvis. \( P = 0.038 \) and \( r = -0.408 \) show a negative significant correlation, i.e., if FT4 will increase fat mass in the pelvis decreases.

For FT3 we detected significant correlations (\( p \leq 0.05 \)) with no parameter.

TSH was positively correlated with bone mass but not significantly, the second significance level was not reached. The only significant correlation for TSH and the lean mass of the lower limbs was a positive correlation \( (r = 0.415, p = .035) \).

**CONCLUSIONS**

1. Complex biological effects of thyroid hormones on bone, incompletely understood, motivate the need to approach the study of the changes in bone mass and bone metabolism markers in thyrotoxic osteoporosis, that is a consequence of an excess of thyroid hormones;

2. As for thyrotoxicosis, regardless of the clinical form, the first line treatment aims the cancellation of the excessive production of thyroid hormones in order to suppress their metabolic and visceral effects;

3. In thyrotoxic osteoporosis there are significantly elevated values of the biochemical markers of bone turnover;

4. The evaluation of the biochemical markers in thyrotoxic osteoporosis provides useful information on the bone remodeling process and on monitoring the antiosteoporotic therapy results;

5. In all patients with thyrotoxic osteoporosis significant inverse correlations between serum FT4 levels and body weight and between the FT4 values and T-score of the upper limbs were found;

6. The Whole Body DEXA determination proved to be useful in exploring the relationship between lean and fat mass, respectively regional bone mass, but also in assessing body composition changes in thyrotoxic osteoporosis;

7. First line therapy in osteoporosis associates antithyroidian and antiosteoporotic medication;
8. It requires periodic review (annual) of bone mineral density and biochemical markers of bone turnover in patients older than 40 years, with pathological history of hyperthyroidism;

9. Whole Body DEXA determination is a modern alternative in the study of body composition (lea and, fat tissue compartments and bone mass) that tends to become the new standard for investigating the body structure.

Curriculum Vitae

Name: Vasile Ionut-Silviu
Date of Birth: 27/01/1976
Marital status: Single
Address: Craiova, Alex. Macedonski No. 17
E-mail: ionut_vasile@hotmail.com
Phone: 0747 77 77 15
Education: High School Nicholas Balcescu Craiova
Faculty of Medicine, UMF Craiova 2001
At present - Assistant Professor, Discipline of Endocrinology, Faculty of Medicine, UMF Craiova
- Endocrinology Specialist at Emergency County Hospital Craiova,
Department of Endocrinology
Member of scientific societies:
- Founding member of the Association of Clinical Endocrinologists in Romania
- Member of Romanian Society of Endocrinology