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The Role of Real-Time Thyroid Ultrasonography in the Assessment and Management of Patients with Hashimoto's Thyroiditis

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1. Introduction

The most common cause of hypothyroidism is the autoimmune disorder Hashimoto's thyroiditis, the stages of which can be accurately and objectively assessed by serial, real-time thyroid ultrasonography. Early stages of chronic thyroiditis include; increased vascularity and a patchy heterogeneous texture reflecting the inflammatory infiltrations, enlargement of the thyroid gland and sometimes associated lymphadenopathy. As the autoimmune destruction of the thyroid gland continues the normal thyroid texture progressively changes until the tissue is replaced by empty spaces, so called end-stage. We can follow the course of the thyroiditis, which typically proceeds over several years, correlating with clinical features, thyroid [thyroid peroxidase (TPO), thyroglobulin (Tg)] antibody titres and serum levels of thyroid stimulating hormone (TSH) and free thyroxin (T4). We can confirm change in thyroid status from Hashimoto's thyroiditis to Graves' disease when TSH-receptor antibodies are additionally produced, document remission in young patients with Hashimoto's thyroiditis and we can obtain diagnostic information in patients with the rare but serious Riedel's thyroiditis. In the hands of an experienced operator real-time thyroid ultrasonography can provide information about the underlying autoimmune process. For example, ultrasound abnormalities can be correlated with; the eye changes that are found in about 25% of patients (1), serum levels of calsequestrin and collagen XIII antibodies (2-5), serum levels of thyroid antibodies and other parameters of the autoimmune process including phenotypes and numbers of infiltrating T lymphocytes in the thyroid.

In this chapter, we will highlight the use of real-time ultrasound in the assessment of patients with Hashimoto's thyroiditis, not only for clinical purposes but also to provide information about the pathogenesis of Hashimoto's thyroiditis and its variants such as silent and post partum thyroiditis and Riedel's thyroiditis.

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2. Serial studies in Hashimoto's thyroiditis

In the hands of a single operator using standard criteria for assessing the ultrasound changes of Hashimoto's thyroiditis, real-time thyroid ultrasonography is a valuable new tool for diagnostic and management purposes. Images can be stored and changes compared serially in individual patients and correlated with immune parameters in cohorts of patients in research studies. Fine needle aspiration (FNA) biopsy can characterise any nodules and features of the Hashimoto's thyroiditis process itself, such as numbers of lymphocytes and other mononuclear cells and overall architectural changes. Typically, the most classical appearance in early thyroiditis is the formation of small cystic areas throughout the gland which reflect the lymphoid infiltrations (fig 1) which progresses to a stage of multi-cystic disease (fig. 2). Later, there is increased destruction of the thyroid follicles, scarring and pseudo nodule formation (fig. 3) and the gland becomes shrunken and avascular (fig 4). Finally, in long standing cases, there may be tissue calcification (fig. 4). The full process takes from many months to 2-3 yr although this needs to be shown in a long term prospective study of patients who were diagnosed early, i.e. with no symptoms, normal TSH and positive serum thyroid antibodies, correlating ultrasound changes with parameters of thyroid function and the autoimmune reactions. We have followed a few such patients

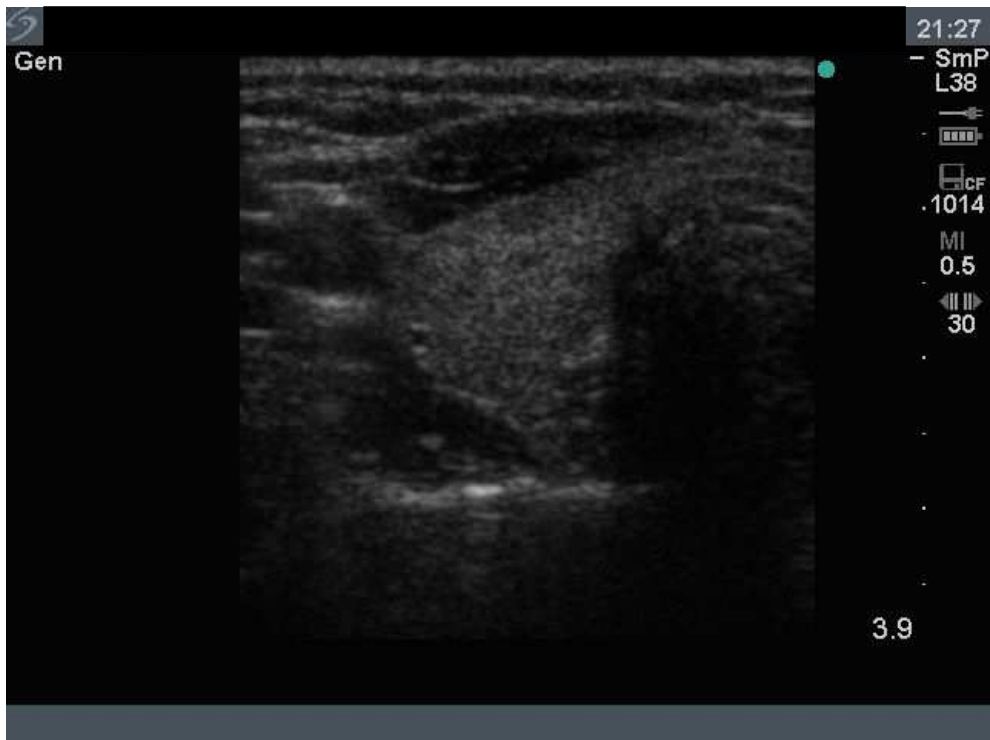


Fig. 1. Thyroid ultrasound changes in a 23 yr old female with early Hashimoto's thyroiditis and subclinical hypothyroidism (normal FT4, TSH 4.5) showing minimal cystic changes and a patchy texture, reflecting the autoimmune reactions.

with Hashimoto's thyroiditis over a course of the natural history of the disease before and after treatment with thyroxin, observing that the correlation between findings on real time ultrasound, thyroid function and thyroid antibody levels are indeed close (Wall, Champion *et al* unpublished observations). Moreover, ultrasonographic changes correlate closely with serum TSH and T4 values and clinical features of both the thyroiditis (tender painful gland, goitre) and hypothyroidism and can indicate accurately the stage of the disease and whether or not a patient needs to be treated with thyroxin.



Fig. 2. Ultrasound changes in a 30 yr old male with more severe Hashimoto's thyroiditis and overt hypothyroidism showing extensive cystic changes throughout the lobe, especially in the upper parts, scarring and pseudo nodule formation.



Fig. 3. Typical ultrasound changes in a 50 yr old female with long standing hypothyroidism due to Hashimoto's thyroiditis. The thyroid tissue has been destroyed and replaced by empty spaces (seen as black areas) and linear scarring, giving the appearance of pseudo nodules. This can be called "end stage" disease. In this patient, the gland is slightly enlarged although with time it becomes shrunken and small.



Fig. 4. Late stage Hashimoto's thyroiditis in a 45 yr old female showing chronic, egg shell, calcification seen as a 1 cm calcified ball with shadowing (due to inability of the ultrasound waves to penetrate the calcified material).

3. Thyroid nodules in Hashimoto's thyroiditis

There is an increased prevalence of thyroid cancer in patients with Hashimoto's thyroiditis (6) so any nodules (fig. 5) should be carefully documented, assessed for signs of malignancy and ultrasound-guided fine needle aspiration biopsy (FNA) performed where appropriate. The possibility that the number and/or size of any nodules might reflect the severity and extent of the autoimmune process or represent a surrogate for the development of ophthalmopathy, could be studied.



Fig. 5. A suspicious hypo echoic nodule in the thyroid of a 35 yr old female patient with early Hashimoto's thyroiditis. Apart from a few small cystic areas around the nodule and mild patchiness throughout, the texture of the gland itself is relatively normal

4. Conversion of Hashimoto's thyroiditis to Graves' hyperthyroidism

Changes in the status of the autoimmune reactions of Hashimoto's thyroiditis can be quantified by measurement of serial TPO, Tg and TSH-receptor antibodies and some patients show dramatic changes from one disorder to the other, particularly development of Graves' disease even after the apparent destruction of the thyroid gland by the Hashimoto's thyroiditis process. We have studied a 14 yr old female patient who presented with profound hypothyroidism due to Hashimoto's thyroiditis with high levels of TSH and unmeasurable T4 and ultrasound appearances typical of end stage Hashimoto's thyroiditis who later converted to Graves' hyperthyroidism with the development of TSH-r antibodies (7). We were able to show by serial real time thyroid US, destruction of the thyroid gland initially then re filling with newly formed follicular cells through the action of the TSH receptor antibodies, followed by overall thyroid enlargement and finally, the typical heterogeneous appearance of Graves' hyperthyroidism that reflect the lymphoid infiltration,

including increased vascularity (fig. 6a, 6b). This is the first documented observation of change from hypothyroidism to hyperthyroidism recorded by real time thyroid ultrasonography (7).

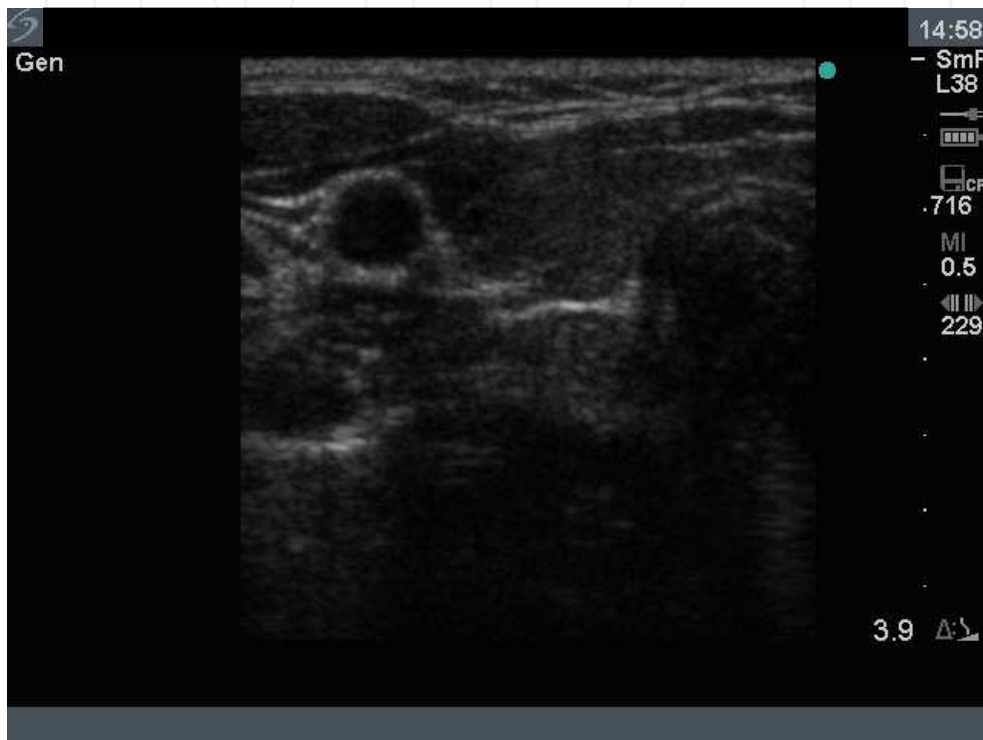


Fig. 6a. Ultrasound appearance of the thyroid gland in a 14 year old female patient 10 months after presenting with Hashimoto's thyroiditis and profound hypothyroidism and 9 months after biochemical and clinical conversion to Graves' hyperthyroidism. The typical appearances of Hashimoto's thyroiditis namely, a small, shrunken lobe and isthmus and generalized hypoechoicity due to inflammation of the thyroid tissue, are still present.



Fig. 6b. Thyroid ultrasonography 16 months later (30 months after biochemical and clinical conversion from Hashimoto's hypothyroidism to Graves' hyperthyroidism). The thyroid is larger, particularly the isthmus, more hyper echoic throughout and typical of fully established Graves' hyperthyroidism

5. Remission in young patients with Hashimoto's thyroiditis

We have studied a 12 yr old girl with Hashimoto's thyroiditis was initially euthyroid and later treated with 50 µg l-thyroxin (L-T4) when her fT4 had declined from 17 to 7 pmol/L (normal range, 8-22 pmol/L). At this time her TSH was 4.1 mIU/L (normal range, 0.30-4.0 mIU/L) and thyroid ultrasonography demonstrated features of early inflammation. Two years later, while on the same dose of T4, ultrasound examination revealed severe end-stage Hashimoto's thyroiditis (fig 7a) and thyroid function tests showed a T4 of 14.0 pmol/L and TSH of 0.81 mIU/L. Twelve months later, however, the thyroid ultrasound had returned to almost normal with only minimal features of inflammation (fig 7b). Thyroid function tests showed an fT4 of 12.8 pmol/L and TSH of 0.75 mIU/L. Her T4 treatment was then stopped. Eight, 17, and 30 weeks after this, her fT4 levels were 16.8, 9.7, and 13.9 pmol/L, respectively. Twelve months later her goitre suddenly enlarged and became tender; ultrasound revealed that she now had features of end stage disease with a huge empty

thyroid gland (fig 7c) and fT4 level was low (8 pmol/L) and TSH elevated (11 mU/L) and she was again treated with thyroxin, this time permanently. This is the first recording of serial thyroid ultrasound changes in a patient with Hashimoto's thyroiditis that paralleled changes in thyroid function. This case (8) indicates that thyroiditis can have a fluctuating course, including go into remission in some children. Thyroid ultrasound may be useful to make presumptive therapeutic decisions in children and adolescents with Hashimoto's thyroiditis whose dose of thyroid hormone seems to be less than is full replacement. Thyroid function tests, however, should ultimately guide T4 dosage. It is well recognised that Hashimoto's thyroiditis can be transient in about a third of young patients whereas it is presumed that in adults in all cases it is progressive into end stage destruction and hypothyroidism which is permanent. Use of real time thyroid ultrasonography provides an additional aid to studies of cohorts of children and teenagers to objectively characterise the natural history of the disease.

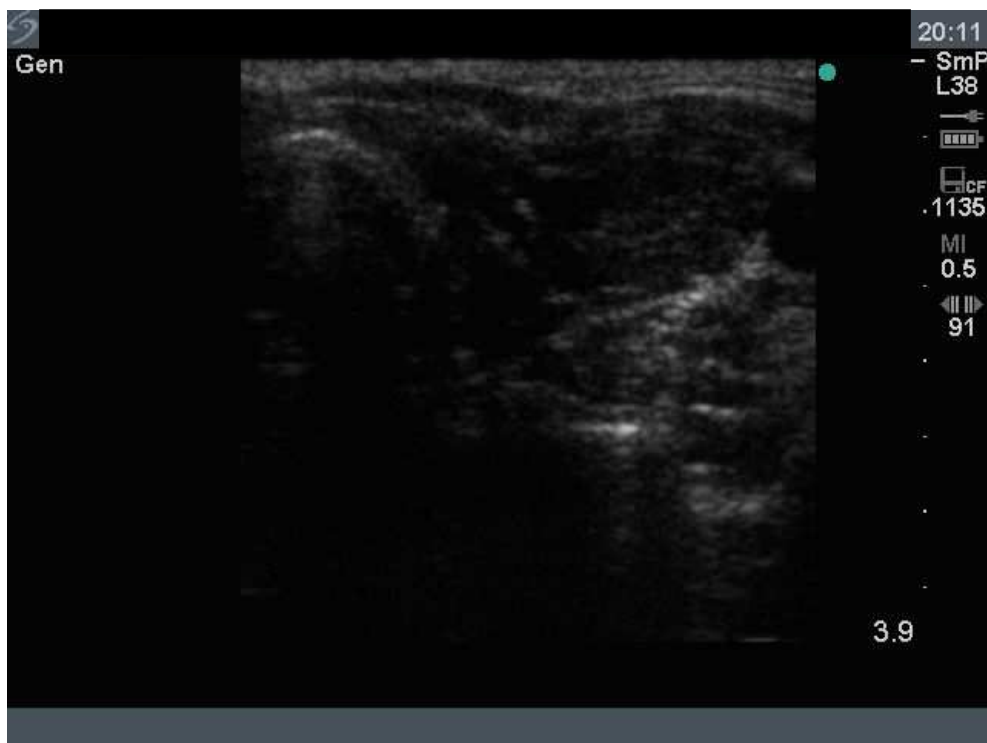


Fig. 7a. Thyroid ultrasonography in a 12-year-old girl with Hashimoto's thyroiditis who was initially euthyroid and later treated with 50 µg l-thyroxin (L-T4) when her fT4 had declined from 17 to 7 pmol/L (normal range, 8-22 pmol/L). At this time her TSH was 4.1 mIU/L (normal range, 0.30-4.0 mIU/L) and thyroid ultrasonography demonstrated features of severe thyroiditis similar to those seen in fig. 3.

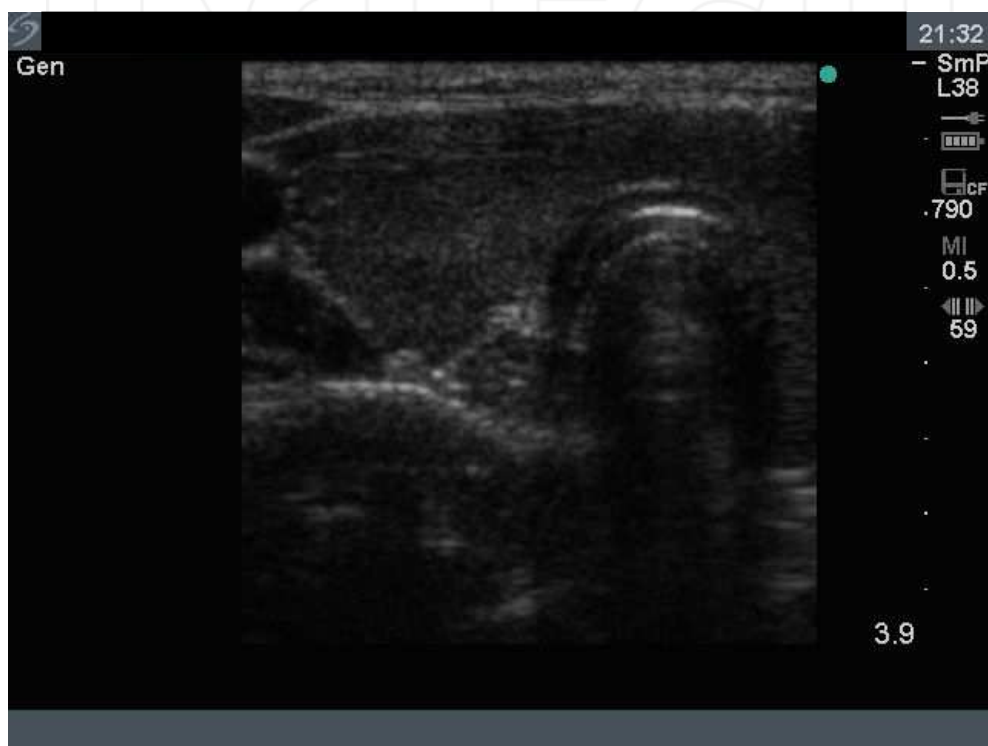


Fig. 7b. Eighteen months later, the thyroid ultrasound in this patient has returned to almost normal with only minimal features of inflammation. Thyroid function tests showed an fT4 of 12.8 pmol/L and TSH of 0.75 mIU/L and she was clinically euthyroid and well.



Fig. 7c. Twelve months later this patient's goitre suddenly enlarged greatly and was tender; ultrasound revealed that she now had features of end stage disease with a huge empty thyroid gland and fT4 level was low (8 pmol/L) and TSH elevated (11 mU/L) and she was again treated with thyroxin, this time permanently.

6. Riedel's thyroiditis

A female aged 25 with a very large, firm goitre, strongly positive thyroid antibodies and marked and resistant hypothyroidism was studied by ultrasound. Her gland was non-tender, stony hard to palpation, diffusely enlarged with no associated adenopathy. (fig. 8). On ultrasound (fig. 8), the texture was quite different to that found in classical Hashimoto's thyroiditis (see above) and consistent with massive fibrosis. Indeed, this patient also had evidence for generalised fibrotic process with radiologically and biopsy proven retroperitoneal fibrosis causing bilateral ureteric obstruction. She was treated with thyroxin as well as glucocorticoids and azathiaprine to control her systemic fibrotic process. Tamoxifen, with anti-transforming growth factor (TGF) beta properties, is also another potential therapeutic strategy.

Riedel thyroiditis, or Riedel's thyroiditis, is a rare, chronic inflammatory disease of the thyroid gland characterized by a dense fibrosis that replaces normal thyroid parenchyma (9). At the Mayo clinic, 37 cases were diagnosed in a series of 57,000 thyroidectomies that were performed between 1920 and 1984. The operative incidence was 0.06% and the overall

incidence in outpatients was 1.06 per 100,000 (10). The fibrotic process invades adjacent structures of the neck and extends beyond the thyroid capsule. This feature differentiates Riedel's thyroiditis from other inflammatory or fibrotic disorders of the thyroid. Because of the encroachment beyond the thyroid capsule, other problems can be associated with Riedel's thyroiditis, including hypoparathyroidism, hoarseness (due to recurrent laryngeal involvement), and stridor (due to tracheal compression). Approximately one third of Riedel's thyroiditis cases are associated with clinical findings of multifocal fibrosclerosis at the time of diagnosis. Riedel's thyroiditis is also associated with other fibrous inflammatory processes, including retroperitoneal fibrosis, orbital pseudotumor, mediastinal fibrosis, sclerosing cholangitis and fibrosis in other organ systems.



Fig. 8. Thyroid ultrasound in a 32 yr old woman with Riedel's thyroiditis, a very large goiter, a systemic fibrotic reaction, strongly positive thyroid antibodies and marked and resistant hypothyroidism. The isthmus is 2.20 cm thick, approximately 3 times normal, and the texture of the thyroid contents is quite different from that found in classical end-stage Hashimoto's thyroiditis (see above), with large oblong hypo echoic spaces scattered among more iso echoic areas, consistent with a combination of thyroiditis and diffues fibrosis, respectively.

7. Eye changes in patients with Hashimoto's thyroiditis

Mild eye signs (ophthalmopathy) are common in patients with Hashimoto's thyroiditis (1) if looked for (since the main and sometimes only sign is upper eyelid lag) and correlate fairly

closely with a variety of eye muscle antibodies which are probably secondary to the putative inflammation of the levator palpebrae superioris muscle. We have studied patients with Graves' hyperthyroidism, addressing whether the thyroid size - as a surrogate for the severity of the "thyroiditis" - is a marker for associated ophthalmopathy (Olliffe, Wall submitted). While we did not demonstrate a significant correlation between bigger thyroid size and ophthalmopathy we have not yet studied patients with Hashimoto's thyroiditis in whom goitre size varies a lot and could - in the early stages before destruction - provide a better marker for subsequent eye signs. Ultrasound changes can also be correlated with serum titres of calsequestrin and collagen XIII antibodies and eye signs in patients with Hashimoto's thyroiditis.

8. Relationship between thyroid and orbital immune reactions in pregnant patients with Hashimoto's thyroiditis

Changes in the thyroid and orbital inflammatory processes may run in parallel or diverge in pregnancy and real-time ultrasound has been used to study patients with Graves' disease and Hashimoto's thyroiditis from pre-pregnancy through pregnancy and in the post-partum period. Changes in the status of Hashimoto's thyroiditis is common during pregnancy and afterwards. We are studying whether these abnormalities are reflected in ultrasound changes, goitre size and thyroid antibody titres and whether they run parallel to changes in eye signs and serum titres of calsequestrin and collagen XIII antibodies or run divergent courses. Preliminary results suggest that thyroid and eye muscle antibody levels fall in parallel during pregnancy and rebound together in the post partum period and correlate with changes in eye signs in patients with Graves' disease and Hashimoto's thyroiditis (Wall, Champion et al., unpublished observations). This suggests that the ophthalmopathy of both Graves' disease and Hashimoto's thyroiditis is closely linked with the thyroid autoimmune process in both disorders, although this study is ongoing. In Hashimoto's thyroiditis the eye changes are usually mild and confined to the upper eyelids with mild proptosis, but the underlying process seems to be the same. While most workers (11-13) believe that the reason for the association is due to cross reactive antibodies targeting the TSHr in the thyroid follicular cell and orbital fibroblast and pre adipocyte TSHr antibodies are not always detected in patients with eye signs (1). For this reason we propose that there may be a primary eye muscle reaction against calsequestrin. and possibly collagen XIII (2-5, 14).

9. Conclusions

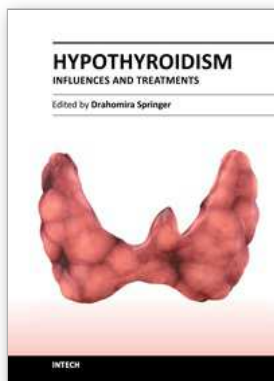
Real-time thyroid ultrasonography is an under utilised tool for the assessment of Hashimoto's thyroiditis and hypothyroidism in individual patients and in research studies. Use of real-time thyroid ultrasonography gives us a unique opportunity to directly observe the consequences of the thyroid autoimmune process in the thyroid gland. We have shown how the ultrasonographic changes closely reflect the nature of the immune reactions, their effects on thyroid follicles and tissue architecture in general and on the ability of the thyroid gland to produce thyroid hormones.

There are limitations to ultrasonography, in particular that we have not proven that the observed visual changes can be directly extrapolated to the immune reactions in the thyroid. However, as technology improves, for example when we can characterise and quantify the

lymphoid patches, we can expect to be able to better correlate what is seen on ultrasound with the underlying autoimmune reactions.

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Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

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