



## THYROID-STIMULATING HORMONE WITHIN NORMAL RANGE DOES NOT AFFECT BONE TURNOVER IN EUTHYROID POSTMENOPAUSAL WOMEN WITH OSTEOPOROTIC FRACTURE - A PRELIMINARY REPORT

Agnieszka Pater<sup>1</sup>, Wieslaw Nowacki<sup>2</sup>, Grazyna Sypniewska<sup>1</sup>

1. Department of Laboratory Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
2. Department of Orthopaedics and Traumatology, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

### **Corresponding author's address**

Agnieszka Pater  
Department of Laboratory Medicine, Collegium Medicum, Nicolaus Copernicus University  
Sklodowskiej-Curie 9  
85-094 Bydgoszcz  
Poland  
Phone +48 52 585 40 46  
Fax +48 52 585 36 03  
E-mail: [agnieszka.chrapkowska@wp.pl](mailto:agnieszka.chrapkowska@wp.pl)

### **Abstract**

**Background:** Pathogenic role of TSH suppression in the damaged bone tissue, in contrast to increased concentrations of thyroid hormones is still unknown. The aim of study was to evaluate the relationship between serum TSH and biochemical bone turnover markers in postmenopausal women with normal thyroid function and to answer whether the differences in TSH concentration within reference range may affect bone metabolism.

**Material and Methods:** 34 women (60-93 years old) admitted to the hospital after osteoporotic fracture participated in the study. Serum propeptide of type 1 procollagen (P1NP) as a bone formation marker and crosslinked C-terminal telopeptides (CTX-I), as a bone resorption marker and TSH were assayed.

**Results:** Median P1NP ( $p=0,05$ ) was significantly higher in the 1st tertile of TSH values (0,35 -1,88 mIU/mL). In the 3rd tertile of TSH concentrations (3,42 -4,94 mIU/mL), the highest CTX-I value was found that exceeded the reference range for age. No differences were found in bone markers between a group of euthyroid and a group of subjects with  $TSH < 0,35$  mIU/mL. No relationship was observed between TSH and bone formation and resorption markers in the whole group of euthyroid postmenopausal women, however bone formation was found to be in the lower reference range for age in the euthyroid subjects as well as in these with decreased TSH. Weight and BMI correlated negatively with CTX ( $r=-0,68$   $p < 0,03$ ) in fractured women in the 1st tertile of TSH.

**Conclusion:** We found no consistent evidence that TSH concentrations within reference range was associated with changes in bone turnover markers.

## INTRODUCTION

Over recent years, there has been a growing number of reports indicating a relationship between serum thyrotropin and bone remodeling [1-9]. Animal studies have shown that reduced expression of the TSH receptor leads to the development of osteoporosis, in accordance with the hypothesis that TSH deficiency may inhibit bone turnover [4,5]. Biologically active TSH receptors are present in the osteoblasts and the administration of recombinant TSH leads to reduced bone resorption and increased bone formation [6,7]. Moreover, the results of research in post-menopausal women with serum TSH in the lower range of normal values suggest a decreased bone mineral density and increased fracture risk [8,9] as well as in 65 years or older men with subclinical hyperthyroidism or hypothyroidism increased risk for hip fracture was observed [10]. Recent results in postmenopausal Italian women who had vertebral fractures indicated the existence of the relationship between TSH and fractures independently of thyroid hormone levels, age and bone mineral density [2]. Pathogenic role of TSH suppression in the damaged bone tissue, in contrast to increased levels of thyroid hormones is still unknown. The aim of our preliminary study was to verify the relationship between serum TSH and biochemical bone turnover markers in postmenopausal women with normal thyroid function who sustained an osteoporotic fracture to assess whether the differences in TSH concentration within the reference range may affect bone metabolism.

## MATERIAL AND METHODS

34 women aged 60-93 years, admitted to the Department of Orthopaedics and Traumatology at the University Hospital in Bydgoszcz for osteoporotic fracture, were included in the study. All were euthyroid postmenopausal women that did not receive drugs affecting bone metabolism before fracture. Inclusion criteria were: osteoporotic fracture, no treatment with anti-osteoporotic drugs, no previous treatment with drugs potentially causing osteoporosis and fragility fractures, no clinical history of recent significant trauma or prolonged immobilization. Only few of them had diabetes mellitus (3), renal insufficiency (1), rheumatoid arthritis (1). 89% had femoral neck fracture and 11% fractures of hip or knee.

A written informed consent from each participant was obtained. The study was approved by the Bioethics Committee at Collegium Medicum, Nicolaus Copernicus University.

From all women included in the study blood was taken within 18 hours after fracture. Serum was obtained within less than 2 hours to avoid proteolysis and stored deep-frozen in small aliquots until assayed but no longer than 3 months. In the serum samples, directly after thawing, the following markers were measured: propeptide of type 1 procollagen (P1NP) (ELISA Kit for Procollagen I N-Terminal Propeptide PINP; Uscn, Life Science Inc.; detection limit was 6,9 pg/ml; reference range for postmenopausal women <45,0 ng/mL) as a bone formation marker, C-terminal telopeptide of type 1 collagen (CTX), (CTX ELISA, Immunodiagnostic Systems Ltd; detection limit 0,02 ng/mL; mean value for postmenopausal women 0,439 ng/ml; range 0,142-1,351 ng/mL) as a bone resorption marker. TSH was assayed using the ARCHITECT TSH assay (Abbott Diagnostics; detection limit 0,01 mIU/mL, which meets the requirements of a third generation TSH assay; reference range at postmenopause 0,35-4,94 mIU/mL, according to the manufacturer data).

Statistical analysis was performed using Statistica 6.0 for Windows (Stat Soft). All data are presented as median and 25<sup>th</sup> and 75<sup>th</sup> percentile. U-Mann-Whitney test was used to compare differences between groups. Spearman correlation test was used.

## RESULTS

Study group consisted of 29 women with TSH within the reference range (0,35-4,94 mIU/mL) and additionally of 5 women with TSH concentration < 0,35 mIU/mL.

Median age in group with TSH within the reference range was 80 (71-85) years, height 1,61 (1,56-1,64) m, weight 70 (60-79) kg and BMI 27 (23-29) kg/m<sup>2</sup>. In all euthyroid women median value of CTX-I was 0,535 (0,400-0,817) ng/mL and was within the reference range for their age, whereas median P1NP concentration of 31,2 (27-39,8) ng/mL was in

the lower reference range. Median TSH was 0,96 (0,66-1,81) mIU/mL whereas the values within 5-95th percentile were found to be from 0,46- 3,40 mIU/mL.

Median age in women with TSH level < 0,35 mIU/mL was 81 (65-86) years, height 1,63 (1,62-1,64) m, weight 80 (63-98) kg and BMI 30 (23-37) kg/m<sup>2</sup>. Median value of CTX-I was 0,491 (0,472-0,535) ng/mL and was within the reference range for their age, whereas median P1NP concentration of 35,6 (35-38,6) ng/mL was in the lower reference range. TSH concentration was 0,24 (0,14-0,29) mIU/mL.

Next, euthyroid post-menopausal women with osteoporotic fracture were divided into 3 groups according to TSH values: 1st tertile from 0,35 to 1,88 mIU/mL, 2nd from 1,89 to 3,41 mIU/mL and 3d from 3,42 to 4,94 mIU/mL (Tab.1).

**Table 1.** Values of biochemical bone turnover markers in euthyroid postmenopausal women with osteoporotic fracture according to TSH tertiles; Median (25th- 75th percentiles)

	TSH		
	1st tertile 0,35 to 1,88 mIU/mL	2nd tertile 1,89 to 3,41 mIU/mL	3rd tertile 3,42 to 4,94 mIU/mL
N	23	4	2
Age (years)	80 (71-86)	69 (63-83)	84 (83-85)
Height (m)	1,61 (1,53-1,64)	1,70 (1,66-1,74)	1,59 (1,57-1,60)
Weight (kg)	62 (60-79)	75 (70-80)	66 (56-76)
BMI (kg/m <sup>2</sup> )	27 (23-29)	26 (25-27)	26 (22-31)
P1NP (ng/mL)	35,0 (27,6 – 39,8)	23,9 (23,4-27,3)	39,9 (31,2-48,6)
CTX-I (ng/mL)	0,555 (0,400 – 0,817)	0,342 (0,179-0,757)	1,183 (0,535-1,831)
TSH (mIU/mL)	0,73 (0,59 – 1,01)	2,19 (2,14-2,30)	3,88 (3,41-4,36)

U-Mann-Whitney test has shown higher median P1NP (p=0,05) in the 1st tertile and higher CTX-I in the 3rd tertile. There was no significant differences in concentration of bone turnover markers between group of women with TSH level <0,35 mIU/mL and those euthyroid postmenopausal women in the 1st tertile.

No relationship was observed between TSH and bone formation and resorption markers in all groups of euthyroid postmenopausal women. Instead, weight and BMI correlated negatively with TSH (r=-0,77 p<0,006 and r=-0,73 p<0,02 respectively) and CTX (r=-0,68 p<0,03) in women in the 1st tertile. No relationship was also observed between TSH and bone formation and resorption markers in a group of women with TSH level <0,35 mIU/mL. P1NP positively correlated with CTX in this group (r=0,9 p<0,04).

## DISCUSSION

It has been found that in hypothyroidism the duration of the remodeling cycle increases. The duration of the resorption process is extended 2-fold and bone formation is prolonged 4-fold [11]. However in hyperthyroidism bone formation and resorption processes are accelerated and remodeling cycle is shortened [11].

In this study we measured serum concentrations of propeptide of type 1 procollagen (P1NP) as a bone formation marker and crosslinked C-terminal telopeptide (CTX-I), as a bone resorption marker in elderly euthyroid women with osteoporotic fracture (mainly of the femoral neck) in attempt to find a relationship between TSH and bone turnover markers. Fracture may have an influence on concentration of bone markers which in the immediate postfracture period does not alter but clearly increase during fracture healing. To exclude any influence of fracture consequences and repair on bone turnover markers, especially P1NP and CTX-I concentrations, we collected blood samples within 18 hours after fracture.

The association between TSH concentration and bone turnover markers in relation to the risk of fragility fracture is still a matter of debate. The association of thyrotropin with bone mineral density and bone markers in postmenopausal women was very recently reported by Baqi et al [12,13]. They observed that bone mineral density (BMD) and the concentrations of biochemical bone turnover markers were significantly more favorable in patients with TSH in the range of 0,35-6,3 mIU/mL than in those with TSH<0,3 mIU/mL which is consistent with the view that TSH itself possibly plays a positive role influencing the BMD in adult women [13]. This is however, not consistent with the results of our preliminary study because we observed similar P1NP and CTX concentrations in the group with TSH concentration <0,35 mIU/mL and these women with TSH of 0,35-4,94 mIU/mL. Differences may result because of the fact that in the study of Baqi et al women were without fractures whereas our subjects had fractures and because of small numbers of patients in both groups, only 5 and 29 with TSH of 0,35-4,94 mIU/mL.

In another study Murphy et al determined the relationship between thyroid status and bone parameters and fractures [1]. There was an increased bone turnover reflected by osteocalcin, P1NP and CTX concentrations in women with TSH below 0,5 mIU/mL compared to women with TSH of at least 0,5 mIU/mL. However, after adjusted regression analysis TSH was no longer associated with bone turnover [1]. Bauer et al found no consistent evidence that low TSH was associated with accelerated bone loss in older ambulatory women [3]. Those findings are similar to ours, because we also observed no relationship between TSH and bone formation and resorption markers in euthyroid postmenopausal women as well as in women with TSH concentration <0,35 mIU/mL. However, it is worth to note that in our subjects with fractures, whether they were euthyroid or had decreased TSH, bone resorption was as expected for their age (0,535 and 0,491 ng/mL, respectively) whereas bone formation was in the lower reference range (31,2 and 35,6 ng/mL). In the study of Martinez et al performed in a large cohort of Spanish postmenopausal women the mean concentration of P1NP in women between 70-85 years of age was found to be 43-50 ng/mL and mean concentration of CTX was 0,36-0,44 ng/mL [14].

Median TSH in a group with TSH within 0,35-4,94 mIU/mL was a little lower 0,96 (0,66-1,81) mIU/mL compared to women with vertebral fractures in Mazziotti study 1,1 mIU/mL (0,66-3,10) [2].

Our study had several limitations: a small number of euthyroid women with fractures and in the group with TSH concentration <0,35 mIU/mL, which may influenced on these preliminary results. As TSH concentration is characterized by a circadian rhythm and the blood collection should be performed at fasting state we could only include in the study those women in which blood collection was performed at the same time of a day. BMD and concentrations of thyroid hormones (fT4, fT3) were not measured; TSH was measured only once.

## CONCLUSIONS

We found no consistent evidence that in euthyroid postmenopausal women with osteoporotic fractures TSH concentrations within the reference range were associated with changes in bone turnover markers.

## ACKNOWLEDGMENTS

This work was supported by grant (MN-13WF) from the Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland.

## References

1. Murphy E, Glüer CC, Reid DM, Felsenberg D, Roux C, Eastell R, Williams GR. Thyroid function within the upper normal range is associated with reduced bone mineral density and an increased risk of nonvertebral fractures in healthy euthyroid postmenopausal women. *J Clin Endocrinol Metab.* 2010;95(7):3173-81
2. Mazziotti G, Porcelli T, Patelli I, Vescovi PP, Giustina A. Serum TSH values and risk of vertebral fractures in euthyroid post-menopausal women with low bone mineral density. *Bone.* 2010;46(3):747-51
3. Bauer DC, Nevitt MC, Ettinger B, Stone K. Low thyrotropin levels are not associated with bone loss in older women: a prospective study. *J Clin Endocrinol Metab.* 1997;82(9):2931-6
4. Agrawal M, Zhu G, Sun L, Zaidi M, Iqbal J. The role of FSH and TSH in bone loss and its clinical relevance. *Curr Osteoporos Rep.* 2010;8(4):205-11
5. Abe E, Marians RC, Yu W, Wu XB, Ando T, Li Y, Iqbal J, Eldeiry L, Rajendren G, Blair HC, Davies TF, Zaidi M. TSH is a negative regulator of skeletal remodeling. *Cell.* 2003 17;115(2):151-62.
6. Mazziotti G, Sorvillo F, Piscopo M, Cioffi M, Pilla P, Biondi B, Iorio S, Giustina A, Amato G, Carella C. Recombinant human TSH modulates in vivo C-telopeptides of type-1 collagen and bone alkaline phosphatase, but not osteoprotegerin production in postmenopausal women monitored for differentiated thyroid carcinoma. *J Bone Miner Res.* 2005;20(3):480-6
7. Martini G, Gennari L, De Paola V, Pilli T, Salvadori S, Merlotti D, Valleggi F, Campagna S, Franci B, Avanzati A, Nuti R, Pacini F. The effects of recombinant TSH on bone turnover markers and serum osteoprotegerin and RANKL levels. *Thyroid.* 2008;18(4):455-60.
8. Bauer DC, Ettinger B, Nevitt MC, Stone KL. Risk for fracture in women with low serum levels of thyroid-stimulating hormone. *Ann Intern Med.* 2001 3;134(7):561-8
9. Murphy E, Williams GR. The thyroid and the skeleton. *Clinical Endocrinology* 2004 61; 285–298
10. Lee JS, Buzková P, Fink HA, Vu J, Carbone L, Chen Z, Cauley J, Bauer DC, Cappola AR, Robbins J. Subclinical thyroid dysfunction and incident hip fracture in older adults. *Arch Intern Med.* 2010 22;170(21):1876-83
11. Gogakos AI, Duncan Bassett JH, Williams GR. Thyroid and bone. *Arch Biochem Biophys.* 2010 1;503(1):129-36
12. Baqi L, Payer J, Killinger Z, Hruzikova P, Cierny D, Susienkova K, Langer P. Thyrotropin versus thyroid hormone in regulating bone density and turnover in premenopausal women. *Endocr Regul.* 2010;44(2):57-63.
13. Baqi L, Payer J, Killinger Z, Susienkova K, Jackuliak P, Cierny D, Langer P. The level of TSH appeared favourable in maintaining bone mineral density in postmenopausal women. *Endocr Regul.* 2010;44(1):9-15
14. Martínez J, Olmos JM, Hernández JL, Pinedo G, Llorca J, Obregón E, Valero C, González-Macías J. Bone turnover markers in Spanish postmenopausal women: the Camargo cohort study. *Clin Chim Acta.* 2009;409(1-2):70-4