

## REVIEW

# Fragility fractures in older persons with altered thyroid function

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Thyroid hormones are pleiotropic peptides with complex action on the human economy. The skeleton is a target tissue for thyroid hormone's action, which is illustrated by the consequences of thyroid hormone excess and deficiency during development and during aging. Thyroid disorders are more frequently observed in older than in younger persons. Thyrotoxicosis is an established cause of secondary osteoporosis. Overt hyperthyroidism and iatrogenic hyperthyroidism due to over-replacement of thyroid hormone may result in fragility fractures. Endogenous or exogenous subclinical hyperthyroidism is associated with reduced bone density, especially in cortical bone in older women. Fragility fracture risk seems to be closely related to the degree of thyroid-stimulating hormone suppression and to other risk factors, including older age. Overt hyperthyroidism and endogenous subclinical hyperthyroidism in older persons should be treated to reduce the risk for fragility fractures, atrial fibrillation and related mortality risk. The risk for fragility fractures in older people, especially in postmenopausal women, taking suppressive doses of levothyroxine for thyroid cancer can be diminished by treatment with the minimal effective suppressive dose and in some cases, by adding an antiresorptive or bone forming therapy where indicated. Replacement therapy for overt hypothyroidism should be regularly adjusted to avoid TSH suppression and consequent increased risk of fragility fractures.

**Key words:** Aging, Fracture, Thyroid, Osteoporosis, Hip fracture, Subclinical hyperthyroidism

## INTRODUCTION

The relationship between thyroid function and bone has been empirically known for ages. Even if only in 1883 the Nobel Laurate Theodor Kocher defined “cachexia strumipriva” as an illness characterized by decreased growth and height after thyroidectomy <sup>1</sup>, the use of burnt sponge and seaweed in the treatment of goiter started as early as 1600 BC in China <sup>2</sup>. The description of “cachexia strumipriva” finally led to the first substitution therapy with thyroid tissue preparations in 1891 by George Murray <sup>3</sup>; however, there is evidence that thyroid tissue was used as a treatment for goiter as early as the VII century AD in China. Also in 1891, Friedrich Von Recklinghausen reported for the first time a young woman who died from thyrotoxicosis with multiple fractures, and described the associated “worm

eaten” appearance of long bones <sup>4</sup>, identifying for the first time the relationship of thyroid hyperfunction and bone fragility fractures (FF) in the adult skeleton. The clinically overt hyperthyroid bone disease became less frequent after the introduction of effective treatment for hyperthyroidism with antithyroid drugs, surgery and radioiodine in the 1940's <sup>5</sup>. Nevertheless, bone loss and FF have been reported recently associated with overt and subclinical hyperthyroidism caused either by nodular toxic goiter or, more frequently, by over-replacement of thyroid hormone. Postmenopausal older women, who constitute a substantial portion of those on thyroid hormone, are remarkably prone to accelerated bone loss, while inadequately high doses of thyroid hormone may further increase their already high risk for FF. Fragility fractures embody a major public health concern expected to continue increasing due to aging of

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the population <sup>6</sup>. The substantial burden associated with FF is caused by derived morbidity and disability, which also entail high social costs. Fragility fractures significantly compromise patients' quality of life and financially overwhelm health care systems. Over half of patients never regain their previous functional capacity after a hip fracture and near one quarter move to long-term care facilities <sup>7</sup>. One year mortality rates after hip fracture are estimated as 14-36% <sup>6,8</sup>. The direct costs of FF in the US were estimated in 19 billion dollars (2005) with an expected 50% increase by 2025 <sup>9</sup>. The cost of osteoporosis in the EU in 2010 was estimated at € 37 billion, while in Italy it was estimated at near € 7 billion <sup>6</sup>. Major risk factors for osteoporosis include age, reduced physical activity, previous FF, a family history of osteoporotic fracture, the use of corticosteroids, and alcohol abuse <sup>10</sup>. Altered thyroid function, more frequently observed in older than in younger persons, is also a risk factor for FF, which can be particularly unfavorable in older people. Its detection and treatment is crucial especially because it is a potentially reversible cause of FF. The present review briefly explores the relationship of thyroid function alterations and fragility fracture risk in older age.

## THYROID FUNCTION, BONE, AND AGING

The direct action of thyroid hormone on the skeleton is certainly evidenced by the delayed epiphyseal development and poor growth of infants with congenital hypothyroidism or with thyroid hormone resistance <sup>11</sup>. Skeletal tissue expresses all isoforms of thyroid hormone receptor (TR), which possibly interact with other nuclear receptors (i.e., vitamin D and retinoids receptors) <sup>12,13</sup>. Circulating osteocalcin levels and mRNA are associated with thyroid status, with osteocalcin mRNA expression in bone being stimulated by the active thyroid hormone 3,5,3'-L- triiodothyronine (T3) in specific locations, such as the hip, which is particularly predisposed to osteoporosis in hyperthyroid patients <sup>13</sup>. Studies in mutant mice have established the concept that T3 has anabolic actions during growth and catabolic effects on adult bone. Thyroid-stimulating hormone (TSH) receptor is expressed in many extrathyroidal tissues including bone and it has been suggested that TSH may have direct actions on bone turnover <sup>14</sup>, and on immunomodulatory responses in the bone marrow <sup>15</sup> and bone cells <sup>16</sup>. Actions of T3 and TSH in osteocytes have not been investigated; in chondrocytes, T3 inhibits proliferation and stimulates chondrocyte differentiation, while TSH may inhibit proliferation and matrix synthesis; T3 stimulates bone resorption but it is currently uncertain whether T3 acts directly in osteoclasts or indirectly

via its effects on the osteoblasts. Most studies indicate that T3 stimulates osteoblast differentiation and bone formation, while there is inconsistent observations suggesting that TSH may stimulate, inhibit or have no effect on osteoblast differentiation and function <sup>17</sup>. Thyroid hormone metabolism in the osteoblast is a fine tune mechanism for the maintenance of intracellular T3 concentrations, through the expression of deiodinases D2 (activator) and D3 (inactivator), which activities vary in the euthyroid, hypothyroid or hyperthyroid state <sup>18</sup>. In organ culture, T3 directly stimulates bone resorption <sup>19</sup>, most probably through nuclear TR <sup>20</sup>. Studies in experimental animals lacking TR-alpha or TR-beta suggest that bone resorption is mediated by TR-alpha <sup>21</sup>. Thyroid hormone may alter calcium metabolism by a direct action on osteoclasts, or via its action on osteoblasts, which consecutively stimulate osteoclastic bone resorption <sup>22</sup>. Another mediator of thyroid hormone-stimulated bone loss is the elevated concentration of interleukin-6 in hyperthyroidism <sup>23</sup>. Table I summarizes the effects of thyroid hormone deficiency or excess on bone turnover, growth, bone mass and fracture risk.

## THYROID HYPERFUNCTION IN OLDER AGE

Thyroid disorders are more common in older than in younger populations, predominantly in women, and they are frequently disregarded because their signs and symptoms often mimic age-associated modifications or disease of other organs. For example, hypothyroidism may induce or worsen cognitive and physical decline, constipation, cold intolerance, body weight gain, and anemia or lipid disorders, all frequently observed in euthyroid older people. Likewise, thyroid hyperfunction may manifest as arrhythmia and congestive heart failure, which may be interpreted as the expression of cardiac disease, very frequent in old age. Weight loss associated with hyperthyroidism may be taken as part of the normal aging process, undernutrition or neoplasia, also frequent in old age. Thyroid hyperfunction may as well be asymptomatic or "apathetic" presented merely with subtle signs, again frequently misinterpreted as normal age-associated changes, or as reduced thyroid function. Indeed, older people may have similar manifestations that correspond to increased or decreased thyroid function, such as, mental confusion, depression, falling and FF, walking disturbances, urinary incontinence from immobility, congestive heart failure, constipation or diarrhea. These signs also correspond to other disorders commonly observed in older people <sup>24</sup>. Overt or, more frequently, subclinical hyperthyroidism may increase significantly the risk for FF, which may be ascribed to other risk factors present in older people.

Hyperthyroidism is found in 0.5% to 3% of all older patients<sup>25-27</sup>. These numbers are higher when considering older people living in long-term care facilities, even if studies in this setting are few and most include a limited number of patients<sup>28</sup>. It is noteworthy that in two studies<sup>29,30</sup> unnecessary therapy with levothyroxine was disclosed in 15.4%<sup>29</sup> and 50%<sup>30</sup> of nursing home residents, with important implications for health and quality of life, perhaps increasing the risk for FF and atrial fibrillation in this already high risk population. Hence, the detection of subclinical thyroid dysfunction, and overt disease, is essential to correctly identify the subjects at true risk. It is also possible that subtle thyroid alterations in younger people may evolve to overt clinical manifestation during aging. For example, non-toxic goiter starting as a diffuse thyroid enlargement during early life may acquire nodularity and autonomous function with aging and may progress, although not frequently, to toxic nodular goiter. Before becoming clinically apparent, toxic goiter may show only slight laboratory modifications conforming subclinical states of thyroid dysfunction. Comorbidity and polypharmacy may further mask or mimic the presentation of thyroid disease. The lack of evident clinical manifestations of thyroid dysfunction in the older adults requests an attentive clinical evaluation and a high index of suspicion to identify their presence, with the appropriate confirmation by means of reliable laboratory testing. Nevertheless, thyroid tests may also have minimal changes with age and caution in the interpretation of such changes is warranted<sup>24</sup>.

#### OVERT HYPERTHYROIDISM

This condition is certainly associated with accelerated bone turnover, decreased bone mineral density (BMD) (reported as 10-28%), and increased fracture rate. BMD reduction may or may not be reversible with hyperthyroidism therapy. Overt hyperthyroidism is associated with hypercalciuria and, infrequently, hypercalcemia. A histomorphometric study showed a small reduction in trabecular bone volume (-2.7%) with a marked increased cortical bone resorption (+40%) and porosity (+32%), with no changes in osteoid volume<sup>31</sup>. Osteoclastic resorption is strikingly activated overcoming osteoblastic action with a 50% reduction in the cycle duration and about 10% loss of mineralized bone in each cycle<sup>32</sup>. Conversely, there is a 17% increase in mineralized bone for each cycle in hypothyroidism. Some studies have shown normalization of BMD after treatment of hyperthyroidism<sup>33-36</sup>. However, there are other studies reporting only partial recovery of BMD after treatment<sup>37-41</sup>. A more recent cross-sectional study showed that women with a past history of hyperthyroidism had a higher prevalence of BMD in the range of osteoporosis<sup>42</sup>. The heterogeneity of these results

is probably due to different duration of hyperthyroidism before treatment, various time intervals of follow up, and diverse techniques and sites of BMD. Even with the variability of BMD, a past history of hyperthyroidism increases the risk for FF<sup>(43-45)</sup>, and may help to explain the higher later mortality in these patients<sup>46</sup>. Interestingly, a study showed that hyperthyroid patients treated with radioiodine had an increased risk of forearm and vertebral fractures compared to patients also treated with methimazole, in whom there was no increase in fractures<sup>47</sup>. This may reflect a tendency of overtreatment in patients with levothyroxine replacement therapy after radioiodine ablation. Likewise, a prospective study of women aged over 65 years followed for 3.7 years showed that those with TSH lower or equal to 0.1 mU/L at baseline had an increased risk for hip (RR = 3.6) and vertebral (RR = 4.5) fractures<sup>48</sup>. Increased bone resorption in patients with hyperthyroidism may lead to hypercalcemia (although not frequently), reduction of parathyroid hormone secretion, and hypercalciuria with a consequent negative calcium balance<sup>49</sup>, and reduced activation of 25-OH-vitamin D<sup>50</sup>. Osteoprotegerin<sup>51</sup>, fibroblast growth factor-23<sup>52</sup>, and urinary excretion of bone collagen-derived pyridinium cross-links<sup>53</sup> have been found increased in overt hyperthyroidism.

Therefore, patients with overt hyperthyroidism should receive adequate amounts of dietary or supplemental calcium and vitamin D.

#### SUBCLINICAL HYPERTHYROIDISM

The finding of TSH levels below 0.45 mU/L in the presence of thyroid hormones in the normal or high borderline range is indicative of subclinical hyperthyroidism, which is more frequent than overt disease<sup>54,55</sup>. The most common causes of subclinical hyperthyroidism are an initial Graves' disease, initial nodular toxic goiter, excessive TSH suppressive therapy with levothyroxine for benign thyroid nodular disease or for differentiated thyroid cancer, or hormone over-replacement in patients with hypothyroidism. However, other causes of a low TSH, such as non-thyroidal illness, fasting, and the use of drugs (i.e., glucocorticoids) should be excluded before making the diagnosis. Subclinical hyperthyroidism in older people may be associated with relevant signs and symptoms of excessive thyroid hormone action, and in particular, with an increased risk of FF, atrial fibrillation, and increased mortality risk<sup>24,54,55</sup>. Indeed, it is becoming increasingly apparent that subclinical hyperthyroidism may decrease BMD and accelerate the development of osteoporosis and FF, particularly in postmenopausal women with a preexisting predisposition<sup>56,57</sup>; hence, patients with low TSH levels should be carefully evaluated (Fig. 1).

A study investigating nursing home residents with low

**Table I.** Summary of effects of thyroid hormone deficiency or excess on bone turnover, growth, bone mass and fracture risk.

	<b>Hypothyroidism</b>	<b>Hyperthyroidism</b>
<b>Bone turnover</b>	Reduced	Increased
<b>Bone remodeling cycle</b>	Prolonged	Reduced
<b>Young skeleton</b>		
• <b>Growth velocity</b>	Reduced	Increased
• <b>Bone mineralization</b>	Reduced	Increased
• <b>Bone age</b>	Reduced	Increased
• <b>Final height</b>	Reduced, disproportioned	Reduced, proportioned
<b>Adult skeleton</b>		
• <b>Bone mass</b>	Increased	Reduced
• <b>FF risk</b>	Increased (by stiffness)	Increased (by fragility)

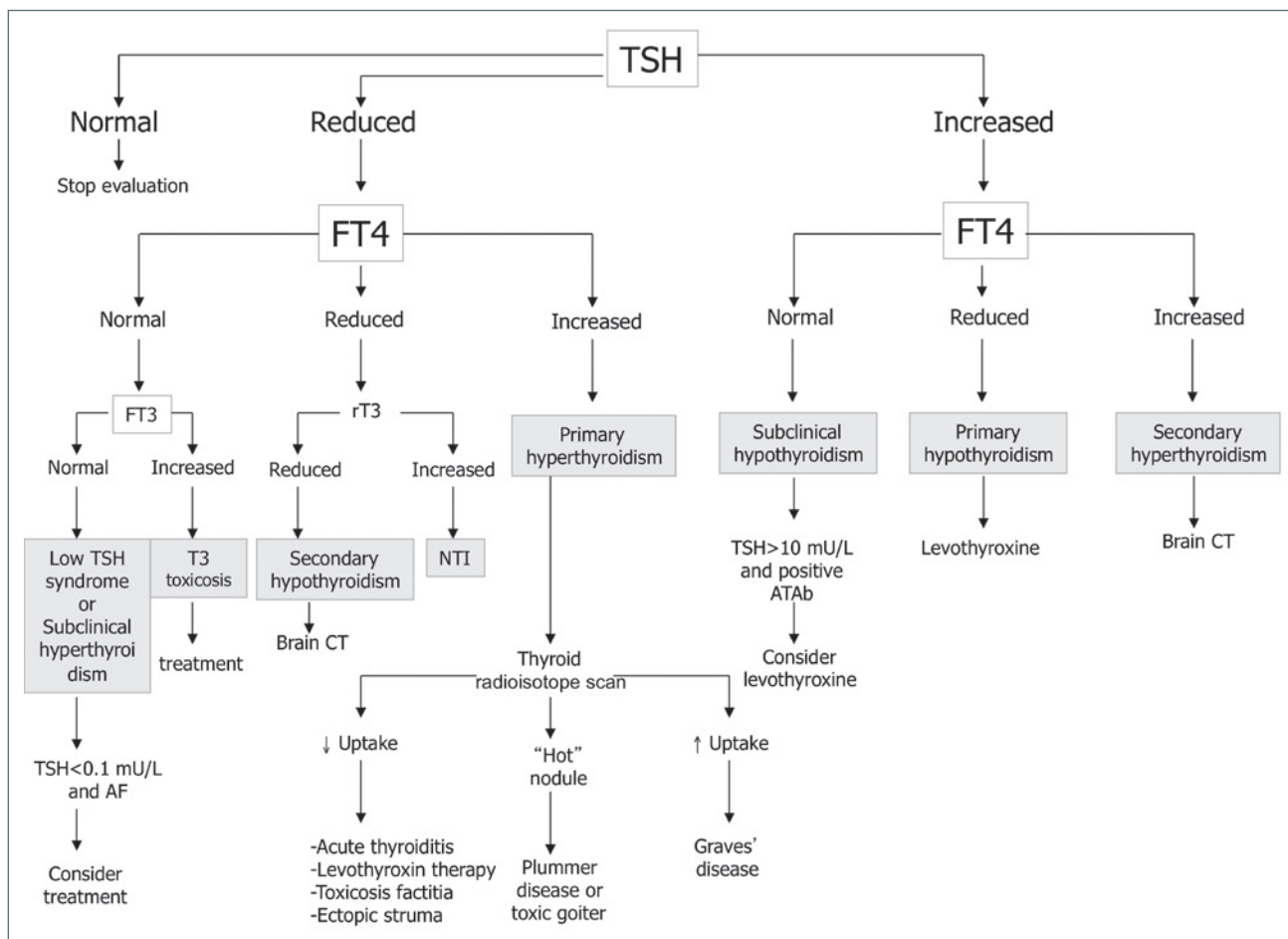
TSH and normal total 3,5,3',5'-L-tetraiodothyronine (thyroxine, T4) levels showed that only 3 out of 40 patients with subclinical hyperthyroidism became overt hyperthyroid. However, 17.5% of patients with subclinical hyperthyroidism died during the first 4 months of follow-up compared to 7.5% in a control group<sup>58</sup>. In a meta-analysis of studies in men with subclinical hyperthyroidism, excess all-cause mortality was related to the years since diagnosis and to advanced age<sup>59</sup>. There are variable results regarding BMD and subclinical hyperthyroidism, but most suggest an associated low BMD<sup>56,60</sup>. Interestingly, in healthy euthyroid postmenopausal women from the Osteoporosis and Ultrasound Study (OPUS) those in the highest quintile of normal free T4 (FT4) at baseline had lower BMD after 6 years of follow-up compared with women in the lowest quintile of FT4<sup>61</sup>. A recent meta-analysis of 13 prospective cohort studies from the US, Europe, Australia, and Japan (n = 70,298), compared participants with euthyroidism (TSH 0.45-4.49 mIU/L) to those with endogenous subclinical hypothyroidism and hyperthyroidism in the incidence of FF after a median follow-up of 12.1 years. Considering all participants and after adjusting for age and sex, there was a significant increased risk of hip (HR = 1.36, 95% CI:1.13-1.64), and any (HR = 1.28, 95% CI:1.06-1.53) fracture for participants with subclinical hyperthyroidism vs. euthyroidism. The increased risk was even higher for those with TSH < 0.10 mIU/L (HR = 1.61, 95% CI:1.21-2.15 for hip fracture; HR = 1.98, 95% CI:1.41-2.78 for any fracture; HR = 3.57, 95% CI:1.88-6.78 for vertebral fracture). For endogenous subclinical hyperthyroidism (excluding those on thyroid medications) there was an increased risk of hip (HR = 1.52, 95% CI:1.19-1.93), any (HR = 1.42, 95% CI 1.16-1.74), and vertebral (HR = 1.74, 95% CI 1.01-2.99) fractures<sup>62</sup>. No association was found between subclinical hypothyroidism and

fracture risk. Besides the effects of thyroid hormone on bone turnover and BMD, which may help explain the increased FF incidence, it is pertinent to consider also an increased risk of falls through effects on muscle strength and coordination.

In view of the fact that subclinical hyperthyroidism and its related clinical manifestations are reversible, may cause in some cases significant morbidity and mortality, and may be prevented by timely treatment, it is important to consider the possible benefit of treatment on an individual basis. Most authors agree regarding considering treatment of older patients with subclinical hyperthyroidism and a clearly suppressed TSH level (< 0.1 mIU/L) and follow up for patients with TSH levels between 0.1 and 0.4 mIU/L<sup>54,55</sup>. Further studies are needed to determine whether treating subclinical hyperthyroidism can prevent fractures.

## EXOGENOUS THYROID HORMONE THERAPY

Subclinical hyperthyroidism due to levothyroxine therapy is not uncommon, with potential increased bone resorption, reduced BMD, and increases FF risk. The risk of FF seems to be linked to the degree of TSH suppression and to other factors (i.e., advanced age), which further increase that risk. There are variable results regarding BMD changes associated with over-replacement with thyroid hormone therapy. However, most studies have demonstrated that even moderate suppressive doses of T4 can cause bone loss in postmenopausal women. Two meta-analyses of studies exploring BMD in patients with subclinical hyperthyroidism due to T4 therapy are available<sup>63,64</sup>. A significantly reduced BMD was found only in postmenopausal women, similar to previous findings in cross-sectional studies. The meta-analysis by Uzzan et al. found a reduced BMD



**Figure 1.** Algorithm for the diagnosis of altered serum TSH concentrations. TSH: thyroid stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; rT3: reverse triiodothyronine; AF: atrial fibrillation; NTI: non-thyroidal illness; ATAb: anti-thyroid antibodies.

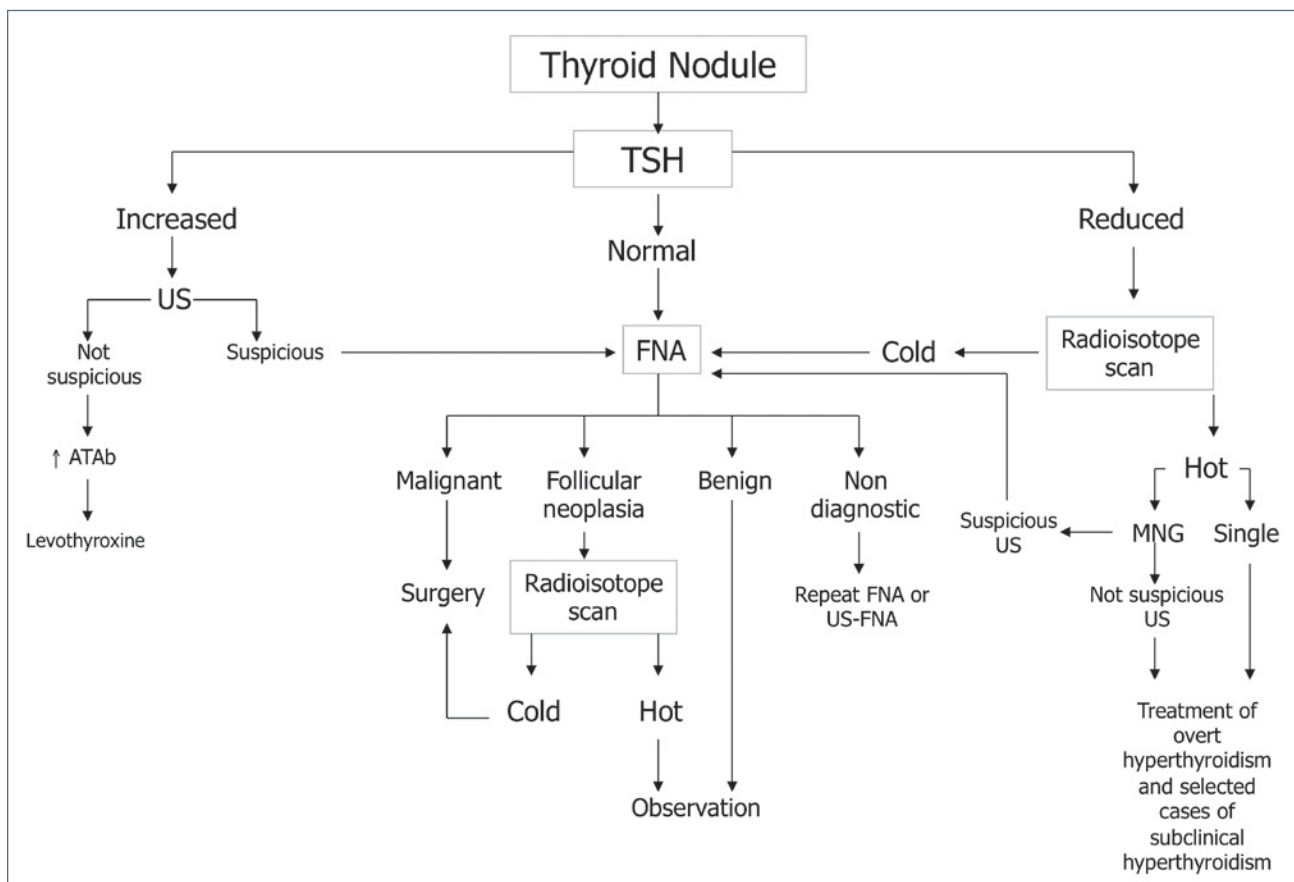
in postmenopausal and also in premenopausal women with levothyroxine replacement therapy<sup>64</sup>.

Regarding FF risk, the results are not uniform with some<sup>48,65</sup> but not all<sup>66</sup> studies showing an increased fracture risk in patients with subclinical hyperthyroidism due to exogenous thyroid hormone therapy. The inconsistent results may be due to diverse populations studied and different degrees of TSH suppression. For example, in a study involving 17,648 patients on levothyroxine therapy those with undetectable TSH had a twofold increased risk of FF when compared to those with TSH between 0.04 and 0.4 mU/L<sup>65</sup>.

A study involving 1,180 patients on levothyroxine therapy showed that near 60% had a TSH < 0.05 mU/L<sup>66</sup>. In this study, even if women aged over 65 years with suppressed TSH values had 2.5% FF vs 0.9% of those with normal TSH values, the difference did not reach statistical significance. In another study of 686 women aged over 65 years, those with TSH ≤ 0.1 mU/L had a 4-fold increased risk of FF vs. those with normal TSH<sup>48</sup>.

## THYROID NODULE AND LEVOTHYROXINE THERAPY

Most of thyroid nodules (~ 95%), which occur with increasing frequency in older age, are benign. Nonetheless, clinical evaluation has been considered for all thyroid nodules given the potential risk of evolving into thyroid malignancy (Fig. 2). The prevalence of palpable thyroid nodules is near 5% in women and 1% in men living in iodine-sufficient areas. Conversely, the prevalence increases to 19-68% for thyroid nodules detected by high-resolution ultrasound, with higher frequency in women and older people<sup>67,68</sup>. It has been estimated that approximately 7-15% of thyroid nodules may evolve into thyroid malignancy depending on sex, age, history of radiation exposure, and family history among others<sup>69,70</sup>. The risk of malignancy is similar for solitary nodules and multinodular goiters; urgent referral to secondary care is necessary only if the nodule is growing rapidly (over few weeks) or associated with stridor,



**Figure 2.** Algorithm for the diagnosis and management of thyroid nodule. FNA: fine-needle aspiration; MNG: multinodular goiter; TSH: thyroid-stimulating hormone; US: ultrasound; ATAb: anti-thyroid anti-bodies.

hoarseness, or cervical lymphadenopathy<sup>71</sup>. Generally, goiter size increases with aging and thyroid nodularity develops, with the largest goiters observed in the oldest age groups living in iodine deficient areas. The prevalence of diffuse and nodular goiter in young adults participating in an iodine deficient area survey (Pescopagano study) was 30% in young adults and increased up to 75% in the age group 55-65 years, with nodular goiter accounting for about one third of the total<sup>72</sup>. Multinodular goiter, usually longstanding, is frequently seen in old age, and thyroid hormone suppressive therapy not only is not indicated but may contribute to exogenous hyperthyroidism with heart and bone adverse effects. A nodule(s) in multinodular goiter may become autonomous with aging and progress to overt thyrotoxicosis, while large goiters may cause obstructive symptoms. The physical examination of women with goiter may be complicated by hyperkyphosis and changes in posture associated with osteoporosis; if the thyroid gland can be palpated in an older woman, it is probably enlarged. Calcification of large goiters may be associated to dyspnea, dysphagia, or dysphonia

and can be misdiagnosed as cancer metastases to lymphoid nodes, hence, Fine-needle aspiration biopsy (FNA) is recommended to determine the nature of calcified lesions<sup>73</sup>.

According to the American Thyroid Association (ATA) guidelines, thyroid ultrasound should not be performed as a screening test; however, patients with a palpable thyroid nodule should undergo ultrasound examination. Management depends mainly on the results of FNA but should also take into consideration the clinical and ultrasound features. Solid hypoechoic nodules and nodules with suspicious sonographic appearance (irregular margins, microcalcifications, taller than wide shape, rim calcifications, or evidence of extrathyroidal extension) should undergo FNA when  $\geq 1$  cm (as determined by largest dimension). Nodules with sonographic appearance suggesting a low risk for thyroid cancer can be undergo FNA when larger ( $\geq 1.5$  to 2 cm). Spongiform nodules  $\geq 2$  cm could also be evaluated by FNA, although observation without FNA is an alternative option<sup>74</sup>. When a goiter is asymptomatic, follow-up is the choice, while treatment is necessary in case of toxic

goiter or compressive symptoms.  $^{131}\text{I}$  is the first choice treatment for thyroid autonomy and hyperthyroidism, whereas surgery is advised for large non-toxic goiters causing significant compressive symptoms.  $^{131}\text{I}$  therapy has been proposed in order to reduce thyroid volume in non-toxic goiters, with satisfactory results, even in the presence of structural and functional heterogeneity, and large variability in  $^{131}\text{I}$  dose. Pretreatment with recombinant TSH (rhTSH) may increase the efficacy of  $^{131}\text{I}$  therapy <sup>75</sup>. FNA is the most accurate method in the evaluation of a thyroid nodule, helping to determine which patients should be referred for surgery. Its accuracy is improved by high-resolution ultrasound guidance, which can also add useful information <sup>71</sup>.

Thyroid cancer is mostly (> 90%) differentiated, which includes papillary and follicular cancer <sup>76</sup>. Thyroid cancer in old age is also generally well-differentiated, but their course is frequently less predictable than in younger patients. Lymphoma of the thyroid and undifferentiated cancers, even if rare, occur with increasing frequency in old age. The incidence of thyroid cancer in the US has tripled from 1975 to 2009 with most of new cases being papillary thyroid cancer. The proportion of tumors lower or equal to 1 cm was 25% in the period 1988–1989 vs + 39% in 2008–2009 <sup>77</sup>. This may be attributable to the rising use of neck ultrasonography and other imaging techniques, which may help to improve the long-term health outcomes for patients with thyroid neoplasms. However, a comprehensive and rational evaluation of thyroid nodule is needed to avoid excessively alarming the patients and improper overuse of imaging exams.

A recent prospective, multicenter, observational study included 992 consecutive patients with 1 to 4 asymptomatic ultrasound and cytologically benign thyroid nodules. Participants were recruited from eight hospital-based thyroid-disease referral centers in Italy between 2006 and 2008. Available results correspond to the first 5 years of follow-up. The primary end point was nodule growth assessed with yearly thyroid ultrasound. Significant size changes were considered as  $\geq 20\%$  modifications in at least two nodule diameters, with a minimum increase of 2 mm. Baseline factors associated with nodule growth were identified. Secondary end points were the sonographic detection of new nodules and the diagnosis of thyroid cancer during follow-up. From the 1,567 original nodules, only 174 (11.1%) increased in size. Nodule growth was associated with the presence of multiple nodules (OR, 2.2 for 2 nodules; OR, 3.2 for 3 nodules; and OR, 8.9 for 4 nodules), and male sex (OR, 1.7). Age equal or higher than 60 years was associated with a lower risk of nodule growth compared to nodules in persons younger than 45 years (OR, 0.5). Thyroid cancer was diagnosed in 5 original nodules (0.3%), and only two of them had grown. New nodules developed

in 93 patients (9.3%), with detection of only one cancer. Therefore, in this large prospective study, the majority of ultrasound or cytologically benign thyroid nodules exhibited no significant size increase during 5 years of follow-up and thyroid cancer was rare <sup>78</sup>. These findings strongly supported consideration of revision of current guideline recommendations for follow-up of asymptomatic thyroid nodules. In the latest ATA guidelines, recommendation 25 explicitly states that “routine TSH suppression therapy for benign thyroid nodules in iodine sufficient populations is not recommended. Though modest responses to therapy can be detected, the potential harm outweighs benefit for most patients (Strong recommendation, High-quality evidence)” <sup>74</sup>. Ultrasound monitoring of benign thyroid nodules is initially recommended at 12 months, then at increasing intervals (e.g., 2 to 5 years, with the shorter interval for large nodules or nodules with suspicious ultrasound features and the longer interval for smaller nodules with benign ultrasonographic features). Repeated FNA might be performed only when there is substantial growth (> 50% change in volume or 20% increase in at least two nodule dimensions), new suspicious ultrasound features, or new symptoms attributed to a nodule.

## TSH SUPPRESSION IN THYROID CANCER

Another important issue regards the cardiac and skeletal effects of long-term TSH suppression used to reduce thyroid cancer recurrence. According to recent guidelines from the ATA, it is necessary to consider age, the presence of preexisting cardiovascular and skeletal risk factor, and the aggressiveness of thyroid cancer to decide the TSH target, and to better balance the benefit vs. the potential adverse effects of long-term TSH suppression. In addition, adequate intake of calcium and vitamin D to prevent osteoporosis should be encouraged <sup>79</sup>. Many authors in the past have recommended that patients with thyroid cancer should maintain very low serum TSH concentrations (less than 0.01 mU/L). However, in one report, serum thyroglobulin concentrations did not fall further when serum TSH was suppressed below 0.1 mU/L <sup>80</sup>. This emphasizes the importance of tailoring the levothyroxine dose to the extent of the disease and the likelihood of recurrence. The ATA initial risk stratification system estimates the risk of persistent/recurrent disease. This system is designed to stratify patients as having either low (papillary thyroid cancer confined to thyroid), intermediate (regional metastases, worrisome histologies, extrathyroidal extension, or vascular invasion), or high (gross extrathyroidal extension, distant metastases, or postoperative serum thyroglobulin suggestive of distant metastases) risk of

recurrence, primarily based upon clinicopathologic findings<sup>74</sup>.

After initial thyroidectomy, whether or not radioiodine therapy is administered, thyroid hormone (levothyroxine) therapy is required in most patients to prevent hypothyroidism and to minimize potential TSH stimulation of tumor growth, as follows:

- for patients with low-risk disease treated with thyroidectomy who have detectable serum thyroglobulin levels (with or without remnant ablation), the serum TSH initially can be maintained between 0.1 and 0.5 mU/L. For similar patients who have undetectable serum thyroglobulin levels (with or without remnant ablation) or who were treated with lobectomy, TSH can be maintained in the mid to lower half of the reference range (0.5 to 2.0 mU/L). In the later setting, thyroid hormone treatment may be unnecessary if a patient can maintain their TSH in this range;
- for patients with intermediate-risk disease, the serum TSH initially can be maintained between 0.1 and 0.5 mU/L;
- for patients with high-risk disease, the serum TSH initially should be less than 0.1 mU/L.

TSH concentrations are measured annually and 6-8 weeks after any dose adjustments of levothyroxine. Although TSH should be maintained < 0.1 mU/L in patients with a structurally incomplete response, patients with a better response to therapy can have their TSH goal modified, for example:

- for patients initially with high-risk disease but who have an excellent or indeterminate clinical response to therapy, a TSH goal of 0.1 to 0.5 mU/L for up to 5 years is acceptable, after which time the degree of suppression can be further relaxed (with continued surveillance for recurrence);
- for patients initially with low-risk disease and who have an excellent clinical response to therapy, a TSH goal of 0.5 to 2 mU/L is acceptable;
- for patients with a biochemically incomplete response, the serum TSH should be maintained between 0.1 and 0.5 mU/L<sup>74</sup>.

## CONCLUSIONS

The skeleton is a target tissue for thyroid hormone's action, certainly verified by the consequences of thyroid hormone excess and deficiency during development and during aging. Old age may be associated with a number of thyroid function alterations. However, it is not simple to discern whether and to what extent these changes are expression of the aging process per se or of an age-associated thyroidal and/or nonthyroidal illness and polypharmacy. There is often significant delay

and difficulty in the diagnosis of thyroid disorders in old age because clinical presentation is paucisymptomatic and attributed to normal aging, and because atypical presentations are not uncommon. Routine screening of asymptomatic, healthy adults is not recommended; however, physicians should maintain a high index of suspicion for testing thyroid function in subjects at risk. Thyroid diseases in older patients differ from those observed in younger patients in their prevalence, which is higher especially among women, and clinical expression, while their treatment often deserves special attention because of the increased risk of complications (i.e. cardiac arrhythmia, cognitive decline, bone loss). Subclinical abnormalities of thyroid function are more prevalent than overt disease in older populations.

Subclinical hyperthyroidism appears to be a significant risk factor for cardiac arrhythmia, especially atrial fibrillation, and FF in old age. The risk is particularly high among those with TSH levels below 0.10 mIU/L. The benefits of treatment of subclinical disease are not completely elucidated. Treatment of thyroid disease deserves especial attention in old-old patients because of the increased risk of complications and the lack of evidence-based data in this population.

Even if most of thyroid nodules in older persons are benign, clinical evaluation should be considered to timely identified thyroid malignancy. FNA remains the cornerstone of thyroid cancer diagnosis, which accuracy may be improved by high-resolution ultrasound evaluation.

Thyroid hormones may lead to accelerated bone turnover and over-replacement of levothyroxine can result in increased FF risk. The majority of cytologically benign thyroid nodules do not have significant size increase and in these nodules thyroid cancer was rare after a 5-year follow up. The risk for osteoporosis in postmenopausal women taking suppressive doses of levothyroxine for thyroid cancer can be minimized by treatment with the minimal effective suppressive dose and eventual institution of antiresorptive or bone forming therapy where indicated, emphasizing the importance of tailoring the levothyroxine dose to the extent of the disease and the likelihood of recurrence.

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