Journal of Nuclear Medicine, published on February 12, 2021 as doi:10.2967/jnumed.120.251504

# The Role of Nuclear Medicine in the Clinical Management of Benign Thyroid Disorders. Part 2. Nodular Goiter, Hypothyroidism, and Subacute Thyroiditis

Giuliano Mariani<sup>1</sup>, Massimo Tonacchera<sup>2</sup>, Mariano Grosso<sup>3</sup>, Emilio Fiore<sup>2</sup>, Pierpaolo Falcetta<sup>2</sup>, Lucia Montanelli<sup>2</sup>, Brunella Bagattini<sup>2</sup>, Paolo Vitti<sup>2</sup>, H. William Strauss<sup>4</sup>

(<sup>1</sup>) Regional Center of Nuclear Medicine, Department of Translational Research and Advanced Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

(<sup>2</sup>) Endocrinology and Metabolism Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

(<sup>3</sup>) Regional Center of Nuclear Medicine, University Hospital of Pisa, Pisa, Italy

(<sup>4</sup>) Molecular Imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

No reprints available. Address all correspondence to: Giuliano Mariani, MD Regional Center of Nuclear Medicine Department of Translational Research and Advanced Technologies in Medicine and Surgery University of Pisa Via Roma 57 I-56126 Pisa, Italy Tel: +39-347-0509632 Email: giuliano.mariani@med.unipi.it

The authors have received no financial support for this work

Running title: Nuclear medicine in benign thyroid disease

## ABSTRACT

**Goiter**, an enlargement of the thyroid gland, is a common endocrine abnormality. Constitutional factors, genetic abnormalities, and/or dietary and environmental factors may contribute to the development of nodular goiter. Most patients with non-toxic nodular goiter are asymptomatic or have only mild mechanical symptoms ("globus pharyngis"). Work-up of these patients includes measurement of TSH, fT3, fT4, thyroid auto-antibodies, ultrasound imaging, thyroid scintigraphy, and fine-needle aspiration biopsy of nodules with certain ultrasound and scintigraphic features. Treatment for multinodular goiter includes dietary iodine supplementation, surgery, radioiodine therapy (to decrease thyroid size), and mini-invasive ablation techniques.

**Hypothyroidism** ranges from rare cases of myxedema to more common mild forms (subclinical hypothyroidism). Primary hypothyroidism often has an autoimmune etiology. Clinical presentations differ in the neonate, children, adults and elderly patients. Work-up includes thyroid function tests and ultrasound imaging. Nuclear medicine is primarily used to locate ectopic thyroid tissue in congenital hypothyroidism, or to detect defects in iodine organification with the perchlorate discharge test. Treatment consists of thyroid replacement therapy with L-Thyroxine, adjusting the daily dose to the individual patient's metabolic and hormonal requirements.

**Subacute thyroiditis** is a self-limited inflammatory disorder of the thyroid gland, often associated with painless or painful swelling of the gland and somatic signs/symptoms. Inflammation disrupts thyroid follicles resulting in a rapid release of stored T4 and T3 causing an initial thyrotoxic phase – often followed by transient or permanent hypothyroidism. Although subacute thyroiditis is often related to a viral infection, no infective agent has been identified. Subacute thyroiditis may be caused by a viral infection in genetically predisposed individuals. Work-up includes lab tests, ultrasound imaging, and radionuclide imaging. Thyroid scintigraphy demonstrates different findings depending on the phase of the illness, ranging from very low-to-absent tracer uptake in the thyroid gland in the hyperthyroid phase, to normal appearance in the late recovery phase. Since subacute thyroiditis is self-limited, treatment is directed toward relief of pain. High-dose nonsteroidal anti-inflammatory drugs are usually the first-line treatment. If severe pain persists, a course of corticosteroids may be necessary. Permanent hypothyroidism develops in up to 15% of patients with subacute thyroiditis, even more than 1 year following presentation.

**Key Words:** diffuse and nodular goiter; primary autoimmune hypothyroidism; subacute, destructive thyroiditis; lab tests for benign thyroid disorders; ultrasound imaging; radionuclide imaging; fine-needle aspiration biopsy; therapy of diffuse and nodular goiter; therapy of hypothyroidism; therapy of subacute thyroiditis

#### **GOITER AND THYROID NODULES**

#### **Epidemiology and Clinical Presentation**

Goiter, an enlargement of the thyroid gland (>20 mL in men and >15 mL in women) with or without nodules, is one of the most common endocrine abnormalities. If thyroid function is normal, it is described as non-toxic nodular goiter. The incidence of new nodular goiter (NG) cases in adults in the US is 0.1-1.5% of the general population per year (1). Goiter is more common in women than men (2). In areas of iodine deficiency the incidence of thyroid nodules increases with age (without genderrelated difference) (3), whereas in iodine-sufficient areas the prevalence of NG decreases with age (4). Constitutional factors, genetic abnormalities, and/or dietary/environmental factors may contribute to the development of NG (2-5). Thyroid nodules may become autonomous, possibly evolving to cause thyrotoxicosis.

Clinically, goiter is categorized into diffuse, solitary nodular, or the most prevalent phenotype, multinodular goiter. Most patients with non-toxic nodular goiter are asymptomatic or have mild mechanical symptoms ("globus pharyngis"). Nodular goiter is often discovered incidentally during an ultrasound scan performed for other reasons. Symptoms of compression of the trachea, esophagus, great vessels, and recurrent laryngeal nerve in the presence of a goiter suggest that a long-term NG has partially migrated to the retrosternal and/or upper mediastinal regions.

#### **Etiology and Pathophysiology**

Worlwide the most important environmental factor for goiter development is iodine deficiency (2,3,6), and there is an inverse correlation between iodine intake and the prevalence of goiter (7). Other factors include genetic susceptibility, female gender, increased body mass, and smoking (6,8,9). Smoking promotes goiter development probably due to thiocyanate in cigarette smoke, which block iodination, leading to a compensatory increase in secretion of the thyroid-stimulating hormone (TSH) (10).

#### Lab Tests

TSH, free T4 (fT4) and free T3 (fT3) should be measured. If the TSH is reduced and fT4 and/or fT3 are elevated, the patient has progressed to a toxic nodular goiter. In iodine-deficient areas, nodules may become autonomous because of persistent stimulus from elevated TSH due to reduced thyroid hormone production.

The presence of antibodies recognizing thyroid-peroxidase (TPO-Ab), thyroglobulin (Tg-Ab), and/or the TSH-receptor suggests the coexistence of Hashimoto's disease or Graves' disease.

#### **Ultrasound Imaging**

Ultrasonography is used to determine thyroid volume and the echogenicity, margins, shape, content, calcifications, vascularity, size, and elasticity of nodules in addition to the status of regional lymphnodes (Fig. 1 and Supplemental File-1). The European Thyroid Association (11), the American College of Radiology (12), and the American Thyroid Association (ATA) (13) have issued guidelines (with slight differences) for stratifying the risk of malignancy of thyroid nodules according to the so-called "thyroid imaging reporting and data system" (TI-RADS). The ultrasound-based criteria (Tables 1 and 2) stratify thyroid nodules into five categories of risk for malignancy, a change from prior consensus guideline that stratified the ultrasound risk of malignancy into three categories (14); examples of thyroid nodules can be classified as benign by ultrasound criteria alone, and nodules with low-risk features have a false negative risk of only 0.3% (11). It is still debated which TI-RADS version provides better outcome (15, 16). Ultrasound guidance is crucial to localize sites for fine-needle aspiration biopsy (FNAB) (17) and mini-invasive therapeutic procedures (18).

#### **Fine-needle Aspiration Biopsy of Thyroid Nodules**

The prevalence of thyroid cancer in patients referred for goiter evaluation is 4%–18% (19). FNAB should be performed in suspicious nodules with high-risk ultrasound features, especially if combined with the scintigraphic features described further below. Table 3 summarizes the main features of the two most widely employed systems for classifying the cytology findings according to the risk of malignancy, the Bethesda system and the British Thyroid Association (BTA) system. Approximately 20% of FNABs of thyroid nodules have indeterminate cytology (Bethesda III, or BTA Thy3a-f), with a rate of malignancy of 10%–30% (20). Molecular testing for gene mutations (e.g., BRAF, RAS, RET/PTC, PPAR $\gamma$ ) enhances the accuracy of FNAB in nodules with indeterminate cytology (21,22).

#### **Diagnostic and Therapeutic Radionuclide Procedures**

*Thyroid Scintigraphy with* <sup>123</sup>*I-Iodide or* <sup>99m</sup>*Tc-Pertechnetate*. Thyroid scintigraphy provides a map of functioning thyroid parenchyma (Fig. 2), including hypofunctioning nodules ("cold" areas on the scan) or autonomously functioning nodules ("hot" areas on the scan, with variable uptake in the extra-nodular thyroid parenchyma – up to complete suppression). Combined with ultrasonography,

thyroid scintigraphy can determine which thyroid nodules should be characterized with FNAB (23). Nodules that appear as "warm/hot" on thyroid scintigraphy are rarely malignant (24); therefore, FNAB of such lesions is not indicated (Fig. 3).

In areas with sufficient dietary iodine intake, thyroid scintigraphy is not necessary in patients with diffuse or (multi)nodular goiter when serum TSH is normal, because all such nodules usually appear as cold areas on the scan and should be evaluated with FNAB if exhibiting a high TI-RADS score and exceeding 10 mm in any diameter (25,26). However, in iodine-deficient areas the serum TSH level alone may not be sufficient to exclude the presence of autonomously functioning thyroid nodules (27), and thyroid scintigraphy should be performed in all patients with nodular goiter. A meta-analysis showed a 50% prevalence (95% CI: 32%–68%) of normal TSH values in patients with autonomously functioning thyroid nodule(s) (28).

*PET/CT with <sup>18</sup>F-FDG in Patients with Nodular Goiter.* "Incidentalomas" – when an <sup>18</sup>F-FDG PET/CT scan performed for reasons not related to the thyroid (usually in patients with non-thyroid cancers) shows increased tracer uptake in the thyroid gland – as it occur in 1%–2% of all <sup>18</sup>F-FDG scans. Two patterns of <sup>18</sup>F-FDG uptake have been observed, diffuse and focal (Fig. 4). Diffuse <sup>18</sup>F-FDG uptake in the thyroid gland is usually associated with autoimmune thyroiditis and has little or no clinical relevance (*29-31*). Focal <sup>18</sup>F-FDG uptake in the thyroid gland can be found in nodular goiter, and about 35% of these "incidentalomas" are thyroid cancer (*32*). Therefore, these cases should be further investigated for unequivocal characterization (*33*). The occurrence of thyroid incidentalomas during a PET/CT scan is not unique to <sup>18</sup>F-FDG, as they can be observed also with other PET tumor imaging agents, e.g. <sup>18</sup>F-fluorocholine, <sup>68</sup>Ga-DOTA-TOC, and <sup>68</sup>Ga-PSMA-ligand (*34-36*) (Fig. 5).

<sup>18</sup>F-FDG-avid thyroid nodules that cannot be classified with FNAB cytology are more likely to be malignant than a nodule without enhanced [<sup>18</sup>F]FDG uptake (Fig. 6); whereas, a similar thyroid nodule without increased [<sup>18</sup>F]FDG uptake is <u>highly unlikely</u> to be malignant (*37-39*). Although any focal [<sup>18</sup>F]FDG uptake above the normal thyroid background is interpreted as positive and a high SUV<sub>max</sub> increases the risk of malignancy (*38,40*), no specific SUV<sub>max</sub> threshold has been identified to reliably discriminate malignant from benign thyroid nodules.

#### **Therapy of Nodular Goiter**

*Surgery*. Compressive symptoms are a major indication for surgery, as stated by the ATA and by the German Society for General and Visceral Surgery (41).

Radioiodine Therapy for Reduction of Goiter Volume. In patients with either diffuse or nodular goiter with mechanical symptoms, who cannot undergo surgery because of comorbidities (42), can be treated with radioiodine. A practical approach to determine the activity to be administered is based on the assumption of a target activity of 3.7 MBq (100  $\mu$ Ci) of radioiodine per gram of functioning thyroid tissue 24 h after administration. The initial estimate (i.e. 3.7 MBq × volume of functioning thyroid tissue as assessed by thyroid scintigraphy) is corrected by the 24-h radioiodine uptake (RAIU) value. More personalized dosimetry-based approaches to determine the activity of radioiodine for therapy (43) have been discussed in the companion CE article (44). Whereas in Graves' disease the target absorbed dose necessary to ablate hyperfunctioning thyroid tissue is between 200–400 Gy, data derived from external beam radiation therapy for cancers of the head and neck suggest that an absorbed dose between 100–150 Gy is sufficient for tissue ablation of normal thyroid parenchyma (45,46).

This treatment causes an average 30%–40% volume reduction within one year post-treatment, with further reduction up to 50%–60% of the initial thyroid volume/mass in the following year (42). To increase radioiodine uptake in multinodular glands, an off-label use of recombinant human TSH (rhTSH), administered i.m. as a single 0.3 mg dose 24 h before radioiodine therapy, has been suggested (47-51). An advantage of pre-treatment with rhTSH is that the activity of administered radioiodine is reduced by about half the activity that should be administered without rhTSH pre-treatment – with consequent reduction in overall radiation dosimetry (52,53).

Besides the usual contraindication in pregnant/lacating women, some conditions must be fulfilled before submitting patients to this treatment:

- Evaluation for malignancy (ultrasonography, thyroid scintigraphy, and FNAB if necessary) must be performed prior to radioiodine therapy.
- The total thyroid volume/mass must be evaluated for bulky goiters extending to the upper mediastinum (which may include MRI, or CT without contrast agent).
- The "active" thyroid volume/mass should be evaluated by thyroid scintigraphy, considering that cystic lesions and other low-uptake areas are not expected to respond to radioiodine therapy.

Since most patients treated with radioiodine develop hypothyroidism within 2–3 years after therapy, all patients receiving radioiodine therapy should be followed with semi-annual serum TSH assays (42,54).

#### Medical Therapy of (Nodular) Goiter

Once their benign nature has been established, goiters with small nodules usually do not require treatment and can safely be monitored with regular follow-up. Since iodine deficiency has a key role in thyroid enlargement, iodine supplementation may reduce goiter size (55,56).

Historically, TSH-suppressive therapy with L-Thyroxine was used with the aim of reducing stimulation of thyroid parenchyma and nodules. Although this approach was widely embraced in the past (56-59), the long-term outcomes of this approach are still controversial (59). Current ATA guidelines do not recommend the routine use of L-Thyroxine for the treatment of benign thyroid nodules (13), although it may remain a feasible option for young patients in case of mild iodine deficiency (59,60).

#### **Mini-invasive Treatments for Nodular Goiter**

Tissue "ablation" techniques have been developed to induce necrosis/apoptosis of specific thyroid nodules. Recent mini-invasive techniques induce thermal ablation with different forms of energy such as microwaves, radiofrequency, high-intensity focused ultrasound, or laser energy (13).

#### HYPOTHYROIDISM

#### **Epidemiology and Clinical Presentation**

Hypothyroidism is a systemic condition caused by transient or permanent: i) thyroid failure (primary hypothyroidism); ii) deficiency of thyrotropin secretion (TSH) (secondary, or central hypothyroidism); or iii) resistance of peripheral target tissues (Supplemental File-3).

The spectrum of hypothyroidism ranges from severe overt hypothyroidism (myxedema) to milder forms, subclinical hypothyroidism. Primary hypothyroidism accounts for 95%–99% of thyroid failure and has usually an autoimmune etiology. Deficiency of pituitary or hypothalamic function (secondary or tertiary hypothyroidism), and peripheral resistance to thyroid hormones, or their inactivation due to auto-antibodies, are rare.

The prevalence of hypothyroidism in the US (defined as TSH levels >4.5 mIU/L) is 3.7% of the general population *(61)*. In Europe it is 0.65% (95% CI: 0.38%–0.99%) for overt and 4.11% (95% CI: 3.05%–5.31%) for subclinical hypothyroidism *(62)*.

*Congenital hypothyroidism.* Congenital hypothyroidism is the most frequent congenital endocrine disorder (1:2.200–2.500 live births). Delayed diagnosis leads to growth retardation and severe neurological and psychiatric impairment.

*Children and Adolescent Hypothyroidism.* Hypothyroidism in children and adolescents is characterized by retarded growth and short stature, variable but usually declining school performance, and signs/symptoms similar to those occurring in adults. In addition to the history and physical examination, laboratory evaluation should include TSH, fT4 and fT3. In the presence of abnormal findings, the patient should be referred to a pediatric endocrinologist.

*Hypothyroidism in Adults*. Thyroid hormone deficiency reduces function in almost every organ system depending on the degree of hypothyroidism (Table 4).

*Hypothyroidism in the Elderly*. The most frequent signs/symptoms are fatigue, muscle weakness, cold intolerance, dry skin, hair loss, constipation, poor appetite, depression and/or mental deterioration, hearing loss, cardiomegaly and congestive heart failure.

Drug-Induced Hypothyroidism. The large amount of iodine released from amiodarone (an iodine-rich drug used for treating tachyarrythmias) may fail to escape the Wolff-Chaikoff effect (see below) and thus cause iodine-induced hypothyroidism, especially in patients with preexisting autoimmune thyroiditis (63,64). Lithium therapy may cause hypothyroidism by blocking both release and synthesis of thyroid hormones (65). Interferon may precipitate hypothyroidism, either by aggravating preexisting autoimmune thyroiditis and/or by a direct cytotoxic effect on thyroid follicular cells (66). Tyrosine kinase inhibitors (TKI) may induce hypothyroidism by mechanism(s) not fully understood (67).

#### Pathophysiology

The most frequent cause of hypothyroidism in adults is autoimmune thyroiditis (Ord-Hashimoto disease). It most probably results from a combination of a predisposing genetic background with exogenous and endogenous factors *(68)*. Infiltration of thyroid tissue by amyloidosis, hemochromatosis, sarcoidosis, cystinosis, scleroderma, or leukemia may also cause hypothyroidism and goiter.

Hypothyroidism may result from either severe iodine deficiency or iodine excess. In severe iodine deficiency, large goiters and variable degrees of hypothyroidism may be observed at any age. Excess iodine intake (>1–2 mg/day) acutely inhibits iodine organification and thyroid hormone synthesis (Wolff-Chaikoff effect) as well as thyroid hormone release. In most euthyroid subjects iodine excess does not cause hypothyroidism due to an adaptive mechanism (escape, usually at ~10 days after iodine loading); nevertheless, patients with preexisting thyroid abnormalities may fail to escape the Wolff-Chaikoff effect and thus develop hypothyroidism.

Iatrogenic hypothyroidism can be observed following treatment of hyperthyroidism with antithyroid drugs or radioiodine, as well as after total thyroidectomy or external beam radiation therapy of the head and neck region.

#### Lab Tests

*TSH.* Primary hypothyroidism is characterized by increased TSH and decreased FT4; in subclinical hypothyroidism TSH is increased (generally between 5–10 mIU/L) and FT4 is normal. In central hypothyroidism low FT4 is associated with low-to-inappropriately normal TSH.

*Antibodies*. Thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab) are positive in most patients with autoimmune thyroiditis.

*Lipids.* In both overt and subclinical hypothyroidism the lipid profile shows increased total LDL cholesterol levels with increased or normal HDL levels. Triglyceride levels are normal or slightly elevated.

#### **Ultrasound Imaging**

In hypothyroidism the thyroid volume can be normal, increased (goiter) or reduced (atrophic form of chronic autoimmune thyroiditis, hypoplasia or hemiagenesis) (Supplemental File-4). Inhomogeneous hypoecogenicity is typical of chronic autoimmune thyroiditis. Ultrasonography can also identify ectopic thyroid tissue in congenital hypothyroidism.

## **Radionuclide Techniques in Hypothyroidism**

Nuclear medicine currently has a limited role in hypothyroidism, since the diagnosis is based on signs/symptoms and on thyroid hormonal profile (TSH, fT3, fT4). The only current application of radionuclide imaging in hypothyroidism concerns congenital hypothyroidism *(69)*. Thyroid scintigraphy with either <sup>99m</sup>Tc-Pertechnetate or preferably <sup>123</sup>I-Iodide constitutes the best standard for ascertaining thyroid agenesis or locating ectopic thyroid tissue in the mediastinum, or base of the tongue – especially in newborns/children.

When the thyroid gland is in its normal location in a patient with congenital hypothyroidism, the cause of hypothyroidism can be genetic mutation(s), over 25 of which have been described (70,71). The perchlorate discharge test explores defects in the intrathyroidal organification process of iodide as a cause of congenital hypothyroidism. Once iodide is "trapped" in the thyroid gland following active transport mediated by sodium/iodide symporter (NIS), iodine binds to thyroglobulin – therefore no longer requiring active transport for intracellular retention. Perchlorate ions inhibit NIS-mediated iodide transport and cause loss of iodide not bound to thyroid hormones. Evaluating the release of

radioiodine caused by perchlorate allows evaluation of non-organified intrathyroidal iodide and thus assessment of an iodide-binding defect (69).

#### **Thyroid Replacement Therapy in Hypothyroidism**

Approximately 85  $\mu$ g of L-Thyroxine is secreted by the thyroid gland daily. Of the total daily T3 production (about 33  $\mu$ g in normal man), approximately 80% arises from peripheral conversion from T4, and only about 20% derives from direct thyroidal secretion. Synthetic L-Thyroxine is recommended as the preparation of choice to treat hypothyroidism, due to its efficacy, favourable side-effect profile, ease of administration, good intestinal absorption, long serum half-life, and low cost. L-Thyroxine is converted in-vivo into its active metabolite T3. Nevertheless, a subgroup of hypothyroid patients are not satisfied with L-Thyroxine therapy alone (72); in these patients, combination therapy with L-Thyroxine (L-T3) might be considered (73,74).

Hypothyroid patients with minimal endogenous thyroid function require L-Thyroxine doses of  $1.6-1.8 \ \mu g/kg$  of body weight (ideal body weight being a better predictor than actual body weight). Patients with L-Thyroxine dose requirements much higher than expected should be evaluated for gastrointestinal disorders such as *Helicobacter pylori*–related gastritis, atrophic gastritis, celiac disease, lactose intolerance, and intestinal giardiasis. Serum TSH monitoring is advisable when starting medications such as phenobarbital, phenytoin, carbamazepine, rifampin, and sertraline.

Symptoms, such as cold intolerance or dry skin lack sensitivity and specificity, therefore are not recommended for judging adequacy of replacement in the absence of biochemical assessment. About 6-8 weeks after a change in L-Thyroxine dosage Serum TSH should be checked.

#### SUBACUTE THYROIDITIS

Subacute thyroiditis is a self-limited inflammation of the thyroid gland, often associated with painless or painful swelling of the gland and somatic signs/symptoms including fever and malaise (75). Painless subacute thyroiditis may be overlooked or misdiagnosed, especially when occurring in the post-partum – occasionally related to postpartum psychosis or depression (76).

Originally described in 1895 by Mygind as "thyroiditis akuta simplex" (77), the pathology of subacute thyroiditis was first depicted in 1904 by the Swiss surgeon Fritz de Quervain, whose name is associated with the disorder. The inflammatory process causes disruption of thyroid follicles resulting

in a rapid release of stored T4 and T3 causing an initial thyrotoxic phase – often followed by transient or permanent hypothyroidism.

#### **Epidemiology and Clinical Presentation**

The incidence of subacute thyroiditis is 4.9/100,000 per year (78). Its prevalence is highest in middle-aged women (female:male ratio between 4:1–7:1). Subacute thyroiditis often occurs after an upper respiratory viral illness – thought to trigger the disease.

Anterior neck pain is the cardinal feature of de Quervain's subacute thyroiditis. The inflammation can start in one lobe and then migrate to the contralateral lobe. Dysphagia is occasionally reported. The gland is firm and tender on palpation. In the early phases there can be signs of thyrotoxicosis (tachycardia, tremor, increased skin warmth), sometimes requiring the use of a beta-blocker. The thyrotoxic phase may be followed by hypothyroidism that is usually transient, although it can occasionally be permanent. In patients with hypothyroid symptoms, L-Thyroxine replacement should be started – with frequent TSH monitoring to assess possible tapering or continuation of replacement therapy.

#### **Etiology and Pathophysiology**

Although subacute thyroiditis has been related to a viral infection (79), so far no infective agent has been clearly identified (80). The destructive events of subacute thyroiditis may trigger thyroid autoimmunity in subjects with a genetic background, occasionally resulting in chronic autoimmune thyroiditis with hypothyroidism (81), or in Graves' disease (82).

About 72% of patients with subacute thyroiditis present the HLA-BW35 antigen (83), and familial subacute thyroiditis can be associated with HLA-B35 (84), suggesting that the disease may be caused by a viral infection in genetically predisposed individuals. Therapies potentially affecting the immune system may be associated with subacute thyroiditis (85), as in patients with chronic hepatitis B or C treated with interferon and/or ribavirin (66).

#### Lab Tests

Laboratory exams show a moderate leukocytosis, elevated erythrocyte sedimentation rate, and elevated serum C-reactive protein levels. In the thyrotoxic phase, suppressed serum TSH is associated with normal or elevated free T3 and free T4. The thyrotoxic phase typically lasts four to eight weeks. Thyroglobulin levels are elevated because of the destruction of thyroid follicles.

#### **Ultrasound Imaging**

Thyroid ultrasound shows heterogeneous, diffuse, hypoechoic and confluent areas, with no increase in the vascularity on color Doppler (86). These abnormalities often revert to a near-normal pattern when the condition resolves (Fig. 7).

#### **Radionuclide Imaging**

Thyroid scintigraphy is characterized by very low-to-absent tracer uptake in the thyroid gland in the thyrotoxic phase – a pattern shared by other conditions of destructive thyroiditis (e.g, type-2 amiodarone-induced thyroid dysfunction). Depending on the phase of the illness, there can be absent tracer uptake in the whole gland or in part of the gland. Even when subacute thyroiditis affects primarily one lobe of the thyroid, the scan may show completely absent tracer uptake in the whole gland (Fig. 7), because of suppressed TSH levels due to a thyrotoxic phase of the disease.

#### **Therapy of Subacute Thyroiditis**

Since subacute thyroiditis is self-limited, in most cases the thyroid gland spontaneously resumes normal thyroid hormone production. Treatment is directed toward relief of thyroid pain. High-dose nonsteroidal anti-inflammatory drugs are usually the first-line treatment (75). If neck pain does not improve after a few days, or if the patient presents with severe neck pain, corticosteroids may be considered (80), which leads to improvement within two days. After 5–7 days of high-dose prednisone, the dose is tapered over the next 2–4 weeks. As the dose is tapered, most patients have no recurrence of symptoms, but occasionally this does occur and the dose must be increased again.

Thyroid hormone supplementation is generally not necessary for the transient hypothyroid phase of subacute thyroiditis, unless patients are symptomatic. However, permanent hypothyroidism develops in up to 15% of patients, even more than one year following presentation (75).

#### FINANCIAL DISCLOSURE

The authors have no financial conflicts of interest to disclose.

#### REFERENCES

- Hurley DL, Gharib H. Evaluation and management of multinodular goiter. *Otolaryngol Clin* North Am. 1996;29;527-40.
- Knudsen N, Bulow I, Jorgensen T, Laurberg P, Ovesen L, Perrild H. Goitre prevalence and thyroid abnormalities at ultrasonography: a comparative epidemiological study in two regions with slightly different iodine status. *Clin Endocrinol (Oxf)*. 2000;53:479-85.
- 3. Aghini-Lombardi F, Antonangeli L, Martino E, et al. The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. *J Clin Endocrinol Metab.* 1999;84:561-6.
- Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)*. 1995;43:55-68.
- 5. Brix TH, Kyvik KO, Hegedüs L. Major role of genes in the etiology of simple goiter in females: a population-based twin study. *J Clin Endocrinol Metab.* 1999;84:3071-5.
- 6. Carlé A, Krejbjerg A, Laurberg P. Epidemiology of nodular goitre. Influence of iodine intake. *Best Pract Res Clin Endocrinol Metab.* 2014;28:465-79.
- 7. Fiore E, Tonacchera M, Vitti P. Influence of iodization programmes on the epidemiology of nodular goitre. *Best Pract Res Clin Endocrinol Metab.* 2014;28:577-88.
- 8. Hegedüs L, Brix TH, Paschke R. Etiology of simple goiter. *Thyroid*. 2009;19:209-11.
- Knudsen N, Brix TH. Genetic and non-iodine-related factors in the aetiology of nodular goitre. Best Pract Res Clin Endocrinol Metab. 2014;28:495-506.
- Christensen SB, Ericsson UB, Janzon L, Tibblin S, Melander A. Influence of cigarette smoking on goiter formation, thyroglobulin, and thyroid hormone levels in women. *J Clin Endocrinol Metab.* 1984;58:615-8.
- 11. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. *Eur Thyroid J.* 2017;6:225-37.
- 12. Tessler FN, Middleton WD, Grant EG, et al. ACR thyroid imaging, reporting and data system (TI-RADS): white paper of the ACR TI-RADS committee. *J Am Coll Radiol*. 2017;14:587-95.
- 13. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. The

American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;26:1-133.

- 14. Gharib H, Papini E, Garber JR, et al. American Association of Clinical Endocrinologists, American College of Endocrinology and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules – 2016 update. *Endocr Pract.* 2016;22(Suppl 1):1-60.
- 15. Magi F, Chytiris S, Croce L, et al. Performance of the ACR TI-RADS and EU TI-RADS scoring systems in the diagnostic work-up of thyroid nodules in a real-life series using histology as reference standard. *Eur J Endocrinol*. 2020;183:521-8.
- 16. Tan L, Tarn YS, Tan S. Diagnostic accuracy and ability to reduce unnecessary FNAC: A comparison between four Thyroid Imaging Reporting Data System (TI-RADS) versions. *Clin Imaging*. 2020;65:133-7.
- 17. Carmeci C, Jeffrey RB, McDougall IR, Nowels KW, Weigel RJ. Ultrasound-guided fine-needle aspiration biopsy of thyroid masses. *Thyroid*. 1998;8:283-9.
- 18. Barile A, Quarchioni S, Bruno F, et al. Interventional radiology of the thyroid gland: critical review and state of the art. *Gland Surg.* 2018;7:132-46.
- 19. Brito JP, Yarur AJ, Prokop LJ, McIver B, Murad MH, Montori VM. Prevalence of thyroid cancer in multinodular goiter versus single nodule: a systematic review and meta-analysis. *Thyroid.* 2013;23:449-55.
- 20. Ho AS, Sarti EE, Jain KS, et al. Malignancy rate in thyroid nodules classified as Bethesda category III (AUS/FLUS). *Thyroid*. 2014;24:832-9.
- 21. Roth MY, Witt RL, Steward DL. Molecular testing for thyroid nodules: review and current state. *Cancer*. 2018;124:888-98.
- 22. Ferris RL, Baloch Z, Bernet V, et al. American Thyroid Association statement on surgical application of molecular profiling for thyroid nodules: current impact on perioperative decision making. *Thyroid*. 2015;25:760-8.
- 23. Noto B, Eveslage M, Pixberg M, et al. Prevalence of hyperfunctioning thyroid nodules among those in need of fine needle aspiration cytology according to ATA 2015, EU-TIRADS, and ACR-TIRADS. *Eur J Nucl Med Mol Imaging*. 2020;47:1518-26.
- 24. Ashcraft MW, Van Herle AJ. Management of thyroid nodules. II: Scanning techniques, thyroid suppressive therapy, and fine needle aspiration. *Head Neck Surg.* 1981;3:297-322.

- 25. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;26:1-133.
- 26. Giovanella L, Avram AM, Iakovu I, et al. EANM practice guideline/SNMMI procedure standard for RAIU and thyroid scintigraphy. *Eur J Nucl Med Mol Imaging*. 2019;46:2514-25.
- 27. Chami R, Morenio-Reyes R, Corvilain B. TSH measurement is not an appropriate screening test for autonomous functioning thyroid nodules: a retrospective study of 368 patients. *Eur J Endocrinol.* 2014;170:593-9.
- Treglia G, Trimboli P, Verburg FA, Luster M, Giovanella L. Prevalence of normal TSH value among patients with autonmously functioning thyroid nodule. *Eur J Clin Invest*. 2015;45:739-44.
- 29. Agrawal K, Weaver J, Ngu R, Krishnamurthy Mohan H. Clinical significance of patterns of incidental thyroid uptake at <sup>18</sup>F-FDG PET/CT. *Clin Radiol*. 2015;70:536-43.
- 30. Małkowski B, Serafin Z, Glonek R, Suwała S, Łopatto R, Junik R. The role of <sup>18</sup>F-FDG PET/CT in the management of the autoimmune thyroid diseases. *Front Endocrinol (Lausanne)*. 2019 Apr 5;10:208.
- 31. Albano D, Treglia G, Giovanella L, Giubbini R, Bertagna F. Detection of thyroiditis on PET/CT imaging: a systematic review. *Hormones (Athens)*. 2020;19:341-9.
- 32. Pattison DA, Bozin M, Gorelik A, et al. <sup>18</sup>FDG-avid thyroid incidentalomas: The importance of contextual interpretation. *J Nucl Med.* 2018;59:749-55.
- 33. Trimboli P, Knappe L, Treglia G, et al. FNA indication according to ACR-TIRADS, EU-TIRADS and K-TIRADS in thyroid incidentalomas at <sup>18</sup>F-FDG PET/CT. *J Endocrinol Invest*. 2020;43:1607-12.
- 34. Bertagna F, Albano D, Giovanella L, et al. <sup>68</sup>Ga-PSMA PET thyroid incidentalomas. *Hormones* (*Athens*). 2019;18:145-9.
- 35. Bertagna F. Albano D, Giovanella L, Giubbini R, Treglia G. F18-choline/C11-choline PET/CT thyroid incidentalomas. *Endocrine*. 2019;64:203-8.
- 36. Ciappuccini R, Edet-Sanson A, Saguet-Rysanek V, Gauthé M, Stéphane Bardet S. Thyroid incidentaloma on <sup>18</sup>F-fluorocholine PET/CT and <sup>68</sup>Ga-PSMA PET/CT revealing a medullary thyroid carcinoma. *Clin Nucl Med.* 2019;44:663-5.

- 37. Vriens D, Adang EM, Netea-Maier RT, et al. Cost effectiveness of FDG-PET/CT for cytologically indeterminate thyroid nodules: a decision analytic approach. J Clin Endocrinol Metab. 2014;99:3263-74.
- 38. Castellana M, Trimboli P, Piccardo A, Giovanella L, Treglia G. Performance of <sup>18</sup>F-FDG PET/CT in selecting thyroid nodules with indeterminate fine-needle aspiration cytology for surgery. A systematic review and a meta-analysis. *J Clin Med.* 2019;8:1333.
- 39. Piccardo A, Puntoni M, Dezzana M, et al. Indeterminate thyroid nodules. The role of <sup>18</sup>F-FDG PET/CT in the "era" of ultrasonography risk stratification systems and new thyroid cytology classifications. *Endocrine*. 2020;69:553-61.
- 40. Sager S, Vatankulu B, Erdem Sahin O, et al. Clinical significance of standardized uptake values in thyroid incidentaloma discovered by F-18 fluorodeoxyglucose positron emission tomography/computed tomography. *J Cancer Res Ther*. 2018;14:989-93.
- 41. Bartsch DK, Luster M, Buhr HJ, et al. Indications for the surgical management of benign goiter in adults. *Dtsch Arztebl Int*. 2018;115:1-7.
- 42. Bonnema SJ, Hegedüs L. A 30-year perspective on radioiodine therapy of benign nontoxic multinodular goiter. *Curr Opin Endocrinol Diabetes Obes*. 2009;16:379-84.
- 43. Hammes J, van Heek L, Hohberg M, et al. Impact of different approaches to calculation of treatment activities on achieved doses in radioiodine therapy of benign thyroid diseases. *EJNMMI Physics*. 2018;5:32.
- 44. Mariani G, Tonacchera M, Grosso M, Orsolini F, Vitti P, Strauss HW. The role of nuclear medicine in the clinical management of benign thyroid disorders. Part 1. Hyperthyroidism. J Nucl Med. In press.
- 45. Boomsma MJ, Bijl HP, Langendijk JA. Radiation-induced hypothyroidism in head and neck cancer patients: A systematic review. *Radiother Oncol.* 2011;99:1-5.
- 46. Xu Y, Shao Z, Tang T, et al. A dosimetric study on radiation-induced hypothyroidism following intensity-modulated radiotherapy in patients with nasopharyngeal carcinoma. *Oncol Lett.* 2018;16:6126-32.
- 47. Bonnema SJ, Nielsen VE, Boel-Jørgensen H, et al. Improvement of goiter volume reduction after 0.3 mg recombinant human thyrotropin-stimulated radioiodine therapy in patients with a very large goiter: a double-blinded, randomized trial. *J Clin Endocrinol Metab.* 2007;92:3424-8.

- 48. Ceccarelli C, Antonangeli L, Brozzi F, et al. Radioiodine <sup>131</sup>I treatment for large nodular goiter: recombinant human thyrotropin allows the reduction of radioiodine <sup>131</sup>I activity to be administered in patients with low uptake. *Thyroid*. 2011;21:759-64.
- 49. Bonnema SJ, Nielsen VE, Boel-Jørgensen H, et al. Recombinant human thyrotropin-stimulated radioiodine therapy of large nodular goiters facilitates tracheal decompression and improves inspiration. *J Clin Endocrinol Metab.* 2008;93:3981-4.
- 50. Lee Y-Y, Tam K-W, Lin Y-M, et al. Recombinant human thyrotropin before <sup>131</sup>I therapy in patients with nodular goitre: a meta-analysis of randomized controlled trials. *Clin Endocrinol (Oxf)*. 2015;83:702-10.
- 51. Xu C, Wang P, Huikai Miao H, et al. Recombinant human thyrotropin-stimulated radioiodine therapy in patients with multinodular goiters: A meta-analysis of randomized controlled trials. *Horm Metab Res.* 2020;52:841-9.
- 52. Nieuwlaat W-A, Hermus AR, Ross HA, et al. Dosimetry of radioiodine therapy in patients with nodular goiter after pretreatment with a single, low dose of recombinant human thyroid-stimulating hormone. *J Nucl Med.* 2004;45:626-33.
- 53. Fast S, Hegedüs L, Grupe P, et al. Recombinant human thyrotropin-stimulated radioiodine therapy of nodular goiter allows major reduction of the radiation burden with retained efficacy. *J Clin Endocrinol Metab.* 2010;95:3719-25.
- 54. Bonnema SJ, Hegedüs L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. *Endocr Rev.* 2012;33:920-80.
- 55. Hintze G, Kobberling J. Treatment of iodine deficiency goiter with iodine, levothyroxine or a combination of both. *Thyroidology*. 1992;4:37–40.
- 56. Diehl LA, Garcia V, Bonnema SJ et al. Management of the nontoxic multinodular goiter in Latin America: comparison with North America and Europe, an electronic survey. J Clin Endocrinol Metab. 2005;90:117–23.
- 57. Gharib H, James EM, Charboneau JW, et al. Suppressive therapy with levothyroxine for solitary thyroid nodules. A double-blind controlled clinical study. *N Engl J Med.* 1987;317:70-5.
- 58. Papini E, Petrucci L, Guglielmi R, et al. Long-term changes in nodular goiter: a 5-year prospective randomized trial of levothyroxine suppressive therapy for benign cold thyroid nodules. *J Clin Endocrinol Metab.* 1998;83:780-3.

- 59. Bandeira-Echtler E, Bergerhoff K, Bernd Richter B. Levothyroxine or minimally invasive therapies for benign thyroid nodules. *Cochrane Database Syst Rev.* 2014 Jun 18;(6):CD004098.
- 60. Gharib H, Papini E, Garber JR, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and managmenet of Thyroid nodules – 2016 update. *Endocr Pract.* 2016;22:622-39.
- 61. https://www.medscape.com/answers/122393-11267/what-is-the-prevalence-of-hypothyroidismin-the-us. Accessed June 20, 2020.
- 62. Mendes, D, Alves C, Silverio N, Batel Marquesa F. Prevalence of undiagnosed hypothyroidism in Europe: A systematic review and meta-analysis. *Eur Thyroid J.* 2019;8:130-43.
- 63. Leung AM, Braverman LE. Consequences of excess iodine. *Nat Rev Endocrinol*. 2014;10:136-42.
- 64. Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. *Endocr Rev.* 2001;22:240-54.
- 65. Lazarus JH. Lithium and thyroid. Best Pract Res Clin Endocrinol Metab. 2009;23:723-33.
- 66. Tomer Y, Menconi F. Interferon induced thyroiditis. *Best Pract Res Clin Endocrinol Metab.* 2009;23:703-12.
- 67. Torino F, Barnabei A, Paragliola R, Baldelli R, Appetecchia M, Corsello SM. Thyroid dysfunction as an unintended side effect of anticancer drugs. *Thyroid*. 2013;23:1345-66.
- 68. Ajjan RA, Weetman AP. The pathogenesis of Hashimoto's thyroiditis: further developments in our understanding. *Horm Metab Res.* 2015;47:702-10.
- 69. Keller-Petrot I, Leger J, Sergent-Alaoui A, de Labriolle-Vaylet C. Congenital hypothyroidism: role of nuclear medicine. *Semin Nucl Med.* 2017;47:135-42.
- 70. Targovnik HM, Citterio CE, Rivolta CM: Thyroglobulin gene mutations in congenital hypothyroidism. *Review Horm Res Paediatr*. 2011;75:311-21.
- 71. Targovnik HM, Citterio CE, Rivolta CM. Iodide handling disorders (NIS, TPO, TG, IYD). Best Pract Res Clin Endocrinol Metab. 2017;31:195-212.
- 72. Peterson SJ, Cappola AR, Castro MR, et al. An online survey of hypothyroid patients demonstrates prominent dissatisfaction. *Thyroid*. 2018;28:707-21.
- 73. Tarik A, Wert Y, Cheriyat P, Joshi R. Effects of long-term combination LT4 and LT3 therapy for improving hypothyroidism and overall quality of life. *South Med J.* 2018;111:363-9.

- 74. Jonklaas J, Tefera E, Shara N. Short-term time trends in prescribing therapy for hypothyroidism: Results of a survey of American Thyroid Association Members. *Front Endocrinol.* 2019;10; 30 January 2019.
- 75. Volpé R. The management of subacute (DeQuervain's) thyroiditis. Thyroid. 1993;3:253-5.
- 76. Felicetta JV. Painful, painless, and postpartum thyroiditis. Distinct entities or merely variants? *Postgrad Med.* 1989;86:269-72.
- 77. Mygint H Thyroiditis acute simplex. *Journal of Laringology, Rhinology and Otology* 1895;181-93.
- 78. Fatourechi V, Aniszewski JP, Fatourechi GZ, Atkinson EJ, Jacobsen SJ. Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota, study. J Clin Endocrinol Metab. 2003;88:2100-5.
- 79. Fraser R, Harrison RJ. Subacute thyroiditis. *Lancet*. 1952;23:382-6.
- 80. Ogawa E, Katsushima Y, Fujiwara I, Iinuma K. Subacute thyroiditis in children: patient report and review of the literature. *J Pediatr Endocrinol Metab.* 2003;16:897-900.
- 81. Gozariu L, Stroe M, Vladutiu T, et al. Late hypothyroidism following subacute thyroiditis. *Exp Clin Endocrinol*. 1986;87:48-52.
- 82. Bartalena L, Bogazzi F, Pecori F, Martino E. Graves' disease occurring after subacute thyroiditis: report of a case and review of the literature. *Thyroid*. 1996;6:345-8.
- 83. Nyulassy S, Hnilica P, Buc M, Guman M, Hirschová V, Stefanovic J. Subacute (de Quervain's) thyroiditis: association with HLA-Bw35 antigen and abnormalities of the complement system, immunoglobulins and other serum proteins. *J Clin Endocrinol Metab.* 1977;45:270-4.
- 84. Kramer AB, Roozendaal C, Dullaart RP. Familial occurrence of subacute thyroiditis associated with human leukocyte antigen-B35. *Thyroid*. 2004;14:544-7.
- 85. Vassilopoulou-Sellin R, Sella A, Dexeus FH, Theriault RL, Pololoff DA. Acute thyroid dysfunction (thyroiditis) after therapy with interleukin-2. *Horm Metab Res.* 1992;24:434-8.
- 86. Cappelli C, Pirola I, Gandossi E, Formenti AM, Agosti B, Castellano M. Ultrasound findings of subacute thyroiditis: a single institution retrospective review. *Acta Radiol*. 2014;55:429-33.



**FIGURE 1.** Ultrasonography of a multinodular thyroid gland (axial view). Right lobe: single welldefined isoechoic nodule surrounded by a hypoechoic rim (halo sign). Left lobe: mixed nodule, cystic with echogenic solid component. SDM: skin, dermis and muscles forming the superficial layer in the neck. SN: solid nodule in right lobe. MN: mixed nodule in left lobe. TW: tracheal wall. TL: tracheal lumen.



**FIGURE 2.** Thyroid scintigraphy (anterior view) acquired 15 min after IV injection of <sup>99m</sup>Tcpertechnetate in a patient with diffuse, non-nodular goiter and normal thyroid function, showing global hyperplasia of the thyroid with homogeneous tracer distribution within the gland. The right lobe is larger than the left, with a longitudinal axis measuring about 70 mm.



**FIGURE 3.** Thyroid scintigraphy in two patients with nodular goiter (anterior view). Left panel: <sup>99m</sup>Tc-Pertechnetate scan acquired 15 min after IV injection, showing moderately enlarged gland with reduced tracer uptake in lower half of left lobe, corresponding to a palpable nodule (green broken line); in case of suspicious ultrasound features of this nodule, the patient should be referred for FNAB. Right panel: scan acquired with pinhole collimator 24 h after oral administration of 1.85 MBq <sup>131</sup>I-iodide to a candidate for radioiodine therapy of multinodular goiter with autonomously functioning nodule(s); only the nodule at the apex of right lobe (red broken line) shows increased tracer uptake, whereas nodule at base of right lobe and at the isthmus (green broken lines) do not concentrate radioiodine ("cold" nodules); FNAB was performed because of intermediate-risk EU-TIRADS score, and showed both nodules to be benign.



**FIGURE 4.** Thyroid incidentalomas observed in 2 patients undergoing <sup>18</sup>F-FDG PET/CT for thyroidunrelated oncological conditions (top: axial fused PET/CT; bottom: whole-body MIP image). Yellow arrows indicate the unexpected findings of focally increased tracer uptake (left) and diffuse tracer uptake (right). While diffusely enhanced tracer uptake is generally associated with thyroiditis, any focal increase in tracer uptake must be further evaluated with ultrasound and possibly FNAB, because of the relatively high rate of thyroid malignancy.



# <sup>18</sup>F-Fluoro-Choline <sup>68</sup>Ga-PSMA-11 <sup>68</sup>Ga-DOTA-TOC

**FIGURE 5.** Thyroid incidentalomas (yellow arrows) observed in 3 patients evaluated with PET tracers other than <sup>18</sup>F-FDG for oncological conditions (top: axial fused PET/CT; bottom: coronal fused PET/CT). Left panel: a patient with biochemical recurrence of prostate cancer. Previously he had a left hemithyroidectomy because of nodular goiter; histology showed chronic autoimmune thyroiditis; diffusely enhanced <sup>18</sup>F-fluorocholine uptake in residual right thyroid lobe corresponds to autoimmune thyroiditis. Center panel: focally increased <sup>68</sup>Ga-PSMA11 uptake within multinodular goiter prevalent in left lobe. Right panel: focally increased <sup>68</sup>Ga-DOTA-TOC uptake in right thyroid lobe [courtesy of Drs. Paola A. Erba and Roberta Zanca, Regional Center of Nuclear Medicine, University of Pisa, Pisa, Italy].



**FIGURE 6.** Evaluation of 30-y-old woman with family history of familial papillary thyroid carcinoma. Ultrasonography (A: axial view; C: longitudinal view) shows a 25-mm mixed iso-hypoechoic solid nodule of right lobe, with microcalcifications (small white arrow). Serum calcitonin was undetectable, and TSH was 2.7 μIU/mL; FNAB showed high-risk undetermined lesion (BTA Thy3f). <sup>18</sup>F-FDG PET/CT showed intense focal uptake (SUV<sub>max</sub> 12) in thyroid nodule of right lobe (B: coronal fused image). An additional focus of increased <sup>18</sup>F-FDG uptake (D: coronal fused image) was noted in a deeper plane, corresponding to a small lymph node of the central compartment not detected at ultrasonography. The patient underwent thyroidectomy and lymph node dissection of the central compartment, which revealed a BRAF-mutated papillary thyroid carcinoma with multiple lymph node metastases [courtesy of Dr. Arnoldo Piccardo, Nuclear Mecicine Department, "Galliera" Hospital, Genoa, Italy].



**FIGURE 7.** Ultrasound and scintigraphy images of a 46-y-old woman with subacute thyroiditis arising in a pre-existing chronic autoimmune thyroiditis. At presentation the patient had a tender goiter and pain whilst swallowing, but no fever. Abnormally increased leukocyte count and ESR, but normal PCR. TSH level 0.01 mIU/L, with increased fT3 (almost 2-fold upper normal limit) and fT4 (1.5-fold upper normal limit). Left: ultrasound axial (top) and longitudinal views (bottom), showing markedly hypoechoic area in left thyroid lobe, with poorly defined margins. Center: anterior view <sup>99m</sup>Tc-Pertechnetate scintigraphy at presentation, showing minimal tracer uptake in the thyroid gland, with physiologic visualization of the parotid and submandibular salivary glands; the downward-pointing triangle indicates the sternal notch. Right: axial (top) and longitudinal views (bottom) of ultrasonography obtained one year later, showing almost complete recovery of the abnormalities observed in the baseline ultrasound scan. Thyroidal hormonal profile was completely normal at this time.

Composition *	Points	Echogenicity *	Points	Shape *	Points	Margins *	Points	Echogenic foci §	Points
Cystic or almost completely cystic	0	Anechoic	0	Wider-than-tall	0	Smooth	0	None or large comet- tail artifacts	0
Spongiform	0	Hyperechoic or isoechoic	1	Taller-than-wide	3	Ill-defined	0	Macrocalcifications	1
Mixed cystic and solid	1	Hypoechoic	2			Lobulated or irregular	2	Peripheral (rim) calcifications	2
Solid or almost completely solid	2	Very hypoechoic	3			Extra-thyroidal extension	3	Punctate echogenic foci	3

**TABLE 1.** TI-RADS Ultrasound Features of Thyroid Nodules According to the American College of Radiology (2017)

(\*) choose only one score(§) choose all scores that apply

**TABLE 2.** Comparison of Categories and Risk of Malignancy of Thyroid Nodules According to the American College of Radiology criteria TI-RADS Versus the European Thyroid Association (ETA) EU-TIRADS Criteria.

Cat	egory		Features	_Risk of mali	gnancy	Indicatio	n to FNAB
ACR	ETA	ACR	ETA	ACR	ETA	ACR	ETA
TR1	1	0 points	no nodules	<2%	n.a.	no	n.a.
TR2	2	2 points	anechoic or entirely spongiform	<2%	0%	no	no, unless compressive
TR3	3	3 points	oval shape, smooths margins, entirely isoechoic or hyperechoic	5%	2%-4%	yes if ≥25 mm; surveillance if ≤15 mm	yes if >20 mm
TR4	4	4–6 points	mildly hypoechoic	5%-20%	6%-17%	yes if ≥15 mm; surveillance if ≥10 mm	yes if >15 mm
TR5	5	≥7 points	any of the followings: - non-oval/round shape ("taller-than-wide"); - irregular margins; - microcalcifications; - markedly hypoechoic	>20%	26%-87%	yes if≥10 mm; surveillance if≥5 mm	yes if >10 mm; active surveillance if <10 mm

#### Descriptive ACR category

TR1: benign; TR2: not suspicious; TR3: mildly suspicious; TR4: moderately suspicious; TR5: highly suspicious

#### Descriptive ETA category

1: normal (no nodules); 2: benign; 3: low risk; 4: intermediate risk; 5: high risk

Category		Features		<b>Risk of malignancy</b>		
Bethesda	BTA	Bethesda	BTA	Bethesda	BTA	
Ι	Thy1	nondiagnostic	nondiagnostic	1%-4%	4.5%-8.5%	
II	Thy2	benign	non-neoplastic	0%-3%	0%-3%	
III	Thy3a	atypia of undetermined significance/follicular lesion of undetermined significance	nondiagnostic atypia	5%-15%	pprox 10%	
IV	Thy3f	follicular neoplasm/suspicious for follicular neoplasm	suspected follicular neoplasm	15%-30%	35%-40%	
V	Thy4	suspicious for malignancy	suspicious of malignancy	60%-75%	68%-70%	
VI	Thy5	malignant	diagnostic of malignancy	97%-99%	98%-99%	

**TABLE 3**. Comparison of Prognostic Stratification of Cytology Findings after FNAB of Thyroid Nodules According to the Bethesda Reporting System versus the British Thyroid Association Reporting System.

Bethesda: Bethesda reporting system BTA: British Thyroid Association reporting system

**TABLE 4** – Summary of Major Pathophysiologic and Clinical Changes in Moderate/Severe

 Hypothyroidism

Target tissues/organs	Deficient thyroid hormone				
All tissues/organs	Decreased basal metabolic rate and thermogenesis (increased sensitivity to cold); weight gain; fatigue				
Cardiovascular and Renal function	Bradycardia; reduced contractility; dyspnea on exertion; reduced exercise tolerance; reduced glomerular filtration rate				
Nervous system	Impaired cognitive and memory functions; somnolence; vertigo; headache; numbness/tingling in extremities; decreased peripheral reflexes;				
Gastrointestinal tract	Constipation/obstipation; increased gallstone formation				
Skin and skin annexes	Dry skin; hair thinning/loss; edema of hands, face, eyelids; pallor				
Musculoskeletal	Muscle weakness; muscle aches, tenderness and stiffness; joint pain; carpal tunnel syndrome				
Reproductive apparatus	Oligo-dysmenorrhea; infertility (in females and males); miscarriages				

# Supplemental File 1: Ultrasound evaluation of goiter



Ultrasonography of a diffuse, non-nodular goiter (axial view). Outline of the thyroid gland is indicated by the broken line. Inhomogeneous ultrasound pattern, without clear nodules but with isoechoic and hypoechoic pseudonodules. TG: thyroid gland (right and left lobes). SDM: skin, dermis and muscles forming the superficial layer in the neck. TL: tracheal lumen. BV: major blood vessels of the neck.

<u>Supplemental File 2: examples of different ultrasound scores of thyroid nodules according to</u> <u>EU-TIRADS criteria of the European Thyroid Association</u>



Ultrasound features of thyroid nodules (indicated by open arrows) according to EU-TIRADS criteria. A) spongiform nodule; B) isoechoic solid nodule; C) mildly hypoechoic nodule; D) hypoechoic nodule with microcalcifications (small white arrow); E) hypoechoic nodule with taller-than-wide shape and extrathyroidal extension (small white arrow); F) markedly hypoechoic nodule with extrathyroidal extension (small white arrow). Cytology of nodules in A), B), and C) was consistent with benign (colloid) nodules, whereas nodules depicted in D), E), and F) were papillary thyroid carcinomas.

# **Supplemental File 3: Classification of Hypothyroidisms**

# Primary hypothyroidism

Congenital

- Thyroid dysgenesis
  - Aplasia; hypoplasia; ectopic gland
- Thyroid dyshormonogenesis
  - Sodium-iodide symporter defect; thyroid peroxidase defect; hydrogen peroxidase generation defects (DUOX2, DUOXA2 gene mutations); pendrin defect; thyroglobulin defect; iodotyrosine deiodinase defect
- Resistance to TSH binding or signaling
  - TSH receptor defect; G protein defect (type 1A and 1B pseudo-hypoparathyroidism)

# Acquired

- Thyroiditis
  - Autoimmune
    - Hashimoto's thyroiditis (goiter and atrophic forms)
    - Painless and post partum thyroiditis (transient, rarely permanent)
    - Subacute thyroiditis (transient, rarely permanent)
- Thyroid infiltration
  - Amyloidosis; hemochromatosis; sarcoidosis
- Iodine deficiency; goitrogens in foodstuffs; pollutants
- Iodine excess
- Iatrogenic
  - <sup>131</sup>I-iodide therapy
  - Surgery
  - Esternal irradiation for nonthyroidal malignancy
  - Drugs
    - Antithyroid drugs (methimazole, carbimazole, propylthiouracil)
    - Amiodarone, lithium, iodide, interferon-α, tyrosine kinase inhibitors

# **Central hypothyroidism**

Congenital

- Isolated TSH deficiency
- Congenital hypopituitarism (combined pituitary hormone deficiencies)

# Acquired

- Pituitary (secondary) or hypothalamic (tertiary) disorders
- Bexarotene (retinoid X receptor agonist)
- Dopamine or severe illness

# Peripheral congenital hypothyroidism

- Thyroid hormone cell membrane transport defect (MCT8 gene mutations)
- Thyroid hormone resistance (thyroid hormone receptor  $\alpha \in \beta$  gene mutations)

# Supplemental File 4: examples of ultrasound patterns in hypothyroidism



Ultrasound patterns observed in hypothyroidism (axial views). Upper panel: chronic autoimmune thyroiditis, showing enlarged thyroid lobes with diffuse, moderate hypoechogenicity and marked inhomogeneity. Middle panel: chronic autoimmune thyroiditis, showing the atrophic form. Lower panel: thyroid hemiagenesis, showing a normal right lobe and isthmus, but completely absent left thyroid lobe.