Short focus on thyroid function in menopause: impact on bone health

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Summary

The assessment of thyroid status is particularly crucial in some phases of female life. For example, thyroid function in pregnancy had been largely investigated and nowadays its importance is widely recognized. Perimenopausal period seems to be even critical in the context of thyroid illness, not only for the consequences of thyropathies *per sé*, but also for the possible impact on climacteric symptoms.

KEY WORDS: bone loss; thyroid; menopause.

Physiological modifications of thyroid secretion, such as the reduced capability of iodine uptake and hormonal synthesis, were usually described in perimenopause (1-3). Besides, the increase of median level of reverse triiodothyronine (rt3) (the inactive form of thyroid hormone triiodothyronine T3) in association with related less free tetraiodothyronine (fT4) catabolism, tend to raise Thyroid Stimulating Hormone (TSH) above normal upper level (3). These events represent the possible explanations for increase of diagnosis of overt or subclinical hypothyroidism observed in that period. At the same time, thyroid autoimmune diseases have been reported to be slightly more common in menopause (1). Lowering progesterone may be involved in this phenomenon, as it is usually considered one of the most important regulator of autoimmune activity (4).

Although thyroid hormones (TH) are not directly involved in pathogenesis of menopausal complications, some consequences of climacterium, like coronary atherosclerosis and bone loss, may be aggravated by thyroid alterations (5).

In particular, overt or subclinical hyperthyroidism, likely due to autoimmune disease (Graves-Basedow) or iatrogenic - usually produced by inappropriate suppressive therapy with TH strongly reducing TSH, in order to prevent relapse of thyroid cancer after surgical treatment of differentiated thyroid carcinoma or enlargement of thyroid nodules in thyroid goiter is an important condition to be avoided in menopause (6). In fact, chronic excess of circulating TH may induce a reduction of bone strenght, changing mineral and energy metabolism (6). Higher level of TH usually causes higher bone turnover state, shortening bone remodeling cycle in favour of increased resorption: in that manner, the duration of bone formation process becomes insufficient to ensure an adequate bone mineralization, leading to increased bone fragility and fracture risk (6).

It is well known overt hyperthyroidism, such as peripheral excess of TH (fT4 and fT3) with TSH below its reference range, may cause osteoporosis and higher fracture risk in adults: however, bone loss resulting from untreated thyrotoxicosis is now rare, because of early diagnosis and treatment of that severe clinical condition (6).

In the case of subclinical hyperthyroidism, occurring when fT4 and fT3 levels are within their reference ranges, but TSH concentration is suppressed, most studies evaluating premenopausal women did not show significant consequences on BMD, at any anatomical site, of TSH- suppression therapy (7). Despite this, data on bone strenght about levothyroxine therapy used for this scope before climacteric period remain controversial.

On the contrary, there are important evidences about the endogenous and/or exogenous excess of TH in postmenopause (8). Different population studies about postmenopausal women with subclinical hyperthyroidism revealed:

- increased bone turnover
- reduced BMD
- increased fracture risk.

A recent large meta-analysis of data from 70,298 patients showed TSH value below 0.01 mU/L was associated with a 2- and 3.5-fold increased risk of hip and spine fractures, respectively (8). Another study demonstrated fracture risk significantly increased for each standard deviation unit decrease in TSH (hazard ratio 1.45, $p < 0.001$ for hip fracture; HR 1.32, $p< 0.001$ for major osteoporotic fracture) in euthyroid subjects (8).

As concerns the impact of higher levothyroxine dosage on bone health, it seems to be more clear in the elderly (> 70 years). In that population, higher suppression of TSH was associated with a 2-fold to 3-fold increased risk of fractures (8).

Another 1-year prospective study of 93 women with differentiated thyroid cancer showed that TSH-suppressive therapy resulted in accelerated bone loss in postmenopausal women, underlying the possible deleterious effect on bone metabolism of high-dose of TH required in these cases to prevent tumor recurrence (9). However, these aspects need to be further elucidated because of the great heterogeneity of data and dosage used in different studies (9).

In an interesting manner, Murphy et al. (10) observed in 1278 healthy euthyroid postmenopausal women, higher fT4 and fT3, even in the euthyroid reference range, were associated with lower femoral bone mineral density (BMD) and increased risk of non-vertebral fractures by 20% ($p= 0.002$) and 33% ($p= 0.006$) respectively. However, also these findings need to be further elucidated.

It would be advisable to assess thyroid status in perimenopausal period, especially in symptomatic women, not only to exclude overt or subclinical hyperthyroidism and prevent its possible negative effect on bone, but also as some typical climacteric symptoms due to hormonal fluctuations – like hot flashes, tachycardia, sleeplessness – can be confused or exacerbated in presence of any thyroid hyperfunction (2).

Estrogen Therapy (ET) (for postmenopausal women who have had hysterectomies) or Hormone Replacement Therapy (HRT) (for postmenopausal women with intact uteri), if not contraindicated, is fundamental to treat vasomotor symptoms. In case of oral ET/HRT assumption in women with every kind of thyroid dysfunction, the effect of estrogens on thyroid status should be considered, as they can theoretically produce modifications of TSH, fT3 and fT4 because of augmented Thyroxine Binding Globulin (TBG) partly linking circulating TH, due to its hepatic first-pass effect. That phenomenon may produce an increase of levotiroxine dosage requirements of women being treated for hypothyroidism, owing to the possible reduction of the free bioactive fraction of circulating thyroxine (2). It should be useful to periodically assess thyroid function, in the first year of treatment with ET/HRT, even if follow-up of each thyropathy requires anyway regular follow-up. In some patients, the choice of transdermal ET/HRT which do not influence the bound fraction of TH, may represent a valid option to reasonably customize therapy (2).

However, the co-occurrence of thyroid disease should not influence the decision to initiate HT, and the treatment must be conducted according to generally recognized international standards (2).

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