

Effect of combined treatment with calcitonin on bone densitometry of patients with treated hypothyroidism

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SUMMARY - INTRODUCTION. Thyroid hormones (TH) may affect bone metabolism and turnover, inducing a loss of bone mass among hyperthyroid and in hypothyroid patients under hormone replacement treatment. Thyroid dysfunction leads to changes in the dynamics of parathyroid hormone (PTH) and calcitonin (CT) secretion.

OBJECTIVE. The objective of the study was to determine the usefulness of CT as adjuvant therapy in the prevention of bone loss during the treatment of hypothyroidism.

MATERIAL AND METHODS. We studied 16 female patients with recently diagnosed primary hypothyroidism, divided into two groups: group G1 (n=8) submitted to treatment with thyroxine (L-T4), and Group 2 (n=8) that, in addition to being treated with L-T4, received a nasal CT spray. All

patients were submitted to determination of TSH, free T4, bone mineral densitometry (BMD) and total bone calcium (TBC) at the time of diagnosis, after 6 to 9 months of treatment, and after 12 months of treatment.

RESULTS. No statistical significant differences were detected in either group between the total BMD values obtained for the femur and lumbar spine before and after treatment. However, group G1 presented a statistical significant TBC loss after 12 months of treatment compared to initial values. In contrast, no TBC loss was observed in the group treated with LT-4 in combination with CT, a fact that may suggest that CT was responsible for the lower bone reabsorption during treatment of hypothyroidism.

KEYWORDS: Calcitonin. Osteoporosis. Hypothyroidism

INTRODUCTION

Thyroid hormones (TH) affect bone metabolism and turnover, increasing the number of bone remodeling cycles, activating and increasing the number of osteoclasts and altering the relation between bone reabsorption and bone formation^{2,5,24,25}. This effect induces a loss in bone mass in hyperthyroid individuals^{2,6,8,18,20,24} and also among hypothyroid patients submitted to hormonal replacement therapy^{2,5,7,18,29}.

Parathyroid hormone (PTH) is released by the parathyroid glands depending on serum calcium and its major action is to stimulate bone reabsorption through the osteoclasts¹. In hypothyroidism, basal PTH and its response to hypocalcemia are higher than in normal individuals, and this exaggerated response does not normalize even after 6 months of replacement treatment with TH^{8-12,33-35}.

Calcitonin (CT) is a hormone mainly produced by the parafollicular cells of the thyroid (C cells) and is a potent inhibitor of bone reabsorption; its secretion is stimulated by calcium. In hypothyroidism there is a lower CT reserve and its response to a hypercalcemic stimulus is significantly

reduced¹³, probably due to the destruction of C cells by the process of chronic thyroiditis. Hypothyroid patients, when starting hormonal replacement therapy, may present bone remodeling of high turnover owing to the action of TH. Mundy, in 1976²⁵, showed that CT inhibits TH-induced bone reabsorption in vitro. Since CT mainly acts by suppressing the osteoclastic activity of bone, it may be assumed that patients with osteoporosis involving a high turnover may benefit more rapidly from CT treatment than patients with less severe disorders of bone remodeling^{1,28}.

The aim of the present study was to assess the possible loss of bone mass occurring during treatment of hypothyroidism and to clarify the probable role of calcitonin in the prevention of osteopenia and its possible use as an adjuvant in the treatment of hypothyroidism.

MATERIAL AND METHODS

Patients: We studied 20 female patients with recently diagnosed primary hypothyroidism, seen at the Endocrinology Outpatient Clinic of UNIFESP-EPM from May 1993 to August 1995. The patients were matched for age and basal thyro-

Tabela 1 – BMD (Zscore) of the lumbar spine (L2-L4) and of the femoral neck in group G1 (median and range).

Initial		6 to 9 Months		12 Months	
Spine	femur	spine	femur	spine	Femur
-0.22	0.43	-0.13	0.29	0.00	0.03
(-0.86 to 0.64)	(-0.98 to 1.32)	(-0.95 to 0.55)	(-0.60 to 0.82)	(-0.92 to 0.46)	(-0.68 to 1.66)

Tabela 2 – BMD (Zscore) of the lumbar spine (L2-L4) and of the femoral neck in group G2I (median and range).

Initial		6 to 9 Months		12 Months	
Spine	femur	spine	femur	spine	Femur
0.30	0.12	0.51	0.03	0.66	0.27
(-3.05 to 3.33)	(-1.78 to 2.19)	(-2.96 to 4.06)	(-2.24 to 1.47)	(-2.68 to 3.22)	(-2.09 to 1.68)

tropin (TSH) and free thyroxine (T4L) concentration and divided into two groups. The patients in group G1 (n=10) received L-thyroxine at the dose of 1.6 to 2.0 µg/kg/day, while the patients in group G2 (n=10) received L-thyroxine at the same dose in combination with calcitonin nasal spray at the dose of 100 IU three times a week. The patients were submitted to determination of TSH and T4L, to bone densitometry of the lumbar spine (BMDc), of the femur (BMDf) and of the entire body (BMDt) and to determination of total bone calcium (TBC) at the beginning of the study, after 6 to 9 months and after 12 months of treatment. Four patients (two from each group) were excluded from the evaluations because of lack of compliance with treatment. All other patients continued to be euthyroid during follow-up.

Laboratory determinations: serum T4L and TSH were determined by an ultrasensitive immunofluorimetric method, using commercial Delfia kits (Pharmacia, Turku, Finland).

Bone densitometry: Bone densitometry was determined by DEXA using a LUNAR DPX-L densitometer. The results are reported as g/cm² and the z score standard deviation was used.

Statistical analysis: The Friedman test was applied to the changes obtained in BMDc, BMDf and BMDt data along time in each group. The initial and final BMDc, BMDf, BMDt, TBC and body weight values were compared by the Wilcoxon test in each group, and the Mann-Whitney test was used for comparison between groups. The level of significance was set at =.05 in all analyses.

RESULTS

No patients reported any complaints about complications and/or side effects caused by calcitonin. No statistical significant variation in body weight occurred in the patients of either group during the study. The initial median weight of G1

patients was 63,87 Kg (range: 52,0 - 73,0) and the median at the end of the study was also 63,87 Kg (range: 51,0 to 75,0). The initial median weight of G2 patients was 66,75 Kg (range: 49, 0 to 77,0) and the median at the end of the study was 64,5 Kg (range: 49,0 to 74,0).

No significant differences between groups were observed with respect to the initial values of BMDc, BMDf, BMDt and TBC.

No significant differences in total, spinal or femoral BMD (reported as g/cm² and z score) were observed during the study period within groups. Also, no significant differences were observed between initial and final values (Tables 1 and 2).

Group G1 presented a significant loss (P<0.01) of total bone calcium during the study period (Table 3), with significantly lower values (p<0.02) at 12 months (median 815 - range 680 to 980 g) compared to initial values (median 867.5 - range 713-980 g). In group G2 there was no statistical difference between the initial (median 876.5 ; range 626-1057 g) and end values (median 837.5 ; range 607-1011 g) of TBC.

DISCUSSION

Osteoporosis is a highly common skeletal disorder of multifactorial etiology which mainly affects women²³ and with important effects in terms of patient morbidity and mortality. Because of the multifactorial nature of the disorder, whenever possible the association of osteopenic factors should be avoided and, depending on the cause, treatment should be combined with pro-osteogenic or antireabsorptive drugs.

Changes in thyroid function affect the osteomineral metabolism^{7,15,17,28,36}, leading to changes in the dynamics of PTH and CT secretion^{8,11,13}, with a direct action of TH on bone tissue²⁵ as well as potentiation of the action of PTH on bone reabsorption³². In hypothyroid subjects, the dynamics

Tabela 3 – Total bone calcium (g) determined in group G1 patients

Patient no	Initial	at 6 to 9 months	at 12 months
1	830	807	807
2	883	825	815
3	852	806	815
4	713	713	680
5	969	909	895
6	885	884	891
7	806	798	799
8	980	971	969

Tabela 4 – Total bone calcium (g) determined in group G2 patients

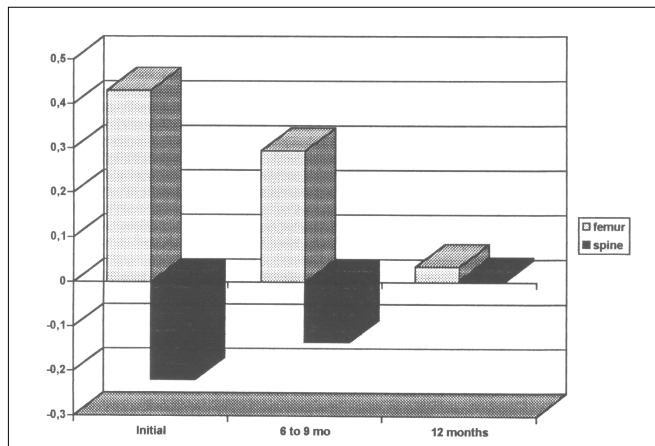
Patient no	Initial	at 6 to 9 months	at 12 months
1	882	856	845
2	871	829	828
3	1011	950	957
4	1057	1007	1011
5	626	618	607
6	812	802	830

of PTH secretion continues to be altered even after 6 months of euthyroid status¹¹, favoring the exposure of bone tissue to relatively high quantities of PTH associated with normal TH levels, with consequent greater bone reabsorption.

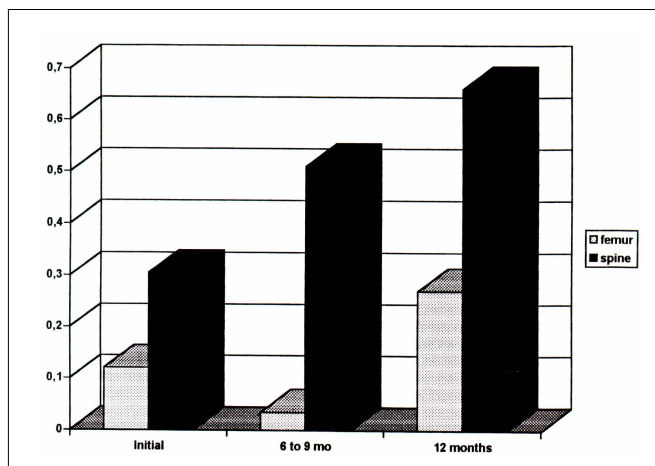
Calcitonin is a potent inhibitor of bone reabsorption and its partial or total deficiency may represent the loss of an important bone-protecting factor among patients, with bone tissue becoming more vulnerable to the action of hormones that stimulate its reabsorption. In hypothyroidism there is a lower calcitonin reserve, with a significantly decreased response to the hypercalcemic stimulus¹³, which justifies the therapeutic use of CT in hypothyroid patients under hormonal replacement treatment.

CT is an effective therapeutic agent in various diseases characterized by accelerated bone reabsorption²³. Its therapeutic use in the treatment of osteoporosis is questionable, although this pathology is frequently associated with an increase in bone reabsorption. Results obtained in patients with accelerated bone reabsorption treated with CT have shown normalization of the loss of bone mass similar to that obtained with the use of other bone reabsorption inhibitors (estrogens and bisphosphonates)³¹. Other reports have demonstrated an increase in bone mass in the vertebrae and long bones^{16,22,26}, a reduced fracture rate^{19,30} and relief of the syndromes accompanied by bone pain²¹.

Even though the evaluation of our patients did



Graf. 1 – BMD (Z score) of the lumbar spine (L2-L4) and of the femoral neck in group G1 (hypothyroid patients that received only L-thyroxine)



Graf. 2 – BMD (Z score) of the lumbar spine (L2-L4) and of the femoral neck in group G2 (hypothyroid patients that received L-thyroxine in combination with calcitonin)

not reveal a significant alteration of BMDt and of lumbar spine and femur BMD, the TBC measurement showed that hypothyroid female patients presented a significant bone calcium loss after 1 year of replacement treatment with TH (group G1).

The combined use of CT in the treatment of hypothyroidism seems to be useful for the prevention of greater bone loss, especially in patients with other risk factors for osteopenia. This was demonstrated by the follow-up of our G2 patients treated with CT in combination with thyroid hormone, who did not show a significant TBC loss after 1 year of treatment.

Evaluation of TBC is considered to be the most sensitive determination for the assessment of bone mass. It is expressed in grams and may present alterations with a change in patient body

weight. The patients in the two groups studied here did not present significant differences in weight during the study.

On the basis of these data, we may infer that a loss of bone calcium occurs in hypothyroid patients submitted to hormonal replacement, a fact that can be minimized when CT is administered in combination. Since CT is an antireabsorptive hormone, it is not expected to produce a significant increase in bone mass, but rather to maintain bone mass by the prevention or reduction of later bone losses²³. It has been demonstrated that the use of CT can stabilize or modestly increase the indices of cortical and trabecular bone mass and total bone calcium when administered to patients over a period of 1 to 2 years^{23,26,27}. Burckhardt & Burnand³ demonstrated that in all controlled studies in which CT was used there was a decrease in the rate of vertebral fractures, although the difference was not statistically significant.

As a potent antiosteoclastic drug, CT seems to be relatively harmless when compared to the potential complications caused by the other drugs used in the treatment or prevention of osteoporosis³⁷. Among the side effects reported with the use of CT, the most important ones are nausea, gastric discomfort and skin rashes¹, which, however, were substantially reduced when the nasal spray was introduced^{4,37}. None of the patients followed up by us complained about side effects of calcitonin.

Although our study followed the patients for one year, a more prolonged prospective study with a larger number of patients would be necessary to definitely confirm whether calcitonin is a hormone that could, or should, be added to the treatment of hypothyroidism, especially among patients with proven osteopenia.

ACKNOWLEDGEMENTS

The authors thank Dr. Marcus Magliano from Sandoz S.A. for his collaboration in Calcitonin (Miacalcic®) supplying.

RESUMO

Influência da terapêutica associada com calcitonina sobre a densitometria óssea de pacientes com hipotireoidismo tratado.

INTRODUÇÃO. Os hormônios tireoidianos (HT) podem influenciar o metabolismo e o "turnover" ósseo, induzindo perda de massa óssea em hipertiróides e em hipotiróides na vigência de reposição hormonal. As disfunções tireoidianas levam a alterações na dinâmica de secreção de parator-

mônio (PTH) e de calcitonina (CT).

OBJETIVO. Esclarecer a utilidade da CT como terapêutica coadjuvante na prevenção de perda óssea durante o tratamento do hipotireoidismo.

MATERIAL E MÉTODOS. Dezesseis pacientes do sexo feminino com hipotireoidismo primário recém-diagnosticados, divididos em dois grupos: grupo G1 (n=8) tratado com tiroxina (L-T4) e grupo G2 (n=8) que recebeu, além de L-T4, CT "spray" nasal. Todos os pacientes foram avaliados com TSH, T4 livre, densitometria mineral óssea (BMD) e cálcio ósseo total (TBC) ao diagnóstico após 6 a 9 meses de terapêutica e com 12 meses de tratamento.

RESULTADOS. Em ambos os grupos não foram encontradas mudanças estatisticamente significativas entre as medidas da BMD total antes e após o tratamento, assim como no fêmur e na coluna lombar. Entretanto, o grupo G1 apresentou perda significativa do TBC após 12 meses de tratamento em relação aos valores iniciais. Já no grupo que usou terapêutica associada com CT, não houve perda de cálcio ósseo total, o que pode sugerir que a CT foi responsável por uma menor reabsorção óssea durante o tratamento do hipotireoidismo. [Rev Ass Med Bras 2000; 46(2): 177-81]

NOTICE

The authors hereby confirm that neither the manuscript nor any part of it has been published or is being considered for publication elsewhere. By signing this letter each of us acknowledges that he or she participated sufficiently in the work to take public responsibility for its content.

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