CLINICAL PRACTICE GUIDELINES

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Management of
THYROID DISORDERS

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STATEMENT OF INTENT

These clinical practice guidelines (CPGs) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient, based on the clinical picture presented by the patient and the management options available locally.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the Web version of this document, which is the definitive version at all times. This version can be found at the websites mentioned above.

UPDATING THE CPG

These guidelines were issued in 2019 and will be reviewed in a minimum period of four years (2023) or sooner if new evidence becomes available. When they are due for updating, the Chairman of the CPG or National Adviser of the related speciality will be informed about it. A discussion will be held on the need for a revision, including on the scope of the revised CPG. A multidisciplinary team will be formed, and the latest systematic review methodology used by MaHTAS will be employed.

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KEY RECOMMENDATIONS

The following recommendations were highlighted by the guidelines Development Group as the key clinical recommendations that should be prioritised for implementation.

HYPERTHYROIDISM

- In patients with suspected hyperthyroidism, serum TSH and fT4 should be obtained at the initial evaluation. fT3 should be measured when TSH is suppressed but fT4 is within normal range.
- Patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: ATDs, RAI therapy, or thyroidectomy.
- If ATD is chosen as the primary therapy for GD, the medication should be continued for approximately 12–18 months, and then discontinued if the TSH levels are normal at that time.
- If surgery is chosen as the primary therapy for GD, near total or total thyroidectomy is the procedure of choice and should be referred to a high-volume thyroid surgeon.
- Patients with overtly TMNG or TA should be treated with RAI therapy or thyroidectomy. On occasion, long-term, low-dose treatment with MMI may be appropriate.
- A differential WBC count should be obtained during febrile illness and at the onset of pharyngitis in all patients taking antithyroid medication.
- Liver function and hepatocellular integrity should be assessed in patients taking MMI or PTU who experience pruritic rash, jaundice, light-coloured stool or dark urine, joint pain, abdominal pain or bloating, anorexia, nausea, or fatigue.

HYPOTHYROIDISM

- Levothyroxine is the recommended preparation of choice and the mainstay of treatment of hypothyroidism.

The three main aims of therapy are:

    i) To provide resolution of signs and symptoms, including biological and physiological markers of hypothyroidism

    ii) To achieve normalisation of serum TSH with improvement in thyroid hormone concentrations

    iii) To avoid iatrogenic thyrotoxicosis or overtreatment particularly in the elderly

- Levothyroxine is best taken on empty stomach (1 hour before breakfast or at bedtime, at least 3 hours after the last meal of the day) because absorption is impaired if taken with food. Compliance may be enhanced however, by instructing patients to consistently take it before breakfast each day.

- Levothyroxine replacement therapy can be started as an initial full replacement or as partial replacement with gradual dose increments titrated using serum TSH as the goal. Dose adjustments should be made when there are significant changes in body weight, and with pregnancy and ageing. Serum TSH should be reassessed 4–8 weeks after any dose adjustments.

SUBCLINICAL THYROID DISORDERS

- When TSH is persistently <0.1 mIU/L, treatment of SCHyper is recommended in all individuals >65 years of age.
- Antithyroid drugs should be the first line and initial treatment for subclinical hyperthyroidism, whatever the aetiology.
- Radioactive iodine therapy should be considered in those with persistent and progressive subclinical hyperthyroidism due to autonomous nodule and multinodular goitre.
- Investigation of raised TSH requires repeated measurements to establish a firm diagnosis of subclinical hypothyroidism.

THYROID NODULES/GOITRE

- All patients with a suspected thyroid nodule/nodular goitre or radiographic abnormality suggesting a thyroid nodule incidentally detected on another imaging study should undergo a dedicated thyroid/neck US that encompasses the thyroid as well as the central and lateral neck compartments.
- Surgery is recommended in:
    i.   symptomatic compression or large goitres (>80 g)
    ii. relatively low uptake of RAI
    iii. when thyroid malignancy is documented or suspected (e.g. suspicious or indeterminate cytology)
    iv. large thyroid nodules, especially if greater than 4 cm or if nonfunctioning, or hypofunctioning on ^{123}I or [99]mTc pertechnetate scanning
    v.   coexisting hyperparathyroidism requiring surgery
    vi. especially if TRAb levels are particularly high
    vii. patients with moderate-to–severe active Graves' Ophthalmopathy (GO)
- Surgery is not recommended for patients with substantial comorbidity such as cardiopulmonary disease, end-stage cancer, or other debilitating disorders, or where there is lack of access to a high-volume thyroid surgeon.
- Subacute thyroiditis should be suspected in all patients who present with painful goitre.

THYROID EMERGENCIES

Thyroid Storm

- The diagnosis of thyroid storm is clinical. Both the BWPS and JTA diagnostic tools could be used to aid diagnosis, but we recommend the use of BWPS as this scoring tool is more sensitive.
- High doses of PTU (500–1000 mg loading, then 250 mg, 4–6 hourly) should be used in thyroid storm. In the presence of contraindications, high doses of MMI (60–80 mg/day) can be used.
- β-adrenergic receptor antagonists such as propranolol should be administered in thyroid storm to control heart rate and inhibit other peripheral action of thyroid hormone.
- Shorter acting intravenous esmolol or diltiazem can be used to control heart rate when there are contraindications to β-adrenergeic receptor antagonists.
- High doses of glucocorticoids (IV hydrocortisone 100 mg, 6 hourly or dexamethasone 2 mg, 6 hourly) should be given in thyroid storm.
- 5–10 drops of Lugols iodine 6–8 hourly for the first 10 days, should be given after administration of antithyroid drugs for rapid improvement of thyrotoxicosis in thyroid storm.
- All patients with thyroid storm should have early definitive therapy with RAI. In patients with large obstructing goitre or contraindications to RAI, early thyroidectomy should be considered instead.

Myxoedema Coma

- Intravenous hydrocortisone 200 mg start then 100 mg 6–8 hourly should be administered prior to levothyroxine.
- Initial intravenous levothyroxine of 200–400 μg followed by 1.6 mcg/kg/day (75% if administered intravenously) should be given thereafter. If intravenous levothyroxine is not available, oral levothyroxine can be given as 500 mcg loading followed by maintenance dose.
- Intravenous liothyronine (when available) may be given in addition to thyroxine. Loading dose recommended is 5–20 mcg followed by 2.5–10 mcg every 8 hours till patient regains consciousness.

Pre-/Perioperative Management

- All elective surgery should be postponed until euthyroidism or near euthyroid state is achieved.
- In patients who are hyperthyroid and require urgent surgery, rapid control with high dose MMI or PTU, β-blockers, Lugol's iodine and glucocorticoids are recommended.

THYROID DISORDERS IN PREGNANCY

- Pregnant women with OH should be treated with LT4.
- For maternal SCHypo, LT4 treatment is recommended in the following situations to reduce the risk of miscarriage and preterm delivery:
  a) Pregnant women with negative TPOAb:
     - LT4 is recommended if TSH is >10 mIU/L
     - LT4 may be considered if TSH is above the pregnancy specific reference range or 4.0 mIU/L
  b) Pregnant women with positive TPOAb:
     - LT4 is recommended if TSH is above the pregnancy specific reference range or 4.0 mIU/L
     - LT4 may be considered if TSH is >2.5 mIU/L
- For hypothyroid women already treated with LT4 before conception, we recommend a TSH goal of not more than 2.5 mIU/L before conception and during first trimester as the trimester specific reference range for Malaysian population is not available.
- During the second and third trimester, a TSH goal of 3.0 mIU/L or below can be adopted.
- Pregnant women who are already treated with LT4 before conception are recommended to have their LT4 dosage increased by 30%–50% upon conception with a higher percentage being considered for post ablative hypothyroidism and lower percentage for autoimmune hypothyroidism.
- When a suppressed TSH and elevated fT4 are detected in the first trimester, clinical history and physical examination should be performed to determine the aetiology. Graves' disease is differentiated from gestational thyrotoxicosis clinically. TRAb supports the diagnosis of Graves' disease.
- Management of gestational transient thyrotoxicosis is mainly through supportive therapy: rehydration and hospitalisation if needed in the presence of hyperemesis gravidarum; and β-blocker if very symptomatic. Antithyroid drug is not recommended.
- In pregnant women in whom ATD needs to be continued; PTU is recommended throughout the first trimester.
- The lowest effective dose of ATD should be used for thyrotoxicosis during pregnancy, targeting fT4 at or moderately above the reference range.
- In postpartum thyroiditis
  - Women in thyrotoxic phase of PPT who are symptomatic should be treated with β-blockers; ATDs are not recommended.
  - Women in hypothyroid phase of PPT and who are symptomatic should be treated with thyroxine. Women with mild symptoms who choose not to be treated need to have their TFT checked every 4–8 weekly until euthyroidism is restored.

ACQUIRED HYPOTHYROIDISM AND HYPERTHYROIDISM IN CHILDREN AND ADOLESCENTS

- **Hypothyroidism secondary to Hashimoto's thyroiditis:** Levothyroxine is recommended as the medication of choice with the recommended dose is based on the body weight or body surface area. The recommended target range for TSH is in the lower half of the reference range while for free T4 is in the upper half of the reference range. Levothyroxine is effective in reducing the thyroid gland size/goitre.

- **Non-goitrous euthyroid Hashimoto's thyroiditis:** One should monitor for goitre, antithyroid antibodies and pattern of thyroid function; treatment with thyroxine is controversial.

- **Hyperthyroidism:** The first-line initial treatment is ATD, which is carbimazole or its active metabolite MMI. Methimazole/carbimazole dose typically used is 0.2–0.5 mg/kg daily, with a range from 0.1 mg/kg to 1.0 mg/kg daily (maximal initial dose: 30 mg daily). After 2–4 weeks, when the thyroid hormone levels have normalised, the initial dose should gradually be reduced by 30%–50%. TSH levels may take 2–4 months to appear in the serum and should not be used to titrate the dose. If children develop serious adverse reactions to MMI, RAI or surgery should be considered, because the risks of PTU are considered greater than the risks of RAI or surgery.

- **Hyperthyroidism:** Propylthiouracil (PTU) should not be used in children. If it is used, it should be stopped immediately and liver function should be assessed in children who develop anorexia, pruritus, rash, jaundice, light coloured stool or dark urine, joint pain, right upper quadrant pain or abdominal bloating, nausea or malaise due to the risk of idiosyncratic liver failure.

- **Hyperthyroidism:** Definitive therapy available for GD is RAI or thyroidectomy. Indications for definitive treatment in children include relapse after an appropriate duration of ATD, a lack of compliance on the part of the patient/ caretakers or adverse effects of ATD. The issue of how long ATDs should be used in children before considering either RAI or surgery is controversial.

THYROID DISORDERS IN THE ELDERLY

In subclinical hypothyroidism

- In patients aged >70 years, if serum TSH is ≥10 mIU/L, consider L-thyroxine treatment if patients have clear symptoms of hypothyroidism or high vascular risk.

- In patients aged >70 years, if serum TSH is ≤10 mIU/L, observe and repeat TFTs in 6 months.

- In patients aged ≤70 years, if serum TSH is ≥10 mIU/L, consider L-thyroxine treatment.

- In patients aged ≤70 years, if serum TSH is ≤10 mIU/L and symptoms of hypothyroidism are present, consider a 3-month trial of L-thyroxine, then assess response to treatment.

- In patients aged ≤70 years, if serum TSH is ≤10 mIU/L and there are no symptoms of hypothyroidism, observe and repeat TFTs in 6 months.

DRUG-INDUCED THYROID DISORDERS

- Monitor TFTs before and 3–4 months after starting amiodarone and at 3–6 months interval thereafter. Monitor for up to 1 year after stopping amiodarone.

GRAVES OPTHALMOPATHY

- Assessment of GO includes assessment of activity and severity using standardised criteria. Graves opthalmopathy is categorised as active or inactive; mild, moderate, severe or sight threatening.
- Euthyroidism should be restored as soon as possible in patients with GO.
- Oral prednisolone prophylaxis of 0.4–0.5 mg/kg/day for a total of 3 months is recommended in patients with mild-to–moderate GO who are undergoing radioiodine therapy.

LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees
SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE 2001	

FORMULATION OF RECOMMENDATION

In line with new development in CPG methodology, the CPG Unit of MaHTAS is in the process of adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group.

In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:
- Overall quality of evidence
- Balance of benefits versus harms
- Values and preferences
- Resource implications
- Equity, feasibility, and acceptability

GUIDELINE DEVELOPMENT AND OBJECTIVES

GUIDELINE DEVELOPMENT

The members of the Development Group (DG) for these CPG were from the Ministry of Health (MoH) and Ministry of Higher Education (MoHE).

A systematic literature search was carried out using the following electronic databases/platforms: Guidelines International Network (G-I-N), Medline via Ovid, Cochrane Database of Systemic Reviews (CDSR), and Pubmed. The inclusion criteria are all thyroid diseases/disorders regardless of study design. The search was limited to literature published in the last 10 years and on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched and experts in the field contacted to identify relevant studies. All searches were conducted from 1 March 2017 to 31 December 2017. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

Reference was also made to other guidelines as listed below:
- Ministry of Health Malaysia–CPG on Management of Thyroid Dysfunction During Pregnancy and Postpartum 2007
- American Thyroid Association–Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis 2016
- American Thyroid Association–Guidelines for the Treatment of Hypothyroidism 2014
- American Thyroid Association–Guidelines for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum 2017
- European Thyroid Association–Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism 2015
- European Thyroid Association Guideline: Management of Subclinical Hypothyroidism 2013

These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used for reference.

A total of 138 clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. The DG members met 11 times throughout the development of these guidelines. All literature retrieved was appraised by at least two DG members using the Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed at each DG meeting. All statements and recommendations formulated after that were agreed upon by the DG. Where evidence was insufficient, recommendations were made by consensus of the DG. Any differences in opinion are resolved consensually. The CPG was based largely on the findings of systematic reviews, meta-analyses, and clinical trials, with local practices taken into consideration.

The literature used in these guidelines was graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001). The writing of the CPG follows strictly the requirement of AGREE II.

On completion, the draft CPG was reviewed by external reviewers. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (Available at: http://www.moh.gov.my/penerbitan/mymahtas/CPG_MANUAL_MAHTAS.pdf).

OBJECTIVES

The objectives of the CPGs are to provide evidence-based recommendations on thyroid diseases on these aspects:
i. Screening and diagnosis
ii. Management (non-pregnant adults, pregnancy, adolescents, and children)

TARGET GROUP/USER

This CPG intends to guide those involved in the management of thyroid diseases either in primary or secondary/tertiary care, namely:
i. Medical officers and specialists in public and private practice
ii. Allied health professionals
iii. Trainees and medical students
iv. Patients and their advocates
v. Professional societies

HEALTHCARE SETTINGS

Outpatient, inpatient, and community settings

DEVELOPMENT GROUP

CHAIRPERSON

Prof. Dato' Dr. Mafauzy Mohamed
Senior Consultant Endocrinologist,
Hospital Universiti Sains Malaysia,
Kubang Kerian, Kelantan

MEMBERS *(alphabetical order)*

Dr. Foo Siew Hui
Consultant Physician & Endocrinologist,
Hospital Selayang,
Selayang, Selangor

Dr. Hanisah Abdul Hamid
Chemical Pathologist,
Hospital Tengku Ampuan Rahimah,
Klang, Selangor

Dr. Ijaz Hallaj Rahmatullah
Physician & Endocrinologist,
Hospital Raja Permaisuri Bainun,
Ipoh, Perak

Assoc. Prof. Dr. Jeyakantha Ratnasingam
Consultant Endocrinologist,
University Malaya Medical Centre,
Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur

Dr. Kuan Yueh Chien
Endocrinologist & Physician,
Hospital Umum Sarawak,
Kuching, Sarawak

Dr. Lim Shueh Lin
General Physician & Endocrinologist,
Hospital Pulau Pinang,
George Town, Pulau Pinang

Dr. Mohammad Arif Shahar
Consultant Physician & Endocrinologist,
Avisena Specialist Hospital,
Shah Alam, Selangor

Assoc. Prof. Dr. Muhammad Yazid Jalaludin
Consultant Paediatric Endocrinologist,
Department of Paediatrics,
Faculty of Medicine, University Malaya,
Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur

Assoc. Prof. Dr. Noor Shafina Mohd Nor
Paediatric Endocrinologist,
Faculty of Medicine, Universiti Teknologi MARA,
Sungai Buloh, Selangor

Prof. Dr. Nor Azmi Kamaruddin
Senior Consultant Endocrinologist,
Universiti Kebangsaan Malaysia Medical Centre,
Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur

Dr. Nor Faizah Ghazali
Family Physician,
Klinik Kesihatan Tanglin,
Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur

Dr. Norhaliza Mohd Ali
Consultant Physician & Endocrinologist,
Hospital Sultanah Aminah,
Johor Bahru, Johor

Dr. Siti Rohani Mohammad Alias
Family Physician,
Klinik Kesihatan Jinjang,
Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur

Dr. Siti Sharina Anas
Chemical Pathologist,
Hospital Putrajaya,
Putrajaya, Wilayah Persekutuan Putrajaya

Dr. Suhaimi Hussain
Paediatric Endocrinologist,
Hospital Universiti Sains Malaysia,
Kubang Kerian, Kelantan

Dr. Tong Chin Voon
General Physician & Endocrinologist,
Hospital Melaka,
Melaka

Dr. Yong Sy Liang
Endocrinologist,
Hospital Tengku Ampuan Rahimah,
Klang, Selangor

Dr. Wong Sze Lyn Jeanne
Paediatric Endocrinologist,
Hospital Putrajaya,
Putrajaya, Wilayah Persekutuan Putrajaya

Dr. Zanariah Hussein
Consultant Physician & Endocrinologist,
Hospital Putrajaya,
Putrajaya, Wilayah Persekutuan Putrajaya

EXTERNAL REVIEWERS

The following external reviewers provided feedback on the draft:

Dr. Azriyanti Anuar Zaini
Consultant Paediatric Endocrinologist,
University of Malaya Medical Centre,
Kuala Lumpur

Dr. Florence Tan
Consultant Endocrinologist,
Sarawak General Hospital,
Kuching

Dr. Janet Hong Yeow Hua
Consultant Paediatric Endocrinologist,
Hospital Putrajaya,
Putrajaya

Professor Dr. Khoo Ee Ming
Primary Care Physician,
University of Malaya Medical Centre,
Kuala Lumpur

Dr. Khor Hui Min
Consultant Geriatrician,
University of Malaya Medical Centre,
Kuala Lumpur

Dr. Leslie Charles Lai Chin Loy
Consultant in Chemical Pathology and Metabolic Medicine,
Gleneagles Medical Centre,
Kuala Lumpur

Prof. Dr. Liza Sharmini Ahmad Tajudin
Professor and Senior Consultant Ophthalmologist,
Hospital Universiti Sains Malaysia,
Kota Bharu

Assoc. Prof. Dr. Mohd Pazudin Ismail
Head of Department/Consultant,
Department of Obstetrics & Gynaecology,
Hospital Universiti Sains Malaysia,
Kota Bharu

Dr. Muniswaran Ganeshan,
Maternal Fetal Medicine Specialist,
Obstetrician & Gynaecologist,
Women & Children's Hospital,
Kuala Lumpur

Dr. Nani Draman
Family Medicine Specialist,
Hospital Universiti Sains Malaysia,
Kota Bharu

Dr Nazrila Hairiana Nasir
Consultant Radiologist,
Radiology Department,
Hospital Putrajaya,
Putrajaya

Dr. Nik Nor Izah Nik Ibrahim
Medical Lecturer in Pharmacology,
Universiti Sains Malaysia,
Kota Bharu

Puan Noraini Mohamad
Head of Pharmacy,
National Cancer Institute,
Putrajaya

Dr. Norasyikin A. Wahab
Consultant Endocrinologist,
Universiti Kebangsaan Malaysia Medical Centre,
Kuala Lumpur

Prof. Dr. Norlela Sukor
Professor and Consultant Endocrinologist,
Universiti Kebangsaan Malaysia Medical Centre,
Kuala Lumpur

Dr. Nor Aina Emran
Consultant Breast & Endocrine Surgeon,
Hospital Kuala Lumpur

Prof. Dr. Nor Azlin Mohamed Ismail
Maternal Fetal Medicine Unit,
Dept. of Obstetrics & Gynaecology,
Universiti Kebangsaan Malaysia Medical Centre,
Kuala Lumpur

Prof. Dr. Rohaizak Muhammad
Consultant Breast and Endocrine Surgeon,
Universiti Kebangsaan Malaysia Medical Centre,
Kuala Lumpur

Assoc. Prof. Dr. Rosediani Muhamad
Head, Family Medicine Department,
Hospital Universiti Sains Malaysia,
Kota Bharu

Dr. Rozita Zakaria
Consultant Family Medicine Specialist,
Klinik Kesihatan Putrajaya Presint 18,
Putrajaya

Dr. Wan Fatihah Wan Sohaimi
Nuclear Medicine Physician,
Hospital Universiti Sains Malaysia,
Kota Bharu

Dr. Wan Mariny W Md Kasim,
Consultant Ophthalmologist
Ophthalmology Department,
Hospital Serdang

Dr. Yahya Mohd Aripin
Consultant General, Breast and Endocrine Surgeon,
Universiti Teknologi MARA Specialist Medical Centre,
Kuala Lumpur

Dr. Yau Weng Keong
Consultant Physician & Geriatrician,
Head of Department of Medicine and
Head of Geriatric Service, Ministry of Health Malaysia,
Hospital Kuala Lumpur

Prof. Dr. Zarina Abdul Latiff
Senior Consultant Paediatrician and Clinical Geneticist,
Head, Thalassaemia Centre,
Universiti Kebangsaan Malaysia Medical Centre,
Kuala Lumpur

1. THYROID DISORDERS: THE DISEASE

1.1 EPIDEMIOLOGY OF THYROID DISORDERS IN MALAYSIA

A large cross-sectional multicentre study done recently demonstrated that the prevalence of thyroid dysfunction in Malaysia is 3.4%: 0.6% had overt hyperthyroidism and 2.8% subclinical hyperthyroidism. On the other hand, the prevalence of hypothyroidism is 2.1% (0.5% overt and 1.6% subclinical hypothyroidism). Except for overt hyperthyroidism, the majority of subjects with thyroid dysfunction were newly diagnosed. The proportion of those who were newly diagnosed with thyroid dysfunction was as high as 68%. Females were found to have a higher prevalence of thyroid dysfunction compared to their male counterparts (female: 4.1% vs. male: 1.9% for hyperthyroidism and 2.6% vs. 1.2% for hypothyroidism).[1 (Level III)]

The same study looked at the prevalence of goitre and thyroid nodule. The prevalence of goitre and thyroid nodule in the Malaysian population is 9.3% and 3.6%, respectively. Despite having an abnormality at the anterior neck, as high as 62% of those with grade 2 goitre and 68% of those with thyroid nodule were newly diagnosed. In the Malaysian population, there was a higher prevalence of goitre in the Indian population and those aged less than 45 years. There was also a higher prevalence of goitre with positive thyroid antibodies in coastal and urban areas, indicating increased iodine exposure. On the other hand, there may also be pockets of iodine-deficient areas in rural regions, where a high prevalence of goitre was not associated with positive thyroid antibodies.[2 (Level III)]

The prevalence of thyroid antibodies in the Malaysian population was 12.2% for anti-thyroid peroxidase (anti-TPO) and 12.1% for anti-thyroglobulin (anti-TG). Females have a higher prevalence of positive thyroid antibodies compared to males (female: 15.2% vs. male: 3.0% for anti-TPO and 15.7% vs. 6.0% for anti-TG). Surprisingly, those with Indian ethnicity had a significantly higher prevalence of anti-TPO compared from other ethnic groups. Coastal and urban regions reported a higher prevalence of thyroid antibodies (as high as 16.1% for anti-TPO and 17.8% for anti-TG), supporting the possibility of higher iodine exposure in these areas.[3 (Level III)]

2. HYPERTHYROIDISM

2.1 OVERT HYPERTHYROIDISM

2.1.1 Causes Of Thyrotoxicosis

Thyrotoxicosis occurs due to inappropriately high thyroid hormone action in tissues secondary to elevated thyroid hormone levels, as opposed to hyperthyroidism, which is a subset of thyrotoxicosis due to inappropriately high thyroid hormone synthesis and secretion by the thyroid gland.[4 (Level I)]

Thyrotoxicosis can be broadly divided into four main causes:[4(Levell)]

A. Activation Of Thyroid Hormone Synthesis And Secretion, Which Leads To Autonomous Release Of Excessive Thyroid Hormone

Graves' disease remained the most common cause of primary hyperthyroidism. Its prevalence can be as high as 70%–84% in different countries.[5,6 (Level III, II)] Graves' disease occurs due to the presence of anti-TSH receptor antibodies. *Yersinia enterocolitica* infection has been associated with Graves' disease.[7 (Level II)] Other causes of primary hyperthyroidism include toxic adenoma and toxic multinodular goitre. Genetic analysis of resected nodules revealed a mutation in the TSH receptor gene, which leads to basal activation of the protein kinase A pathway and increased T4 production and increased cellular proliferation. In addition, the mutation leads to increased TSH receptor affinity to TSH, thus increasing thyroid hormone synthesis.[8 (Level II)] Not all of these hot nodules are actually benign. Some may be malignant, and further workout is necessary. The risk of malignancy in hot nodules may be underestimated, and a literature review reported that a weighted rate of 3.1% (0–12.5%) of hot nodules are graded as thyroid cancer.[9(Level I)] Thyroid papillary carcinoma can cause hyperthyroidism.[10 (Level III)] Graves' disease can co-exist with toxic adenoma and is termed as Marine–Lenhart syndrome.[11 (Level III)] And, finally, there is a small group of patients with diffuse non-autoimmune hyperthyroidism due to a genetic mutation leading to the production of thyroid hormone without any TSH ligand.[12 (Level III)]

B. Thyroid Stores Of Preformed Hormone Are Passively Released In Excessive Amounts Due To Autoimmune, Infective, Chemical, Or Physical Insults

Destruction of the thyroid follicle cells can result in the hyperthyroid stage of any thyroiditis. It could be due to autoimmune processes such as Hashimoto's thyroiditis; infective like subacute thyroiditis (viral) or even *Mycobacterium tuberculosis*,[13,14 (Level III)] cellulitis of the skin anterior to the neck or due to physical insult from a rapidly growing anaplastic carcinoma of the thyroid gland or primary thyroid lymphoma.[15, 16 (Level III)]

C. Exposure To Extrathyroidal Sources Of Thyroid Hormone Either Endogenous Or Exogenous

Endogenous sources of thyroid hormones include struma ovarii, which is actually teratoma of the ovaries composed mainly of thyroid tissue[17 (Level III)] and metastatic thyroid carcinoma secreting thyroid hormones. These are actually rare, with fewer than 100 cases reported since 1946.[18 (Level III)] Exogenous sources of thyroid hormones are becoming commoner nowadays. Over-the–counter supplements containing thyroid support/thyroid supplements/thyroid health actually contain various amounts of T3 and/or T4 that are readily available over the Internet – via online purchases.[19, 20 (Level III,II)] They are cheap, there is no need for a prescription, and people have more privacy in managing their own health. People purchase it

based on testimonials. These supplements may not mention the actual ingredients used.[20,21 (Level II,III)] In addition, exogenous sources of thyroid hormones can come from cooked animals' thyroid gland, as reported in an epidemic of thyrotoxicosis after ingesting thyroid hormone-containing beef hamburger.[22 (Level III)]

D. The Thyroid Gland Is Excessively Stimulated By Trophic Factors Such As Thyrotropin-Stimulating Hormone (TSH) And Other Factors.

TSHoma, which is pituitary gland thyrotrophs adenoma secreting excessive amounts of TSH leading to secondary hyperthyroidism is rare. Besides, gestational trophoblastic disease, which secretes β-HCG (which has partial molecular similarity with TSH) can lead to thyrotoxicosis. It is also rare, as only 2.0 per 1000 pregnancies have gestational trophoblastic disease, of which only 7% have biochemical thyrotoxicosis.[23 (Level III)] Iodinated contrast materials are increasingly being used during CT scans and angiographic procedures. Amiodarones are used frequently for various types of tachyarrhythmia. The iodine content in radiographic contrast materials and amiodarone is much higher than the amount human beings actually require. This excess iodine will lead to Jod–Basedow thyrotoxicosis.[24, 25 (Level III)] The prevalence of contrast iodine-induced subclinical hyperthyroidism can reach up to 2.66%[26, 27 (Level II)] and contrast iodine-induced hyperthyroidism up to 1.7%.[28,29 (Level II,III)] Amiodarone-induced thyrotoxicosis is more prevalent, and is in the range of 3.0%–20.8%.[30, 31, 32, 33 (Level III)] There are other rare case reports of thyrotoxicosis such as due to L-asparaginase chemotherapy, which leads to transient thyrotoxicosis.[34 (Level III)]

2.1.2 How To Diagnose Hyperthyroidism?

2.1.2.1 Biochemical Evaluation For Diagnosis Of Hyperthyroidism

Serum thyroid-stimulating hormone (TSH) measurement has the highest sensitivity and specificity of any single blood test and is used as an initial screening test for hyperthyroidism.[35 (Level III)] However, diagnostic accuracy is improved when serum TSH and free T4 (fT4) are assessed at initial evaluation. If fT4 is within the normal range and TSH is suppressed, then free T3 (fT3) should be measured. In overt hyperthyroidism, serum fT4, fT3, or both are elevated and serum TSH is suppressed (usually <0.01 mIU/L).[4(Level III)]

2.1.2.2 Diagnostic Testing For Aetiology Of Hyperthyroidism

Thyroid Ultrasound

When expertise is available and there is no stigmata of Graves' disease and the aetiology not clear by history, thyroid ultrasound comprising both conventional greyscale and colour flow Doppler examination is recommended as the imaging procedure for hyperthyroidism work-up. Thyroid vascularity (Table 1) and peak systolic velocity (PSV) of the inferior thyroid artery are useful markers to distinguish between Graves' disease and thyroiditis, especially in the setting of pregnancy or

Figure 1: Algorithm for the investigations of suspected hyperthyroidism.[4 (Level III)]

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                    ┌─────────────────────┐
                    │     Suspected       │
                    │   hyperthyroidism   │
                    └─────────────────────┘
                              │
                    ┌─────────────────────┐
                    │     Measure TSH     │
                    │       and fT4       │
                    └─────────────────────┘
                              │
              ┌───────────────┴───────────────┐
      ┌───────────────┐              ┌───────────────┐
      │     ↑fT4      │              │   Normal fT4  │
      │     ↓TSH      │              │     ↓TSH      │
      └───────────────┘              └───────────────┘
              │                              │
      ┌───────────────┐              ┌───────────────┐
      │     Overt     │              │  Measure fT3  │
      │ hyperthyroidism│             └───────────────┘
      └───────────────┘                      │
                              ┌──────────────┴──────────────┐
                      ┌───────────────┐            ┌───────────────┐
                      │     ↑fT3      │            │   Normal fT3  │
                      └───────────────┘            └───────────────┘
                              │                            │
                      ┌───────────────┐            ┌───────────────┐
                      │     Overt     │            │  Subclinical  │
                      │ hyperthyroidism│           │ hyperthyroidism│
                      └───────────────┘            └───────────────┘
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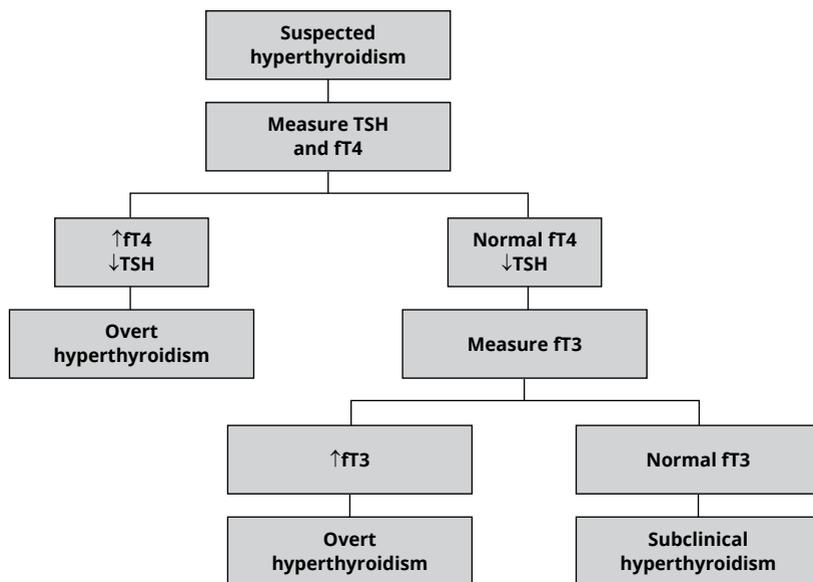
Table 1: Thyroid vascularity grading and pattern by ultrasound (Adapted from Ref: 36 [Level II])

Grading	Vascular pattern	
Grade 1	Absent intraparenchymal vascularity or minimal spots	Low or normal vascularity
Grade 2	Presence of parenchymal blood flow with patchy uneven distribution	
Grade 3	Mild increase of colour flow Doppler signal with patchy distribution	Increased vascularity
Grade 4	Markedly increased colour flow Doppler signal with diffuse homogenous distribution	

lactation, where nuclear imaging is contraindicated.[36 (Level II)] Peak systolic velocity of inferior thyroid artery >40 cm/s is suggestive of Graves' disease.[36 (Level II)] According to Hari Kumar *et al*., colour flow Doppler and ultrasound parameters correlated significantly with pertechnetate scan results, demonstrating a comparable sensitivity of 96% and specificity of 95%.[36 (Level II)] However, thyroid ultrasound has its limitation, as it may miss early Graves' disease and resolving thyroiditis.[37 (Level III), 38 (Level III)]

TSH Receptor Antibodies (TRAbs)

TRAbs are specific biomarkers for the diagnosis of Graves' disease.[39(Level III); 40(Level III)] They are also useful for predicting the risk of relapse and guide definitive treatment for Graves' disease.[41(Level III)] There are two methods for measuring TRAbs:competitive binding assay (TSH binding inhibiting immunoglobulin, TBII) and cell-based bioassay (Thyroid stimulating immunoglobulin, TSI). Most immunoassays today use a competitive binding assay (TBII). TBII only reports the presence or absence of TRAbs and their concentrations, but does not indicate their functional activity.[42 (Level III); 43 (Level III)] The third generation TBII has 99% sensitivity and 99% specificity for the diagnosis of Graves' disease in hyperthyroidism.[44 (Level III)] In contrast, highly sensitive cell–based bioassays (TSI) exclusively differentiate between the TSH-R-stimulating Ab (TSAb) and TSH-R-blocking Ab (TBAb).[45 (Level III); 46 (Level III)]

Figure 2: Categories of TRAbs. (Adapted from Ref: [47 [Level III]])
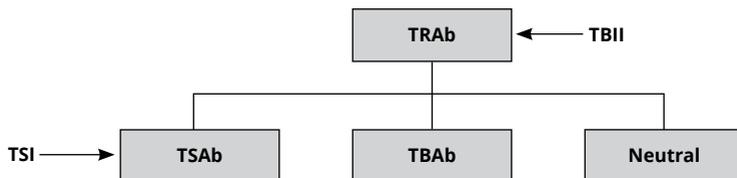
TBII: TSH-binding inhibiting immunoglobulin; TSI: Thyroid-stimulating immunoglobulin; TSAb: TSH-R-stimulating Ab; TRAb: TSH receptor Ab; TBAb: TSH-R-blocking Ab.

Thyroid Scintigraphy

Thyroid scintigraphy is the only technique that allows the assessment of thyroid regional function and detection of areas of autonomously functioning thyroid nodules. Scintigraphy of the thyroid is suggested when thyroid nodularity coexists with hyperthyroidism. However, thyroid scintigraphy is significantly less sensitive for diagnosing thyroid nodules measuring less than 1–1.5 cm.[48 (Level III)] The most used radionuclides in scintigraphy according to the American Association of Clinical Endocrinologists/European Thyroid Association (AACE/ETA) guideline are ^{123}I or [99m]Tc. The advantages of ^{99m}Tc include the high availability in the nuclear medicine department, low energy of gamma photons, and the relatively short half-life (six hours). These characteristics make [99m]Tc a more preferred option compared to [123]I.[49 (Level III)]

Recommendations

- In patients with suspected hyperthyroidism, serum TSH and fT4 should be obtained at the initial evaluation. fT3 should be measured when TSH is suppressed but fT4 is within the normal range

Figure 3: Algorithm for diagnostic testing for aetiology of hyperthyroidism.[36 (Level II);39(Level III); 49 (Level III)]

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                        ┌─────────────────────────┐
                        │  Overt hyperthyroidism  │
                        └─────────────────────────┘
                 ┌──────────────┴──────────────────┐
        ┌─────────────────┐              ┌──────────────────────┐
        │ Stigmata of     │              │ No stigmata of Graves'│
        │ Graves' disease │              │ disease and aetiology │
        └─────────────────┘              │ not clear by history  │
                 │                       └──────────────────────┘
        ┌─────────────────┐
        │ Graves' disease │
        └─────────────────┘
```

- **Thyroid US and Doppler**
  - **Positive** → Graves' disease
  - **Negative** → Other causes of hyperthyroidism
    - Toxic adenoma
    - Toxic multinodular goitre (MNG)
    - Thyroiditis

- **TRAb**

- **Thyroid scintigraphy**
  - **Increase uptake**
    - Diffuse uptake → Graves' disease
    - Focal uptake → Toxic adenoma/ Toxic MNG
  - **Normal or reduce uptake**

Assess vascularity and peak systolic velocity (PSV) of inferior thyroid artery
- ↑Vascularity and PSV >40 cm/s → Graves' disease
- ↓Vascularity and PSV <40 cm/s → Thyroiditis

Nodules → Thyroid scintigraphy

Painful thyroid → Subacute thyroiditis

Painless thyroid
- Normal or elevated serum thyroglobulin
  - Postpartum thyroiditis
  - Hashimoto thyroiditis
- Low or undetectable serum thyroglobulin → Factitious thyrotoxicosis

- Thyroid ultrasonography with colour flow Doppler has reasonable sensitivity and specificity to distinguish between Graves' disease and thyroiditis and is recommended in situations wherein scintigraphy is not available or feasible (e.g. pregnancy or lactation)
- In overt hyperthyroidism without stigmata of Grave's disease, TSH receptor antibody (TRAb) is useful to distinguish between Graves' disease and other causes of hyperthyroidism
- Thyroid scintigraphy should be obtained if the clinical presentation suggests a toxic adenoma or toxic multinodular goitre or whenever the diagnosis is in doubt

2.1.3 How To Treat Hyperthyroidism?

In patients in whom the diagnosis of thyrotoxicosis is strongly suspected or confirmed, treatment with propranolol, atenolol, metoprolol, or other beta-blockers leads to a decrease in heart rate, systolic blood pressure, muscle weakness, and tremors, as well as improvement in the degree of irritability, emotional lability, and exercise intolerance.[50 (Level II)] Oral administration of calcium-channel blockers, both verapamil and diltiazem, has been shown to affect heart rate control in patients who do not tolerate or are not candidates for β-adrenergic blocking agents.[4 (Level II)]

Recommendation

- Beta-adrenergic blockade is recommended in all patients with symptomatic thyrotoxicosis, especially elderly patients and thyrotoxic patients with resting heart rates in excess of 90 beats per minute or coexistent cardiovascular disease

2.1.3.1 How To Treat Graves' Hyperthyroidism (GD)?

Once it has been established that the patient is hyperthyroid and the cause is GD, the patient and physician must choose between three effective and relatively safe initial treatment options: [131]I therapy (radioactive iodine), antithyroid drugs (ATD), or thyroidectomy.[50 (Level II)] The long-term quality of life (QoL) following treatment for GD was found to be the same in patients randomly allocated to one of the three treatment options.[4 (Level II)]

Radioactive Iodine (RAI)

RAI has been used to treat hyperthyroidism and is well tolerated; complications are rare, except for those related to orbitopathy. Thyroid storm occurs only rarely following the administration of RAI. However, RAI can induce a short-term increase of thyroid hormone levels. To prevent a clinical exacerbation of hyperthyroidism, the use of methimazole (MMI) or carbimazole, before and after RAI treatment may be considered in patients with severe hyperthyroidism, the elderly, and individuals with substantial comorbidity that puts them at greater risk for complications of worsening

Table 2: Clinical situations that favour a particular modality as treatment for Graves' hyperthyroidism[4 (Level II)]

Modality	Favour	Contraindication
RAI	• Women not planning a pregnancy in the future (in less than six months, provided thyroid hormone levels are normal) • Individuals with comorbidities increasing surgical risk • Patients with previously operated or externally irradiated necks • Lack of access to a high-volume thyroid surgeon • Patients with contraindications to ATD use or failure to achieve euthyroidism during treatment with ATDs • Patients with periodic thyrotoxic hypokalaemic paralysis, right heart failure, pulmonary hypertension or congestive heart failure	• Pregnancy • Lactation • Coexisting thyroid cancer, or suspicion of thyroid cancer • Individuals unable to comply with radiation safety guidelines • Used with informed caution in women planning a pregnancy within 4–6 months
ATDs	• Patients with a high likelihood of remission (especially women, with mild disease, small goitres and negative or low-titre TRAb) • Pregnancy • Elderly or others with comorbidities increasing surgical risk or with limited life expectancy • Individuals in nursing homes or other care facilities who may have limited longevity and are unable to follow radiation safety regulations • Patients with previously operated or irradiated necks • Patients with lack of access to a high-volume thyroid surgeon • Patients with moderate-to–severe active Graves' ophthalmopathy (GO) • Patients who need more rapid biochemical disease control	• Previous known major adverse reactions to ATDs

Table 2: Clinical situations that favour a particular modality as treatment for Graves' hyperthyroidism[4 (Level II)] *Continued from previous page*

Modality	Favour	Contraindication
Surgery	• Women planning a pregnancy in <6 months provided thyroid hormone levels are normal • Symptomatic compression or large goitres (>80 g) • Relatively low uptake of RAI • Thyroid malignancy is documented or suspected (e.g. suspicious or indeterminate cytology) • Large thyroid nodules, especially if greater than 4 cm or if nonfunctioning, or hypofunctioning on ^{99}mTc pertechnetate scanning • Coexisting hyperparathyroidism requiring surgery • If TRAb levels are particularly high • Patients with moderate-to–severe active GO	• Substantial comorbidities such as cardiopulmonary disease, end-stage cancer, or other debilitating disorders • Lack of access to a high-volume thyroid surgeon • (Pregnancy is a relative contraindication, and surgery should only be used in circumstances wherein rapid control of hyperthyroidism is required and antithyroid medications cannot be used. Thyroidectomy is best avoided in the first and third trimesters of pregnancy because of teratogenic effects associated with an aesthetic agents and the increased risk of foetal loss in the first trimester and the increased risk of preterm labour in the third. Optimally, thyroidectomy is performed in the second trimester; however, although it is the safest time, it is not without risk (4.5%–5.5% risk of preterm labour). Thyroid surgery in pregnancy is also associated with a higher rate of complications, including hypoparathyroidism and recurrent laryngeal nerve (RLN) injury.

thyrotoxicosis. The latter includes patients with cardiovascular complications such as atrial fibrillation, heart failure, or pulmonary hypertension and those with renal failure, infection, trauma, poorly controlled diabetes mellitus, and cerebrovascular or pulmonary disease. These comorbid conditions should be addressed with standard medical care and the patient rendered medically stable before the administration of RAI if possible. If possible, iodinated radiocontrast should be avoided at least 4–6 weeks prior to RAI therapy. In addition, beta-adrenergic blocking drugs should be used judiciously in these patients in preparation for RAI therapy. Methimazole and carbimazole have been shown to reduce thyroid hormone levels after RAI treatment

in randomised controlled trials. A special diet is not required before RAI therapy, but nutritional supplements that may contain excess iodine and seaweeds should be avoided for at least seven days. A low-iodine diet may be useful for those with relatively low RAIU to increase the proportion of RAI trapped. Patients who might benefit from adjunctive MMI or carbimazole may be those who tolerate hyperthyroid symptoms poorly. Such patients frequently have free T4 at 2–3 times the upper limit of normal. Young and middle-aged patients who are otherwise healthy and clinically well compensated despite significant biochemical hyperthyroidism can generally receive RAI without pretreatment. If given as pretreatment, MMI and carbimazole should be discontinued before the administration of RAI. Continuation of ATDs up to 2–3 days prior to RAI can prevent a short-term increase of thyroid hormone levels, which is found after six days. In elderly patients or in those with underlying cardiovascular disease, resuming MMI or carbimazole 3–7 days after RAI administration should be considered and generally tapered as thyroid function normalises. In selected patients with Graves' hyperthyroidism who would have been candidates for pretreatment with ATDs because of comorbidities or excessive symptoms, but who are allergic to ATDs, the duration of hyperthyroidism may be shortened by administering iodine (e.g. saturated solution of potassium iodide [SSKI]) beginning a week after RAI administration.[4 (Level II)]

The goal of RAI therapy in GD is to control hyperthyroidism by rendering the patient hypothyroid; this treatment is very effective, provided a sufficient radiation dose is deposited in the thyroid. This outcome can be accomplished equally well by either administering a fixed dose or by calculating the activity based on the size of the thyroid and its ability to trap RAI. The first method is simple, while the second method requires two unknowns to be determined: the uptake of RAI and the size of the thyroid.[4 (Level II)]

Anti-Thyroid Drugs (ATDs)

The goal of the therapy is to render the patient euthyroid as quickly and safely as possible. These medications do not cure Graves' hyperthyroidism; however, when given in adequate doses, they are very effective in controlling hyperthyroidism. When they fail to achieve euthyroidism, the usual cause is nonadherence. The treatment itself might have a beneficial immunosuppressive role, either to primarily decrease thyroid-specific autoimmunity, or secondarily, by ameliorating the hyperthyroid state, which may restore the dysregulated immune system back to normal. Carbimazole is rapidly converted to MMI in the serum (10 mg of carbimazole is metabolised to approximately 6 mg of MMI). They work in an identical fashion, and both are effective as a single daily dose. At the start of MMI therapy, initial doses of 10–30 mg daily are used to restore euthyroidism, and the dose can then be titrated down to a maintenance level (generally 5–10 mg daily). The dose of MMI should be targeted to the degree of thyroid dysfunction because too low dose will not restore a euthyroid state in patients with severe disease and an excessive dose can cause iatrogenic hypothyroidism in patients with mild disease. In addition, adverse drug reactions are more frequent with higher MMI doses. Thus, it is important to use

an MMI dose that will achieve the clinical goal of normalisation of thyroid function reasonably rapidly while minimising adverse drug effects. It is important to monitor serum T3 levels initially because some patients normalise their free T4 levels with MMI, but have persistently elevated serum T3, indicating continuing thyrotoxicosis. Methimazole has the benefit of once-a–day administration and a reduced risk of major side effects compared to propylthiouracil (PTU). Propylthiouracil has a shorter duration of action and is usually administered two or three times daily, starting with 50–150 mg three times daily, depending on the severity of the hyperthyroidism. As clinical findings and thyroid function tests results return to normal, a reduction to a maintenance PTU dose of 50 mg two or three times daily is usually possible. When more rapid biochemical control is needed in patients with severe thyrotoxicosis, an initial split dose of MMI (e.g. 15 or 20 mg twice a day) maybe more effective than a single daily dose because the duration of action of MMI may be less than 24 hours.[4 (Level II)]

The adverse effects of ATDs can be divided into common, minor allergic side effects and rare but serious allergic/toxic events such as agranulocytosis, vasculitis, or hepatic damage. The minor allergic reactions included pruritus or a limited, minor rash. Cutaneous reactions were more common with PTU or higher dose MMI (30 mg/day) compared with lower dose MMI (15 mg/day). Hepatotoxicity was more common with PTU.[4 (Level II)]

A patient is considered to be in remission if they have had a normal serum TSH, free T4, and free T3 for a year after discontinuation of ATD therapy. The remission rate varies considerably between geographical areas. A meta-analysis shows the remission rate in adults is not improved by a course of ATDs longer than 18 months. A lower remission rate has been described in men, smokers (especially men), and those with large goitres (>80 g). Higher initial doses of MMI (60–80 mg/day) do not improve remission rates; they increase the risk of side effects and are not recommended. If a patient experiences a relapse at follow-up, RAI therapy or surgery can be considered.[4 (Level II)]

Surgery

Thyroidectomy has a high cure rate for the hyperthyroidism of GD. Total thyroidectomy has a nearly 0% risk of recurrence, whereas subtotal thyroidectomy may have an 8% chance of persistence or recurrence of hyperthyroidism at five years. The most common complications following near-total or total thyroidectomy are hypocalcaemia due to hypoparathyroidism (which can be transient or permanent), recurrent or superior laryngeal nerve injury (which can be temporary or permanent), postoperative bleeding, and complications related to general anaesthesia.[4 (Level II)]

Recommendations

- Patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: ATDs, RAI therapy, or thyroidectomy

- Medical therapy of any comorbid conditions should be optimised prior to RAI therapy
- Pretreatment with ATDs prior to RAI therapy for GD should be considered in patients who are at increased risk for complications due to worsening of hyperthyroidism. MMI should be discontinued 2–3 days prior to RAI
- Sufficient activity of RAI should be administered in a single application, typically a mean dose of 10–15 mCi (370–555 MBq), to render the patient with GD hypothyroid
- In patients who are at increased risk for complications due to worsening of hyperthyroidism, resuming ATDs 3–7 days after RAI administration should be considered
- MMI/CMZ is the preferred agent in all patients who choose ATD therapy for GD
- Patients should be informed about the side effects of ATDs and the necessity of informing the physician promptly if they develop pruritic rash, jaundice, acholic stools, or dark urine, arthralgias, abdominal pain, nausea, fatigue, fever, or pharyngitis
- If ATD is chosen as the primary therapy for GD, the medication should be continued for approximately 12–18 months, and then discontinued if TSH levels are normal at that time
- If a patient with GD becomes hyperthyroid after completing a course of MMI, consideration should be given to treatment with RAI or thyroidectomy. Continued low-dose ATD treatment for longer than 12–18 months may be considered in patients not in remission who prefer this approach
- If surgery is chosen as treatment for GD, patients should be rendered euthyroid prior to the procedure with ATD pretreatment, with or without beta-adrenergic blockade
- If surgery is chosen as the primary therapy for GD, near-total or total thyroidectomy is the procedure of choice and should be referred to a high-volume thyroid surgeon

2.1.3.2. How Should Overt Hyperthyroidism Due To Toxic Multinodular Goitre (TMNG) Or Toxic Adenoma (TA) Be Managed?

Two effective and relatively safe definitive treatment options exist for TMNG and TA: RAI therapy and thyroid surgery. The decision regarding treatment should take into consideration several clinical and demographic factors as well as patient preference. The goal of therapy is the rapid and durable elimination of the hyperthyroid state. For patients with TMNG, the risk of treatment failure or need for repeat treatment is <1% following near-total and/or total thyroidectomy, compared with a 20% risk for retreatment following RAI therapy.

Euthyroidism is achieved within days after surgery. However, the risk of hypothyroidism and the requirement for exogenous thyroid hormone therapy is

100% after near-total/total thyroidectomy. For patients with TMNG who receive RAI therapy, the response is 50%–60% by three months and 80% by six months. In a large study of patients with TMNG treated with RAI, the prevalence of hypothyroidism was 3% at one year and 64% at 24 years. Hypothyroidism was more common among patients under 50 years of age.[4 (Level II)]

For patients with TA, the risk of treatment failure is <1% after surgical resection (ipsilateral thyroid lobectomy or isthmusectomy). Typically, euthyroidism is achieved within days after surgery. The prevalence of hypothyroidism varies from 2% to 3% following lobectomy for TA. For patients with TA who receive RAI therapy, there is a 6%–18% risk of persistent hyperthyroidism and a 3%–5.5% risk of recurrent hyperthyroidism. There is a 75% response rate by three months and 89% rate by one year following RAI therapy for TA. The prevalence of hypothyroidism after RAI is progressive and hastened by the presence of antithyroid antibodies or a nonsuppressed TSH at the time of treatment.[4 (Level II)]

Table 3: Factors that favour a particular modality as treatment for TMNG or TA[4 (Level II)]		
Modality	**Favour**	**Contraindication**
RAI	• Advanced patient age • Significant comorbidity • Prior surgery or scarring in the anterior neck • Small goitre size • RAIU sufficient to allow therapy • Lack of access to a high-volume thyroid surgeon	• Pregnancy • Lactation • Coexisting thyroid cancer • Unable to comply with radiation safety guidelines • Used with caution in women planning a pregnancy within 4–6 months
Surgery	• Presence of symptoms or signs of compression within the neck • Concern for coexisting thyroid cancer • Coexisting hyperparathyroidism requiring surgery • Large goitre size (>80 g) • Substernal or retrosternal extension • RAIU insufficient for therapy • Need for rapid correction of the thyrotoxic state	• Significant comorbidities, such as cardiopulmonary disease, end-stage cancer, or other debilitating disorders • Lack of access to a high-volume thyroid surgeon • Pregnancy is a relative contraindication, and surgery should only be used in this circumstance when rapid control of hyperthyroidism is required and ATDs cannot be used
ATD	• Advanced age • Comorbidities with increased surgical risk • Associated with decreased life expectancy • Poor candidates for ablative therapy	• Previous known major adverse reactions to ATDs

Recommendations

- Patients with overtly TMNG or TA should be treated with RAI therapy or thyroidectomy. On occasion, long-term, low-dose treatment with MMI may be appropriate

- Because RAI treatment of TMNG or TA can cause a transient exacerbation of hyperthyroidism, beta-adrenergic blockade should be considered even in asymptomatic patients who are at increased risk for complications due to worsening of hyperthyroidism (i.e. elderly patients and patients with comorbidities)

- In addition to beta-adrenergic blockade, pretreatment with MMI prior to RAI therapy for TMNG or TA should be considered in patients who are at increased risk for complications due to worsening of hyperthyroidism, including the elderly and those with cardiovascular disease or severe hyperthyroidism

- In patients who are at increased risk for complications due to worsening of hyperthyroidism, resuming ATDs 3–7 days after RAI administration should be considered

- If surgery is chosen as treatment for TMNG or TA, patients with overt hyperthyroidism should be rendered euthyroid prior to the procedure with MMI pretreatment, with or without β-adrenergic blockade

- MMI should be stopped at the time of surgery for TMNG or TA. Beta-adrenergic blockade should be slowly discontinued following surgery

- Persistent or recurrent hyperthyroidism following surgery for TMNG or TA should be investigated for other possible causes

- RAI therapy should be used for retreatment of persistent or recurrent hyperthyroidism following inadequate surgery for TMNG or TA

- Long-term MMI treatment of TMNG or TA might be indicated in some elderly or otherwise ill patients with limited life expectancy, in patients who are not good candidates for surgery or ablative therapy, and in patients who prefer this option

2.1.4 How To Monitor Treatment Of Hyperthyroidism?

Patients Post RAI

Most patients respond to RAI therapy with a normalisation of thyroid function tests and improvement of clinical symptoms within 4–8 weeks. Hypothyroidism may occur from four weeks onwards. This transition can occur rapidly, but more commonly occurs between two and six months, and the timing of thyroid hormone replacement therapy should be determined by results of thyroid function tests, clinical symptoms, and physical examination. Transient hypothyroidism following RAI therapy can rarely occur, with subsequent complete recovery of

thyroid function or recurrent hyperthyroidism. In such patients, the thyroid gland often remains palpable.

Beta-blockers that were instituted prior to RAI treatment should be tapered when free T4 and free T3 have returned to the reference range. As free T4 and free T3 improve, ATDs can usually be tapered, which allows an assessment of the response to RAI. Most patients eventually develop hypothyroidism, which is indicated by a free T4 below the normal range. At this point, levothyroxine should be instituted. TSH levels may not rise immediately with the development of hypothyroidism and should not be used initially to determine the need for levothyroxine. When thyroid hormone replacement is initiated, the dose should be adjusted based on an assessment of free T4. Overt hypothyroidism should be avoided, especially in patients with active GO.

Once euthyroidism is achieved, lifelong annual thyroid function testing is recommended at least annually, or if the patient experiences symptoms of hypothyroidism or hyperthyroidism. Since TSH levels may remain suppressed for a month or longer after hyperthyroidism resolves, the levels should be interpreted cautiously and only in concert with free T4 and free T3.[4] (Level II)

Response to RAI therapy can be assessed by monitoring the size of the gland, thyroid function, and clinical signs and symptoms. The goal of re-treatment is to control hyperthyroidism with certainty by rendering the patient hypothyroid. Patients who have persistent, suppressed TSH with normal free T3 and free T4 may not require immediate retreatment but should be monitored closely for either relapse or development of hypothyroidism. In the small percentage of patients with hyperthyroidism refractory to several applications of RAI, surgery should be considered.[4] (Level II)

Patients Treated With ATD

Periodic clinical and biochemical evaluation of thyroid status in patients taking ATDs is necessary, and it is essential that patients understand its importance. An assessment of serum free T4 and free T3 should be obtained about 2–6 weeks after initiation of therapy, depending on the severity of the thyrotoxicosis, and the dose of medication should be adjusted accordingly. Serum T3 should be monitored because the serum free T4 levels may normalise despite persistent elevation of serum free T3. Serum TSH may remain suppressed for several months after starting therapy, and it is therefore not a good parameter for monitoring therapy early in the course. Once the patient is euthyroid, the dose of MMI can usually be decreased by 30%–50% and biochemical testing repeated in 4–6 weeks. Once euthyroid levels are achieved with the minimal dose of medication, clinical and laboratory evaluation can be undertaken at intervals of 2–3 months. If a patient is receiving long-term MMI (>18 months), this interval can be increased to 6 months.[4] (Level II)

Recommendations

- Follow-up within the first 1–2 months after RAI therapy for GD/TMNG/TA should include an assessment of free T4 (and free T3 if indicated), and TSH. Biochemical monitoring should be continued at four- to six-week intervals for six months, or until the patient becomes hypothyroid and is stable on thyroid hormone replacement
- When hyperthyroidism due to GD/TMNG/TA persists after six months following RAI therapy, re-treatment with RAI is suggested. In selected patients with minimal response three months after therapy, additional RAI may be considered
- A differential WBC count should be obtained during febrile illness and at the onset of pharyngitis in all patients taking antithyroid medication
- Liver function and hepatocellular integrity should be assessed in patients taking MMI or PTU who experience pruritic rash, jaundice, light-coloured stool or dark urine, joint pain, abdominal pain or bloating, anorexia, nausea, or fatigue

2.1.5 When To Refer Patients

Recommendations

- Hyperthyroidism due to TMNG or TA should be referred to centres with radioiodine facility or surgical expertise
- Hyperthyroidism due to GD treated with ATDs but remaining hyperthyroid despite adequate treatment should be referred to centres with radioiodine facility or surgical expertise
- Hyperthyroidism due to GD treated with ATDs but relapsing after an initial course of ATDs should be referred to centres with radioiodine facility or surgical expertise
- Hyperthyroid patients with other comorbidities or who develop comorbidities should be referred to a tertiary centre

2.2 SUBCLINICAL HYPERTHYROIDISM

Subclinical hyperthyroidism is defined as suppressed serum TSH with normal fT4 and fT3 concentrations.[51(Level II)] It is exclusively based on laboratory findings.

2.2.1 What Is The Prevalence Of Subclinical Hyperthyroidism?

The prevalence of subclinical hyperthyroidism varies between 0.7% in United States[52(Level II)] and 2.91% in Europe[53(Level II)], and it depends on diagnostic criteria, age, sex, TSH assay used, and the iodine intake of the population being studied.[54(Level II)] A local cross-sectional study showed that the prevalence of subclinical hyperthyroidism is 2.8%.[1(Level III)] In other studies, the prevalence of subclinical hyperthyroidism ranges up to 1.3% in moderately iodine-deficient areas amongst Orang Asli in Hulu Selangor[55(Level II)] and 1.9% amongst men in urban areas.[56(Level II)] Subclinical hyperthyroidism occurs more frequently among older females.[57(Level II)]

2.2.2 What Is The Aetiology Of Subclinical Hyperthyroidism?

The aetiology of subclinical hyperthyroidism would be similar to that of overt hyperthyroidism.

Table 4: Causes of a low serum TSH level [Adapted from [(54 Level II); (19 Level III)]]	
Causes of a low serum TSH level	
True subclinical hyperthyroidism	
Endogenous	Graves' disease
	Multinodular goitre
	Autonomous nodule
• Exogenous	
▪ Intentional	Thyroxine suppressive dose for thyroid cancer
▪ Unintentional	Thyroxine replacement dose for hypothyroidism
Others	
Medications	Glucocorticoids
	Dopamine
	Dobutamine
	Octreotide
	Amiodarone
Transient	First trimester of pregnancy
	Destructive thyroiditis
	Post-radioactive iodine therapy for hyperthyroidism
	Severe non-thyroidal illness
Ethnicity	Black (American)
	Pituitary or hypothalamic insufficiency
	Smoking

2.2.3 What Is The Natural History Of Disease (NHOD) For Subclinical Hyperthyroidism?

Subclinical hyperthyroidism normalises in 17%–36% of patients[58(Level II)]; however, there is a 0.5%–5.0% chance of progression to overt hyperthyroidism.[4(Level II)] There is no local data on NHOD for subclinical hyperthyroidism, but in Singapore, 5.3% progress to overt hyperthyroidism and 13.3% revert to normal after a mean follow-up of 18 months.[59 (Level II)] NHOD for subclinical hyperthyroidism may be influenced by the TSH level and its aetiology. In a large retrospective study

conducted among 323 patients with subclinical hyperthyroidism from 2003 to 2010, progression to overt hyperthyroidism was 20.3% for those with TSH <0.1 mIU/L and only 6.8% for those with TSH 0.1–0.39 mIU/L[60 (Level II)], and in another retrospective study of 96 patients with subclinical hyperthyroidism, 9% subclinical Graves' will require treatment by five years as opposed to 21% for multinodular goitre and 61% for autonomous nodule.[61 (Level II)] However, NHOD of subclinical hyperthyroidism was found not to be associated with aetiology and the level of low TSH in a retrospective study in Singapore.[59 (Level II)]

2.2.4 What is the Significance of Subclinical Hyperthyroidism?

Table 5: Association of subclinical hyperthyroidism and events
[Adapted from [58 (Level II); 62 - 82 (Level II)]]

		Prospective studies		Meta-analysis		TSH severity level relationship
		With association	No association	With association	No association	
Mortality	Probable	√	√	√		√ (CHD)
Cardiovascular events						
Atrial fibrillation	Probable	√		√		√
Chronic heart failure	Possible	√	√		√	√
Non-fatal cardiovascular events	Possible	√		√	√	√
Bone						
Bone mass density	Possible	√ Post-menopausal	√ Pre-menopausal	√ Femoral neck only	√ Total hip and lumbar spine	√
Fractures	Probable	√	√	√		√
Others						
Stroke	Unclear	√	√		√	
Cognition	Unclear	√	√	√		
Symptoms	Possible	√				

Mortality

A few prospective studies suggest an association[62 (Level II)] between subclinical hyperthyroidism and mortality, but others do not.[63 (Level II)] A meta-analysis by Collet showed that subclinical hyperthyroidism is associated with increased total mortality (hazard ratio [HR], 1.24 95% CI,1.06–1.46) with higher mortality due to coronary heart disease with TSH <0.10 mIU/L compared with TSH level 0.10–0.44 mIU/L, p<0.03.[64 (Level II)]

Atrial Fibrillation

Prospective studies suggest subclinical hyperthyroidism is associated with atrial fibrillation.[65 (Level II), 66 (Level II)] Both prospective studies and meta-analyses show the TSH severity level relationship.[64 (Level II), 66 (Level II)]

Chronic Heart Failure

A few prospective studies suggest an association of subclinical hyperthyroidism with heart failure[67(Level II)], but some do not.[68(Level II)] A meta-analysis by Gencer *et al*. show an HR of 1.46 (95% CI, 0.94–2.27) (p>0.05), even though the TSH severity relationship suggested lower TSH <0.1 mIU/L is associated with heart failure.[69(Level II)]

Non-fatal Cardiovascular Events

Most prospective studies show an increased hazard ratio for non-fatal cardiovascular events with subclinical hyperthyroidism, but do not reach statistical significance,[68 (Level II)] with the exception of a study in Scotland.[58 (Level II)] Individual participant meta-analysis by Collet showed the HR for coronary heart disease events was 1.21 (95% CI 0.99–1.46) and the TSH severity relationship did not suggest the lower TSH <0.1 mIU/L is associated with a greater risk of events.[64 (Level II)] But another meta-analysis by Li-bo Yang showed an HR of 1.19 (95% CI, 1.10–1.28), p<0.05.[70(Level II)]

Fractures

A prospective Busselton Health Study[71(Level II)] showed no association between subclinical hyperthyroidism and fractures, but the Health, Aging and Body Composition Study by Rodondi[68 (Level II)] showed there is an association with fractures. An individual-participant data meta-analysis by Blum[72(Level II)] revealed an HR for hip fracture of 1.36 (95% CI, 1.13–1.64); any fracture HR 1.28 (95% CI, 1.06–1.53); non-spine fracture HR 1.16 (95% CI, 0.95–1.41); spine fracture HR 1.51 (95% CI, 0.93–2.45). Also, the lower the TSH, the higher the risk of fractures. A recent study further supports the association between subclinical hyperthyroidism and fractures.[73(Level II)]

Bone Mineral Density (BMD)

The Rotterdam study[74(Level II)] showed decreased BMD in subclinical hyperthyroid patients, but the Cardiovascular Health Study[75(Level II)] did not. An individual-participant data meta-analysis by Segna *et al*. showed more BMD loss at the femoral neck only versus euthyroidism, more so amongst those with TSH <0.10 mIU/L. Ruifei Yang *et al*.[73(Level II)] showed that the BMD decrement at the femoral neck and total hip BMD occurred mainly among women.

Stroke

A prospective study by Parle[76(Level II)] suggested an increased risk of stroke. However, another study by Cappola[77(Level II)] suggested otherwise. A meta-analysis by Chaker[78(Level II)] did not reveal any association between subclinical hyperthyroidism and stroke.

Cognition

Kalmijn[79(Level II)] suggested an increased risk of dementia. However, no association was noted by Formiga.[80(Level II)] A meta-analysis by Rieben[81(Level II)] showed an association between subclinical hyperthyroidism and dementia (HR 1.67 [95% CI, 1.04–2.69]).

Symptoms

A prospective study by Stott[82(Level II)] showed subclinical hyperthyroidism is associated with higher mean Wayne scores as compared with euthyroid subjects.

Recommendation

- ECG, echo and bone mineral density assessments are recommended especially for patients with subclinical hyperthyroidism

2.2.5 What Are the Benefits of Treatment of Subclinical Hyperthyroidism?

So far, no large randomised controlled trials have looked into the effects of treatment outcomes on mortality, cardiovascular events, fractures, stroke, and cognition. However, there have been several much smaller studies looking at the effects of treatment on symptoms, cardiac structure and function, heart rate, body composition, and bone mineral density.[83(Level II); 84(Level II); 85(Level II); 86(Level II); 87(Level II); 88(Level II)]

Table 6: Benefits of treatment of subclinical hyperthyroidism
(Adapted from [83(Level II); 84(Level II); 85(Level II); 86(Level II); 87(Level II); 88(Level II)])

Outcome measures	Treatment modality	Benefits	
		Yes	No
Symptoms	Methimazole [83]	√ [83]	
	Propylthiouracil, RAI [84]	√ [84]	
Cardiac function, rates, structure	Methimazole [83]	√ [83]	
	Propylthiouracil, RAI [84]		√ [84]
	Methimazole [86]	√ [86]	
	Propylthiouracil [88]	√ [88]	
Bone mass density	Propylthiouracil, RAI [84]		√ [84]
	RAI [85]	√ [85]	
	Methimazole [86]	√ [86]	
	RAI, thyroidectomy [87]	√ [87]	
Body composition	RAI, thyroidectomy [87]	√ [87]	

Beta-blocker bisoprolol had been used for patients on thyroxine suppressive therapy and found to reduce symptoms, heart rate, and left ventricular hypertrophy.[89(Level II)]

2.2.6 What Is The Approach To Patients With Low TSH Level?

Figure 4: Algorithm for determining aetiology of low TSH level. (Adapted from[4(Level II)])
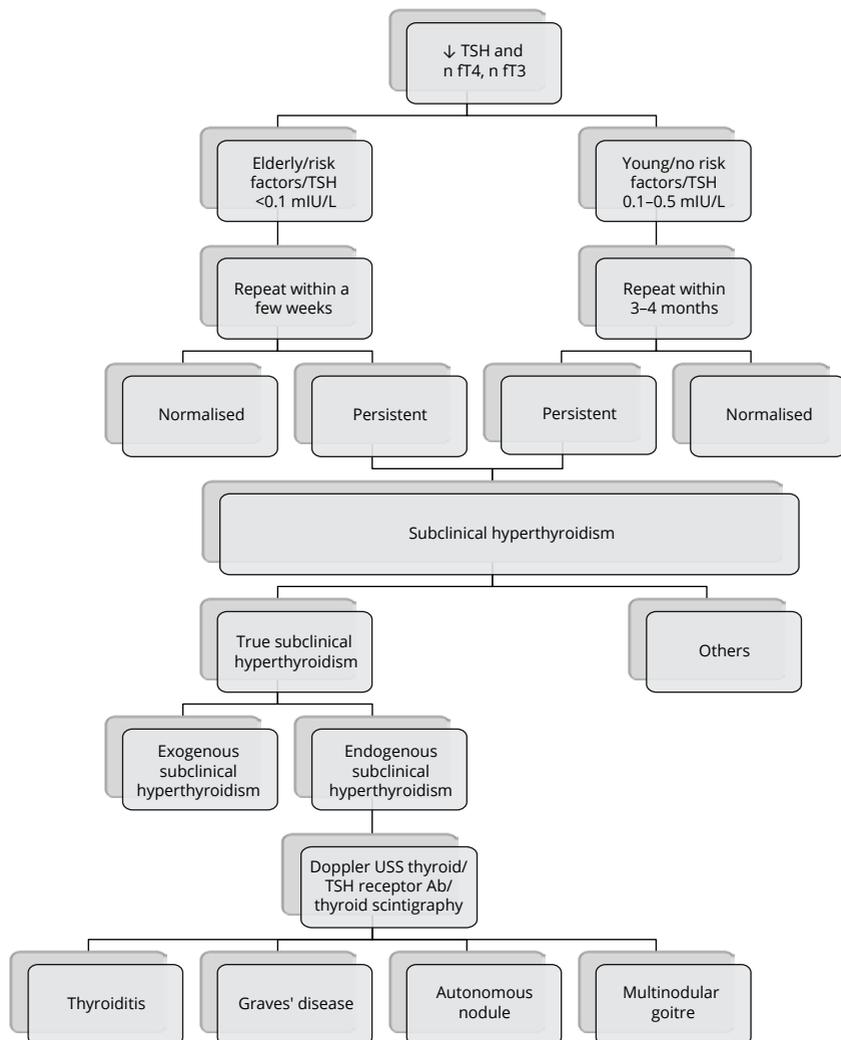
2.2.7 What Is The Treatment Of Subclinical Hyperthyroidism?

According to currently available evidence, subclinical hyperthyroidism is likely to cause atrial fibrillation; may probably increase the risk of mortality and fractures; and possibly cause heart failure and cardiovascular events. However, it is unclear whether subclinical hyperthyroidism causes stroke and dementia. Current studies on treatment outcomes measure only surrogate markers such as symptoms, cardiac structure, function and rate, bone mineral density, and body composition. Therefore, the American Thyroid Association in 2016 suggested when to treat subclinical hyperthyroidism.[4(Level II)]

Table 7: Factors influencing consideration for treatment of subclinical hyperthyroidism [Adapted from [4(Level II)]]

Factor	TSH (<0.1 mIU/L)	TSH (0.1–0.4 mIU/L)
Age >65 years	Yes	Consider treating
Age <65 years with comorbidities	Yes	Consider treating
Heart disease	Yes	Consider treating
Osteoporosis	Yes	Consider treating
Menopausal, not on oestrogens or bisphosphonates	Yes	Consider treating
Hyperthyroid symptoms	Yes	Consider treating
Age <65 years, asymptomatic	Consider treating	Observe

Recommendations

- Treatment should be considered in patients with subclinical hyperthyroidism who are either elderly (age >65 years old) OR with comorbidities (cardiac disease or osteoporosis) OR TSH level less than 0.1 mIU/L
- Patients with subclinical hyperthyroidism at a younger age (age <65 years) AND those without comorbidities (cardiac disease or osteoporosis) AND TSH between 0.1 and 0.5 mIU/L AND asymptomatic should be observed
- β-blockers should be instituted in patients with symptomatic sublinical hyperthyroidism
- Treatment if decided, should be based on aetiology and follow the same outlined principles for overt hyperthyroidism
- Anti-thyroid drugs should be the first-line of treatment and initial treatment for subclinical hyperthyroidism, whatever the aetiology

Figure 5: Algorithm for treatment of subclinical hyperthyroidism. [Adapted from [4(Level II)]]

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                    ┌─────────────────────┐
                    │  True subclinical   │
                    │  hyperthyroidism    │
                    │  (GD, MNG, AN)*     │
                    └─────────────────────┘
                      │                    │
         ┌────────────────────┐    ┌────────────────────┐
         │ Elderly/           │    │ Young and no       │
         │ comorbidities/     │    │ comorbidities      │
         │ TSH <0.1 mIU/L     │    │ and TSH            │
         │                    │    │ 0.1–0.5 mIU/L      │
         └────────────────────┘    └────────────────────┘
                  │                    │              │
            ┌──────────┐        ┌─────────────┐ ┌─────────────┐
            │  Treat   │        │ Symptomatic │ │Asymptomatic │
            └──────────┘        └─────────────┘ └─────────────┘
              │      │                │              │
        ┌────────┐ ┌──────────┐ ┌──────────────┐ ┌──────────┐
        │  GD    │ │ AN/MNG   │ │ Beta-blockers│ │ Observe  │
        └────────┘ └──────────┘ └──────────────┘ └──────────┘
            │          │
        ┌────────┐ ┌──────────────┐
        │  ATD   │ │ ATD/RAI/     │
        │        │ │ surgery      │
        └────────┘ └──────────────┘
```
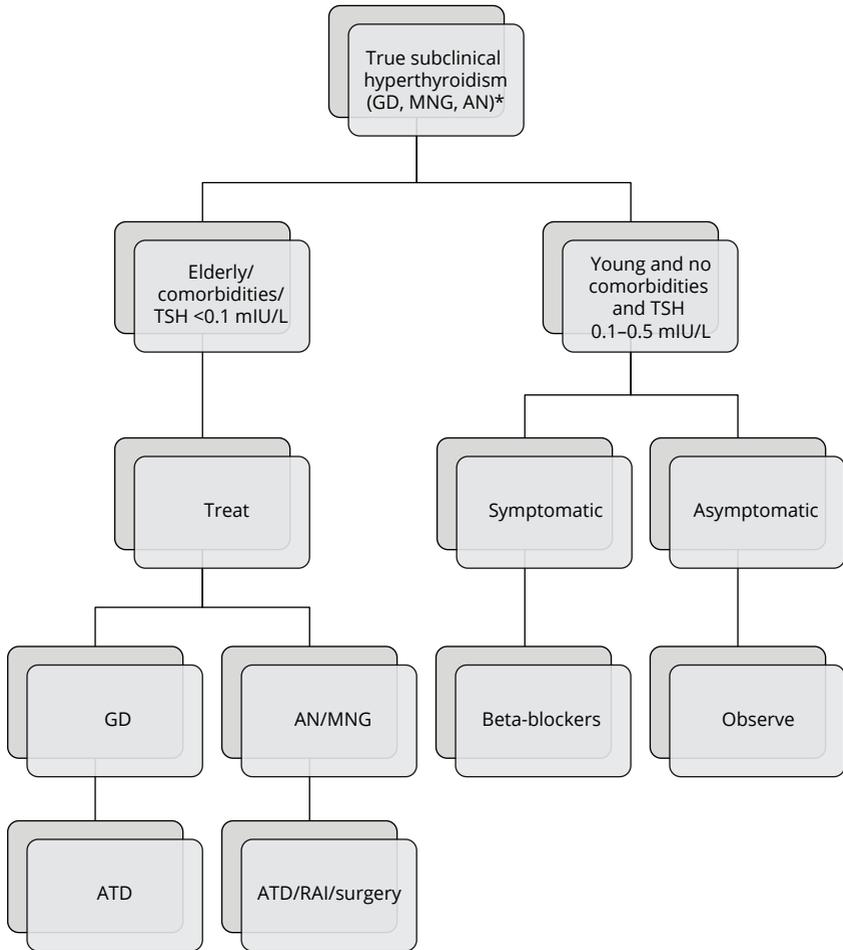
*GD (Graves' Disease); MNG (multinodular goitre); AN (autonomous nodule).

- Radioactive iodine therapy should be considered in those with persistent and progressive subclinical hyperthyroidism due to autonomous nodule and multinodular goitre
- Surgery should be reserved for those with compressive symptoms (dysphagia and shortness of breath) or suspicious of malignancy

3. HYPOTHYROIDISM

3.1 OVERT HYPOTHYROIDISM

3.1.1 What Are The Clinical And Biochemical Goals For Levothyroxine Replacement In Primary Hypothyroidism?

The goals of levothyroxine replacement in primary hypothyroidism are to achieve a state of euthyroidism and normalisation of circulating levels of TSH and thyroid hormones.[91 (Level I)]

Recommendations

• Levothyroxine is the recommended preparation of choice and the mainstay of treatment of hypothyroidism

The three main aims of therapy are:

i) To provide resolution of signs and symptoms, including biological and physiological markers of hypothyroidism

ii) To achieve normalisation of serum TSH with improvement in thyroid hormone concentrations

iii) To avoid iatrogenic thyrotoxicosis or overtreatment, particularly in the elderly

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3.1.2 Are Clinical Parameters Such As Cold Sensitivity And Dry Skin Useful By Themselves For Assessing Adequacy Of Levothyroxine Replacement In Primary Hypothyroidism?

The signs and symptoms associated with hypothyroidism such as dry skin, cold intolerance, constipation, and psychomotor retardation are neither sensitive nor specific and overlap significantly between patients with and without thyroid disease. Therefore, symptoms alone without biochemical assessment lack sensitivity and specificity and should, therefore, not be used for judgeing the adequacy of replacement. However, changes in clinical symptoms should be followed longitudinally and taken into consideration together with serum TSH and thyroid hormones levels, comorbidities, and other potential causes.[91 (Level I)]

3.1.3 How Should Levothyroxine Administration Be Timed With Respect To Meals And Beverages In Order To Maintain Maximum, Consistent Absorption?

When levothyroxine is co-administered with food, absorption is reduced compared with absorption in the fasting state.[92 (level II)] Taking levothyroxine at bedtime has been shown to be just as efficacious as taking it in the morning, with no significant changes in the TSH levels.[93–94 (Level II)] It is important to consider not only when the absorption of levothyroxine would be optimal, but also what timing promotes adherence.

Recommendation

- Levothyroxine is best taken on empty stomach (1 hour before breakfast or at bedtime, at least 3 hours after the last meal of the day) because absorption is impaired if taken with food. Compliance may be enhanced however, by instructing patients to consistently take it before breakfast each day

3.1.4 Are There Medications And Supplements That Should Not Be Co-administered With Levothyroxine In Order To Avoid Impaired Absorption?

Multiple studies have shown that administration of levothyroxine with various medications or beverage such as coffee can impair the absorption of levothyroxine.[95–101 (Level II)]

Recommendation

- Administration of levothyroxine should be separated from other potentially interfering medications and supplements (Table 8). A four-hour separation is advised, but untested

Table 8: Medications and supplements interfering with absorption of levothyroxine [Adapted from [98 (Level II)]]

Interference with absorption		
Bile acid sequestrants (cholestyramine, colestipol, colesevelam)	Calcium salts (carbonate, citrate, acetate)	Diet
Sucralfate	Chromium picolinate	• Ingestion with a meal
Cation exchange resins (Kayexelate)	Charcoal	• Grapefruit juice
Oral bisphosphonates	Orlistat	• Espresso coffee
Proton pump inhibitors	Ciprofloxacin	• High fibre diet
Raloxifene	H_2 receptor antagonists	• Soybean formula (infants)
Multivitamins (containing ferrous sulfate or calcium carbonate)	Malabsorption syndromes • Celiac disease	• Soy
Ferrous sulphate	• Jejunoileal bypass surgery	
Phosphate binders (sevelamer, aluminum hydroxide)	• Cirrhosis (biliary) • Achlorhydria	

3.1.5 Are There Gastrointestinal Conditions That Should Be Considered When A Patient's Levothyroxine Dose Is Much Higher Than Expected?

Several gastrointestinal disorders seem to affect levothyroxine absorption or serum TSH levels possibly mediated through an impact on gastric acidity. Reduction of levothyroxine requirement after eradication of *H. pylori* infection and institution of a gluten-free diet for coeliac disease has been shown in prospective studies.[102-104 (Level II)] Levothyroxine absorption, however, appeared to be preserved in Roux-en-Y surgery and various other gastric bypass procedures. This is consistent with the ileum being the main site of levothyroxine absorption.[105-106 (Level II)] It should also be noted that autoimmune atrophic gastritis is particularly prevalent in older patients with hypothyroidism and Hashimoto's thyroiditis.[107 (Level II)]

Recommendation

- Evaluation for gastrointestinal disorders (*H. pylori*, atrophic gastritis, and coeliac's disease) should be considered in patients requiring a much higher-than-expected dose of levothyroxine. If indeed such disorders are detected and treated successfully, re-assessment of thyroid function is necessary, and the levothyroxine dose adjusted accordingly

3.1.6 What Medications May Alter A Patient's Levothyroxine Requirement By Affecting Either Metabolism Or Binding To Transport Proteins?

Adjustment of levothyroxine dose may be necessary for the use of medications that alter T4 metabolism or change the concentration of thyroxine-binding globulin.[91 (Level I)] The need to increase the levothyroxine dose substantially has been reported in athyreotic patients prescribed tyrosine kinase inhibitors such as imatinib and sunitinib.[90 (Level II)]

Recommendation

- Serum TSH should be reassessed at initiation or discontinuation of oestrogen and androgens (may alter levothyroxine requirement), and at the commencement of agents (such as tyrosine kinase inhibitors) that can affect thyroxine metabolism and thyroxine and tri-iodothyronine deiodination. Monitoring of serum TSH is also advisable when patients are started on drugs that have been shown to increase hepatic metabolism of T4 and T3, i.e. antiepileptics such as phenobarbital, phenytoin, and carbamazepine, or other medications such as rifampicin and sertraline

3.1.7 What Factors Determine The Levothyroxine Dose Required By A Hypothyroid Patient For Reaching The Appropriate Serum TSH Goal?

Many factors can affect the levothyroxine requirement to achieve normalisation of serum TSH levels. The initial dose of levothyroxine should be decided based

on the patient's body weight, lean body mass, pregnancy status, aetiology of hypothyroidism, degree of TSH elevation (in the case of primary hypothyroidism), age, general medical condition – especially the presence of cardiac disease, and the serum TSH goal appropriate for the clinical situation.[91(Level II)]

3.1.8 What Is The Best Approach To Initiating And Adjusting Levothyroxine Therapy?

Multiple factors need to be considered when initiating levothyroxine based on serum TSH levels and weight (full replacement of 1.6 µg/kg when serum TSH levels are markedly elevated and lower doses of 25–50 µg/day in milder degrees of hypothyroidism).[91 (Level I)] Medications taken concurrently may affect the dose required as well.[108 (Level I)]

Recommendation

- Levothyroxine replacement therapy can be started as an initial full replacement or as a partial replacement with gradual dose increments titrated using serum TSH as the goal. Dose adjustments should be made when there are significant changes in body weight, and with pregnancy and ageing. Serum TSH should be reassessed 4–8 weeks after any dose adjustments

3.1.9 What Are The Potentially Deleterious Effects Of Excessive Levothyroxine?

Overtreatment or iatrogenic thyrotoxicosis can result in atrial fibrillation and accelerated bone loss or osteoporosis. Therefore, thyroid hormone excess and subnormal serum TSH level (especially values less than 0.1 mIU/L) should be avoided, particularly in older people and postmenopausal women.

(Refer to the section on subclinical hyperthyroidism and hyperthyroidism in the elderly.)

3.1.10 What Are The Potentially Deleterious Effects Of Inadequate Levothyroxine?

Thyroid hormone deficiency can have detrimental effects on the serum lipid profile and result in the progression of cardiovascular disease. Therefore, adequate doses of levothyroxine should be given to normalise serum TSH levels, to minimise or eliminate these effects.

(Refer to the section on effects of subclinical hypothyroidism.)

3.1.11 What Is The Appropriate Management Of Perceived Allergy To The Constituents Of Levothyroxine Or Intolerance To Levothyroxine?

Allergy to the dye in the tablet has been reported, but rarely occurs.[109 (Level III)]

Recommendation

- If a patient is perceived to be allergic or intolerant to levothyroxine, change in dose or product, including the use of gel capsules and treating concomitant iron-deficiency anaemia, can be tried. Referral to an allergist may be helpful in a few cases, to rule out other allergens, reactions to which may have been attributed to levothyroxine

3.1.12 How Should Levothyroxine Therapy Be Managed In Individuals Who Have Elevated TSH Values Due To Nonadherence?

There are various reports in which patients with raised serum TSH levels while being prescribed levothyroxine were shown to be able to absorb levothyroxine normally and therefore thought to be nonadherent. In such cases, once weekly dosing has been shown to be effective and safe in reducing TSH levels.[110–111 (Level II)]

Recommendation

- Weekly oral administration of the full week's dose of levothyroxine should be considered in patients in whom adherence cannot otherwise be sustained

3.1.13 What Biochemical Goals Should Be Employed For Levothyroxine Replacement In Patients With Secondary Hypothyroidism?

A randomised controlled trial showed that patients given a dose of 1.6 μg/kg/day produced fT4 that reached the upper part of the reference range, and it was associated with lower body weight, lower BMI, lower cholesterol, and fewer clinical signs of hypothyroidism, based on the Zulewski score. However, no differences in well-being and cognitive function were observed.[112 (Level I)] Growth hormone replacement may result in the need to either initiate or increase the dose of levothyroxine in patients with hypopituitarism.[113 (Level II)]

Recommendation

- The primary biochemical goal in patients with secondary hypothyroidism is to maintain serum free thyroxine levels in the upper half of the reference range, but the level may be reduced in older patients or those with comorbidities and those at a higher risk of complications of thyroid hormone excess

3.1.14 What Approach Should Be Taken In Patients Treated For Hypothyroidism Who Have Normal Serum TSH Values But Still Have Unresolved Symptoms?

A prospective case-control study showed that women with Hashimoto's thyroiditis suffer from a high symptom load and that hypothyroidism is only a contributory factor.[114 (Level II)] In addition, it has been shown that individuals referred for thyroid testing by their primary care physicians had rates of psychological distress twice as

high as the general population despite the fact that the rate of hypothyroidism was not higher.[115 (Level II)]

> **Recommendation**
>
> • Acknowledgement of the patients' symptoms and evaluation for alternative causes is recommended

3.1.15 Is There An Unmet Need In L-T4–Treated Patients With Hypothyroidism?

A community-based study from the UK showed that patients taking levothyroxine despite normal serum TSH levels display significant psychological well-being impairment, as measured using the General Health Questionnaire (GHQ-12), compared to controls of similar age and sex. Higher serum fT4 (but not fT3) was associated with lower GHQ-12 scores, implying improved well-being.[116 (Level II)] Another community-based study from Norway suggested a higher prevalence of depression and anxiety, as measured by the Hospital Anxiety and Depression Scale (HADS) scores in hypothyroid women aged 40 years and older taking levothyroxine.[117 (Level II)] In a third study from the USA, levothyroxine-treated women were shown to have decrements in health status, psychological function, working memory, and motor learning compared to euthyroid controls. However, correlations between TSH levels and outcomes were not found.[118 (Level II)] The evidence suggests that despite normal serum TSH levels, psychological distress, impaired well-being, and cognitive disturbances occur more often in patients with hypothyroidism treated with levothyroxine monotherapy than controls and that 5%–10% of patients treated with levothyroxine monotherapy with normal serum TSH can have persistent symptoms related to the disease and therapy.

3.1.16 Is There A Biological Rationale For Persistent Complaints In L-T4–Treated Hypothyroid Patients?

Two most common causes of hypothyroidism are Hashimoto's disease and thyroid ablation in Graves' disease, and therefore most hypothyroid patients have autoimmune thyroid disease. Autoimmune thyroid disease is associated with other autoimmune disorders, with rheumatoid arthritis being the most common coexisting autoimmune disorder. Also, there are significantly increased relative risks for almost all other autoimmune diseases (RR >10 for systemic lupus erythematosus, Addison's disease, pernicious anaemia, coeliac disease, and vitiligo). Due to the nonspecific nature of associated symptoms, many of these conditions may go unnoticed for a long time. Therefore, screening for other autoimmune diseases has been recommended for patients with autoimmune thyroid disease who present with new or unresolving non-specific symptoms.[119–121 (Level II)]

Persistent symptoms despite normal serum TSH levels in patients with hypothyroidism treated with levothyroxine monotherapy have been suggested to be due to the patients' awareness of a chronic disease, thyroid autoimmunity

independent of thyroid function, and inadequacy of levothyroxine treatment to restore physiological T4 and T3 concentrations in serum and tissues.[122 (Level 1)]

3.1.17 When Should Endocrinologists Be Involved In The Care Of Patients With Hypothyroidism?

Consultation with an endocrinologist is recommended in the following situations/ for the following population groups:

- Children and infants
- Patients in whom it is difficult to render and maintain a euthyroid state
- Pregnancy
- Women planning conception
- Cardiac disease
- Presence of goitre, nodule, or other structural changes in the thyroid gland
- Presence of other endocrine diseases, such as adrenal and pituitary disorders
- Unusual constellation of thyroid function test results
- Unusual causes of hypothyroidism, e.g. drug-induced hypothyroidism or by agents such as tyrosine kinase inhibitor[123 (Level I)]

3.1.18 In Hospitalised But Not Critically Ill Patients With Known Pre-existing Hypothyroidism, Should Levothyroxine Therapy Be Re-evaluated Based On An Elevated Serum TSH Measurement?

There is a lack of RCTs and other evidence in the literature regarding the use and monitoring of levothyroxine in hospitalised patients. However, the ATA has provided recommendations for this population of patients in its 2014 guidelines.[91 (Level III)]

Recommendation

- Factors that should be taken into consideration for institution and adjustment of levothyroxine replacement include the degree of clinical and biochemical hypothyroidism, active comorbidities, and details of administration of levothyroxine (e.g., dosage, timing, and other factors affecting absorption).

3.1.19   In Hospitalised But Not Critically Ill Patients Treated With Levothyroxine Replacement, What Formulation And Route Of Administration Are Recommended?

Recommendation

- Oral administration of levothyroxine is recommended, but if this is not feasible, other enteral routes can be used. However, if enteral administration is contraindicated (e.g. perforated viscus) or there are concerns of significant malabsorption, then intravenous levothyroxine (at approximately 75% of oral

dose, assuming enteral levothyroxine dose achieved euthyroidism) may be used till enteral absorption improves.

3.1.20 In Hospitalised But Not Critically Ill Patients About To Be Treated With Levothyroxine, Should The Possibility Of Adrenal Insufficiency Be Excluded?

Recommendation

• The possibility of adrenal insufficiency should be considered and if there is sufficient clinical or biochemical evidence to consider this diagnosis, empiric treatment should be provided.

3.2 SUBCLINICAL HYPOTHYROIDISM

3.2.1 What Are The Causes Of Subclinical Hypothyroidism?

The most common cause of subclinical hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's disease).[124-126 (Level III)] Less common causes include treated Graves' disease, TMNG and TA – radioactive iodine therapy, subtotal thyroidectomy, and antithyroid drugs (intermittent non-compliance); head and neck surgery; radiation therapy to the head, neck or chest area; iodine deficiency; untreated primary adrenal insufficiency; medications: lithium, iodine, amiodarone; secondary hypothyroidism (hypopituitarism); idiopathic and congenital.[124–127 (Level III)] Transient elevations of TSH may occur in subacute or painless thyroiditis, following the withdrawal of L-thyroxine and during recovery from a significant non-thyroidal illness. Repeat measurements of TSH at two-to-three–month intervals from the initial finding of a raised TSH are reasonable.[125 (Level III)]

3.2.2 How To Diagnose Subclinical Hypothyroidism?

Subclinical thyroid disease is a laboratory diagnosis. It is defined as a serum TSH concentration above the statistically defined upper limit of the reference range when serum fT4 and T3 concentrations are within their reference ranges.[126 (Level I); 127 (Level I; 128 (Level I)] However, since an array of factors has been shown to lead to transient abnormalities of serum TSH, investigation for raised TSH requires repeat measurements within two to three months to establish a firm diagnosis.[128 (Level 1)] Transient elevations of TSH may occur in numerous circumstances, such as subacute or painless thyroiditis, following withdrawal of L-thyroxine, during recovery from a significant non-thyroidal illness, and during treatment with various drugs (e.g. lithium, amiodarone).[128 (Level I)] Patients with subclinical disease may have few or no definitive clinical signs or symptoms of thyroid dysfunction.[128 (Level I)] Serum TSH has a log-linear relationship with circulating thyroid hormone levels (a two-fold change in free thyroxine will produce a 100-fold change in TSH).[125 (Level I)] The generally accepted reference range for serum TSH is 0.40–4.2 mIU/L.[125 (Level I); 129 (Level IV)] Determination of anti-TPO antibodies may be helpful in defining the risk of progression (2.6% each year if thyroid peroxidase [TPO] antibodies are absent and

4.3% if they are present).[129 (Level IV); 130 (Level I); 131 (Level IV)] Spontaneous recovery has been described in subjects with subclinical hypothyroidism, and is (more likely in those with negative antithyroid antibodies and serum TSH levels less than 10 mIU/L and within the first two years after diagnosis.[132(Level I)]

> **Recommendations**
>
> - Subclinical hypothyroidism is defined as a serum TSH concentration above the statistically defined upper limit of the reference range when serum fT4 is within its reference range
> - Investigation of raised TSH requires repeat measurements, to establish a firm diagnosis
> - Determination of anti-TPO antibodies may be helpful in defining the risk of progression

3.2.3 What Are The Complications of Subclinical Hypothyroidism?

Despite the clear biochemical pattern suggestive of mild hypothyroidism, few patients with SCHypo have typical hypothyroid symptoms. The only large study to systematically investigate symptoms in patients with overt and SCHypo as compared to euthyroid controls is the Colorado Thyroid Disease Prevalence study. This large questionnaire-based study conducted among 25,862 subjects reported a small but significant difference in symptoms between euthyroid and subclinical hypothyroid patients. The main problems reported were drier skin, poorer memory, slower thinking, weaker muscles, greater tiredness, more muscle cramps, more feeling cold, deeper and hoarser voice, puffier eyes, and more constipation in SCHypo.[133 (Level IV)]

The Tromsö study compared symptoms in 154 controls and 89 SCHypo subjects with a TSH between 3.5 and 10.0 mIU/L using a similar panel of questions. Tiredness, but none of the other symptoms, was significantly different between the groups.[134 (Level IV)] These studies suggest that some patients with subclinical hypothyroidism do indeed develop clinical manifestations of mild thyroid failure.

Patients with SCHypo have a high rate of progression to clinically overt hypothyroidism. In a prospective cohort study by Gerold Huber, Jean-Jacques Staub *et al*., 82 women with subclinical hypothyroidism underwent a follow-up for a mean of 9.2 years. Patients were classified into three groups on the basis of their initial TSH values: $\geq$4 to 6, 6 to 12, and greater than 12 μIU/mL. The 10-year incidence of hypothyroidism was 0%, 42.8%, and 76.9%, respectively, in these three groups.[135 (Level IV)] The rate of progression to overt hypothyroidism was significantly higher in women with a higher baseline serum TSH concentration.[133 (Level IV)] The presence of anti-TPO antibodies was also correlated with a significantly increased incidence of progression to overt hypothyroidism.[135 (Level IV); 136 (Level IV); 137 (Level IV)] However, some people do not show progression and some experience normalisation.[135 (Level IV); 136 (Level IV); 137 (Level IV); 138 (Level IV)]

A TSH level greater than 10 mIU/L predicts a higher rate of progression, and a level of less than 6 mIU/L predicts a lower likelihood of progression.[139 (Level IV)] In a study in men and women older than 55 years with a mean follow-up of 32 months, the TSH level normalised in 52% of those with a serum TSH of less than 10 mIU/L.[139 (Level IV)]

Subclinical hypothyroidism is associated with elevated TC, LDL-C,and TG levels, and these lipid levels decrease with treatment.[140 (Level IV); 141 (Level IV); 133 (Level IV); 142 (Level I)] Higher serum TC, LDL-C, and TG levels increased the risk of coronary heart disease (CHD); therefore, the cardiovascular status of SCHypo patients should be monitored carefully. A meta-analysis involving a total of 40,516 participants showed weak evidence of an association between HDL-C and subclinical hypothyroidism.[142 (Level I)] A systematic review of 7 prospective studies and a meta-analysis of 11 prospective cohort studies showed the risk of CHD events increased significantly with higher levels of TSH, particularly in those with TSH levels ≥10.0 mIU/L (HR 1.89, 95% CI, 1.28–2.80).[140 (Level I); 141 (Level I)] Minimal TSH disturbances between 4.5 and 6.9 mIU/L were not associated with CHD events.[140 (Level I); 141 (Level I)] A meta-analysis of 13 prospective cohort studies found no association between subclinical hypothyroidism and fracture risk.[143 (Level I)] Multiple studies showed no association with anxiety, depression, or cognitive dysfunction.[144 (Level IV)]

4. THYROID NODULES/GOITRE

A thyroid nodule is defined as a discrete lesion within the thyroid gland that is due to an abnormal focal growth of thyroid cells. Thyroid nodules are generally benign hyperplastic (or colloid) nodules or benign follicular adenomas and, uncommonly, carcinoma occurs in 5%–10% of nodules. A nontoxic goitre is defined as any thyroid enlargement characterised by uniform or selective growth of thyroid tissue that is not associated with overt hyperthyroidism or hypothyroidism and that does not result from inflammation or neoplasia.

4.1 HOW COMMON ARE THYROID NODULES/GOITRE?

The prevalence of goitre, diffuse or nodular, differs widely depending on iodine intake by the population. Goitre may occur endemically, due mainly to iodine deficiency, or sporadically. By using ultrasonography as the screening method, a prevalence of up to 30%–50% of an unselected adult population has been described as having goitre, with a higher prevalence noted in iodine-deficient areas and in older people.

Thyroid nodules are a common clinical finding. In large population-based studies, the estimated prevalence of thyroid nodules detected by palpation is 4%–7%.[145–146 (Level II)] Imaging studies identify up to 10 times more nodules, mostly benign. On ultrasonography, detection rates of clinically in-apparent thyroid nodules of 20%–75% have been reported in the general population. Thyroid nodules are more common in elderly individuals, females, subjects from iodine-deficient

geographic areas, and those with a history of radiation exposure.[147 (Level III)] In autopsy studies, thyroid nodules may be present in up to 50%–60% of all adults.[148 (Level II)]

4.2 WHAT IS THE USUAL CLINICAL PRESENTATION OF THYROID NODULES/GOITRE?

In general, thyroid nodules are usually not associated with abnormal thyroid hormone secretion. Therefore, affected patients do not have any symptoms or signs of thyroid dysfunction and present with neck lump or swelling. About 70% of patients with sporadic nontoxic goitre complains of neck discomfort. Some patients have concerns about cosmetic appearance and fear of possible malignancy.

Large goitres may displace or compress the trachea, oesophagus, and neck vessels. There may be compressive symptoms and signs such as inspiratory stridor, dysphagia, or a choking sensation. Compression of the recurrent laryngeal nerve can result in hoarseness of voice due to vocal cord paralysis, usually associated with thyroid malignancy.

4.3 CLINICAL EVALUATION OF THYROID NODULES/GOITRE

The main objective of the evaluation of a thyroid nodule is to differentiate malignant lesions from benign conditions. Most nodules are asymptomatic and benign. The initial evaluation of a patient with a thyroid nodule should include a complete history and physical examination.[149 (Level III)]

Historical features that favour benign disease are a family history of Hashimoto's thyroiditis, benign thyroid nodule/goitre, and symptoms of hypothyroidism/hyperthyroidism. A sudden increase in the size of the nodule with pain and tenderness suggests a cyst or localised thyroiditis.[149 (Level III)]

Historical features that suggest malignancy:

- Young age (<20 years) or old age (>60 years)
- Male gender
- History of external neck radiation during childhood/adolescence
- Rapid growth
- Recent changes in speaking, breathing, or swallowing
- Family history of thyroid cancer or MEN type 2

Physical manifestations of thyroid malignancy:

- Firm to hard consistency of nodule
- Irregular shape
- Fixation to underlying or overlying tissues
- Vocal cord paralysis
- Suspicious regional lymphadenopathy

The presence of multiple nodules does not decrease the likelihood of thyroid cancer. In patients with multiple nodules, the decrease in malignancy rate is approximately proportional to the number of nodules. Thyroid cancers are often in the dominant nodule, but in approximately one-third of cases, the cancer is in a non-dominant nodule.[150 (Level III)]

Recommendations

- A complete history should include:
  - Personal or family history of thyroid disease or cancer
  - Previous head and neck or whole-body irradiation
  - Previous surgery, particularly head and neck or upper oesophageal/thoracic surgery
  - Rate of neck mass growth
  - Use of iodine-containing drugs or supplements
  - Symptoms of hypothyroidism or hyperthyroidism
  - Symptoms of dysphagia, dysphonia, and dyspnoea (at rest, positional, or nocturnal) may be due to compression or invasion of surrounding structures
- Physical examination should include a thorough neck examination focusing on:
  - Thyroid dimensions and consistency
  - Thyroid nodule location, consistency, size, and number
  - Neck tenderness or pain
  - Cervical central and lateral lymph node enlargement

4.4 ULTRASOUND EVALUATION OF THYROID NODULES/GOITRE

When a nodular goitre is clinically present, ultrasound (US) assessment is the preferred and most useful imaging technique to guide disease management and treatment. The pattern of US features associated with nodule confers a risk of malignancy and, combined with nodule size, guides the decision to proceed for Fine Needle Aspiration Biopsy (FNAB).[151 (Level III)]

Recommendation

- All patients with a suspected thyroid nodule/nodular goitre or radiographic abnormality suggesting a thyroid nodule incidentally detected on another imaging study should undergo a dedicated thyroid/neck US that encompasses the thyroid as well as the central and lateral neck compartments

Ultrasound is the gold standard for assessing nodule/gland size and thyroid parenchyma (homogeneous or heterogeneous), location and characteristics of

any nodule(s), and the presence or absence of suspicious cervical lymph nodes in the central and lateral compartments. Nodule characteristics include composition (solid/cystic proportion), echogenicity, shape if taller than wide, margins, and presence of echogenic profile.[151 (Level III)]

4.4.1 How To Describe Ultrasound Findings For Thyroid Nodules?

A structured assessment followed by a practical and standardised reporting format with details of specific sonographic characteristics of thyroid nodules is necessary to standardise diagnosis, risk stratification and the subsequent management decision.

The American College of Radiology ACR TI-RADS 2017 structured reporting system is best recommended as it is easy-to–use, robust and reproducible and widely accepted by radiologists. This reporting system enables assessment of thyroid malignancy risk and helps select patients for FNA and/or surgery, and may substantially reduce the number of unnecessary invasive procedures. The structured reporting greatly facilitates communication between radiologists and physicians, as well as between practitioners and patients.

For patients with multiple nodules (≥4) present, only the four highest scoring nodules, should be scored, reported, and followed up. Follow up shall be according to the highest grade TI-RADS nodule available. Other nodules are also reassessed with ultrasound. Interval enlargement on follow up is significant if there is an increase of 20% and 2 mm in two dimensions, or a 50% increase in volume. If the ACR TI-RADS level increases between scans, an interval scan the following year is again recommended. Ultrasound follow up of a thyroid nodule can be ceased after 5 years if there is no increment in TI-RADS grade and size. Thus stability of the nodule over that time span reliabily indicates that the nodule has a benign characteristic.
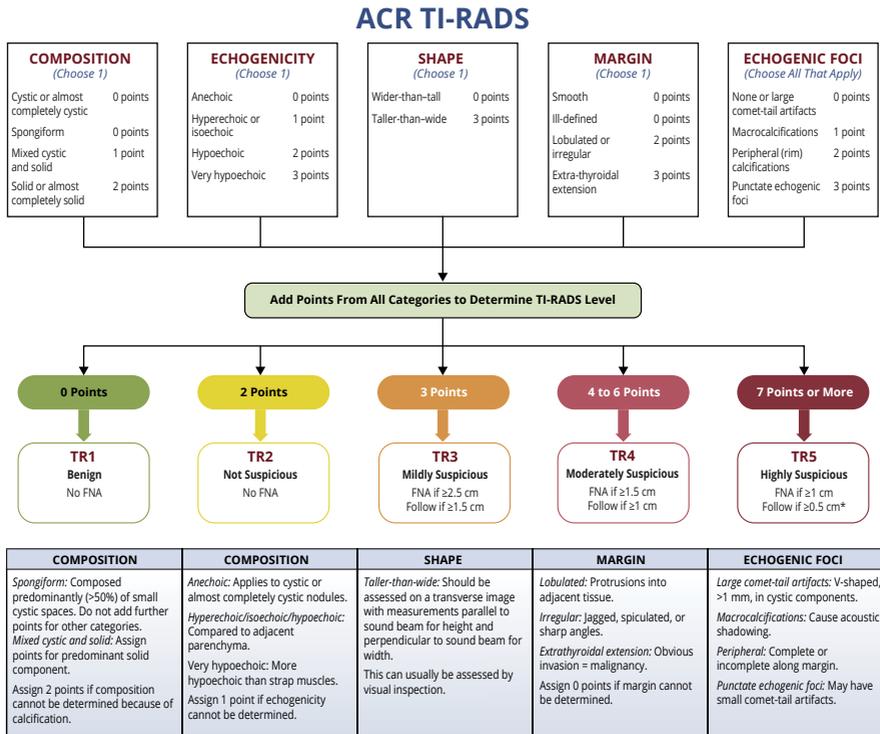
4.5 FINE NEEDLE ASPIRATION BIOPSY (FNAB) OF THYROID NODULES

Fine needle aspiration biopsy (FNAB) of thyroid nodules is the main technique for diagnosing thyroid cancer; it has high sensitivity and specificity rates. The technique is easy to perform and safe. It requires an adequate specimen, which should contain at least five or six groups of 10–15 well-preserved cells. Ultrasound-guided FNAB reduces the possibility of non-diagnostic specimens and is preferred in nodules with a higher likelihood of either non-diagnostic cytology (>25–50% cystic) or sampling error (non-palpable or posterior location).[151 (Level III)]

FNAB is recommended for suspicious lesions (TR3–TR5) with the specific size criteria, according to the ACR Ti-RADS 2017 management algorithm (Refer Figure 6)

- TR1: no FNA required
- TR2: no FNA required

Figure 6: ACR-TI RADS 2017 structured reporting system for ultrasound of thyroid nodules.

ACR TI-RADS

COMPOSITION (Choose 1)		ECHOGENICITY (Choose 1)		SHAPE (Choose 1)		MARGIN (Choose 1)		ECHOGENIC FOCI (Choose All That Apply)	
Cystic or almost completely cystic	0 points	Anechoic	0 points	Wider-than-tall	0 points	Smooth	0 points	None or large comet-tail artifacts	0 points
Spongiform	0 points	Hyperechoic or isoechoic	1 point	Taller-than-wide	3 points	Ill-defined	0 points	Macrocalcifications	1 point
Mixed cystic and solid	1 point	Hypoechoic	2 points			Lobulated or irregular	2 points	Peripheral (rim) calcifications	2 points
Solid or almost completely solid	2 points	Very hypoechoic	3 points			Extra-thyroidal extension	3 points	Punctate echogenic foci	3 points

Add Points From All Categories to Determine TI-RADS Level

0 Points	2 Points	3 Points	4 to 6 Points	7 Points or More
TR1 Benign No FNA	**TR2** Not Suspicious No FNA	**TR3** Mildly Suspicious FNA if ≥2.5 cm Follow if ≥1.5 cm	**TR4** Moderately Suspicious FNA if ≥1.5 cm Follow if ≥1 cm	**TR5** Highly Suspicious FNA if ≥1 cm Follow if ≥0.5 cm*

COMPOSITION	COMPOSITION	SHAPE	MARGIN	ECHOGENIC FOCI
Spongiform: Composed predominantly (>50%) of small cystic spaces. Do not add further points for other categories. *Mixed cystic and solid:* Assign points for predominant solid component. Assign 2 points if composition cannot be determined because of calcification.	*Anechoic:* Applies to cystic or almost completely cystic nodules. *Hyperechoic/isoechoic/hypoechoic:* Compared to adjacent parenchyma. Very hypoechoic: More hypoechoic than strap muscles. Assign 1 point if echogenicity cannot be determined.	*Taller-than-wide:* Should be assessed on a transverse image with measurements parallel to sound beam for height and perpendicular to sound beam for width. This can usually be assessed by visual inspection.	*Lobulated:* Protrusions into adjacent tissue. *Irregular:* Jagged, spiculated, or sharp angles. *Extrathyroidal extension:* Obvious invasion = malignancy. Assign 0 points if margin cannot be determined.	*Large comet-tail artifacts:* V-shaped, >1 mm, in cystic components. *Macrocalcifications:* Cause acoustic shadowing. *Peripheral:* Complete or incomplete along margin. *Punctate echogenic foci:* May have small comet-tail artifacts.

*Refer to discussion of papillary microcarcinomas for 5–9 mm TR5 nodules.

- TR3: ≥1.5 cm follow up, ≥2.5 cm FNAB
  - follow up: 1, 3, and 5 years
- TR4: ≥1.0 cm follow up, ≥1.5 cm FNAB
  - follow up: 1, 2, 3 and 5 years
- TR5: ≥0.5 cm follow up, ≥1.0 cm FNAB
  - annual follow up for up to 5 years

If there are multiple nodules, the two with the highest ACR TI-RADS grades should be biopsied plus if there are any associated suspicious neck nodes (level II, III, IV and VI). If metastatic lymph nodes are suspected, FNA may be indicated for sub-centimetric nodules with a TI-RADS grade 5 or 4 or nodule with the highest TIRADS grade, independent of the size of the nodule.

4.5.1 Cytology Reports Of FNAB Samples From Thyroid Nodules

Standardised reporting of FNA cytology interpretation is necessary and currently utilises the Bethesda system that recognises six diagnostic categories, each having an estimated cancer risk.

- Non-diagnostic
- Benign
- Atypia/follicular lesion of undetermined significance (AUS/FLUS)
- Follicular neoplasm
- Suspicious of malignancy
- Malignant

4.5.2 Molecular Testing Of FNAB Samples

Molecular testing of FNAB specimens for thyroid-related genes might be useful as an adjunct in the assessment of thyroid nodules. Several molecular panels aimed at increasing the accuracy of preoperative cytological diagnosis of thyroid nodules are commercially available. After consideration of clinical and US features, mutational testing for BRAF or the seven-gene mutation marker panel (BRAF, RAS, RET/PTC, PAX8/PPAR-Gamma) may be considered in nodules with cytological interpretation reporting suspicious of malignancy and guide surgical decision-making.[151 (Level III)]

4.6 LABORATORY EVALUATION FOR THYROID NODULES

A. Serum Thyroid-Stimulating Hormone/Thyrotropin (TSH)

Serum TSH levels, measured in a highly sensitive immunometric assay, should always be performed and, if abnormal, fT4 levels should be measured during the initial evaluation of a patient with a thyroid nodule or nontoxic goitre.[151(Level III)] An undetectable TSH should suggest the possibility of toxic, autonomously functioning nodular areas in the goitre. Proceeding with thyroid scintigraphy is recommended.[151(Level III)] Patients with thyroid cancer rarely have abnormalities in serum TSH. Elevated serum TSH in patients with nontoxic goitre suggests the possibility of thyroiditis and hypothyroidism.

B. Serum Thyroid Autoantibodies

Measurement of serum antithyroid peroxidase (TPO) antibody or antithyroglobulin antibody levels may be helpful in the diagnosis of chronic autoimmune thyroiditis. Routine measurement of serum thyroglobulin for initial evaluation of thyroid nodules is not recommended.[151 (Level III)]

C. Serum Calcitonin

Serum calcitonin levels should be measured for patients with a family history or clinical suspicion of medullary thyroid carcinoma (MTC) or multiple endocrine

neoplasia type 2 (MEN2).[152 (Level III)] It is not cost-effective or necessary to measure calcitonin levels in patients with nodular thyroid disease in the absence of clinical suspicion of MTC or abnormal cytologic findings.[151(Level III)]

4.7 WHAT OTHER IMAGING MODALITIES MAY BE NEEDED WHEN EVALUATING THYROID NODULES/GOITRE?

A. Radionuclide Scanning

Thyroid scintigraphy with technetium should be performed in patients with solitary thyroid nodule or multi-nodular goitre with low TSH levels.[152 (Level III)]

B. CT and MRI

In patients with large goitres, conventional radiography of the neck and upper mediastinum should be used to determine tracheal compression. CT and MRI are useful for evaluating invasion into surrounding structures or retrosternal extension or intrathoracic goitre.

It is also recommended in evaluation of occult metastases in mediastinal and retropharyngeal regions in follow up cases of post thyroidectomy with elevation of serum thyroglobulin (Tg) level and negative sonographic finding. Other additional functions of CT and MR is to access other nodal sites that should not be neglected in cases of thyroid carcinoma .These are the lower paratracheal nodes in the superior mediastinum (level VII), and the retropharyngeal and retroesophageal groups which are difficult to access on ultrasound.

4.8 MANAGEMENT OF THYROID NODULES/GOITRE

1. Observation and Monitoring

Patients with small, asymptomatic goitres can be monitored by clinical examination and evaluated periodically with ultrasound measurements. Goitre growth can be variable, and some patients have stable goitres for many years.

2. Thyroid Hormone Suppression Therapy

Regression of sporadic nontoxic diffuse goitre following thyroxine suppression therapy has been established in earlier studies.[153–154 (Level III)] Nodular goitre and thyroid nodules are less responsive to thyroxine suppression therapy for size regression. A subset of patients with younger age, smaller and recently diagnosed nodules are more likely to respond to thyroid hormone suppression therapy.[155 (Level III)] With the discontinuation of therapy, thyroid nodules return to their pretreatment size, and therefore size reduction may require continuous treatment.[151 (Level III)] Long-term thyroid hormone suppression therapy increases the risk of bone loss and cardiac tachyarrhythmia, especially in the elderly.

3. Surgery

Surgery for nontoxic goitre may be necessary if progressive obstructive symptoms develop with a near-total or total thyroidectomy as the operative procedure of choice. Recurrence may be seen in 10%–20% of patients within 10 years if subtotal thyroidectomy is performed.[155 (Level II)]

4. Radioiodine [131]-I therapy

[131]-I therapy for nontoxic diffuse and multinodular goitre is safe and effective with a gradual reduction in goitre size noted in the majority of patients. Initial side effects may present as mild pain and tenderness with transient mild thyrotoxicosis. Hypothyroidism may be a long-term consequence in up to 40% of patients.[156 (Level II)]

5. Alcohol Injection

Percutaneous ethanol injection may be used for recurrent symptomatic cystic nodules.[157 (Level II)]

Figure 7: Algorithm for management of patients with thyroid nodules. (Adapted from [151 (Level III)])
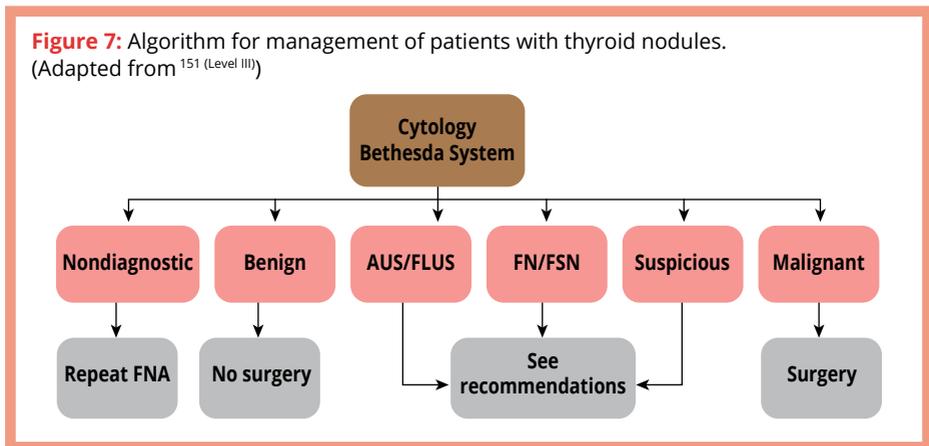
For nondiagnostic nodule
- FNA should be repeated with US guidance and, if available, on-site cytologic evaluation
- Repeatedly nondiagnostic nodules without a high suspicion sonographic pattern require close observation or surgical excision for histopathologic diagnosis
- Surgery should be considered for histopathologic diagnosis if the cytologically nondiagnostic nodule has a high suspicion sonographic pattern, growth of the nodule (>20% in two dimensions) is detected during US surveillance, or clinical risk factors for malignancy are present

For AUS/FLUS, FN/FSN, Suspicious nodule

- For nodules with AUS/FLUS cytology, investigations such as repeat FNA or molecular testing may be used to supplement malignancy risk assessment in lieu of proceeding directly with a strategy of either surveillance or diagnostic surgery. Informed patient preference and feasibility should be considered in clinical decision-making

- Diagnostic surgical excision may be considered for FN/SFN cytology nodules. However, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery. Informed patient preference and feasibility should be considered in clinical decision-making

- If the cytology is reported as suspicious for papillary carcinoma (SUSP), surgical management should be similar to that of malignant cytology, depending on clinical risk factors, sonographic features, patient preference, and possibly results of mutational testing (if performed).

5. THYROID EMERGENCIES AND PERIOPERATIVE MANAGEMENT OF THYROID DISEASES

5.1 THYROID STORM

Life-threatening thyrotoxicosis or thyroid storm is a rare disorder (prevalence: 0.2/100,000/year)[158 (Level III)] characterised by a multisystem disorder with mortality rates in the range of 11%–25%.[158 (Level III); 159 (Level III)] Most thyroid storms result from a triggering event in conjunction with underlying hyperthyroid conditions. The major precipitant for thyroid storm is non-compliance or discontinuation of anti-thyroid drugs, followed by severe infection, cardiac event, thyroidal and non-thyroidal surgery, trauma, administration of iodinated contrast and radioactive iodine, pregnancy and delivery, adrenal insufficiency, and diabetic ketoacidosis.[158(Level III); 159 (Level III); 160 (Level III)]

Multiorgan and acute heart failure are the main cause of mortality.[163 (Level III)] Early recognition and intensive treatment will improve survival in patients with thyroid storm. In view of the high mortality rates, intensive care unit admission and multidisciplinary expertise encompassing endocrinologists, intensivists, cardiologists, hepatologists, and neurologists are required with multiorgan decompensation.

5.1.1 How is Thyroid Storm Diagnosed?

The diagnosis of thyroid storm is made clinically in a thyrotoxic patient with evidence of decompensation. The diagnosis may be challenging, as often there is an overlap with clinical features of other critical medical conditions. To overcome this, more objective diagnostic methods, including the Burch–Wartofsky Point Scale (BWPS)[161 (Level III)] and the newer Japan Thyroid Association (JTA)[158 (Level III)] scoring,

are used. The BWPS quantitatively scores patients based on thermoregulatory, tachycardia/atrial fibrillation, congestive heart failure, central nervous system, gastrointestinal-hepatic, and the presence of a precipitating event (Table 9). A BWPS score ≥45 indicates thyroid storm, 25–44 indicates impending thyroid storm, and <25 indicates that thyroid storm is unlikely.[161 (Level III)] The JTA qualitatively categorises patients into thyroid storm 1 (TS1) and thyroid storm 2 (TS2) with the presence of thyrotoxicosis as a pre-requisite (Table 10).[158 (Level III)] Patients with a BWPS ≥45 or JTA TS1 or TS2 with evidence of decompensation require aggressive multimodal

Table 9: Burch–Wartofsky Diagnostic criteria for thyroid storm* (Adapted from[161 (Level III)])			
Thermoregulatory dysfunction		**Cardiovascular dysfunction**	
Temperature		Tachycardia	
37.2–37.7 (99–99.9)	5	90–109	5
37.8–38.2 (100–100.9)	10	110–119	10
38.3–38.8 (101–101.9)	15	120–129	15
38.9–39.4 (102–102.9)	20	130–139	20
39.5–39.9 (103–103.9)	25	≥140	25
Central nervous system effects		**Congestive heart failure**	
Absent	0	Absent	0
Mild	10	Mild	5
Agitation		Pedal oedema	
Moderate	20	Moderate	10
Delirium		Bibasilar rales	
Psychosis		Severe	15
Extreme lethargy		Pulmonary oedema	
Severe	30	**Atrial fibrillation**	
Seizure		Absent	0
Coma		Present	10
Gastrointestinal-hepatic dysfunction		**Precipitant history**	
Absent	0	Negative	0
Moderate	10	Positive	10
Diarrhoea		*In patients with severe thyrotoxicosis, points are assigned to the highest weighted description applicable in each category and scores totaled. When it is not possible to distinguish the effects or an intercurrent illness from those of the severe thyrotoxicosis *per se*, points are awarded such as to favour the diagnosis of storm and hence, empiric therapy. A score of 45 or greater is highly suggestive of thyroid storm; a score of 25–44 is suggestive of impending storm, and a score, below 25 is unlikely to represent thyroid storm.	
Nausea/vomiting			
Abdominal pain			
Severe	20		
Unexplained jaundice			

Table 10: Diagnostic criteria for thyroid storm of Japan Thyroid Association (Adapted from[158 (Level III)])

Prerequisite for diagnosis		
Presence of thyrotoxicosis with elevated levels of free tri-iodothyronine (FT3) or free thyroxine (FT4)		

Symptoms		
1. Central nervous system (CNS) manifestations: Restlessness, delirium, mental aberration/psychosis, somnolence/lethargy, coma (≥1 on the Japan Coma Scale or ≤14 on the Glasgow Coma Scale)		
2. Fever: ≥38˚C		
3. Tachycardia: ≥130 beats per minute or heart rate ≥130 in atrial fibrillation		
4. Congestive heart failure (CHF): Pulmonary oedema, moist rales over more than half of the lung field, cardiogenic shock, or Class IV by the New York Heart Association or ≥Class III in the Killip classification		
5. Gastrointestinal (GI)/hepatic manifestations: nausea, vomiting, diarrhoea, or a total bilirubin level ≥3.0 mg/dL		

Diagnosis		
Grade of TS	**Combinations of features**	**Requirements for diagnosis**
TS1	First combination	Thyrotoxicosis and at least one CNS manifestation and fever, tachycardia, CHF, or GI/hepatic manifestations
TS1	Alternate combination	Thyrotoxicosis and at least three combinations of fever, tachycardia, CHF, or GI/hepatic manifestations
TS2	First combination	Thyrotoxicosis and a combination of two of the following: fever, tachycardia, CHF, or GI/hepatic manifestations
TS2	Alternate combination	Patients who met the diagnosis of TS1 except that serum FT3 or FT4 level are not available

Exclusion and provisions		
Cases are excluded if other underlying diseases clearly causing any of the following symptoms: fever (e.g., pneumonia and malignant hyperthermia), impaired consciousness (e.g., psychiatric disorders and cerebrovascular disease), heart failure (e.g., acute myocardial infarction), and liver disorders (e.g., viral hepatitis and acute liver failure). Therefore, it is difficult to determine whether the symptom is caused by TS or is simply a manifestation of an underlying disease; the symptom should be regarded as being due to a TS that is caused by these precipitating factors. Clinical judgement in this matter is required.		
TS1, "Definite" TS; TS2, "Suspected" TS.		

treatment. The decision to use aggressive treatment for patients with BWPS 25–44 would depend on clinical judgement, weighing against the risk of adverse events from therapy.[4 (Level III)] Retrospective audits comparing the BWPS versus JTA generally show agreement between the two methods, but there was a tendency for underdiagnosis with the JTA.[159(Level III); 162 (Level III)] If the clinician is unsure whether the symptoms are due to thyroid storm or an underlying disease, symptoms should be regarded as due to thyroid storm. Although measurement of fT4, fT3, and TSH are required, these values may not correlate with the severity of clinical presentation.

Recommendations

- The diagnosis of thyroid storm is clinical. Both the BWPS and JTA diagnostic tools could be used to aid diagnosis, but we recommend the use of BWPS, as this scoring tool is more sensitive
- BWPS score ≥45 or TS1 is definitive of thyroid storm
- BWPS score of 25–44 or TS2, clinical judgement to look for decompensation should be used to diagnose thyroid storm

5.1.2 What Is The Anti-thyroid Drug Of Choice In Thyroid Storm?

Early and aggressive multimodal therapy is required for resolution of thyroid storm. The treatment strategies for thyroid storm are aimed at:

a) Inhibiting synthesis and release of thyroid hormone
b) Inhibiting peripheral action of thyroid hormone
c) Reversing systemic decompensation
d) Treating precipitating event
e) Addressing definitive therapy

High doses of propylthiouracil (PTU) or methimazole (MMI) are mainly targeted at inhibiting the synthesis and release of thyroid hormones. The recommended dosing for PTU is a loading of 500–1000 mg, then 250 mg four-hourly and, for MMI 60–80 mg/day, a single dose or divided into two equal doses.[4 (Level III)] PTU is preferentially used in comparison to MMI in thyroid storm, as the latter has the added benefit of inhibiting type I deiodinase activity in the thyroid gland and other peripheral organs, therefore reducing the conversion of T4 to T3.[4 (Level III); 163 (Level III); 164 (Level III)] T3 levels drop by 45% within one hour of PTU administration, but only about 10%–15% after starting MMI.[163 (Level III)] However, the Japan nationwide survey indicated that there was no difference in outcomes between those treated with PTU vs. MMI.[165 (Level III); 166 (Level III)] MMI has the added benefit of less frequent dosing and less hepatotoxicity.[167 (Level III)] With such large doses of ATD administered, monitoring for adverse events such as liver dysfunction, rash, and agranulocytosis should be carried out.

Recommendations

- High doses of PTU (500–1000 mg loading, then 250 mg, 4–6-hourly) should be used in thyroid storm. In the presence of contraindications, high doses of MMI (60–80 mg/day) can be used.
- Upon improvement of thyroid storm, patients should be transitioned to MMI.

5.1.3 Are Rectal Anti-thyroid Drugs Useful?

In conditions where the absorption of oral PTU or MMI is compromised, such as in ventilated patients or in those with conditions that impair absorption, rectal PTU or MMI can be used. The dose and frequency are similar to those for the oral route. (See guide to prepare rectal PTU in Table 11). The pharmacological levels of rectal and oral preparations are similar, and rectal antithyroids have been reported to resolve thyroid storm.[168 (Level III); 169 (Level III); 170 (Level III); 171 (Level III)]

Table 11: Preparation of rectal PTU
PTU enema: 400 mg of PTU in 90 mL of sterile water[170 (Level II)]
PTU suppository: Polyethylene glycol base (200 mg of PTU in each)[171 (Level III)]

Recommendation

- In circumstances in which absorption is impaired, rectal preparations of PTU or MMI can be used

5.1.4 What Is The Role Of Beta-adrenergic Receptor Antagonists?

Beta-adrenergic receptor antagonists are key to control heart rate and inhibit other peripheral actions of thyroid hormones in thyroid storm. Preferentially β-blockers with the ability to inhibit type 1 deiodinase such as propranolol (60–80 mg/four-hourly) are used.[4 (Level III)] Caution should be exercised with patients in decompensated heart failure. Beta-blockers with selective β-1 blockade such as bisoprolol, landiolol, and esmolol infusion have more favourable cardiovascular benefits in thyroid storm with significant cardiac compromise.[166(Level III)] If there are contraindications to β-blockers, such as in patients with bronchial asthma or chronic obstructive pulmonary disease (COPD), cardioselective calcium-channel blockers such as diltiazem[160(Level III)] or intravenous esmolol with shorter half-lives and easier reversibility can be used in the intensive care setting to control heart rate.[172(Level III)] Intravenous esmolol infusions are given at a loading dose of 250–500 mcg/kg, and thereafter at 50–100 mcg/kg/min of infusion, which is titrated to heart rate and blood pressure. In patients with atrial fibrillation, cardioversion should be considered after ruling out cardiac thrombosis if haemodynamics are impaired. A $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke [double weight]) score ≥2 will require anticoagulation.[166 (Level III); 173 (Level III)]

Recommendations

- Beta-adrenergic receptor antagonists such as propranolol should be administered in thyroid storm to control heart rate and inhibit other peripheral action of thyroid hormone
- Shorter-acting intravenous esmolol or diltiazem can be used to control heart rate when there are contraindications to β-adrenergic receptor antagonists

5.1.5 What Is The Role Of Corticosteroids?

Corticosteroids should be administered in thyroid storm to inhibit both thyroid hormone synthesis and peripheral conversion of T4 to T3.[174 (level III); 175 (level III)] Corticosteroids are also given as prophylaxis for relative adrenal insufficiency caused by a hypermetabolic state in thyroid storm.[166 (level III)] Large doses need to be used; dexamethasone (median dose – 6 mg/day), hydrocortisone (300 mg/day), or prednisolone (25 mg/day) are recommended.[4 (level III); 165 (level III)] Intravenous forms are preferred when rapid action is desired or when there are concerns of gut absorption of glucocorticoids. With the improvement in clinical condition, doses should be reduced and tapered off to prevent adverse effects.

Recommendation

- High doses of glucocorticoids (IV hydrocortisone 100 mg, 6 hourly or dexamethasone 2 mg, 6 hourly) should be given in thyroid storm

5.1.6 What Is The Role Of Inorganic Iodide?

Inorganic iodide (Lugol's iodine/saturated solution of potassium iodide, SSKI) can be used in thyroid storm to rapidly decrease T4 levels by inhibition of iodide oxidation and organification and inhibits release of thyroid hormone.[161 (Level III); 176 (Level III); 177 (Level III); 178 (Level III)] These agents must be used in combination with antithyroid drugs for rapid clinical improvement. Inorganic iodide can reduce thyroid hormone faster than steroids or antithyroid drugs.[161 (Level III)] Recommended dose is 5 drops of Lugol's iodine 6 hourly (6.25 mg iodine/drop) or 10 drops of Lugol's iodine 8 hourly.[161 (Level III); 4 (Level III)] It is important to note that these agents should only be given at least after one hour of antithyroid drug administration, to prevent the use of iodine as a substrate for thyroid hormone synthesis.[178 (Level III)] After clinical improvement, the Lugol's iodine should be tapered and stopped before the antithyroid. Lugol's iodine should not be given beyond 10 days or else this would lead to escape from the Wolff-Chaikoff phenomenon. Patients known to be allergic to inorganic iodide containing drugs should not be given these agents. Inorganic iodide may also be administered via rectal or nasogastric routes in critically ill patients. The solution should be diluted in water or taken with bread to avoid mucosal irritation.

> **Recommendation**
>
> • 5–10 drops of Lugols iodine 6–8 hourly for the first 10 days, should be given after administration of antithyroid for rapid improvement of thyrotoxicosis in thyroid storm

5.1.7 What Is The Role Of Lithium/Cholecystographic Agents?

Lithium can be used as an alternative for patients who cannot tolerate MMI or PTU and works by inhibiting release of thyroid hormone by thyroid gland through unknown mechanisms.[179 (Level III); 180 (Level III)] Recommended doses are lithium 300 mg up to thrice daily. Adverse effects that need to be considered are lithium toxicity and nephrogenic diabetes insipidus. Therefore, lithium levels should be monitored to avoid toxicity. Cholestyramine has been used as an option to improve thyrotoxic state in thyroid storm by reducing enterohepatic recycling of thyroid hormones.[181 (Level III); 182 (Level III); 183 (Level III)] Recommended dose of cholestyramine is 1–4 g/every 6 hourly.

> **Recommendation**
>
> • Lithium and cholestyramine can be used as adjunct treatment for thyroid storm

5.1.8 What Is The Role Of Plasma Exchange?

Total plasma exchange (TPE) is used in patients with severe thyroid storm, rapid clinical worsening or failure or contraindications to standard multimodal therapy.[4 (Level III)] Failure to standard therapy is considered when thyroid storm shows no improvement within 24–48 hours of standard multimodal therapy. Total plasma exchange removes thyroid hormones, antibodies, and circulating cytokines. Total plasma exchange with 40–50 mL/kg of replacement fluid has demonstrated improved outcomes and resolution of thyroid storm and should be continued until clinical improvements are noted.[184 (Level III); 185 (Level III)] fT4 and fT3 should be sampled before and after each session. Two types of replacement therapy: fresh frozen plasma (FFP) or albumin have been used in TPE for thyroid storm. Although there is no randomised study to compare between the two, fresh frozen plasma (FFP) has been preferentially used because it contains thyroid binding globulin (TBG) that will better enhance removal of TBG bound thyroid hormones.[166 (Level III)] Continuous hemodiafiltration (CHDF) is sometimes used in parallel with TPE in haemodynamically compromised patients.[166 (Level III)]

> **Recommendation**
>
> • TPE (with FFP as fluid replacement) should be considered in severe/rapidly deteriorating thyroid storm or with contraindications to standard multimodal therapy

5.1.9 What Is The Role Of Other Supportive Therapy?

Other supportive treatment would also be required in thyroid storm. These include intravenous fluids, respiratory support, and nutritional support. Cooling measures using cooling blankets and with the use of acetaminophen is recommended. The use of salicylates should be avoided as these drugs displace bound thyroxine leading to further elevations of free thyroid hormone.[4 (Level III); 166 (Level III)] Infection should be treated with broad-spectrum antibiotics, tailored to source of infection. In patients with respiratory failure or severe CNS depression, respiratory support with invasive or non-invasive ventilation may be required.

Recommendation

- The use of salicylates should be avoided as these drugs displace bound thyroxine leading to further elevations of free thyroid hormone

5.1.10 What Is The Role Of Early Definitive Therapy And Prevention?

Definitive therapy needs to be considered in all patients presenting with thyroid storm. Urgent or early thyroidectomy is an option in patients who have a contraindication to antithyroid drugs, have a large goitre.[186 (Level III); 187 (Level III)] However, these patients should be rendered close to euthyroid prior to surgery with methods such as TPE in order to minimise risk of thyroid storm. If radioactive iodine is considered and Lugol's iodine has been administered during thyroid storm, the RAI should be deferred until about 3–4 months after.[161 (Level III)] Commonest precipitating factor is non-compliance and patients therefore should be educated on this aspect. Patients undergoing surgery or RAI should be rendered near euthyroid as possible prior to procedure or the procedures should be postponed to prevent thyroid storm.

Recommendation

- All patients with thyroid storm should have early definitive therapy with RAI. In patients with large obstructing goitre, early thyroidectomy should be considered instead

5.2 MYXOEDEMA COMA

5.2.1 How Is Myxoedema Coma Diagnosed?

Myxoedema coma is a rare condition which is diagnosed clinically in patients presenting with hallmarks of reduced conscious level and hypothermia. Thyroid function test will be consistent with hypothyroidism. Other clinical features are hyponatremia and/or hypercapnia. It should be suspected especially in patients with history of hypothyroidism or with any cause for hypothyroidism. Other causes of reduced consciousness should also be excluded.[188–191 (Level III)]

Diagnostic scoring systems have been designed but are not well validated as the incidence is low.[189 (Level III)]

5.2.2 What Are The Complications Of Myxoedema Coma?

Myxoedema coma is a systemic condition that can affect every organ and system.[188,192 (Level III)] Known complications include metabolic decompensation (hypoglycaemia, hyponatraemia), cardiovascular[193 (Level III)] (bradycardia, hypotension, pericardial effusion and heart failure), neurological (psychosis, seizures[194 (Level III)], altered consciousness), respiratory [195–196 (Level III)] (hypoventilation, hypercapnia, sleep apnoea), renal failure and anaemia.[197 (Level III)]

5.2.3 What Are The Best Treatment Modalities For Myxoedema Coma?

Patients who have been diagnosed with myxoedema coma are critically ill and should be nursed in intensive care wards. Absorption of oral medications may be impaired and reduced in these patients due to multiple factors. Therefore, intravenous thyroxine is recommended by most authors.[192 (Level II)-, 188, 198, 190, 91 (Level III)] These patients may also have concurrent hypoadrenalism, thus intravenous hydrocortisone is recommended prior to commencement of thyroid hormones.[188 (Level III)] Ideally a serum cortisol is taken prior to administration of intravenous hydrocortisone.

Recommendations

- Intravenous hydrocortisone 200 mg stat then 100 mg 6–8 hourly should be administered prior to levothyroxine
- Initial intravenous levothyroxine of 200–400 mcg followed by 1.6 mcg/kg/day (75% if administered intravenously) should be given thereafter. If intravenous levothyroxine is not available, oral levothyroxine can be given as 500 mcg loading followed by maintenance dose
- Intravenous liothyronine (when available) may be given in addition to thyroxine. Loading dose recommended is 5–20 mcg followed by 2.5–10 mcg every 8 hours till patient regains consciousness

---

5.2.4 How Should Patients With Myxoedema Coma Be Monitored?

Improvements can be seen within one week of treatment. As with all critically ill patients, multiorgan parameters should be monitored including mental status cardiovascular parameters, respiratory parameters, renal function, metabolic parameters (e.g. electrolytes). Thyroid function test can be monitored every 2 days. Sequential Organ Failure Assessment (SOFA) score is an example of assessment tool that has been used and was found to be more predictive of outcome compared to other tools.[192 (Level II); 190 (Level III)]

5.3 PRE-/PERIOPERATIVE MANAGEMENT: HYPERTHYROIDISM

Surgical stress and anaesthesia can precipitate thyroid storm, cardiac failure or tachyarrhythmias in patients with uncontrolled pre-existing hyperthyroid disorders. Overall morbidity and mortality in well prepared patients are low.[199 (Level III)]

5.3.1 How Is This Best Treated/Risk Minimised?

Combination of antithyroid drugs, beta-blockers, iodine, and glucocorticoids have been shown to rapidly reverse hyperthyroidism in patients planned for surgery.[199(Level III); 200 (Level III); 201 (Level II);202 (Level II)] Beta blockade alone in comparison to anti-thyroids, has been shown to have better peri-operative outcomes in patients with hyperthyroidism.[203 (Level II)]

> **Recommendations**
>
> • All elective surgery should be postponed until euthyroid or near euthyroid state is achieved
> • For urgent surgeries, clinical and biochemical assessment of patient's thyroid state should be ascertained
> • In patients who are hyperthyroid and require urgent surgery, rapid control with high dose MMI or PTU, β-blockers, Lugol's iodine and glucocorticoids are recommended

5.3.2 Is There A Need To Treat Subclinical Hyperthyroid Disease Pre-operatively?

> **Recommendations**
>
> • Only in elderly patients and those with pre-existing cardiac disease/atrial fibrillation, with subclinical hyperthyroidism should be considered to require treatment pre-operatively
> • Beta-blockers are recommended to minimise risk of tachyarrhythmias peri-operatively in the elderly and patients with pre-existing cardiac disease and subclinical hyperthyroidism

5.4 PRE-OPERATIVE MANAGEMENT: HYPOTHYROIDISM

5.4.1 Is There A Role For Universal Screening For Hypothyroidism Preoperatively?

There is insufficient evidence for or against universal screening for hypothyroidism. Different panels of experts differ in their opinions of subpopulation to screen.[127 (Level II), 123 (Level II), 91 (Level II), 204 (Level II)]

Recommendations

- There is no role for universal screening for hypothyroidism preoperatively
- Only patients with risk factors for hypothyroidism or those who exhibit symptoms of hypothyroidism should be screened

5.4.2 What Are The Potential Intra, And Postoperative Complications Of Untreated Hypothyroidism?

Untreated hypothyroidism causes systemic hypometabolism. Potential complications of hypothyroidism include hypotension, cardiovascular collapse, hypoventilation, sensitivity to opioids, sedatives and anaesthesia, and myxoedema coma. Cardiovascular complications are increased in patients with overt hypothyroidism and similar risks have been reported in those with mild hypothyroidism.[205 (Level II); 206 (Level II)] Subclinical hypothyroidism has also been found to be more common among patients with obstructive sleep apnoea; presence of which affects intubation and ventilation.[207 (Level II)]

5.4.3 How Should Perioperative Hypothyroidism Be Managed?

In observational studies, postoperative outcomes vary according to the degree of hypothyroidism. Patients with mild (subclinical hypothyroidism) and moderate (overt) hypothyroidism generally have few adverse effects.[208 (Level II-2); 209 (Level II-3)] Although there is lack of data among these patients, those with severe hypothyroidism (myxoedema coma) should be considered high risk for surgery.

Recommendations

- In mild hypothyroidism i.e., those with subclinical hypothyroidism, surgery should not be postponed
- In moderate hypothyroidism i.e., overt hypothyroidism, urgent surgeries should be undertaken without delays. In elective surgeries, it is recommended that euthyroid state is restored before surgery
- In severe hypothyroidism i.e., myxoedema coma, treatment with both T3 and T4 should be given prior to surgeries

6. THYROIDITIS – SUBACUTE AND ACUTE THYROIDITIS

6.1 SUBACUTE THYROIDITIS (DE QUERVAIN'S THYROIDITIS)

6.1.1 How is Subacute Thyroiditis Diagnosed?

Subacute thyroiditis is one of the causes of painful thyroid gland. Presentation is usually between the age of 40 and 50 years.[210 (Level III); 211 (Level III); 212 (Level III); 213 (Level III); 214 (Level III)] Most series reported higher preponderance for female gender with a ratio as high

as 6:1.[210 (Level III); 212 (Level III); 213 (Level III); 215 (Level III)] The presence of prodromal symptoms associated with upper respiratory tract symptoms is variable. Some studies reported the presence of prodromal symptoms between 20% and 38.5%.[211 (Level III); 212 (Level III)] Only between 12.5% and 46.2% of patients with subacute thyroiditis reported fever.[210 (Level III); 213 (Level III); 214 (Level III)] For the diagnosis of subacute thyroiditis, painful thyroid swelling remained a prominent symptom and is taken as an important diagnostic criterion.[210 (Level III); 211 (Level III); 212 (Level III); 213 (Level III); 214 (Level III); 215 (Level III); 216 (Level III); 217 (Level III); 218 (Level III)]

Patients with subacute thyroiditis usually present during the thyrotoxic phase. The onset of disease is between one and two weeks. Typically, the hyperthyroid state lasts for 2–3 weeks, peaks at 1 week after the onset, followed by a period of hypothyroidism which lasts for 6–12 weeks. Subsequently, euthyroid state ensues.[211 (Level III); 219 (Level III)] Most of studies recorded moderate increase in thyroxine level with suppressed thyroid stimulating hormone, while thyroid storm is rare.[210 (Level III); 211 (Level III); 212 (Level III); 213 (Level III); 215 (Level III); 216 (Level III)] A cross-sectional study comparing the thyroid function of patients with subacute thyroiditis and Graves' disease demonstrates that the free tri-iodothyronine (fT3) to free thyroxine (fT4) was significantly lower in the former. An fT3/fT4 ratio of less than 0.3 has a sensitivity of 52.4% and specificity of 91.3% for destructive thyroiditis.[220 (Level II)] Apart from thyroxine and triiodothyronine, thyroglobulin levels are also elevated.[213 (Level III); 216 (Level III); 219 (Level III)] The presence of thyroid antibodies in subacute thyroiditis varies from study to study (between 4% and 20%).[214 (Level III); 215 (Level III); 217 (Level III)] However, overall, the thyroid antibody titre in destructive thyroiditis is much lower compared from Graves' disease.[219 (Level III); 220 (Level II)]

Raised erythrocyte sedimentation rate (ESR) is one of the important diagnostic criteria. Several studies reported an average ESR of 60 mm in the 1st hour.[210 (Level III); 212 (Level III); 214 (Level III); 215 (Level III); 216 (Level III)] Frates *et al.* reported ESR as high as 100 mm in the 1st hour.[218 (Level III)] Because of the wide range reported, it is difficult to determine what level of ESR is predictive of subacute thyroiditis. Several studies also measured C-reactive protein (CRP). In general, the level of C-reactive protein is also elevated in this condition.[211 (Level III); 214 (Level III); 219 (Level III)]

In terms of imaging, destructive thyroiditis displays low uptake on radio-iodine scan.[217 (Level III); 219 (Level III)] In centres without radio-iodine scan facility, ultrasound of the neck and thyroid may not be helpful as common findings include ill-defined hypoechoic lesion within the thyroid gland.[211 (Level III); 219 (Level III)] However, Doppler ultrasound which shows suppressed vascularity may be of value. A study reported that 77.8% of patients with subacute thyroiditis had ill-defined hypoechoic lesions while 95% had reduce Doppler Colour flow.[218 (Level II)] Another study described "lava flow" appearance on grey scale ultrasound in 100% of their case series (n=22).[221 (Level III)]

Recommendations

- Subacute thyroiditis should be suspected in all patients who present with painful goitre

- All patients with painful thyroid swelling should have thyroid function test done which includes free thyroxine and thyroid stimulating hormone
- An fT3/fT4 ratio of less than 0.3 may be used to help differentiate between subacute thyroiditis and Graves' disease
- An ESR or CRP should be measured in patients with painful thyroid swelling. Elevated ESR and CRP is suggestive of subacute thyroiditis
- Ultrasound should be performed in all patients with painful thyroid swelling to rule out acute/suppurative thyroiditis. A non-suggestive ultrasound within 1 week of onset of illness should be repeated later

6.1.2 How Should Subacute Thyroiditis Be Managed?

Management of subacute thyroiditis is limited by the rarity of the condition and availability of high-quality evidence. Most of the studies were observational retrospective.[212 (Level III); 213 (Level III); 214 (Level III); 215 (Level III); 216 (Level III)] Patients either receive non-steroidal anti-inflammatory drugs (NSAIDs), steroids or expectant management. The American Thyroid Association recommends that NSAIDs are used for mild cases and prednisolone for severe ones.[4 (Level III)] Beta-blocker is used to alleviate significant thyroid symptoms.[210 (Level III); 217 (Level III); 219 (Level III)] In majority of cases, 90% of patients go into remission without any sequelae and only 10% went into permanent hypothyroidism requiring thyroxine replacement.[210 (Level III), 219 (Level III)]

A non-randomised retrospective review of prednisolone vs. loxoprofen (NSAID) for the treatment of subacute thyroiditis was done by Sato *et al.* (2016). The average dose of prednisolone given was 15 mg/day (range: 14–16 mg/day) vs. loxoprofen 180 mg/day. They demonstrated that the time to normalisation of thyroid function was quicker in the prednisolone group (22 vs. 32 days).[213 (Level III)] Similarly, Benbassat *et al*. reported that those who received steroid had faster remission compared with NSAIDs.[215 (Level III)]

Recommendations

- Beta-blocker can be used in patients with symptoms of thyrotoxicosis
- Non-steroidal anti-inflammatory drugs are the first-line therapy and should be used for patients with mild symptoms
- Prednisolone should be used in patients who present with severe symptoms or for those who do not respond to initial NSAID therapy

6.1.3 What Is The Dosage Of Steroid Used To Treat Subacute Thyroiditis?

In a prospective non-randomised clinical trial, Kubota *et al*. demonstrated that 15 mg/day of starting dose for prednisolone is an acceptable option for treatment of subacute thyroiditis. The prednisolone dose was tapered 5 mg/day every 2 weeks. In cases with persistent pain or high C-reactive protein, the dose is extended or increased up to 40 weeks of total treatment. Fifty percent of cases go into remission

within 6 weeks and do not recur. Thirty percent require between 7 and 8 weeks, while 20% require more than 8 weeks to recover.[222 (Level II)] A retrospective study comparing recurrent and non-recurrent subacute thyroiditis revealed that tapering prednisolone from 30 mg per day to 5 mg per day over a longer period (up to 44 days) is associated with no recurrence.[212 (Level III)]

An experimental approach to the treatment of subacute thyroiditis is administration of a mixture of lidocaine and dexamethasone using insulin pen into the thyroid gland.[223 (Level III)] Although the study design is prospective with seemingly favourable outcome, due to its small number (n=36), further study would be needed to clarify its benefits and risks.

Recommendation

- A starting dose of 15 mg/day tapered to 5 mg/day every 2 weeks is recommended. The duration of prednisolone may be prolonged in cases with persistent symptoms or raised ESR or CRP

6.1.4 How Long Should Patients With Subacute Thyroiditis Be Followed-up?

Overall, from retrospective studies, the recurrent rate of subacute thyroiditis is extremely low over the longterm. In a retrospective cohort, the recurrence rate is only 1.6% over a total of 13 years.[211 (Level III)] However, the recurrence rates are higher within the 1st year and tend to reduce over the years. In a retrospective review, the recurrence rate was about 10% over a 5-year period of follow-up.[214 (Level III)] Another study reported a recurrence rate of 10% within 1 year, and 4% after more than a year. The rate of hypothyroidism is as high as 34% in the first year and 15% after 1 year.[216 (Level III)] Therefore, it would be sensible to have frequent follow-up within the first 12 months, with reducing frequency over the next 5 years. Follow-up after 5 years may not be necessary.

Recommendation

- Patients should be monitored for recurrence 6 monthly for the first 1 year and yearly for the next 5 years

6.2 ACUTE/SUPPURATIVE THYROIDITIS

6.2.1 How Is Acute Thyroiditis Diagnosed?

Acute thyroiditis is a rare but life-threatening disorder. The clinical features of acute thyroiditis are quite similar to subacute thyroiditis but are of more severe intensity. Pain is a very prominent feature. Patients may also present with fever and lymphadenopathy. Local inflammation caused by the condition may contribute to upper airway obstruction. Patients may assume a posture to limit neck extension and fluctuance suggest the presence of abscess.[217 (Level III)]

In general, patients with acute thyroiditis are euthyroid. However, there are case reports of patient with hyperthyroidism and thyroid storm.[4 (Level III), 224 (Level III)]

During the acute inflammatory stage, ultrasound may not show a well demarcated hypoechoic lesion, but rather a diffuse hypoechoic area spread throughout the thyroid lobe which may cause erroneous diagnosis of subacute thyroiditis.[217 (Level III); 224(Level III)] Only later, approximately 1 week, the abscess or well demarcated hypoechoic lesion would be obvious. Other modalities that can be used to demonstrate the presence of an abscess are CT scans and MRIs.[217 (Level III); 4 (Level III); 224 (Level III); 225 (Level III)]

Apart from demonstrating thyroid abscess, several authors emphasize the need to identify pyriform sinus fistula which may contribute to recurrence.[225 (Level III); 226 (Level III); 227 (Level III)] The pyriform sinus fistula may be identified using direct endoscopy, barium oesophagography or CT scan.[226(Level III)]

Recommendations

- Acute thyroiditis should be suspected in all patients who present with painful goitre
- All patients with painful thyroid swelling should have thyroid function test done which includes free thyroxine and thyroid stimulating hormone
- Ultrasound should be done in all patients with painful thyroid swelling to rule out acute/suppurative thyroiditis. A non-suggestive ultrasound within 1 week of onset of illness should be repeated later
- In patients who had ultrasound findings suggestive of abscess or acute/suppurative thyroiditis, aspiration should be done; and sample sent for Gram stain, culture, and sensitivity
- In immunocompromised patients with unusual presentation of thyroid abscess; other rare causative organisms such as tuberculosis should be suspected

6.2.2 How Should Acute Thyroiditis Be Managed?

Thyroid fine needle aspiration with Gram staining, culture and sensitivity should be done to identify the causative organism. Among common reported isolates are S*treptococcus pyogenes*, *Staphylococcus aureus,* and *Streptrococcus pneumoniae*.[217 (Level III)] Other Gram-negative organisms such as *Haemophilus influenzae*, *Escherichia coli,* and *Klebsiella* spp. have also been reported.[224 (Level III)] Therefore the use of empirical broad-spectrum antibiotics is appropriate. Tuberculosis has also been reported in less than 1% of cases.[224 (Level III)]

The mainstay of therapy for acute thyroiditis is surgical excision.[217 (Level III), 4 (Level III)] To prevent recurrence, the piriform sinus fistula can be surgically excised or obliterated using chemocauterisation with favourable outcome based on case series.[226 (Level III); 227 (Level III)] With effective antibiotic therapy and elimination of formed abscesses, patients typically have an excellent prognosis if they survive the acute

episode. However, it is difficult to determine the exact morbidity and mortality of this condition due to its low incidence.

Recommendations

- Beta-blocker can be used in patients with symptoms of thyrotoxicosis
- Acute/suppurative thyroiditis should be treated with antibiotics and surgical drainage determined by clinical judgement

7. SPECIAL SITUATIONS

7.1 HYPOTHYROIDISM AND PREGNANCY

7.1.1 What Is The Definition Of Maternal Overt/Subclinical Hypothyroidism (OH/SCHypo)?

Maternal Hypothyroidism is generally defined as the presence of an elevated serum TSH during pregnancy beyond the upper limit of the pregnancy-specific reference range. Overt maternal hypothyroidism is also characterised by a decreased serum fT4 below the lower limit of the pregnancy specific reference range while SCHypo is characterised by an isolated high TSH with fT4 within the pregnancy-specific reference range. At present, serum TSH remains the main determinant used to guide treatment decisions and target. The difficulties lie in the presence of substantial differences in the upper reference limits of pregnancy specific reference range for TSH between populations which varies from 2.15 to 4.68 mIU/L.[228 (Level II)] It is therefore recommended that each institution should establish their own pregnancy-specific reference intervals for each trimester of pregnancy using the local population. If this is not available, an arbitrary level of 4 mIU/L can be used as the TSH upper reference limit. This level represents a reduction of 0.5 mIU/L of the non-pregnant TSH upper reference limit for most assays.[229 (Level II)]

Recommendations

- Each institution should establish their own pregnancy specific reference intervals for each trimester of pregnancy using the local population
- As there is no published data on the pregnancy specific reference range representative of the Malaysian pregnant population, we recommend a TSH upper reference limit of 4 mIU/L

7.1.2 What Are the Prevalence And Common Causes of Maternal Hypothyroidism?

The prevalence of hypothyroidism in pregnancy ranges from 0.3% to 4.8%.[230, 231 (Level III); 232 (Level II); 233 (Level III); 234,235,236 (Level II)] The onset of the disease in pregnancy is rare.[235 (Level II)] The most common cause of hypothyroidism in pregnancy is chronic autoimmune thyroiditis (Hashimoto's thyroiditis).[230, 231, 233 (Level III)] Other causes include previous

surgery, radioiodine ablation, congenital hypothyroidism and rarely, lymphocytic hypophysitis.[230, 233 (Level III)] High pre-pregnancy body mass index (BMI) is a significant risk factor for hypothyroidism in pregnancy.

7.1.3 Is Maternal OH/SCHypo Associated With Adverse Maternal/ Foetal Outcomes?

See ' Appendix 2'.

7.1.4 What Is The Impact Of TPO Ab Positivity on Euthyroid Women Or Women With Subclinical Hypothyroidism In Pregnancy?

See ' Appendix 2'.

7.1.5 Does Treatment With Levothyroxine (LT4) Improve Adverse Outcomes Associated With Maternal Overt/Subclinical Hypothyroidism?

See ' Appendix 2'..

7.1.6 Does Treatment With LT4 Improve Adverse Outcomes Associated With TPO Ab Positivity?

See ' Appendix 2'.

7.1.7 What Is The TSH Goal If Levothyroxine Is Given At Preconception, During Pregnancy And Postpartum?

A retrospective cohort study demonstrated an increased risk of miscarriage with TSH above 2.5 mIU/L at first trimester among pregnant women initiated on LT4 before conception.[266 (Level II)] There was no clinical study to date specifically looking at an optimal TSH goal in second or third trimester. Parallel to the treatment of hypothyroidism in the general population, it is reasonable to target the serum TSH in the lower half of the trimester specific pregnancy reference range for the local population.[229 (Level II)] If this is not available, a TSH goal of not more than 2.5 mIU/L should be achieved before conception and during the first trimester. The TSH goal can be relaxed to 3.0 mIU/L in the second and third trimester.[230 (Level III)] The TSH goal can be reverted to the normal reference range for non-pregnant women after delivery, provided the patient is not immediately planning for another conception.

Recommendations

- For hypothyroid women already treated with LT4 before conception, we recommend a TSH goal of no more than 2.5 mIU/L before conception and during the first trimester as the trimester specific reference range for Malaysian population is not available

- During the second and third trimester, a TSH goal of 3.0 mIU/L or below can be adopted
- The TSH goal can be reverted to the normal reference range for non-pregnant women after delivery

7.1.8 What Is The Levothyroxine Requirement During Pregnancy And Postpartum? How Should It Be Monitored?

An increase in LT4 requirement occurs soon after conception at four to six weeks of gestation. The LT4 requirement gradually increases through mid-gestation between 16–20 weeks and plateaus thereafter in the third trimester until delivery.[267 (Level II)] A retrospective observational study demonstrated a 45%–70% increment in LT4 dosing at the end pregnancy for women who received LT4 before conception.[268 (Level II)] Another retrospective study demonstrated an increment of 13%–27% during the first trimester which further increased to 26%–51% by the second trimester with no significant further increase in the third trimester.[269 (Level II)] The percentage increment in LT4 requirement was generally higher for hypothyroidism post thyroidectomy or radioactive iodine compared to autoimmune thyroiditis.[268 (Level II); 269 (Level II)] A prospective RCT comparing two LT4 dosage increment strategies with increment of LT4 tablets by two tablets per week versus three tablets per week, i.e. 29% versus 43% in early pregnancy showed that both strategies are equally effective in keeping the serum TSH within target, with the first strategy associated with a lower risk of overtreatment resulting in TSH suppression.[270 (Level I)] However, the target TSH in this study was up to 4.9 mIU/L, which is significantly higher than the pregnancy-specific TSH upper reference limit for most populations.[228 (Level II)] This study also showed that a thyroid function testing interval of four-weekly was able to detect more than 90% of all the abnormal values throughout pregnancy.[270 (Level I)] As the increased LT4 requirement during gestation is due to the physiological requirement of an increased total body thyroxine pool during pregnancy, the LT4 dosing should be reduced to pre-pregnant dose upon delivery. However, an observational study on patients with Hashimoto's thyroiditis revealed an increased LT4 requirement postpartum compared to before conception with no reduction versus during pregnancy was possibly related to postpartum exacerbation of autoimmune thyroiditis.[271 (Level II)]

Recommendations

- Pregnant women who are already treated with LT4 before conception are recommended to have their LT4 dosage increased by 30%–50% upon conception with a higher percentage being considered for post ablative hypothyroidism and lower percentage for autoimmune hypothyroidism
- Thyroid function testing should be performed every four weeks from conception until mid-gestation and at least once during the middle of the third trimester
- After delivery, the LT4 dosage can be generally re-adjusted to the prepregnancy requirement

7.1.9 Who Should Be Screened For Maternal Hypothyroidism?

While untreated maternal hypothyroidism has been associated with adverse pregnancy outcomes, the evidence for universal screening for maternal hypothyroidism is yet to be established. A prospective RCT comparing the universal screening versus case-finding approach for detection and treatment of thyroid dysfunction in pregnancy showed no difference in adverse outcomes.[272 (Level I)] Case-finding approach is thus recommended over universal approach for screening of maternal hypothyroidism. The test of choice is TSH as it is the most sensitive test in detection of hypothyroidism. Risk factors that have been shown to be associated with increased risk of maternal hypothyroidism include history of thyroid dysfunction; goitre; known thyroid antibody positivity; age at or above 30 years; type 1 diabetes or other autoimmune disorders; history of pregnancy loss or preterm delivery; infertility; history of thyroid surgery or head and neck radiation; morbid obesity; use of lithium or amiodarone; recent administration of iodinated radiologic contrast; residing in area of moderate-to–severe iodine deficiency; family history of thyroid disorders and two or more prior pregnancies.[273 (Level II); 274 (Level II); 275 (Level II); 276 (Level II); 277 (Level II)]

> **Recommendations**
>
> See 'Appendix 2'

7.2 HYPERTHYROIDISM AND PREGNANCY

7.2.1 What Is the Prevalence Of Hyperthyroidism In Pregnancy?

The prevalence of hyperthyroidism in pregnancy ranges from 0.1% to 1.6% worldwide.[278, 279 (Level II); 230, 280 (Level III); 281 (Level II); 282 (Level III)] In the United States of America, two studies reported the incidence of hyperthyroidism in pregnancy: 5.9 per 1000 women and 3.77 per 1000 women, respectively.[283 (Level II); 284 (Level III); 285 (Level II)] In Malaysia, studies have shown that the incidence of hyperthyroidism in pregnancy is 0.9 per 1000 deliveries.[286 (Level II)] The onset of the disease in pregnancy was rare.[279] Grave's disease was the most common cause.[230, 283, 285 (Level III); 286 (Level II)] Previous history of thyroid disorder and family history of thyroid disorder were associated with thyroid dysfunction.[283 (Level II)]

7.2.2 What Is The Definition Of Maternal Hyperthyroidism?

Maternal hyperthyroidism is defined as suppressed serum TSH level with elevated free tri-iodothyronine (fT3) and/or free thyroxine (fT4). Subclinical hyperthyroidism is defined as suppressed serum TSH with normal fT4 and/or fT3 levels. Subclinical maternal hyperthyroidism has not been associated with adverse maternal or foetal outcomes, and treatment for this condition is not recommended.[287 (Level III)] Serum TSH levels fall in the first trimester of normal pregnancies as a physiological response to the stimulating effect of hCG on the TSH receptor with a peak hCG level between

7 and 11 weeks gestation. The reference ranges for TSH and fT4 also vary between different populations of pregnant women due to assay variations, as well as population-specific factors, such as ethnicity and body mass index. The TSH lower reference limit of the pregnancy-specific reference range between populations varied between 0.02 and 0.41 mIU/L.[228 (Level II)] Thus, any subnormal serum TSH should be evaluated in conjunction with serum fT4 value. It is recommended that population-based, trimester-specific reference ranges for serum TSH and fT4 should be defined through the assessment of the local population data.[229 (Level II); 4 (level II)]

Recommendations

- Each institution should establish its own pregnancy-specific reference intervals for each trimester of pregnancy using local population data
- When a suppressed serum TSH is detected in the first trimester, a medical history should be gathered, and physical examination, and measurement of maternal serum fT4 concentrations should be performed

7.2.3 What Are The Common Causes Of Hyperthyroidism In Pregnancy?

The two most common causes of hyperthyroidism in pregnancy are gestational transient thyrotoxicosis (GTT) and Graves' disease.[229,4, 288 (Level III)] Other causes include toxic multinodular goitre, toxic adenoma and thyroiditis.[229,4 (Level III)] Rare causes in pregnancy include hyperthyroidism induced by beta-HCG in pregnancy such as multiple gestation, molar pregnancy and choriocarcinoma; which are often subclinical.[229,4 (Level III)]

7.2.4 How To Differentiate Gestational Transient Thyrotoxicosis (GTT) From Graves' Disease (GD)?

Gestational transient thyrotoxicosis is a non-autoimmune transient disorder that occurs in the first trimester of pregnancy and is caused by the peak in hCG levels during early pregnancy, leading to biochemical hyperthyroidism.[289(LevelIII)] It is generally asymptomatic, mild and self-limiting.[4(Level III)] However, more severe degrees of GTT are associated with hyperemesis; whereby patients may develop signs and symptoms of hyperthyroidism.[4(Level III)] In the presence of an elevated T4 and suppressed TSH in early pregnancy, GTT needs to be differentiated from Graves' disease, since these are the two most common causes of hyperthyroidism in pregnancy.[4, 289(Level III)] As they may have similar clinical manifestations such as palpitations, anxiety, tremor and heat intolerance, a careful history and physical examination is very important in establishing the aetiology.[4, 229 (Level III)]

The most likely aetiology in patients without a prior history of thyroid disease and stigmata of Graves' disease (goitre and ophthalmopathy) and in the absence of TSH-receptor antibody (TRAb) is GTT.[289,4,229 (Level III)] The presence of TRAb is highly suggestive of Graves' disease. Anti-thyroid peroxidase antibody (anti-TPO) can be present in both conditions.[230 (Level III)] No study has shown usefulness of thyroid

ultrasound in differentiating between GTT and GD.[230 (Level III)] The clinical usefulness of beta-HCG to differentiate between these two conditions is also limited.[290 (Level II)]

Recommendation

• When a suppressed TSH and elevated fT4 are detected in the first trimester, clinical history and physical examination should be performed to determine the aetiology. Graves' disease is differentiated from gestational thyrotoxicosis clinically. TRAb supports the diagnosis of Graves' disease

7.2.5 How To Manage Gestational Transient Thyrotoxicosis (GTT)?

Gestational transient thyrotoxicosis is not associated with adverse pregnancy outcomes.[291, 292 (Level II)] Management of GTT is mainly symptomatic, depending on the severity of symptoms.[4,229 (Level III)] In the presence of hyperemesis gravidarum, antiemetics and intravenous fluids are appropriate treatment. Hospitalisation might be necessary in some cases. Antithyroid drugs (ATDs) are not indicated as no improvement of obstetrical outcome was observed in treated cases, and due to the possibility of increased risk of birth defects with ATD use in early pregnancy.[291; 294 (Level II)] However, there are no studies comparing ATD to supportive therapy.[229 (Level III)] Low dose beta-blockers for a short period may be considered in very symptomatic patients.[4,229,230 (Level III)] Serum T4 returns to normal by 14–18 weeks of gestation.

Recommendation

• Management of gestational transient thyrotoxicosis is mainly supportive therapy: rehydration and hospitalisation if needed in the presence of hyperemesis gravidarum; and beta-blocker if very symptomatic. Antithyroid drugs are not recommended

7.2.6 What Are The Complications Of Hyperthyroidism In Pregnancy?

Hyperthyroidism in pregnancy can lead to poor maternal and foetal outcomes, especially when it is uncontrolled.[291 (Level II)] Maternal complications include miscarriages, preterm delivery, hypertension, heart failure, and thyroid storm.[291 (Level III)] Foetal transfer of TRAb that stimulate the thyroid gland can cause foetal hyperthyroidism which can lead to intrauterine growth retardation, stillbirth, low birth weight.[291,229,295 (Level II)] On the contrary, foetal hypothyroidism can occur as a result of transfer of ATD used to treat the mother, especially when the mother is made euthyroid.[295 (Level III)]

7.2.7 How to Manage Graves' Disease Prior to Conception?

In pregnancy, both hyperthyroidism and its treatment may result in complications. Therefore, all women with hyperthyroidism who are in their reproductive age should be given pre-conception counselling, which includes the importance of stable euthyroid state before attempting pregnancy and the association of birth

defects with ATD during pregnancy.[229,4 (Level III)] A stable euthyroid state can be indicated by two sets of normal thyroid function tests, at least one month apart with no change of therapy within the tests.[229,4 (Level III)] The pre-conception counselling should also include discussion on the therapeutic options for the management of hyperthyroidism in patients desiring pregnancy, whether to be treated with ATD or with definitive therapy, i.e. radioactive iodine therapy or thyroidectomy.[229,296 (Level III)] Each treatment option has its own advantages and disadvantages (Table 12).

In patients who prefer ATD, the increased risk of teratogenicity with both PTU and CMZ should be informed. Patients who are well-controlled on CMZ and plan to conceive could switch to PTU before trying to conceive.[4 (Level III)] See 'Appendix 2'. Women with thyrotoxicosis who require high dose of ATD to achieve a euthyroid state should be considered for definitive therapy before pregnancy.[4 (Level III)] Definitive therapy with radioactive iodine or surgery has the advantage of allowing patients to become pregnant without the concern of teratogenicity risk of ATD. After radioactive iodine therapy, conception should be delayed for at least 6 months and until a stable

Table 12: Therapeutic options for Graves' disease patients planning for pregnancy (Adapted from[229[Level III]])

Therapy	Advantages	Disadvantages
Antithyroid drugs	Effective treatment to euthyroid state within 1–2 months	Birth defects associated with use during pregnancy
	Often induces gradual remission of autoimmunity (decreasing antibody titres)	Medication adverse effects
	Easily discontinued or modified. Ease of treatment; cheap	Relapse after drug withdrawal likely in 50%–70% of the cases
Radioactive iodine (RAI)	Future relapse of hyperthyroidism very rare	Rising antibody titres following treatment may contribute to worsening ophthalmopathy or foetal risk
		Need to defer pregnancy until at least 6 months post RAI
		Some may not be in stable euthyroid state within the first year after RAI (might be hypothyroid or may remain hyperthyroid)
		Lifelong need of levothyroxine therapy following ablation
Thyroidectomy	Definitive therapy of hyperthyroidism. Stable euthyroid state easily achieved on replacement levothyroxine therapy	Life-long need for levothyroxine supplementation
	Gradual remission of autoimmunity occurs after surgery	Risks of thyroidectomy such as hypoparathyroidism, recurrent laryngeal nerve injury

euthyroid state is achieved. TSH-receptor antibody (TRAb) level may remain elevated for months following radioactive iodine therapy.[229, 4,297 (Level III)] Therefore surgery may be a better option for definitive therapy in patients with high TRAb levels.[229,4 (Level III)]

Recommendations

- Women with hyperthyroidism should be counselled on the importance of euthyroid state before attempting pregnancy. The risks and benefits of all treatment options to achieve a euthyroid state (radioactive treatment, thyroidectomy and ATD therapy) should also be discussed
- Women with hyperthyroidism who require high doses of ATD to achieve a euthyroid state should be considered for definitive therapy before becoming pregnant
- Women who are well-controlled on carbimazole and who desire pregnancy could switch to PTU before trying to conceive

7.2.8 How To Manage Graves' Disease During Pregnancy?

Anti-thyroid drugs are the mainstay of treatment for hyperthyroidism in pregnancy. The greatest risk with the usage of ATD in pregnancy is the teratogenicity potential. Besides, aplasia cutis, a syndrome of carbimazole embryopathy that includes dysmorphic facies has also been described. Recent large studies from Japan[294 (Level II-2)] and Denmark[298,300 (Level II-2)] have shown that CMZ-associated birth defects are more common than anticipated, affecting 1/30 children exposed to the drug in the weeks 6–10 of pregnancy. The risk observed included various types of abdominal wall defects, aplasia cutis, atresias of digestive tract, urinary tract, respiratory (choanal atresia) and circulatory (ventricular septum) defects.[298,300 (Level II-2)]

The Danish study also noted an almost similar incidence rate of teratogenicity after exposure to PTU[298 (Level II-2)], which was previously considered non-teratogenic. However, these defects were less severe and consisted of face and neck malformations (preauricular sinus and cysts) and urinary tract malformations (only in boys). As the majority of PTU-associated defects had been detected when the children developed complications and received surgery for the defect later in childhood,[293,298 (Level II-2)] studies relying solely on birth defects at birth will not find this association.[299 (Level III)]

The major period of teratogenicity due to ATD was gestational weeks 6–10, the period of organ formation. Therefore, consideration on treatment strategy is appropriate. A woman who is on ATD should test for pregnancy and immediately contact her caregiver to make a plan, once pregnancy is confirmed.[300,228 (Level III)]

Many patients on ATD therapy gradually enter remission when made euthyroid. Although half of the hyperthyroid patients eventually relapse when the medication is withdrawn after 1–2 years of therapy, only a few patients who have become TRAb

negative during therapy will relapse within the first months.[229 (Level III)] Therefore, ATD withdrawal is an option if the GD is considered to be in remission based on (i) recent thyroid function results and TRAb measurement, (ii) the need of only a low dose of ATD, and (iii) the clinical condition. After stopping ATD, thyroid function testing needs to be closely monitored during the remaining first trimester. However, ATD should not be stopped in some pregnant women who are at high risk of hyperthyroidism relapse if ATD is withdrawn.[304 (Level III)] This will include: women who were started on ATD therapy recently (<6 months), still have suppressed TSH, have a relatively high serum T3, high levels of TRAb, large goitre, active ophthalmopathy or other signs of active disease.

If ATD has to be continued or started in early pregnancy to treat overt hyperthyroidism, the drug of choice is PTU. There is a risk of liver failure with the use of PTU, but the risk of liver failure or agranulocytosis in pregnancy is much lower than the risk of birth defects.[293 (Level II)] Patients on CMZ should be replaced with PTU in early pregnancy, using a dose ratio of 1:10[301 (Level III)] e.g. 200 mg PTU per day to replace 20 mg CMZ. Because the half-life of PTU is considerably shorter, it should be used twice or thrice daily.

Recommendations

- Women taking ATD should be instructed to perform a pregnancy test as soon as possible, after a missed period. If the pregnancy test is positive, pregnant women should contact their caregiver immediately

- During early pregnancy, consider discontinuation of antithyroid drugs in a patient who is euthyroid on low dose of CMZ (≤10 mg daily) or PTU (≤100 mg daily), due to the potential teratogenic effects. Other factors to be considered before discontinuation of ATD include disease history, goitre size, duration of treatment, recent thyroid function tests results, TRAb measurement and other clinical factors

- If antithyroid medication is stopped, thyroid function testing and clinical examination should be performed monthly to ensure the pregnant woman remains clinically and biochemically euthyroid

- In pregnant women in whom ATD needs to be continued, PTU is recommended throughout the first trimester

- After first trimester, no recommendation can be made whether PTU should be continued or changed to CMZ

7.2.9 How To Monitor Patients With Graves' Disease On ATD In Pregnancy?

All ATD cross the placenta.[229,4,230,302 (Level III)] Therefore, foetal thyroid function might be affected. When patient is made euthyroid, the foetus is often overtreated, leading to foetal hypothyroidism and goitre.[302 (Level III)] Therefore, ATD dosage should be adjusted with the aim of maternal fT4 at or just above the pregnancy-specific upper limit of normal.[229,4,230,302,303 (Level III)] The smallest dose of ATD should be used

to avoid foetal overtreatment. Antithyroid drug discontinuation is possible in the last trimester as the incidence of GD becomes very low due to decrease in thyroid autoimmunity.[304 (Level II-2)]

When the trimester-specific fT4 is not available, the use of the non-pregnant reference range is recommended.[229,4 (Level III)] fT4 should be monitored every 4–6 weeks after initiation of therapy and after achieving target value.[229,4,230,303 (Level III)]

> **Recommendation**
>
> • The lowest effective dose of ATD should be used during pregnancy, targeting fT4 at or just above the reference range

7.2.10 What Is The Role Of Thyrotropin Receptor Antibody (TRAb) Assays In Pregnancy?

The measurement of TRAb is helpful in clarifying the aetiology of thyrotoxicosis and a positive result strongly supports the diagnosis of Graves' disease (GD). In pregnancy, as in the non-pregnant state, TRAb are a hallmark of GD.[305 (Level II)] GD occurs before pregnancy in 0.4%–1% of women and in 0.2%–0.4% during pregnancy, representing the most common cause (85%) of either overt or subclinical hyperthyroidism in women of reproductive age.[306,307 (Level III)] Regarding the behaviour of the TRAb, it is remarkable to note that due to the pregnancy-induced immunosuppression, autoantibody levels tend to decrease throughout pregnancy. The most typical scenario is that the TRAb are detectable in the first trimester, but their levels decrease after 20 weeks of gestation becoming undetectable towards full term.

Table 13: Indications and timing for TSH receptor antibody (TRAb) assays in pregnancy [232,312 (Level III)]

Indication for TRAb	Timing	TRAb level at the risk for foetal hyperthyroidism
Past history of Graves' disease treated with ablation (radioiodine or surgery)	Early in pregnancy, repeat test at weeks 18–22	**>3 times upper limit of normal**
Patient on antithyroid drugs (ATDs) for treatment of Graves' hyperthyroidism when pregnancy is confirmed	Early in pregnancy	
Patient requires treatment with ATDs for Graves' disease through midpregnancy	Repeat test at weeks 18–22	
Elevated TRAb at weeks 18–22 or the mother is taking ATD in the third trimester	Repeat test at weeks 30–34	

TRAb should be checked in a pregnant woman with a past history of GD or active GD. If TRAb levels are low or undetectable in early pregnancy, no further TRAb testing is recommended.[229] If maternal TRAb is elevated or patient is being treated with ATDs, TRAb should be measured again between weeks 18 and 22. In those with levels near 3–4 times above upper limit of normal (ULN), TRAb should be checked again during weeks 30–34. Maternal TRAb serum concentration greater than 3 times the upper limit of the reference range in the third trimester is a risk factor for neonatal hyperthyroidism.[306,229,308] (Level III)

Recommendations

- If the patient has a past history of GD treated with ablation (radioiodine or surgery), a maternal serum determination of TRAb is recommended at initial thyroid function testing during early pregnancy
- If TRAb levels are low or undetectable in early pregnancy, no further TRAb testing is recommended
- If maternal TRAb is elevated or patient is being treated with ATDs, TRAb should be measured again between weeks 18 and 22
- If elevated TRAb is detected at weeks 18–22 or the mother is taking ATD in the third trimester, a TRAb measurement should again be performed in late pregnancy (weeks 30–34) to evaluate the need for neonatal and postnatal monitoring

7.2.11 Should Additional Foetal Ultrasound Monitoring For Growth, Heart Rate And Goitre Be Performed?

Foetal well-being may be affected in the presence of uncontrolled hyperthyroidism and elevated TRAb.[229,307] (Level III) The diagnosis of foetal hyperthyroidism should be made on clinical grounds based on maternal history, serum TRAb levels and foetal ultrasonography.

Foetal goitre is the earliest sonographic sign of foetal thyroid dysfunction.[4] (Level III) Other signs of potential foetal hyperthyroidism that may be detected by ultrasonography include foetal tachycardia (heart rate >170 bpm, intrauterine growth restriction, accelerated bone maturation, signs of congestive heart failure and foetal hydrops.[229] (Level III)

Recommendation

- Foetal surveillance should be performed in women who have uncontrolled hyperthyroidism in the second half of pregnancy and elevated TRAb levels at any time during pregnancy (more than 3x upper limit of normal). Monitoring may include ultrasound to assess heart rate, growth, amniotic fluid volume, and the presence of foetal goitre

7.2.12 How To Manage Thyrotoxicosis Patients Who Are Breastfeeding?

Antithyroid drugs are the mainstay of treatment for thyrotoxicosis during the post-partum period.[229,303,296,310,311] (Level III) Both PTU and MMI can be detected in the breast milk of treated hyperthyroid women, but only in a very small amount.[229,309] (Level III) Neither of the two ATDs cause any alterations in thyroid function, physical and mental development of infants breastfed by lactating mothers with thyrotoxicosis. The largest study investigating the effects of ATD consumption during lactation measured neonatal thyroid function in the breastfed offspring, showed no difference in the IQ or physical development of the breastfed children of mothers on ATD compared to the control children.[229] (Level III) Continuation of breastfeeding is safe and should be encouraged in hyperthyroid mothers taking ATD.[310] (Level III)

> **Recommendation**
>
> - When antithyroid drug is indicated, both CMZ and PTU can be administered to breastfeeding women with thyrotoxicosis. However, the lowest effective dose should always be used since a small amount of these medications are transferred into the breast milk

7.3 POSTPARTUM THYROIDITIS (PPT)

7.3.1 What Is Postpartum Thyroiditis (PPT) And What Is Its Natural History?

Postpartum thyroiditis (PPT) is the occurrence of thyroid dysfunction, excluding GD, in the first postpartum year in women who were euthyroid prior to pregnancy. Transient thyrotoxicosis is followed by transient hypothyroidism with a return to the euthyroid state by the end of the initial postpartum year (classical form). Incidence in the general population is 5.4%. About 22% of patients present with the classical form, 30% with isolated thyrotoxicosis, and 48% with isolated hypothyroidism.[312] (Level III) The thyrotoxic phase of PPT typically occurs between 2 and 6 months postpartum. All episodes of thyrotoxicosis resolve spontaneously. The hypothyroid phase of PPT occurs from 3 to 12 months postpartum with about 20%–40% of cases resulting in permanent hypothyroidism in the ensuing 3–12 years.[313] (Level III) A prospective study reported that 50% of women with PPT remained hypothyroid at the end of the first postpartum year.[314] (Level III)

7.3.2 What Is The Aetiology?

It is an autoimmune disorder associated with the presence of thyroid antibodies (TPOAb and TgAb), lymphocyte abnormalities, complement activation, increased levels of IgG1, increased Natural Killer (NK) cell activity, and specific Human Leukocyte Antigen (HLA) haplotypes.[313] (Level III) Women who are thyroid Ab positive in the first trimester have a high risk of developing PPT, ranging from 33% to 50%.[313] (Level III) Women with the highest Ab titres also have the highest risk of PPT. A histological study of fine-needle aspirates of PPT reveals a lymphocytic thyroiditis,

similar to that seen in individuals with silent thyroiditis. The incidence of PPT is 3- to 4-fold higher in women with type 1 DM.[312 (Level III)] It is also associated with other autoimmune diseases such as Systemic Lupus Erythematosus (SLE) and chronic viral hepatitis.[312 (Level III); 315 (Level III)] Antipituitary antibodies have been found in 25% of women with previous history of PPT.[316 (Level II)]

7.3.3 How To Differentiate From Graves' Disease (GD) And What Are The Investigations?

TSH receptor antibodies are positive in GD in nearly all cases and are typically negative in PPT, although some mixed-type disease is seen. An elevated T4:T3 ratio suggests the presence of PPT. Physical stigmata of GD, such as goitre with a bruit or ophthalmopathy, are diagnostic when present. The radioiodine uptake is elevated or normal in GD and low in the thyrotoxic phase of PPT.[313 (Level II)]

7.3.4 What Is The Management?

During the thyrotoxic phase of PPT, symptomatic women may be treated with beta-blockers.[313 (Level III); 312 (Level III); 230 (Level III)] A beta-blocker that is safe for lactating women, such as propranolol or metoprolol, at the lowest possible dose to alleviate symptoms is the treatment of choice. Therapy is typically required for a few weeks. Antithyroid drugs are not recommended for the treatment of the thyrotoxic phase of PPT.[313 (Level III); 312 (Level III); 228 (Level III)] LT4 treatment should be started during the hypothyroid phase of PPT if the patient is symptomatic, lactating or if the patient is considering another conception. Asymptomatic women or women with mild symptoms who choose not to be treated need to have their TFT checked every 4- to 8-weekly until a euthyroid state is restored.[313 (Level III); 312 (Level III); 228 (Level III)] Length of time that LT4 should be continued has not been systematically evaluated. Maintain a euthyroid state in women who are attempting pregnancy or are pregnant. Tapering LT4 doses in order to determine whether the hypothyroid phase of PPT was transitory or permanent can begin by 12 months postpartum. Tapering should be gradual and TSH should be monitored every 6–8 weeks.[313 (Level III)]

Recommendations

- Women in thyrotoxic phase of PPT who are symptomatic should be treated with beta blockers. Antithyroid drugs are not recommended
- Women in hypothyroid phase of PPT and who are symptomatic should be treated with LT4. Women who are not treated need to have their TFT checked every 4- to 8-weekly until a euthyroid state is restored
- Women who choose to get pregnant again while in hypothyroid phase of PPT or who are breastfeeding should be treated with LT4
- Women in hypothyroid phase of PPT who have been initiated on LT4 should start tapering down LT4 after 12 months postpartum and TFT monitored 6- to 8-weekly

7.3.5 When To Monitor?

Following the resolution of the thyrotoxic phase of PPT, serum TSH should be measured in approximately 4–8 weeks (or if new symptoms develop) to screen for the hypothyroid phase. Nearly 10%–50% of women in whom the hypothyroid phase of PPT initially resolves will ultimately go on to develop permanent hypothyroidism.[313 (Level III); 314 (Level III)] Factors associated with an increased risk of developing permanent hypothyroidism are multiparity, thyroid hypoechogenicity on ultrasound, greater severity of the initial hypothyroidism, higher TPOAb titre, greater maternal age, and a history of pregnancy loss.[313 (Level III)] Women with a prior history of PPT should have TSH testing annually to evaluate for the development of permanent hypothyroidism.[313 (Level III)] Women who have had a prior history of PPT, who have another autoimmune disease, or are known to be TPO-Ab-positive should be screened at 3 months for PPT with a TSH and fT4. If they are euthyroid and TPO-Ab-negative, no further screening is indicated. However, if they are TPO-Ab-positive and euthyroid, TSH levels should be obtained at 6 and 9 months after delivery.[312 (Level III)]

Recommendations

- Women with a history of autoimmune disease (T1DM, SLE etc.) should be screened for postpartum thyroiditis
- Women with a history of postpartum thyroiditis in previous pregnancies or with positive thyroid antibody titres should be screened for PPT
- Women with a prior history of PPT with TPO-Ab negative should have their TFT checked at 3 months postpartum. If TFT is normal, no further screening is indicated. If they are TPO-Ab positive and euthyroid, TSH should be checked at 6 months and 9 months after delivery
- Women with resolution of PPT and high risk of permanent hypothyroidism should have TFT screened annually to monitor for development of permanent hypothyroidism
- Resolution of thyrotoxic phase should be followed by TFT monitoring in 4–8 weeks to screen for the hypothyroid phase

7.3.6 Is PPT Associated With Postpartum Depression?

There is no clear relationship between PPT and depression. Studies evaluating the relationship of PPT to postpartum depression have been inconsistent.[313 (Level III); 313 (Level III)] Two studies have reported a significant association between the presence of thyroid antibodies and depression, irrespective of thyroid function, whereas another study showed no association between the presence of microsomal antibodies and postpartum depression.[313 (Level III)] However, since hypothyroidism is an easily treatable cause of depression, all patients with postpartum depression should be screened for thyroid dysfunction.[312 (Level III)]

> **Recommendation**
>
> • Women with postpartum depression should be screened for hypothyroidism by having TFT measured

7.4 ACQUIRED HYPOTHYROIDISM AND HYPERTHYROIDISM IN CHILDREN AND ADOLESCENTS

7.4.1. Acquired Hypothyroidism In Children And Adolescents

7.4.1.1 What Is The Prevalence Of Hashimoto's Thyroiditis In Children And Adolescents?

Hypothyroidism is the most common disturbance of thyroid function in children. The overall prevalence of hypothyroidism in young people less than 22 years of age is 0.135%; and in the group aged 11–18 years, it is 0.113%.[317 (Level II-2)] Acquired hypothyroidism is most often caused by autoimmune thyroiditis. In the National Health and Nutrition Examination Survey (NHANES III) from 1988 to 1994, 6.3% of adolescents (12–19 years of age) had positive antithyroglobulin antibodies and 4.8% had positive antithyroid peroxidase antibodies. The incidence of antithyroid antibodies was highest in Hispanic-American adolescents and lowest in black non-Hispanic adolescents. Non-Hispanic whites had an incidence rate between these two groups.[52 (level II-2)]

7.4.1.2 What Are The Clinical Features Of Hashimoto's Thyroiditis In Children And Adolescents?

The most common manifestation of hypothyroidism in children is declining height velocity that results in short stature which tends to be insidious in onset and may present for several years before other symptoms occur. Other common symptoms are altered school performance, sluggishness, lethargy, cold intolerance, constipation, dry skin, brittle hair, facial puffiness and muscle pain.[318 (Level II-2)]

The commonest physical finding at presentation is a diffusely enlarged thyroid gland/goitre in 39.5% in one series. Other physical findings are short stature; apparent overweight; puffy facies with dull, placid expression; bradycardia; pseudohypertrophy of the muscles and delayed deep tendon reflexes.[319 (Level II-2)]

Pubertal development is delayed in most patients; however, some children have precocious puberty characterised by breast development and vaginal bleeding in girls and macro-orchidism in boys.[320 (Level II-2)]

> **Recommendation**
>
> • The clinical features of hypothyroidism in children and adolescents are similar to adults; however, in children, evaluations of height and puberty are essential since growth retardation and abnormal puberty are common

7.4.1.3 What Is The Natural History Of Hashimoto's Thyroiditis In Children And Adolescents?

Hashimoto's thyroiditis is more common in girls than boys (2.8:1) and in whites than blacks. Among all children, euthyroid goitre is more common than hypothyroidism.[52 (Level II-2)] Hashimoto's thyroiditis with thyrotoxicosis (Hashitoxicosis) in general has a definitive resolution of hyperthyroidism in an average of eight months.[318 (Level II-2)] In patients with Hashimoto's thyroiditis with euthyroidism, 64.8% remains euthyroid after 5 years. Predictive factors for future development of hypothyroidism are presence of goitre, elevated TPO antibodies, ATG antibodies, and progressive increase in TSH.[318 (Level II-2)]

An unusual outcome of Hashimoto's is the conversion to Graves' disease in 7% of children and adolescents, which is due to alteration in the biological activity of the TSH receptor antibody from predominantly a TSH receptor-blocking antibody during the hypothyroid phase to a thyroid-stimulating antibody when Graves' disease manifests.[318 (Level II-2)]

In Hashimoto's thyroiditis with subclinical hypothyroidism at the end of five-year follow-up, 89.6% had thyroid dysfunction. Those associated with Turner (without Turner 63.6% vs. with Turner 100%) or Down syndrome (without Down 63.6% vs. with Down 97.6%) had increased likelihood of having thyroid dysfunctions.[319 (Level II-2)]

In contrast, idiopathic subclinical hypothyroidism frequently is a benign condition, in which 61.9% became euthyroid at the end of five-year follow-up.[319 (Level II-2)]

Recommendation

- It is recommended to examine for goitre, measure antithyroid antibodies, and evaluate TSH pattern, as these are the predictive factors for future development of hypothyroidism

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7.4.1.4 How To Diagnose And Investigate Hashimoto's Thyroiditis In Children And Adolescents?

With compatible history, diagnosis can be confirmed by measuring antithyroid antibodies, in which case approximately 85%–90% of children and adolescents have high serum TPO antibody, and 30%–50% have positive ATG antibody levels.

In one study, eight out of 83 children (9.2%) with autoimmune thyroiditis had positive TSH receptor-blocking antibodies.[321 (Level II-2)]

Thyroid ultrasonography and radionuclide scanning are rarely indicated in children. In a study of 105 children with antibody-positive Hashimoto's thyroiditis, only one-third showed typical ultrasound changes at diagnosis.[322 (Level II-2)]

If the patient has a markedly asymmetric goitre or a prominent nodule, or a smaller nodule that enlarges during follow-up, fine needle aspiration biopsy is indicated. Bone age is performed to assess skeletal maturation and in hypothyroidism during childhood and adolescence the height age is less than the chronological age.[323 (Level 11-2)]

Recommendations

- The diagnosis of Hashimoto's thyroiditis in children and adolescents is based on the compatible history and confirmed with measurement of antithyroid antibodies
- Ultrasound and isotope scans are not routinely performed unless other issues, such as markedly asymmetrical goitre, thyroid nodule or malignancy, are suspected

7.4.1.5 What Is The Pattern Of Thyroid Function In Hashimoto's Thyroiditis In Children And Adolescents?

In a retrospective, multicentre study involving a total of 608 subjects, 69% were pubertal, 58% were asymptomatic, 9% associated with chromosomal disorders (Turner syndrome, Down syndrome), and 17.6% had other autoimmune conditions. With regard to thyroid functions, 52.1% were euthyroid and 47.9% had thyroid dysfunction. In those with thyroid dysfunction, 41.4% were overt and subclinical hypothyroid, and 6.5% were overt and subclinical hyperthyroid. Significant factors associated with an increase in the likelihood of thyroid dysfunction were age <10 years, prepubertal status, and chromosomal disorders.[324 (Level II-2)]

7.4.1.6 What Is The Treatment Of Hypothyroidism Secondary To Hashimoto's Thyroiditis In Children And Adolescents?

Levothyroxine (L-T4) is the treatment of choice in children with hypothyroidism. The goals of the treatment are to restore normal growth, development, and normal pubertal progression. The rate of clearance of L-T4 is higher in children than adults and as a result, the daily replacement on a weight basis is higher.

Age 1–3 years: 4–6 mcg/kg body weight

Age 3–10 years: 3–5 mcg/kg body weight

Age 10–16 years: 2–4 mcg/kg body weight

Alternatively, the dose can be calculated based on the body surface area as approximately 100 mcg/m^2/day. The recommended target range for TSH is in the lower half of the reference range, optimally 0.5–2.0 mIU/L; and for free T4, it is in the upper half of the reference range.[325 (Level II-1)] Once growth and pubertal development are complete, thyroid hormone treatment can be discontinued and thyroid function re-evaluated a month later. Treatment with thyroxine, in hypothyroid patients with goitre, results in reduced thyroid volume.[326 (Level 1)]

Recommendations

- Levothyroxine is recommended as the medication of choice for treating Hashimoto's thyroiditis
- The recommended dose of levothyroxine is based on the body weight or body surface area
- The recommended target range for TSH is in the lower half of the reference range
- The recommended target range for free T4 is in the upper half of the reference range
- Levothyroxine is effective in reducing the thyroid gland size/goitre

7.4.1.7 What Is The Treatment Of Non-goitrous Euthyroid Hashimoto's Thyroiditis?

Treatment of non-goitrous euthyroid Hashimoto's thyroiditis with thyroxine at a dose of 1.44±0.5 mcg/kg body weight results in lower thyroid volume compared to control. Within the control group, thyroid volume and TSH levels increased after two years of follow-up.[327 (Level 1)] However, in another trial, treatment of non-goitrous euthyroid Hashimoto's thyroiditis had no effect on the thyroid volume at the end of three years of treatment.[326 (Level 1)]

Recommendations

- Monitor for goitre, antithyroid antibodies, and pattern of thyroid function in non-goitrous euthyroid Hashimoto's thyroiditis
- Treatment of non-goitrous euthyroid Hashimoto's thyroiditis with thyroxine is controversial

7.4.1.8 What Is The Treatment Of Euthyroid Hashimoto's Thyroiditis With Goitre?

Treatment of euthyroid Hashimoto's thyroiditis with goitre results in a reduction of thyroid volume.[326 (Level 1)] In another trial, treatment of euthyroid Hashimoto's thyroiditis at a dose of 1.6±0.8 mcg/kg adjusted to keep TSH within the normal range of 0.4–4.0 mlU/L resulted in a decline in the thyroid volume in the treated group.[328 (Level 1)]

Recommendation

- Levothyroxine is effective for the treatment of euthyroid Hashimoto's thyroiditis with goitre

7.4.1.9 What Is The Risk Of Hypothyroidism In Turner Syndrome (TS)?

Turner syndrome (TS) has been linked to increased risk of autoimmunity, especially in case of the thyroid gland. Hashimoto's thyroiditis (HT) is the commonest reported autoimmune disease in girls with TS. A study involving 41 TS girls aged 6–18 years confirmed a high incidence of thyroid autoimmunity (26.8%).[329 (Level II)] Another long-term follow-up study reported a higher incidence, whereby 42% of TS girls had elevated thyroid autoantibodies.[330 (Level II)] Amongst the positive autoantibodies group, 65% had hypothyroidism compared to only 24% out of the total TS population, irrespective of the autoantibodies level. Hyperthyroidism was detected in only 2.5% of the total TS girls. The same study reported that thyroid dysfunction was first noted from the age of eight years.

Among Asians, more than half of the Japanese women with TS in adulthood had thyroid autoantibodies. Of the 37 women with thyroid autoantibodies (57%), three had Graves' disease and 20 were hypothyroid and diagnosed with Hashimoto's thyroiditis.[331 (Level II)]

The spontaneous evolution of thyroid function in TS girls with Hashimoto's thyroiditis seems to be characterised by a significant worsening of the thyroid status, both in children presenting with euthyroidism as well as those presenting with subclinical hypothyroidism (SCHypo).[332 (Level II)] An association with TS is shown to worsen the long-term prognosis of thyroid function in girls with HT.

7.4.1.10 When To Screen For Hypothyroidism In Turner Syndrome?

The International Turner Syndrome Consensus Group recommends screening for hypothyroidism at diagnosis and then annually with fT4 and TSH measurements beginning in early childhood and throughout the lifespan.[333 (Level III)]

The TS Study Group suggested that all individuals with TS should require continued annual monitoring of thyroid function throughout the lifespan, starting as young as four years of age. This is in line with the reported case of autoimmune thyroid disease in a four-year–old TS patient.[334 (Level III)]

An observational study, on the other hand, suggested that thyroid function should be evaluated yearly in girls with TS, past the age of eight years, and more frequently in those with positive thyroid autoantibodies.[330 (Level II)] Some other studies acknowledged the importance of monitoring the thyroid function in view of the risk of developing hypothyroidism.[329 (Level II); 331 (Level II); 335 (Level II)]

Massa *et al*. indicated that some TS women had goitre or biochemical hypothyroidism even without detectable antibodies. Therefore, they concluded that the absence of thyroid autoantibody did not exclude a disturbance of thyroid function.[336 (Level II)] Screening of the thyroid function of these women with TS regularly, even if they were negative for thyroid autoantibody, is recommended.

Recommendations

- All individuals with TS should need continued annual monitoring of thyroid function throughout their lifespan starting at diagnosis
- Screening of TS patients for hypothyroidism even in the absence of positive autoantibodies is recommended

7.4.1.11 What Is The Risk Of Hypothyroidism In Down Syndrome (DS)?

Down syndrome (DS) or trisomy 21 children are at an increased risk of primary thyroid dysfunction. The prevalence of hypothyroidism in DS increases with age and is projected as no less than 5.7% among children and adolescents in Scotland.[337 (Level II)] Lughetti *et al*. reported that the probability of hypothyroidism increased from 7% to 24% at ten years.[338 (Level II)]

Subclinical hypothyroidism (SCHypo) is also a known thyroid dysfunction linked to DS. Subclinical hypothyroidism is diagnosed in asymptomatic patients with serum TSH concentration between 5 mIU/L and 10 mIU/L and normal free or total T4. The prevalence of SCHypo is even more frequently reported in children with trisomy 21, with prevalence between 19.6% and 60%.[339 (Level II); 340 (Level III)] However, in a majority of them, the thyroid function tends to normalise overtime. In a cohort of 53 children with DS between six months and five years of age, the SCHypo normalised in >70%, with a higher remission rate in patients without goitre and autoimmunity.[341 (Level III)]

7.4.1.12 When To Screen For Hypothyroidism In Down Syndrome?

Regular monitoring of thyroid function in patients with trisomy 21 is recommended.[342(Level III)] Many children with DS have mildly elevated TSH and normal free T4 levels. Verification of the results of newborn thyroid function screening is important in view of increased risk of acquired thyroid disease. Repeat thyroid function test at 6 and 12 months and then annually is recommended by the guidelines.[342(Level III); 343 (Level III)] Lughetti *et al*. suggested that DS children should be carefully monitored annually to allow early identification of thyroid dysfunction.[338 (Level II)]

Recommendations

- Regular monitoring of thyroid function in patients with trisomy 21 is recommended
- Repeat thyroid function test at 6 and 12 months of age and then annually is recommended

7.4.1.13 How To Treat Hypothyroidism In Down Syndrome?

The decision on whether or not to treat should be taken after careful discussion with the parents on the risks and potential benefits of treatment. To date, there is insufficient data to recommend treatment in the majority of children with

SCHypo, in whom the serum TSH concentration is <10 mIU/L and in whom the TT_4/fT4 concentration is normal. Management of children with abnormal TSH or T4 concentrations should be discussed with a paediatric endocrinologist.[342 (Level III)]

Recommendation

- There is insufficient evidence to recommend treatment in the majority of children with SCHypo, in whom the serum TSH concentration is <10 mIU/L and in whom the TT_4/fT4 concentration is normal

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7.4.1.14 What Is The Risk Of Hypothyroidism In Klinefelter Syndrome (KS)?

To the best of our knowledge, there had been mainly reports on the association of Klinefelter syndrome (KS) with autoimmune conditions, including hypothyroidism. A study in adult men found significantly higher rates of several autoimmune diseases in men with KS, including rheumatoid arthritis (rate ratio [RR 3.3]), lupus (RR 18.1), multiple sclerosis (RR 4.3), Addison's disease (RR 11.7), Sjogren's syndrome (RR 19.3), autoimmune hypothyroidism (RR 2.7), and type 1 diabetes mellitus (RR 6.1).[344 (Level II)]

Although the autoimmune diseases are all significantly higher in adult men with KS compared to men in the general population, most of these conditions are known to have a higher female predominance, and the risk of these autoimmune diseases is similar to women in the general population.[345 (Level II)] However, there are no studies evaluating the autoimmune diseases in children with KS to date.

7.4.1.15 When To Screen For Hypothyroidism In Klinefelter Syndrome?

An interdisciplinary expert panel of specialists under the auspices of the Italian Society of Andrology and Sexual Medicine recommended screening for primary hypothyroidism in adolescents and adults with KS.[346 (Level III)] However, evidence is lacking to recommend this in paediatrics.

A review of KS in children recommended thyroid function screening every 1–2 years starting at age ten years, or sooner or more frequently, if symptoms are present.[347 (Level III)] It is important to be aware of the increased prevalence of autoimmune diseases in KS. Therefore, evaluation of thyroid function is required if suggestive symptoms are present.

Recommendations

- It is important to be aware of the increased prevalence of autoimmune diseases in KS. Therefore, evaluation of thyroid function is required if suggestive symptoms are present
- Thyroid function screening should be performed at diagnosis or at every 1–2 years after the age of ten years

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7.4.1.16 What Is The Risk Of Hypothyroidism In Prader–Willi Syndrome (PWS)?

Hypothalamic dysfunction may increase the risk of central hypothyroidism in Prader–Willi Syndrome (PWS) patients. There are varying studies reporting the prevalence of hypothyroidism in PWS that range from 4.8%[348 (Level III)] to as high as 20%–30%.[349 (Level IV)] However, a small study looking at thyroid status in PWS patients up until two years of life reported that in 72.2% patients, serum TT4 and/or fT4 levels were below the 2.5th percentile of the reference population.[350 (Level III)] This study suggests that transient or definitive TSH-releasing hormone (TRH)–TSH thyroid axis dysfunction may frequently be present in young PWS patients. Awareness of this dysfunction in this critical period of thyroid hormone action on neurological development is important among paediatricians.

Evaluation of thyroid function in children with PWS, before and during GH treatment, was carried out in a study of 75 PWS children. It was found that during GH treatment, fT4 decreased significantly to low-normal levels, while TSH levels remained normal. T3 levels were relatively high or normal, both before and during GH treatment, which may indicate that PWS children have increased conversion of T4 to T3.[351 (Level III)]

7.4.1.17 When To Screen For Hypothyroidism In Prader–Willi Syndrome?

An open international multidisciplinary expert meeting held in October 2006 in Toulouse, France, represented by 37 invited speakers had outlined recommendations for the screening of thyroid status in PWS population. They recommended that PWS patients required screening with TSH, fT_4, and fT_3 measurements, especially before and while on GH treatment.[352 (Level III)]

A review suggested screening for hypothyroidism to be performed within the first three months of life, and then yearly, especially if on GH therapy.[353 (Level III)]

Recommendations

- Screening for hypothyroidism is recommended at diagnosis
- Hypothyroidism in PWS may be of central or peripheral origin. Therefore, PWS patients require screening with TSH, fT4, and fT3 measurements before and while on GH treatment

7.4.1.18 How To Treat And Monitor Hypothyroidism In Prader–Willi Syndrome?

Treatment with levothyroxine at typical replacement doses based on age and weight should be done if the thyroid function is indicative of hypothyroidism.[352 (Level III), 353 (Level III)]

7.4.2 Hyperthyroidism in Children And Adolescents

7.4.2.1 How Is Graves' Disease Diagnosed In Children And Adolescents?

Symptoms of hyperthyroidism may be subtle and present for months or years before the diagnosis is made. School-aged children and adolescents could present with poor concentration, deterioration in school performance, irritability, fatigue, palpitations, heat intolerance, fine tremor, and goitre. Younger prepubertal children more commonly present with poor weight gain and frequent bowel movements and tend to be diagnosed later.[353 (Level III); 354 (Level III)] In the paediatric age group, hyperthyroidism can also affect growth, puberty, and bone density.[353 (Level III)] Increase in height velocity with advanced bone age, is related to the duration of hyperthyroidism. As in adults, children with GD may have a lower than normal bone mass; however, bone mass is often restored to normal levels after two years of an euthyroid state.

The size of the thyroid gland is variable. It is usually symmetrically enlarged, firm, uniformly smooth, and not tender. Ophthalmic abnormalities are usually less severe in children than in adults.[355 (Level III)] Thyrotoxicosis crisis and pretibial myxoedema are rare in childhood.

A suppressed serum TSH and an elevated free T4 or T3 or both confirms the diagnosis of hyperthyroidism. With paediatric patients, it is important that free T4 levels are interpreted according to the reference range for age. There also exists a variation in the reference levels with different manufacturer assays. Some patients, especially prepubertal children, may have elevated serum T3, but normal free T4 levels (isolated T3 toxicosis).[4 (Level III)] In a patient with a symmetrically enlarged thyroid, recent onset of orbitopathy, and moderate-to–severe hyperthyroidism, the diagnosis of GD is likely and further evaluation of the aetiology is often unnecessary.[4 (Level III)] If the diagnosis is not apparent, further diagnostic tests depending on available resources include measurement of TSH-receptor antibody, determination of radioactive iodine uptake (RAIU), or measurement of thyroid blood flow on ultrasonography is needed.[4 (Level III)] If the diagnosis of GD is unclear, TSH receptor antibodies (TRAb) should be measured.[4 (Level III); 356 (Level III)] They are sensitive and specific biomarkers for the diagnosis of GD in childhood and reflect disease severity and activity.[356 (Level III)] There is a positive correlation reported between serum TRAb and fT4 levels and significantly higher levels in young children ≤5 years of age.[357 (Level II)]

Measurement of TSH receptor antibodies may be useful in differentiating GD from the toxic phase of chronic lymphocytic thyroiditis and subacute thyroiditis.[358 (Level III)] However, TSH-receptor antibodies can be negative in mild or initial presentation of GD. A negative result may also be due to assay insensitivity. Other thyroid antibodies, antithyroglobulin and antithyroid peroxidases, are also often present but are not specific in the diagnosis of GD.

Thyroid ultrasonography in GD usually shows a diffusely enlarged thyroid gland, often homogeneous. Ultrasound is recommended for any GD patient with thyroid

gland asymmetry or a palpable nodule. If a significant nodule is confirmed, fine-needle aspiration biopsy and a thyroid scan should be considered.[4 (Level III); 358 (Level III); 359 (Level III)] Although uncommon, patients with GD or an autonomous nodule, may have concurrent differentiated thyroid cancer (DTC). Adolescents with GD have been reported to present with DTC.[359 (Level III)] Given the debate on whether nodules found in the setting of autoimmune thyroid disease have an increased risk of malignancy, a thorough evaluation of the nodule(s) is recommended.

Imaging with radioisotopes is not required for the diagnosis of GD. A thyroid scan should be considered for patients with unclear aetiology and negative TSH-receptor antibody, or if the clinical presentation suggests a thyroid adenoma or multinodular goitre.[4 (Level III), 359 (Level III)]

Recommendations

- The diagnosis is based on the clinical suspicion and confirmed by elevated free T4 and/or T3 levels with suppressed TSH
- Free T4 levels must be interpreted according to reference range for different ages and after consideration of the variation with different manufacturer assays
- In a patient with a symmetrically enlarged thyroid, recent onset of ophthalmopathy and moderate-to–severe hyperthyroidism, the diagnosis of GD is likely and further evaluation of the aetiology is often unnecessary
- However, if the aetiology of hyperthyroidism is unclear, TSH receptor antibodies, which are specific to GD, should be measured
- Ultrasound is recommended for any patient with thyroid gland asymmetry or a palpable nodule

7.4.2.2 How Should Graves' Disease Be Managed In Children And Adolescents?

Three treatment options available for GD are antithyroid drugs (ATD), radioiodine therapy (RAI) and thyroidectomy. First-line initial treatment is ATD, which is carbimazole or its active metabolite methimazole (MMI). Propylthiouracil should be avoided in children, except in selected circumstances, because of the risk of idiosyncratic liver failure. Methimazole/carbimazole dose typically used is 0.2–0.5 mg/kg daily, with a range from 0.1 mg/kg to 1.0 mg/kg daily.[4 (Level III);359 (Level III); 360 (Level III)] The initial starting dose is usually 0.5–1 mg/kg/day, with a maximal dose of 30 mg/day.[361; 362 (Level III)] Because most side effects of MMI are dose-related and occur within the first three months of treatment, high doses of MMI (>30 mg for an adolescent or adult) should rarely be used initially.[4 (Level III); 361 (Level III); 362 (Level III)] Methimazole/carbimazole could be administered once daily, which provides better compliance.[4 (Level III)] Administration in divided doses has not been proven to be superior, compared to once-daily dosing. However, when a more rapid biochemical control is needed in patients with severe thyrotoxicosis, an initial split dose of MMI/carbimazole

(e.g. 15 mg twice a day) may be more effective than a single daily dose because the duration of action of MMI/carbimazole may be less than 24 hours.[4 (Level III)]

Treatment with β-blocker such as atenolol, propranolol, or metoprolol is recommended for children experiencing significant symptoms of hyperthyroidism, e.g. tachycardia, muscle weakness, tremor, or neuropsychological changes. In patients with asthma or reactive airway disease, cardio-selective β-blockers, such as atenolol or metoprolol, should be used cautiously.[4 (Level III); 360 (Level III); 361 (Level III); 362 (Level III)]

Meta-analyses suggest a higher prevalence of adverse events using block-and–replace regimen than dose titration.[4 (Level III)] This is likely due to higher doses of MMI/carbimazole and the dose-related complications associated with MMI/carbimazole, hence this practice should not be routinely used.

Propylthiouracil should only be used for a short course in patients with adverse reaction to MMI who are not candidates for radioiodine therapy or surgery.[361 (Level II)] This is because PTU has a higher risk of liver failure in one in 2000–4000 children taking the medication.[363, 364, 365 (Level II)]

Recommendations

- The first-line initial treatment is ATD, which is carbimazole or its active metabolite MMI
- Methimazole/carbimazole dose typically used is 0.2–0.5 mg/kg daily, with a range from 0.1 mg/kg to 1.0 mg/kg daily (maximal initial dose: 30 mg daily)
- After 2–4 weeks, when the thyroid hormone levels have normalised, the initial dose should gradually be reduced by 30%–50%
- TSH levels may take 2–4 months to appear in the serum and should not be used to titrate the dose
- Propylthiouracil (PTU) should be avoided in children, except in selected circumstances because of the risk of idiosyncratic liver failure
- The block-and–replace regimen should not be routinely used
- Beta-adrenergic blockade should be considered for children with significant symptoms of hyperthyroidism at diagnosis or relapse, especially if there is tachycardia. In patients with asthma or reactive airway disease, cardioselective β-blockers, such as atenolol or metoprolol, should be used cautiously

7.4.2.3 How Should Children With Graves' Disease On Antithyroid Drugs Be Monitored?

After 2–4 weeks, when thyroid hormone levels have normalised, the initial dose is gradually reduced by 30%–50%. Hypothyroidism may occur if the ATD dose is not reduced as serum fT4 levels normalise. TSH levels may take 2–4 months to appear in the serum and should not be used to titrate the dose. After initiation of ATD, thyroid function should initially be monitored 2–6 weeks once, and then every

2–3 months, once the dose is stabilised.[4 (Level III); 359 (Level III); 361 (Level III)] Carbimazole dose could be adjusted based on one tablet (5 mg), half tablet (2.5 mg) or even a quarter tablet (1.25 mg) in infants.[361 (Level III)]

Propylthiouracil-induced liver injury can be of rapid onset and rapidly progressive; routine monitoring of liver function tests and transaminase levels has not been shown to be useful in surveillance for PTU-related liver injury.[4 (Level III)] Adverse effects of MMI are more often reported in the first 3–6 months of treatment and associated with a higher dose. Methimazole/carbimazole is associated with minor reactions (rash, urticaria, arthralgia, and gastrointestinal problems) in about 5%–25% of cases. The frequency of agranulocytosis, the most severe side effect, is between 0.2% and 0.5%. Other major side effects are rare and are observed mostly with PTU, which should be avoided in children; they include drug-induced hepatitis, liver failure, and the production of cytoplasmic antineutrophil antibody. Ab-positive vasculitis is rare.[4 (Level III); 359 (Level III); 361 (Level III)] (see Table 14 for the side effects of antithyroid medications).

Table 14: Side effects of antithyroid medications (MMI and carbimazole)[359 (Level III)]	
Minor	**Severe**
Rash	Agranulocytosis
Pruritus	Neutropaenia
Hives	Thrombocytopaenia
Hair loss	Steven-Johnson syndrome
Nausea	Cholestatic jaundice
Decreased taste	Hepatitis
Joint paint	
Arthralgia	

The frequency of side effects may be dose related and is very low in patients receiving MMI at a dose <10 mg/day. In one centre, Steven-Johnson syndrome had been reported in three out of 100 patients on MMI, but with large doses >30 mg/day.[366 (Level III)] Side effects of ATD should be informed to caretakers/patients preferably in writing, and to seek medical attention if they develop pruritic rash, jaundice, acolic stools or dark urine, arthralgias, abdominal pain, nausea, fatigue, fever, or pharyngitis.

Prior to initiating ATD therapy, a baseline complete blood cell count, including WBC count with differential, and a liver profile including bilirubin, transaminases, and alkaline phosphatase should be done.[4 (Level III)] While routine monitoring of WBC counts may occasionally detect early agranulocytosis, it is not recommended because of the rarity of the condition and its sudden onset, which is generally symptomatic. For this reason, measuring WBC counts during febrile illnesses and at the onset of pharyngitis has become the standard approach for monitoring.[4 (Level III)]

In general, PTU should not be used in children. However, if used, it should be stopped immediately, and liver function assessed in children who experience anorexia, pruritus, rash, jaundice, light-coloured stool or dark urine, joint pain, right upper quadrant pain, abdominal bloating, nausea or malaise.[4] (Level III) Propylthiouracil should be discontinued if transaminase levels reach 2–3 times the upper limit of normal. After discontinuing the drug, liver function tests (i.e. bilirubin, alkaline phosphatase, and transaminases) should be monitored weekly.[4] (Level III) If there is no evidence of resolution, referral to a hepatologist is warranted.[4 (Level III)]

Practitioners should also monitor the weight of children treated with ATDs. Excessive weight gain within six months of treatment is seen in children treated for GD, and the gain in weight can persist.[366 (Level II)] Persistent minor cutaneous reactions to MMI therapy in children should be managed by antihistamine treatment or cessation of the medication and changing to therapy with RAI or surgery.[4 (Level III)] In the case of a serious adverse reaction to an ATD, prescribing the other ATD is not recommended. If children develop serious adverse reactions to MMI, RAI or surgery should be considered, because the risks of PTU are considered greater than the risks of RAI or surgery.[4 (Level III)]

In special circumstances, in which the patient appears to be at risk for thyroid storm and ATD therapy is needed in a child with a serious adverse reaction to MMI, PTU may be considered for short-term therapy to control hyperthyroidism.[4 (Level III)] In this setting, families should be informed of the risks of PTU.

Recommendations

- After initiation of ATD, thyroid function should initially be monitored once in 2–6 weeks, and then every 2–3 months, once the dose is stabilised

- Since most of the side effects of MMI are dose-related and occur within the first three months of treatment, high doses of MMI (>30 mg/day for an adolescent or adult) should rarely be used initially

- A baseline full blood count (FBC), including WBC count with differential and liver function test (LFT) should be obtained before initiating ATD. Routine monitoring of FBC and LFT is not recommended because of the unpredictable development of adverse effects

- White blood cell counts should be measured in children who develop fever, arthralgias, mouth sores, pharyngitis, or malaise with consideration of withholding ATDs

- Patients and caretakers should be counselled on the potential adverse effects of ATD, preferably in writing

- Persistent minor cutaneous reactions to MMI therapy in children should be managed by concurrent antihistamine therapy or cessation of the medication and changing the therapy to RAI or surgery. In the case of a serious adverse reaction to an ATD, prescribing another ATD is not recommended

- In general, PTU should not be used in children. But if it is used, it should be stopped immediately, and liver function assessed in children who develop anorexia, pruritus, rash, jaundice, light-coloured stool or dark urine, joint pain, right upper quadrant pain or abdominal bloating, nausea or malaise

7.4.2.4 When Is Definitive Therapy Indicated?

Definitive therapy available for GD is RAI or thyroidectomy. Indications for definitive treatment in children include relapse after an appropriate duration of ATD, a lack of compliance on the part of the patient/caretakers or adverse effects of ATD. The issue of how long ATDs should be used in children before considering either RAI or surgery is controversial.

The American Thyroid Association 2016 guideline recommends paediatric patients with GD, who are not in remission following at least 1–2 years of MMI/carbimazole, be considered for definitive treatment. Alternatively, MMI/carbimazole may also be used for longer duration if there are no adverse effects.[4 (Level III)] Patients and caretakers should be counselled of the therapeutic options to make a best-informed decision.

In children, when ATDs are used for 1–2 years, remission rates reported are generally not high, that is, at around 20%–30% with remission defined as being euthyroid for one year after cessation of therapy.[4 (Level I); 367 (Level II)] However, a study from France had reported remission rates of 20%, 37%, 45%, and 49% after 4, 6, 8, and 10 years follow-up, respectively, of 154 children treated with ATD.[368 (Level II)] Thus, while definitive therapy should be considered after 1–2 years of MMI, treatment for longer periods is also reasonable if ATD is tolerated. Retrospective studies have suggested that the chance of remission after two years of ATDs is low if; the thyroid gland is large (more than 2.5 times the normal size for age), the child is young (<12 years), prepubertal, or not Caucasian, has high serum TRAb levels on therapy and substantially elevated free T4 levels (>4 ng/dL, 50 pmol/L) at diagnosis (Table 15).[359 (Level III)]

Table 15: Predictors of poor remission (Adapted from [359 [Level III]])
Predictors of poor remission for children and adolescents with Graves' disease
Large thyroid gland (>2.5x the normal size for age)
Young age <12 years
Prepubertal
Non-Caucasian
High serum TRAb levels
Significantly elevated free T4 level (>50 pmol/L) at diagnosis

Persistence of GD in children is reported to correlate with the persistence of TRAb.[369 (Level III)] However, a low TRAb level does not necessarily predict successful remission, whereas monitoring of TRAb levels while on ATD has been shown to be useful in adult patients for predicting the likelihood of remission or relapse of GD after stopping the medication. This approach is yet to be validated in children.

Recommendations

- Definitive therapy available for GD is RAI or thyroidectomy
- Indications for definitive therapy in children include relapse after an appropriate duration of ATD, compliance issues, or adverse effects of ATD
- Paediatric patients who are not in remission following two years of MMI/ carbimazole could be considered for definitive treatment with RAI or thyroidectomy
- Alternatively, MMI/carbimazole may be used for longer duration (>2 years) if the hyperthyroid state is controlled with no medication side effects
- Patients on prolonged ATD therapy should be re-evaluated every 6–12 months and when transitioning to adulthood

7.4.2.5 What Are The Clinical Considerations For RAI Therapy?

The ATA 2016 guideline recommends avoiding RAI in very young children aged <5 years because of concerns of increased susceptibility of the thyroid gland to the proliferative effects of ionising radiation.[4 (Level III)] It may be considered in children between five and ten years of age if the calculated RAI administered activity is <10 mCi (<473 MBq).[4 (Level III)] If RAI therapy is chosen as the treatment for GD in children, sufficient RAI should be administered in a single dose to render the patient hypothyroid.[4 (Level III); 359 (Level III); 370 (Level III)] This is due to concerns that lower administered activities of RAI result in residual, partially irradiated thyroid tissue that is at an increased risk for thyroid neoplasm development.

Children with GD having total T4 levels of >20 ng/dL (260 nmol/L) or free T4 >5 ng/dL (60 pmol/L) who are to receive RAI therapy should be pretreated with MMI/carbimazole and β-blocker, until total T4 and/or free T4 normalise before proceeding with the RAI treatment.[4 (Level III)] Although the frequency of short-term worsening of hyperthyroidism following pre-treatment with ATD therapy is not known, there are rare reports of paediatric patients with severe hyperthyroidism who have developed thyroid storm after receiving RAI.[4 (Level III); 371 (Level III)] When children receiving MMI/carbimazole are to be treated with RAI, the medication should be stopped 2–3 days before treatment.[4 (Level III)] At that time, patients should be placed on beta-blockers, until total T4 and/or free T4 levels normalise following RAI therapy.[371 (Level III)] Thyroid hormone levels in children begin to fall within the first week, following RAI therapy, and usually take 2–4 months to normalise. Although

some physicians restart ATDs after treatment with RAI, this practice is seldom required in children.[371 (Level III)]

The activity of RAI administered should be based on thyroid size and uptake and not reduced because of age in young individuals. Attempts to minimise the RAI activity will result in undertreatment and the possible need for additional RAI therapy and radiation exposure. The administered activity of RAI to patients with large goitres is high. The size of the gland may be underestimated, resulting in insufficient administration of RAI activities. Therefore, surgery may be preferable to RAI in children with goitres larger than 80 g.[4 (Level III)]

Physicians at some centres administer a fixed dose to all children, whereas others calculate the activity from estimation or direct measurement of gland size. To assess thyroid size, especially of a large gland, ultrasonography is recommended. There is a lack of data comparing outcomes of fixed versus calculated activities in children. Advantage of calculated versus fixed dosing is that it may be possible to use lower administered activities of RAI and, at the same time, assure that an adequate administered activity is given. Radioactive iodine is excreted in saliva, urine, perspiration, tears, and stool. Significant radioactivity is retained within the thyroid for several days. It is therefore important that patients and families be informed of local radiation safety recommendations.

After RAI therapy, T3, T4, and/or free T4 levels should be obtained every month. Because TSH levels may remain suppressed for several months after correction of the hyperthyroid state, TSH determinations may not be useful. Hypothyroidism usually develops 2–3 months following successful RAI and should be treated with levothyroxine.

Side effects of RAI therapy in children are uncommon apart from the lifelong hypothyroidism which is the goal of therapy. Less than 10% of children complain of tenderness over the thyroid in the first week after therapy, which can be treated with acetaminophen or non-steroidal anti-inflammatory agents for 24–48 hours.[4(Level III)]

If residual thyroid tissue remains in young children after RAI treatment, a theoretical risk of development of thyroid cancer exists. Increased rates of thyroid cancer and thyroid nodules were observed in young children exposed to radiation after Hiroshima and the Chernobyl nuclear reactor explosion.[4 (Level III); 359 (level III)] The risk appeared to be age-dependent, greatest for children younger than 5–6 years of age and decreasing progressively through 12 years of age.[359 (Level III)] However, these data do not apply directly when assessing the risks of RAI therapy. It is also important to note that iodine deficiency and exposure to radionuclides other than RAI may have contributed to the increased risk of thyroid cancer in young children after the Chernobyl reactor explosion.[359 (Level III)] Thyroid cancer rates were not increased among 3000 children exposed to RAI from the Hanford nuclear reactor site in an iodine-replete region.[4 (Level III)]

To date, long-term studies of children treated with RAI for GD have not revealed an increased risk of non-thyroid malignancies.[4 (Level III)] If a small risk exists, a sample size of more than 10,000 children who were treated at <10 years of age would be needed to identify the risk, likely exceeding the number of such treated children.[4 (Level III)] Based on cancer risk projections from estimated whole-body, low-level radiation exposure as related to age, it is theoretically possible that there may be a low risk of malignancies in very young children treated with RAI.[4 (Level III)]

Recommendations

- Radioactive iodine therapy should be avoided in very young children (<5 years)
- Radioactive iodine therapy can be considered in children between 5 and 10 years of age when the required activity for treatment is <10 mCi (<370 MBq)
- If RAI therapy is chosen as treatment for GD in children, sufficient RAI should be administered in a single dose to render the patient hypothyroid
- There may be circumstances in which RAI therapy is indicated in young children, such as when a child has developed a reaction to ATD, proper surgical expertise is not available, or the patient is not a suitable surgical candidate
- Children with GD having total T4 levels of >260 nmol/L or fT4 >60 pmol/L who are to receive RAI therapy should be pretreated with MMI and β-adrenergic blockade, until levels normalise before proceeding with RAI treatment

7.4.2.6 What Are The Clinical Considerations For Thyroidectomy?

Thyroidectomy is the preferred treatment for GD in young children (<5 years) when definitive therapy is required, and a high-volume thyroid surgeon can perform the surgery. In individuals with large thyroid glands (>80 g), the response to RAI may be poor and thus surgery may be preferable for these patients. When performed, a total or near-total thyroidectomy is the recommended procedure.[4 (Level III)] MMI is typically given for 1–2 months in preparation for thyroidectomy. Iodides block the release of thyroid hormones and reduce the vascularity of the thyroid gland. Potassium iodine (50 mg iodide/drop) can be given as 1–2 drops (i.e. 0.05–0.1 mL) three times daily for ten days before surgery. It can be mixed in juice or milk.[4 (Level III)]

Surgical complication rates are higher in children than in adults. Younger children are at a higher risk for transient hypoparathyroidism post-thyroidectomy than adolescents or adults.[372 (Level III); 373 (Level III); 374 (Level III)] Calcium levels should be monitored postoperatively and treatment with calcitriol and calcium supplements may be needed. Postoperative hypocalcaemia requiring intravenous calcium infusions had been reported to occur more frequently in children than in adults. Complication rates are reported to be two-fold higher with surgeons without extensive experience.[372(Level III)] Further support that thyroidectomy for GD in children should be performed by experienced thyroid surgeons comes from reports of institutional experience showing low complication rates at high-volume centres.[374 (Level III)]

Recommendations

- Thyroidectomy is the preferred treatment for GD in young children (<5 years) when definitive therapy is required
- Thyroidectomy should also be considered in individuals with large thyroid glands (>80 g), where the response to RAI may be poor
- If surgery is chosen, total or near-total thyroidectomy should be performed
- Referral of a child with GD who requires thyroidectomy to a high-volume thyroid surgery centre with paediatric experience is recommended, especially for young children
- Children with GD undergoing thyroidectomy should be rendered euthyroid with the use of MMI/carbimazole. Potassium iodine drops preparation should be given in the preoperative period
- Postoperatively, younger children are at higher risk of hypoparathyroidism. Calcium levels should be monitored, and treatment with calcitriol and calcium may be needed perioperatively
- Management involving a multidisciplinary team that includes experienced thyroid surgeons, paediatric endocrinologists, and anaesthesiologists is recommended

7.5 THYROID DISORDERS IN THE ELDERLY

7.5.1 What Are The Features Of Overt Hyperthyroidism In The Elderly?

The classical signs and symptoms of hyperthyroidism in the younger age group, like tremor, weight loss, palpitation, diarrhoea and heat intolerance, may be absent in the elderly. The term "apathetic thyrotoxicosis" is used to describe the symptoms of elderly hyperthyroidism patients who present with depression, lethargy, and weight loss. Some elderly patients present with "thyrotoxic encephalopathy" with agitation and confusion. Most thyrotoxic patients have decreased appetite and weight loss. Elderly patients with hyperthyroidism may present with angina pectoris or cardiac failure. Fatigue, weakness, agitation, confusion, dementia, and myopathy are nonspecific signs of hyperthyroidism and are often mistaken as age-related changes.[375 (Level II)] Though the classical symptoms and signs of hyperthyroidism are significantly less prevalent in older patients, they are more prevalent in smokers and subjects with higher free T4 concentrations.[376 (Level II)]

7.5.2 How Should Overt Hyperthyroidism In The Elderly Be Treated?

In a randomised controlled trial of MMI alone versus MMI and a β-adrenergic blocking agent, after 4 weeks, patients taking β-adrenergic blockers had lower heart rates, less shortness of breath and fatigue, and improved "physical functioning" on the SF-36 health questionnaire.[377 (Level I)] Once it has been established that the patient is hyperthyroid and the cause is GD, the patient and physician must

choose between three effective and relatively safe initial treatment options: RAI therapy, ATDs, or thyroidectomy.[4 (Level I)] The long-term quality of life (QoL) following treatment for GD was found to be the same in patients randomly allocated to one of the three treatment options.[4 (Level I)] Currently, no scientific evidence exists to support the recommendation of alternative therapies for the treatment of hyperthyroidism.[4 (Level I)]

Recommendations

- Beta-adrenergic blockade is recommended in all patients with symptomatic thyrotoxicosis, especially in the elderly patients and thyrotoxic patients with resting heart rates in excess of 90 beats per minute or coexistent cardiovascular disease
- Patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: RAI therapy, ATDs, or surgery
- Surgery is recommended in:
  i.   Symptomatic compression or large goitres (>80 g)
  ii.   Relatively low uptake of RAI
  iii. When thyroid malignancy is documented or suspected (e.g. suspicious or indeterminate cytology)
  iv.   Large thyroid nodules, especially if greater than 4 cm or if nonfunctioning, or hypofunctioning on ^{123}I or ^{99m}Tc pertechnetate scanning
  v.   Coexisting hyperparathyroidism requiring surgery
  vi.   Especially if TRAb levels are particularly high
  vii. Patients with moderate-to–severe active Graves' Ophthalmopathy (GO)
- Surgery is not recommended for patients with substantial comorbidity such as cardiopulmonary disease, end-stage cancer, or other debilitating disorders, or where there is lack of access to a high-volume thyroid surgeon
- Because RAI treatment of GD can cause a transient exacerbation of hyperthyroidism, beta-adrenergic blockade should be considered even in asymptomatic patients who are at an increased risk for complications due to worsening of hyperthyroidism
- Long-term MMI treatment of TMNG or TA might be indicated in some elderly or otherwise ill patients with limited life expectancy, in patients who are not good candidates for surgery or ablative therapy, and in patients who prefer this option

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7.5.3 What Are The Risks of Subclinical Hyperthyroidism In The Elderly?

The association between subclinical hyperthyroidism and clinical outcomes remains unclear and controversial. The risks of untreated subclinical hyperthyroidism are progression to overt hyperthyroidism and increase in overall mortality,

cardiovascular disease, arrhythmias, osteoporosis, and fractures. There is an association between subclinical hyperthyroidism and cognitive impairment,[378 (Level II)] increased likelihood of greater frailty status,[379 (Level II)] association with the risk of cognitive impairment including mild cognitive impairment and dementia in elderly subjects.[380 (Level II)] Evena modest thyroid hormone excess is associated with a reduced physical function in elderly men.[381 (Level II)] Older people at high cardiovascular risk with low or very high TSH along with normal free T4 appear at an increased risk of incident heart failure.[382 (Level II)] In elderly patients with endogenous subclinical hyperthyroidism and TSH between 0.1 mIU/L and 0.4 mIU/L, progression to clinical hyperthyroidism is uncommon (approximately 1% per year); spontaneous TSH normalisation may occur, and it is most likely that SCHyper persists for many years.[383 (Level II)] Older men with subclinical hyperthyroidism are at an increased risk for hip fracture;[384 (Level II)] lower serum TSH may be associated with an increased risk of hip fractures in older men;[385 (Level II)] lower TSH levels in the euthyroid range are related to lower BMD and weaker femoral structure in elderly women[386 (Level II)] and low TSH was independently related to decreased bone mineral densities at femoral neck in elderly women without overt thyroid dysfunction.[387 (Level II)] Subclinical hyperthyroidism is an independent risk factor for all-cause mortality in older adults.[388 (Level II);389 (Level II)]

However, among well-functioning community-dwelling elderly, a study found no evidence that subclinical thyroid dysfunction contributes to decreased functional capacity.[390 (Level II)] There is no consistent evidence that subclinical hyper- or hypothyroidism contributes to cognitive impairment or decline in old age.[391 (Level II)] There is neither a beneficial nor a detrimental effect of subclinical thyroid dysfunction in older men[392 (Level II)] and individuals aged 85 years with subclinical hyperthyroidism did not have a significantly worse survival over 9 years compared to their euthyroid peers.[393 (Level II)] There was no association between subclinical hypothyroidism or subclinical hyperthyroidism and hip fracture risk or BMD in older men and women.[394 (Level II)] In one study, it did not support the disadvantageous effects of subclinical thyroid disorders on physical or cognitive function, depression, or mortality in an older population.[395 (Level II)] Subclinical hyperthyroidism also had no impact on progression of the left ventricular mass and development of left ventricular hypertrophy during the five-year follow-up in subjects aged 45 years or older.[396 (Level II)]

7.5.4 Should Subclinical Hyperthyroidism In The Elderly Be Treated?

Subclinical hyperthyroidism may progress to overt hyperthyroidism and may be associated with increased cardiovascular and skeletal risks. Differences in the degree of TSH suppression, causes of subclinical hyperthyroidism, patient age, and duration of TSH suppression may influence the adverse consequences.[54 (Level II)]

Recent meta-analysis, including those based on large prospective cohort studies, indicate that subclinical hyperthyroidism is associated with an increased risk of coronary heart disease mortality, incident atrial fibrillation, heart failure, fractures,

and excess mortality in patients with serum TSH levels <0.1 mIU/L. Therefore, despite the absence of randomised prospective trials, there is evidence that treatment is indicated in patients older than 65 years with serum TSH levels <0.1 mIU/L to potentially avoid these serious cardiovascular events, fractures and the risk of progression to overt hyperthyroidism.[54 (Level II)] Given the risk of worsening potential cardiovascular events, patients older than 65 years with TSH levels 0.1–0.39 mIU/L should also be treated in the presence of symptoms of hyperthyroidism, heart disease, diabetes, renal failure, previous stroke or transient ischaemic attack, left atrial dilatation, increased risk factors for stroke, heart failure, coronary artery disease, valvular heart disease, and coronary or peripheral arterial disease.[54 (Level II);4 (Level II)]

Recommendations

- When TSH is persistently <0.1 mIU/L, treatment of SCHyper is recommended in all individuals ≥65 years of age
- When TSH is persistently below the lower limit of normal but ≥0.1 mIU/L, treatment of SCHyper should be considered in individuals ≥65 years of age with cardiac disease, osteoporosis, or symptoms of hyperthyroidism

7.5.5 How Should Subclinical Hyperthyroidism In The Elderly Be Treated?

The treatment of SCHyper is similar to the treatment of overt hyperthyroidism. The treatment should be based on the aetiology of the thyroid dysfunction and follow the same principles as for the treatment of overt hyperthyroidism. Radioactive iodine is appropriate for most patients, especially in older patients when TMNG is a frequent cause of SCHyper.[397 (Level II)] There are no data to inform whether elderly patients with SCHyper would benefit from pretreatment with ATDs to normalise thyroid function before RAI therapy. Given the low risk of exacerbation, the risks of ATD therapy may outweigh any potential small benefit.[4 (Level II);54(Level II)] A course of ATD therapy is a reasonable alternative to RAI in patients with GD and SCHyper, especially in younger patients, since remission rates are highest in persons with mild disease.[4 (Level II);54(Level II)]

Recommendations

- Antithyroid drugs should be the first choice in patients older than 65 years with GD and TSH 0.1–0.4 mIU/L because remission of GD has been observed after ATD treatment in 40%–50% of patients with overt hyperthyroidism 12–18 months after therapy
- Radioactive iodine therapy should be considered if ATDs are not tolerated, in case of relapse and in patients with cardiac disease
- Treatment with ATDs or RAI is recommended in patients with GD and TSH <0.1 mIU/L, older than 65 years and when cardiac disease is present, because these patients are at high risk of adverse cardiac events

Figure 8: Algorithm for the management of SHyper. (Adapted from [54] (Level III))
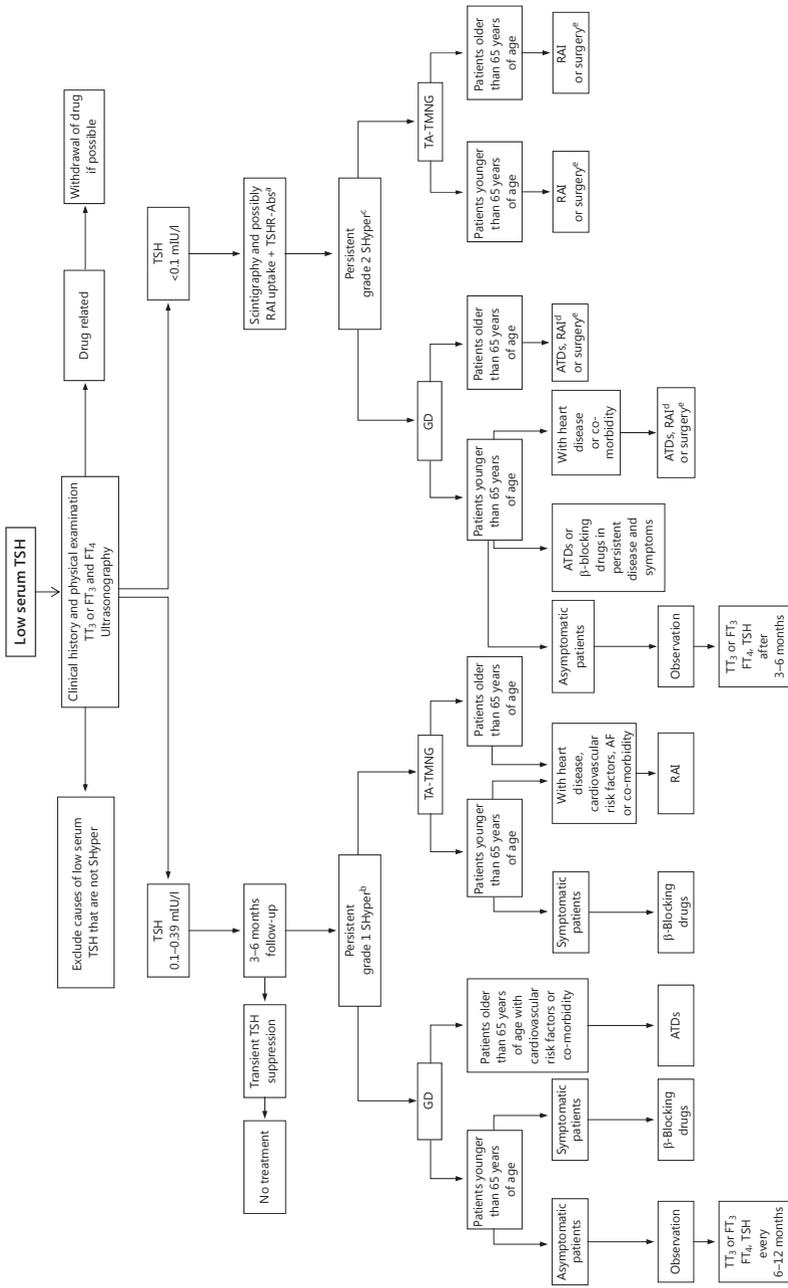
[a]TSHR-Antibody = TSH-receptor antibodies. [b]Grade 1 SHyper (TSH levels: 0.1–0.39 mIU/L). [c]Grade 2 SHyper (TSH levels <0.1 mIU/L). [d]RAI in patients with recurrences or if ATDs are not tolerated. [e]Surgery in patients with large goitre, symptoms of compression, or thyroid malignancies.

- Radioactive iodine therapy or surgery should be the preferred option in patients older than 65 years with SCHyper due to MNG or TA, because these patients are likely to have persistent SCHyper
- In cases where RAI is not feasible (e.g. elderly nursing home patients who may be incontinent and patients with severe comorbidity growing goitre or even pressure symptoms), lifelong low-dose ATDs is a possibility
- Surgery is recommended in patients with SCHyper with a large goitre, symptoms of compression, concomitant hyperparathyroidism, or suspicion of thyroid malignancy. Total thyroidectomy is the treatment of choice in the absence of associated conditions or factors

7.5.6 How Should Overt Hypothyroidism In The Elderly Be Treated?

The elderly are more susceptible to the adverse effects of thyroid hormone excess, especially atrial fibrillation and osteoporotic fractures, so that careful titration of the LT4 dose to avoid iatrogenic thyrotoxicosis is essential in this population.[91 (Level II); 398 (Level II)] Among adults aged 70 years or more, current levothyroxine treatment was associated with a significantly increased risk of fracture, with a strong dose–response relation.[399 (Level I)] In general, levothyroxine should be initiated with low doses, and the dose titrated slowly based on serum TSH measurements. It should be recognised that normal serum TSH ranges are higher in older populations (such as those over 65 years) and that higher serum TSH targets may be appropriate.[91 (Level II);399 (Level II)]

Recommendations

- Small dose of levothyroxine should be started, 25 or 50 µg daily. The dose of levothyroxine should be increased by 25 µg/day every 14–21 days until a full replacement dose is reached
- For older patients (aged >70–75 years), a higher treatment target for serum TSH (around 1–5 mIU/L) is acceptable

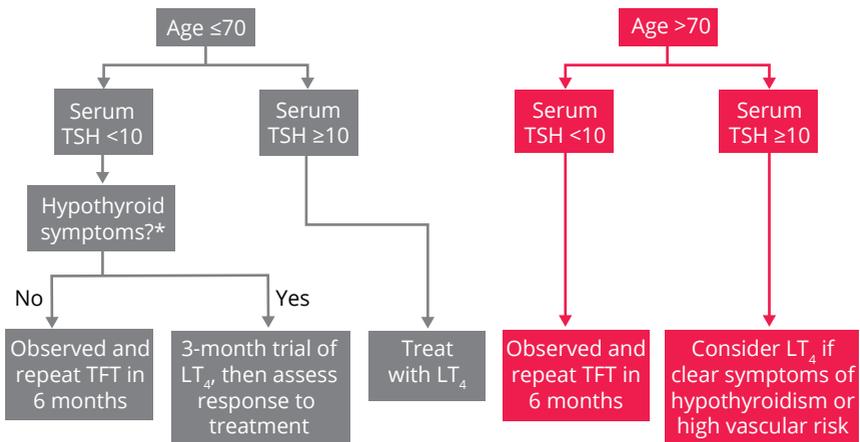### 7.5.7 What Are The Risks Of Subclinical Hypothyroidism In The Elderly?

The risk of subclinical hypothyroidism includes progression to overt hypothyroidism, mood disturbance/mental health, heart failure, dyslipidaemia, CVD, and mortality. Older people with SCHypo appear at an increased risk of incident heart failure[400 (Level II)] and SCHypo persists for four years in just over half of older individuals, with high rates of reversion to euthyroidism in individuals with lower TSH concentrations and TPO Ab negativity.[401 (Level II)] Both SCHypo and subclinical hyperthyroidism are associated with increased mortality in the elderly. A threshold thyroid-stimulating hormone value (>6.35 mIU/L) exists for increased mortality in subclinical hypothyroidism.[402 (Level II)] Deleterious effect of SCHypo on CV events is less evident in moderately older people (<70–75 years) and could vanish in the oldest old people (>80–85 years).[399 (Level II)]

However, a few studies did not show adverse effect of SCHypo. There was no increased risk of CHD, HF, or CV death in older adults with persistent SCHypo.[403 (Level II)] TSH levels increase with age and increase in CHD events, which is less evident in elderly – mainly TSH >10 mIU/L with a lower mortality in oldest olds (>85 years) has been reported.[404 (Level II)] Subclinical hypothyroidism does not appear to be associated with an increased risk of metabolic or neuropsychological derangement in elderly subjects[405 (Level II)] and persons with moderate SCHypo had similar mobility and mobility decline as the euthyroid group.[406 (Level II)] There was no association between subclinical hypothyroidism or subclinical hyperthyroidism and hip fracture risk or BMD in older men and women[394 (Level II)], neither a beneficial nor a detrimental effect of subclinical thyroid dysfunction on mortality in older men.[392 (Level II)] One study did not support disadvantageous effects of subclinical thyroid disorders on physical or cognitive function, depression, or mortality in an older population.[395 (Level II)] A higher TSH and lower fT4 concentrations within the euthyroid range are associated with lower risk of multiple adverse events in older people, including mortality. This suggests tolerance for lower thyroid hormone levels in this age group.[407 (Level II)] It is also unclear whether SCHypo leads to significant mood and cognitive impairments in most older patients,[408 (Level II)] and individuals aged 85 years with both SCHypo and SCHyper do not have a significantly worse survival over nine years than their euthyroid peers.[390 (Level II)]

7.5.8 Should Subclinical Hypothyroidism In The Elderly Be Treated?

There is no evidence for treating elderly subjects with SCHypo with T4 replace-ment therapy to improve cognitive function,[409 (Level I)] and levothyroxine provided no apparent benefits in Hypothyroid Symptom score in older persons with SCHypo.[410 (Level I)]

Figure 9: Suggested management algorithm for SHypo. (Adapted from [398[Level II]])

Age ≤70
- Serum TSH <10
  - Hypothyroid symptoms?*
    - No → Observed and repeat TFT in 6 months
    - Yes → 3-month trial of LT$_4$, then assess response to treatment
- Serum TSH ≥10 → Treat with LT$_4$

Age >70
- Serum TSH <10 → Observed and repeat TFT in 6 months
- Serum TSH ≥10 → Consider LT$_4$ if clear symptoms of hypothyroidism or high vascular risk

The deleterious effect of SCHypo on CV events and mortality appears well established in young adults but is less evident in moderately older people (70–75 years) and could vanish in the oldest old (>80–85 years). Appropriately powered RCT of levothyroxine in SCHypo patients, examining for hard CV endpoints in various classes of age is clearly warranted.[398 (Level II)]

Recommendations

- In patients aged >70 years, if serum TSH is ≥10 mIU/L, consider levothyroxine treatment if clear symptoms of hypothyroidism or high vascular risk are noted
- In patients aged >70 years, if serum TSH is ≤10 mIU/L, observe and repeat TFTs in 6 months
- In patients aged ≤70 years, if serum TSH is ≥10 mIU/L, consider levothyroxine treatment
- In patients aged ≤70 years, if serum TSH is ≤10 mIU/L and have symptoms of hypothyroidism, consider a three-month trial of levothyroxine, and then assess the response to treatment
- In patients aged ≤70 years, if serum TSH is ≤10 mIU/L and there are no symptoms of hypothyroidism, observe and repeat TFT in six months

7.5.9 How Should Subclinical Hypothyroidism In The Elderly Be Treated?

The treatment of subclinical hypothyroidism is similar to the treatment of overt hypothyroidism. Any treatment for this should be individualised, gradual and closely monitored. For older patients (>70–75 years), a higher treatment target of serum TSH (around 1–5 mIU/L) is acceptable.[398 (Level III)]

8. DRUG-INDUCED THYROID DISORDERS

8.1 AMIODARONE INDUCED THYROID DISEASE

8.1.1 What Are The Thyroid Abnormalities Caused By Amiodarone?

Amiodarone is a benzofuranic derivative whose structural formula closely resembles that of T4. It contains approximately 37% iodine by weight. Because approximately 10% of the molecule is deiodinated daily, and the maintenance daily dose of the drug ranges from 200 to 600 mg, approximately 7–21 mg iodide is made available each day, resulting in a marked increase in urinary iodide excretion. Thus, amiodarone treatment releases 50- to 100-fold excess iodine daily.[411 (Level III)] In an euthyroid person receiving amiodarone, serum thyroxine (T4) and free T4 concentrations rise by 20%–40% during the first month of therapy. Serum triiodothyronine (T3) concentrations decrease by up to 30% within the first few weeks of therapy. Serum reverse T3 concentrations increase by 20% soon after the initiation of therapy. The serum TSH concentration usually rises slightly after the initiation of treatment and may exceed the upper limit of normal. After three to six months of therapy, a

steady state is reached in most patients who were euthyroid at baseline:serum TSH concentration normalises, serum total T4, free T4 and reverse T3 concentrations remain slightly elevated or in the upper normal range and serum T3 concentrations remain in the low normal range.[412 (Level I)] Approximately 15%–20% of amiodarone-treated patients develop either thyrotoxicosis (amiodarone-induced thyrotoxicosis, AIT) or hypothyroidism (amiodarone-induced hypothyroidism, AIH).[413 (Level III); 414 (Level III)] Thyroid dysfunction may occur at any time during amiodarone therapy, although AIH is frequently an early phenomenon when chronic autoimmune thyroiditis preexists. Amiodarone-induced thyrotoxicosis may develop early, late during amiodarone treatment, or even many months after drug withdrawal, due to the slow release of amiodarone and its metabolites from the body stores. Occurrence of AIT between 5 and 16 months after stopping amiodarone has been reported. Thus, periodical monitoring of thyroid function is warranted even after amiodarone discontinuation.[415 (Level III); 4 (Level III); 416 (Level III)]

> **Recommendation**
>
> • Monitor TFT before and 3–4 months after starting amiodarone and at 3–6 months interval thereafter. Monitor for up to 1 year after stopping amiodarone.

8.1.2. What Are The Mechanisms Of Amiodarone-Induced Thyrotoxicosis (AIT) and How To Diagnose Them?

Amiodarone-induced thyrotoxicosis (AIT) may develop in patients with underlying thyroid abnormalities (type 1) or in patients with apparently normal thyroid glands (type 2).[411 (Level III)] This disease (AIT) is characterised by suppressed TSH and elevated fT4 and/or fT3 levels. Type 1 AIT (AIT 1) is a form of iodine-induced hyperthyroidism caused by excessive, uncontrolled biosynthesis of thyroid hormone by autonomously functioning thyroid tissue in response to iodine load that typically develops in persons with underlying nodular goitre or latent Graves' disease. Type 2 AIT (AIT 2) is a destructive thyroiditis occurring in an otherwise substantially normal thyroid gland. A mixed/indefinite type is also recognised where patients acquire an overlapping condition of both AIT 1 and AIT 2. Out of the two, AIT 2 is more prevalent in iodine-sufficient areas and, in general, is the most frequent form of AIT.[414 (Level III)] Identification of the different subtypes of AIT is crucial because this affects the therapeutic approach. Thyroid ultrasonography may be useful as it shows the presence or absence of a diffuse or a nodular goitre. Colour flow Doppler ultrasound study of the thyroid is perhaps more reliable. In AIT 2, most cases are characterised by absent hypervascularity, whereas in AIT 1 they usually show an increased vascularity and blood flow velocity.[414 (Level III)] Nuclear imaging using thyroidal 131I uptake (RAIU) is another useful diagnostic tool. The results of RAIU are usually very low (<3%) in AIT 2 and low–normal, normal, or even increased in AIT 1. Other tracers such as 99m pertechnetate (99mTcO4) and 99mTcO4 2-methoxy-isobutyl-isonitrile (MIBI) have also been used.[414 (Level III); 413 (Level III)]

8.1.3 How Should Amiodarone-Induced Thyrotoxicosis (AIT) Be Managed?

Type 1 AIT: It is a form of true hyperthyroidism triggered by the iodine load and is best treated by antithyroid drugs.[413 (Level III)] Since an iodine-replete thyroid gland is less responsive to the inhibitory action of thionamides, higher drug dosages (40–60 mg/day methimazole or equivalent doses of carbimazole or propylthiouracil) and longer periods of therapy (4 weeks to 3–6 months) are required before euthyroidism is restored.[414 (Level III); 4 (Level III)] In countries where potassium perchlorate or sodium perchlorate is available (Europe), it is added in doses not exceeding 1 g per day for 4–6 weeks to accelerate control of hyperthyroidism.[414 (Level III); 4 (Level III)]

Type 2 AIT: Type 2 AIT is best treated with prednisolone, with improvement occasionally seen as early as one week, and usually within a few weeks. In a randomised controlled study that compared treatment groups in AIT 2 with prednisolone alone, perchlorate alone and combination prednisolone and perchlorate, prednisolone treatment resulted in euthyroidism in all patients, while 30% of the patients treated with sodium perchlorate alone needed additional prednisolone treatment to become euthyroid.[417 (Level I)] An earlier retrospective observation showed that a six-week treatment of 42 AIT 2 patients with methimazole alone resulted in euthyroidism in 15% of patients compared to 76% of the patients treated with prednisolone alone.[414 (Level III); 418 (Level III)] The suggested dose of corticosteroids in this setting is equivalent to 40 mg prednisolone given once daily for 2–4 weeks, followed by a gradual taper over 2–3 months, based on the patient's clinical response.[4 (Level III)]

Mixed or indefinite form of AIT: If a precise diagnosis cannot be made, two possible approaches can be proposed. The first one is to start with thionamides (± sodium perchlorate) as for AIT 1 and, in the absence of a biochemical improvement within a relatively short period of time (4–6 weeks), to add glucocorticoids with the assumption that a destructive component is also present superimposed on an underlying thyroid disorder. An alternative approach is represented by a combined treatment (thionamides and glucocorticoids) from the very beginning.[414 (Level III))] Evidence is lacking on the best therapeutic strategy for mixed/indefinite AIT, and randomised clinical trials are warranted. One study had looked at the use of lithium in AIT but the effectiveness is limited and has not been confirmed.[414 (Level III)] Radioiodine treatment is usually not feasible due to the low thyroidal iodine uptake.[415 (Level III)] Patients with AIT who fail to respond to medical therapy should be offered thyroidectomy before they become excessively debilitated from inadequately controlled thyrotoxicosis.[4 (Level III)] A retrospective study on 24 patients who failed medical therapy for AIT underwent total thyroidectomy and the outcome was improved cardiac function in AIT patients with severe LV dysfunction with no mortality.[419 (Level III)] There is neither consensus nor sufficient evidence concerning the decision to either continue or stop amiodarone in AIT patients. Continuing amiodarone may increase the recurrence rate of thyrotoxicosis, causing a delay in the stable restoration of euthyroidism and a longer exposure of the heart to thyroid hormone excess.[420 (Level III)] The decision to continue or stop amiodarone should be individualised and taken jointly by specialist cardiologists and endocrinologists. Amiodarone should be

continued in critically ill patients with life-threatening cardiac disorders responsive to the drug and in AIT 2, as this form is often self-limiting.[414 (Level III)]

Recommendations

- Type 1 AIT should be treated with high-dose carbimazole 40 mg/day or its equivalent
- Type 2 AIT should be treated with corticosteroids: prednisolone 40 mg given once daily for 2–4 weeks, followed by a gradual taper over 2–3 months
- Combined carbimazole and corticosteroids should be used if the patient fails on monotherapy or if the distinction between Type 1 and Type 2 is not clear
- Patients with AIT who are unresponsive to aggressive medical therapy with thionamides and corticosteroids should undergo thyroidectomy
- The decision to stop or continue amiodarone in AIT should be individualised and done in consultation with the treating cardiologist

8.1.4 How Should Amiodarone-Induced Hypothyroidism (AIH) Be Managed?

Clinical features of AIH do not differ from those of patients with hypothyroidism of different causes, although goitre is rare. Underlying chronic autoimmune thyroiditis and female gender are predisposing risk factors for developing AIH.[414 (Level III)] It may be subclinical hypothyroidism or overt hypothyroidism and AIH is easily treated with LT4, and there is no need to discontinue amiodarone, if considered essential for the underlying cardiac disease.[415 (Level III)] Treatment of subclinical hypothyroidism may be unnecessary in some cases, particularly in the elderly, in view of the potential increase in risk of cardiovascular events.[415 (Level III)] Thyroid function should be tested every 4–6 months as there is a risk of progression to overt hypothyroidism. If amiodarone is withdrawn, the LT4 dose may need to be reduced to prevent overtreatment, and in others LT4 may be discontinued, because AIH subsides in about 50% of cases within 2–3 months.[415 (Level III)]

Recommendation

- LT4 treatment is recommended in all cases of overt AIH

8.2 OTHER DRUGS THAT CAUSE THYROID DISORDER

Interferon-alfa, interleukin-2, lithium, tyrosine kinase inhibitor, and checkpoint inhibitor immunotherapy may cause thyroid dysfunction.

a) Interferon alpha (IFN-α): IFN-α is mainly used in the treatment of hepatitis C. The prevalence of thyroid disease during IFN-α treatment is extremely variable, ranging between 1% and 35%.[421 (Level III)] The risk of developing thyroid dysfunction during IFN-α therapy is closely correlated with pre-existing thyroid antibodies.[421 (Level III)] A meta-analysis of the literature by Koh *et al*. showed that about 50% of patients with positive thyroid peroxidase antibodies (TPO Antibody) before IFN-α treatment developed thyroid dysfunction in comparison with 5.4%

in antibody-negative patients.[421 (Level III)] Positive thyroid antibodies with normal thyroid function tests is the most common finding in patients treated with IFN-α. Antibodies that develop during treatment with IFN-α include antithyroglobulin antibodies (Anti Tg) and TSH receptor antibodies (TRAb).[421 (Level III)] Clinical thyroid disease include painless thyroiditis, Hashimoto's thyroiditis, or Graves' disease. The changes in thyroid function test (TFT) usually appear after three months of therapy but can occur as long as IFN-α is given.[422 (Level III)] Hwang *et al.* reported that the mean time to develop thyroid dysfunction was 18 weeks after treatment.[423 (Level III)] A recent study which included 1233 patients who were euthyroid at baseline found that 16.7% developed abnormal TSH values during therapy: 57 had suppressed TSH (4.6%), 70 had hypothyroidism (5.7%), and 79 (6.4%) patients developed biphasic thyroiditis.[424 (Level II)] The average time to develop thyroid dysfunction was 17.5, 18.9, and 22.7 weeks for thyrotoxicosis, biphasic thyroiditis, and hypothyroidism, respectively.[425 (Level II)] The treatment of thyroid dysfunction during IFN-α therapy depends on the aetiology: Graves' disease is treated with antithyroid drugs, thyrotoxic phase of thyroiditis is managed with β-blockers if symptomatic, and hypothyroid phase if symptomatic is treated with levothyroxine.[4 (Level III)] Discontinuation of IFN-α is usually not necessary; however, in some cases of severe thyrotoxicosis where it may be warranted, the hepatologist should be consulted.[430 (Level III)]

b) **Interleukin-2 (IL-2):** Patients with metastatic cancer and leukaemia who are treated with interleukin 2 have been reported to develop thyroid dysfunction ranging from thyroiditis, hypothyroidism, and hyperthyroidism. Studies showed a significant incidence of hypothyroidism after treatment, in the range of 20%–50% with IL-2.[428 (Level III)] Most patients who developed hypothyroidism had positive thyroglobulin or thyroid peroxidase antibodies.[428 (Level III)] Liu *et al.* had reported a case of thyroid storm after initiation of IL-2 with the development of TRAb.[429 (Level III)] The treatment of IL-2-induced thyroid dysfunction is similar to that of IFN-induced thyroid dysfunction.[4 (Level III); 428 (Level III)]

Recommendations

- Monitoring of TFT should be done before treatment and at least 3–4 months after initiating treatment
- Check thyroid antibodies to exclude Graves' Disease and Hashimoto's thyroiditis, if available
- Treatment of IFN-α and IL-2-induced thyroid disorder depends on the aetiology (refer to management of thyroiditis, Graves' disease, and hypothyroidism)
- Discontinuation of IFN-α and IL-2 is usually not necessary

c) **Tyrosine kinase inhibitors (TKIs):** TKIs such as sunitinib, sorafenib, and nilotinib are used to treat malignancies, such as metastatic renal cell carcinoma, hepatoma, thyroid cancers, and GIST. Sunitinib has been reported to induce hypothyroidism in 36%–85% of patients[433 (Level III)] while the figure for sorafenib is 23.1%–67.7%.[431 (Level III)] The mechanism of thyroid dysfunction includes primary

hypothyroidism and destructive thyroiditis.[428 (Level III); 432 (Level III)] Miyake *et al.*[432 (Level III)] reported that out of 69 patients treated with sorafenib for metastatic renal cell carcinoma, 46 patients (66.7%) developed hypothyroidism, either hypothyroidism alone from the outset or following destructive thyroiditis. The median time to develop abnormal TFTs with sorafenib was 1.7 months.[432 (Level III)] Another study found that 6 of 31 patients (19.3%) receiving sunitinib therapy for metastatic renal cell carcinoma developed thyrotoxicosis, including one case of thyroid storm[4 (Level III)] with time to develop thyrotoxicosis between 4 weeks to 15 weeks after starting sunitinib. Thyroid antibodies were not associated with the development of thyroiditis.[431 (Level III)] Management of TKI-induced thyroiditis includes beta-blockers with or without NSAIDs for mild thyrotoxicosis and glucocorticoids in severe cases of thyrotoxicosis phase[4 (Level III); 435 (Level III)] while symptomatic hypothyroidism is treated with levothyroxine.[4 (Level III); 431 (Level III)] There are no clear guidelines or RCTs to recommend discontinuation of TKIs in cases of thyrotoxicosis. Discontinuation of TKIs is usually not necessary;[428 (Level III)] however, in a case series, TKIs has been discontinued in 2 out of 5 patients who developed severe thyrotoxicosis.[431 (Level III)]

Recommendations

- Thyroid function may be evaluated at baseline and monitored every 4–12 weeks thereafter and earlier if symptomatic
- For treatment of TKI-induced thyroiditis and hypothyroidism – refer to management of thyroiditis and hypothyroidism
- Discontinuation of TKI is usually not necessary

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d) Lithium: Patients taking lithium for bipolar disorder are at a high risk of developing thyroid dysfunction, including both hypothyroidism and to a lesser extent thyrotoxicosis. Two published series have identified the development of thyrotoxicosis in 0.6% and 3.0% of patients, respectively.[4 (Level III)] The aetiology of hyperthyroidism is predominantly destructive thyroiditis, although Graves' disease and toxic nodular goitre have been described.[426 (Level III)] Destructive thyrotoxicosis is treated conservatively, with beta-blockers. Corticosteroids are not recommended as it is feared that it may trigger a manic episode.[428 (Level III)] Thyrotoxicosis of other aetiology is treated according to existing guidelines.[4 (Level III)] Lithium inhibits thyroid hormone release, and this may result in the development of goitre and hypothyroidism. A study calculated the incidence of goitre to be 4% per year per 100 patients on continuous lithium therapy.[426 (Level III)] The prevalence of hypothyroidism in lithium-treated patients ranges from 6% to 52%. The risk was higher in older women and women with thyroid antibodies.[426 (Level III)] The management of lithium-induced hypothyroidism is levothyroxine. Lithium-associated goitre is managed in the same manner as any patient with goitre.[426 (Level III)] Discontinuation of lithium is not necessary.[426 (Level III); 428 (Level III)] Monitoring of TFTs should be done before and annually in all patients on lithium therapy or 6 monthly in older women with thyroid antibodies.[4 (Level II); 426 (Level III), (Level III); 427 (Level III)]

Recommendations

- Monitor TFT before and every 6–12 months after initiating lithium
- Goitre is managed as per the guidelines for the management of goitre
- Hypothyroidism is managed with L-thyroxine (see section on Management of Hypothyroidism)
- Hyperthyroidism is managed according to aetiology: thyroiditis, Graves' Disease, toxic MNG
- There is no need to discontinue lithium if thyroid dysfunction develops

e) Immune checkpoint inhibitors (ICI): Drugs in this class are used to treat advanced solid tumours and include cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) inhibitor ipilimumab; programmed cell death protein 1 (2 PD-1) inhibitors: nivolumab and pembrolizumab; and programmed cell death 1 ligand 1 (3 PD-L1) inhibitors: atezolizumab, avelumab, and durvalumab. Combination therapy of ipilimumab plus nivolumab has been approved to treat advanced melanoma. Immune checkpoint inhibitor has been associated with endocrinopathies, such as destructive thyroiditis, adrenal insufficiency, and hypophysitis (leading to secondary hypothyroidism and other associated hormonal deficiencies).[427 (Level III); 434 (Level III)] Thyroid disorder is the most common adverse event associated with ICI. In a meta-analysis involving 38 randomised controlled trials which included over 7500 patients,[434 (Level I)] the overall incidence of hypothyroidism was estimated to be 6.6% and the overall incidence of hyperthyroidism was estimated to be 2.9%. Both thyroid dysfunctions were higher with combination therapy. The American Society of Clinical Oncology recommends monitoring of TFTs at start of therapy and every 4–6 weeks while on therapy. Management of the thyroid disorder is based on the aetiology: for mild asymptomatic hypothyroidism, patients are followed up with close TFTs monitoring.[435 (Level III)] For moderate-to–severe hypothyroidism, treatment with levothyroxine is recommended.[439 (Level III)] For mild asymptomatic hyperthyroidism, patients are followed up with close monitoring of TFTs.[435 (Level III)] For moderate symptoms, beta-blockers for symptomatic relief are recommended and if duration of symptoms exceeds 6 weeks, work up for Graves' disease is required.[435 (Level III)] If severe symptoms or in storm, treatment is as for thyroid storm.[435 (Level III)] In severe cases of both hyperthyroidism and hypothyroidism, it is recommended to withhold ICI.[439 (Level III)]

Recommendations

- Monitor TFT at start of ICI therapy and every 4–6 weeks while on therapy
- Management of ICI-induced thyroid dysfunction depends on the aetiology (see section on Thyroiditis, Graves' Disease, Hypothyroidism)
- Discontinuation of ICI is usually not necessary unless thyroid dysfunction is severe

9. GRAVES' OPHTHALMOPATHY

9.1 WHAT IS THE INCIDENCE OF GRAVES' OPHTHALMOPATHY IN MALAYSIA?

Graves' ophthalmopathy (GO) is also known as thyroid-associated orbitopathy, thyroid-associated ophthalmopathy, and thyroid eye disease. The prevalence of GO in Malaysia was 34.7%.[436 (Level II)] This is very similar to the rate quoted in the literature among the Caucasians, which was 25%–50%.[437 (Level II)] The natural history of GO is one with rapid deterioration followed by gradual improvement towards baseline or with residual stigmata. The commonest presenting features found locally are exophthalmos followed by upper lids retraction and restrictive extraocular myopathy.[436 (Level II)] The risk factors are smoking status at the time of diagnosis of GD; the odd ratio of smokers developing GO is 2.754.[436 (Level II)] Other risk factors are male gender and unstable thyroid function test, especially hypothyroidism.[436 (Level II)]

9.2 WHAT IS THE DEFINITION OF GRAVES' OPHTHALMOPATHY?

Graves' ophthalmopathy is considered present if there is eyelid retraction with either thyroid dysfunction or exophthalmos or optic nerve dysfunction or extraocular muscle involvement. If eyelid retraction is absent, GO is defined as thyroid dysfunction in association with exophthalmos or optic nerve dysfunction or extraocular muscle involvement.[438 (Level II)]

Early symptoms of GO are as follows:

a. Redness in the eyes or lids
b. Swelling or feeling of fullness in one or both upper eyelids
c. Eyelid oedema
d. Eyes seem to be too wide open (thyroid stare)
e. Pain in or behind the eyes[439 (Level II)]

Discriminating points in favour of the diagnosis of GO:

a. Presence of thyroid dysfunction, particularly recent onset (within 18 months)
b. Symptoms not relieved by topical antibiotic
c. Eyelids abnormally wide (upper or lower lid retraction)
d. New bags in upper or lower eyelid or both
e. Change in the appearance of the eyes and eyelids especially eyeball protrusion
f. Presence of other signs such as diplopia and lagophthalmos[439 (Level II)]

9.3 HOW IS THE ASSESSMENT OF ACTIVITY AND SEVERITY?

Assessment of GO activity is best-done using clinical activity score (CAS):[440-443 (Level II)]

1. Spontaneous retrobulbar pain
2. Pain on attempting upward and downward gaze

3. Redness of eyelids
4. Redness of conjunctiva
5. Swelling of caruncle or plica
6. Swelling of eyelids
7. Swelling of conjunctiva (chemosis)

    Inactive GO=CAS <3

    Active GO=CAS ≥3

There are a few approaches to the assessment of GO severity:[441–443 (Level II)]

1. Graves' ophthalmopathy severity assessment according to NOSPECS

No signs or symptoms

Only signs, no symptoms: lid aperture (distance between lid margins in mm with patients looking in primary position, sitting relaxed with distance fixed)

Soft tissue involvement: swelling/redness of the eyes

Proptosis: exophthalmos (in mm: using the same Hertel exophthalmometer and same intercanthal distance for an individual patient)

Extraocular muscle involvement: eye muscle ductions in degree; subjective diplopia score – *intermittent* (diplopia when tired or when first awakening), *inconstant* (diplopia at extreme of gaze), *constant* (continuous diplopia in primary and reading position)

Corneal involvement: absent/punctate keratopathy, ulcer

Sight loss (due to optic nerve involvement): best corrected visual acuity, colour vision, optic disc, relative afferent pupillary defect, visual fields (if optic nerve compression is suspected)

2. Graves' ophthalmopathy severity assessment according to EUGOGO.[441–443 (Level II)]

Mild Graves' ophthalmopathy

Patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually have one or more of the following: minor lid retraction <2 mm, mild soft tissue involvement, exophthalmos <3 mm above normal for race and gender, no or intermittent diplopia and corneal exposure responsive to lubricants.

Moderate-to–severe Graves' ophthalmopathy

Patients without sight threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). They usually have two or more of the following: lid retraction ≥2 mm, moderate-to–severe soft tissue involvement, exophthalmos ≥3 mm above normal for race and gender, inconstant or constant diplopia.

Sight-threatening Graves' ophthalmopathy

Patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown

The clinician needs to decide whether GO is active or inactive and mild, moderate-to–severe or sight-threatening in the assessment of GO.

> **Recommendation**
>
> • Assessment of GO includes assessment of activity and severity using standardised criteria. It is categorised as active or inactive; mild, moderate, severe, or sight threatening

9.4 WHEN TO REFER TO OPHTHALMOLOGIST AND ENDOCRINOLOGIST?

All cases of GO except those with mild GO should be referred to specialised care. Cases where diagnosis of GO is doubtful should be referred too.[439, 442 (Level II)]

Urgent referral should be made if GO is sight threatening, e.g. unexplained deterioration of vision, awareness of change in quality, or intensity of colour vision in one or both eyes, globe subluxation, corneal opacity, significant lagophthalmos, and disc swelling.[439, 442 (Level II)]

9.5 WHAT IS THE TREATMENT FOR GRAVES' OPHTHALMOPATHY?

9.5.1 Non-Specific Treatment/Risk Factors Modification

General treatment includes avoidance of cigarette smoke (active/passive smoking), restoration of euthyroidism as soon as possible, especially avoidance of hypothyroidism.[444-448 (Level I)] Antithyroid drugs and thyroidectomy do not appear to affect the natural course of GO.[449-450 (Level I)] Radioactive iodine confers a small but definite risk of worsening of GO or *de novo* development of new onset GO especially in smokers, in severe hyperthyroidism and in recent onset hyperthyroidism.[449,451-452 (Level I)]

Ocular surface inflammation and dry eyes are common in patients with GO.[453 (Level II)] Use of preservative-free artificial tears with osmoprotective properties, such as sodium hyaluronate or use of eye lubricant gels/ointments to moisture the ocular surface is important.[454 (Level I)]

> **Recommendations**
>
> • All patients with Graves' disease should be urged to quit smoking
> • Euthyroidism should be restored as soon as possible in patients with GO
> • Ocular surface disease is common and should be treated with topical therapy

9.5.2 Mild Graves' Ophthalmopathy

Watchful strategy is sufficient in most patients with mild GO. Attention should be paid to non-specific treatment strategies and risk factors modification as mentioned above.

Sodium selenite 100 mcg bd (corresponding to 93.6 mcg of elemental selenium per day) for 6 months has been shown to improve eye symptoms and quality of life (QoL) as well as prevent the progression of GO. The effect was maintained even at 12 months after selenium was ceased at 6 months. No selenium-related side effects were observed in this large multicentre, randomised, double-blind, placebo-controlled trial. However, the subjects in the study came from a marginally selenium-deficient area.[455-456 (Level I)] In long-standing, inactive mild GO, there is no evidence that selenium is effective.

In cases where objectively mild GO has a profound impact on QoL, these cases may be considered as moderate-to–severe GO and offered immunosuppressive treatment or rehabilitative surgery (refer to moderate-to–severe GO section).[442 (Level III)]

> **Recommendation**
>
> - Topical treatment and measures to control the risk factors are the mainstay of treatment. A 6-month selenium supplement at a dose of 100 mcg bd can be considered

9.5.3 Moderate-to–Severe and Active Graves' Ophthalmopathy

First-Line Treatment

High dose IV glucocorticoids (GC) are currently the first line treatment for moderate-to–severe active GO.[441-442, 457-458, 462-463 (Level I)] The cumulative dose of GCs should not exceed 8 g. Single dose should not exceed 0.75 g and consecutive-day therapy should be avoided. Intravenous GCs are better tolerated and more effective than oral GCs; rate of adverse events are 39% versus 81% with p<0.001.[441-442,458-459 (Level I)] The response rate for intravenous GCs versus oral GCs is 70%–80% versus 50%.[457-459 (Level I)] The contraindications for systemic GCs are recent viral hepatitis, significant hepatic dysfunction, severe cardiovascular morbidity, uncontrolled hypertension or psychiatric disorders.[457-459 (Level II)] Caution should be exercised in diabetic and hypertensive patients. During treatment, proton pump inhibitors to prevent peptic ulcer and bone protection therapy for patients at risk of osteoporosis should be considered.

The recommended schedule for intravenous GCs is a cumulative dose of 4.5 g with IV methylprednisolone 0.5 g weekly for 6 weeks followed by 0.25 g weekly for another 6 weeks.[458 (Level I)] Higher doses with accumulative dose of 7.5 g methylprednisolone given 0.75 g weekly for 6 weeks followed by 0.5 g weekly for 6 weeks can be considered in worst cases within the moderate-to–severe spectrum.[460-461 (Level I)]

In a randomised, single-blind–controlled trial, 35 untreated, active, moderately severe GO patients received IV methylprednisolone 0.5 g weekly for 6 weeks followed by 0.25 g weekly for 6 weeks. Another 35 patients received oral prednisolone at 0.1 g/day then tapering by 0.01 g/week with cumulative dose of 4 g in 12 weeks. At 3 months, 77% in IV group vs. 51% at the oral group showed improvement, p<0.01. Side effects were seen in 17% IV group versus 51% oral group, p=0.005.[458 (Level I)] In another study, 159 subjects with active, moderate-to–severe GO were randomised to cumulative dose of 2.25 g (Low Dose), 4.98 g (Medium Dose) and 7.47 g (High Dose) of intravenous methylprednisolone in 12 weekly infusions. Overall, ophthalmic improvement at 12 weeks were as follows: HD 52% vs. MD 35% p=0.03, and HD 52% vs. LD 28% p=0.01. CAS improvement was 83% (HD), 81% (MD), 58% (LD). Major adverse reaction was seen more commonly in the high-dose group. The authors concluded that high dose IV methylprednisolone provides a short-term benefit over low dose but with more side effects. Hence, the intermediate dose regimen should be used in most cases and the high-dose regimen should be reserved for most severe cases of GO.[461 (Level I)]

Recommendations

- We recommend an intermediate dose of IV methylprednisolone at 0.5 g weekly for 6 weeks followed by 0.25 g weekly for 6 weeks (cumulative dose 4.5 g) in most cases of moderate-to–severe GO
- High-dose regimens of IV methylprednisolone at 0.75 g weekly for 6 weeks followed by 0.5 g weekly for 6 weeks (cumulative dose of 7.5 g) should be reserved for the worst cases with moderate-to–severe GO
- We recommend that a cumulative dose of IV methylprednisolone should not exceed 8 g
- We recommend assessment for viral hepatitis, liver function, cardiovascular dysfunction, blood glucose, and blood pressure to be undertaken before the commencement of IV methylprednisolone

Second-Line Treatment

A second course of IV GC if accumulative dose of 8 g methylprednisolone is not exceeded and patient tolerates GC well.[441-442; 461-462 (Level I)]

Orbital radiotherapy can be considered, especially to improve diplopia and range of ductions in patients with moderate-to–severe GO.[463-464 (Level I)] Randomised clinical trials have shown that orbital radiotherapy could potentiate the effect of systemic GC.[465-466 (Level I)] Cumulative dose of 20 Greys per orbit fractionated in 10 daily doses given over 2 weeks period is commonly used.[441-442(Level II)]

Cyclosporine and oral GCs: Two randomised controlled studies have shown that the combination of cyclosporine and GC was more effective than either agent alone in patients with active, moderate-to–severe GO.[467-468 (Level I)] In one study, 2 groups

of patients were treated with 100 mg per day of prednisolone with tapering down of dose and stopped in 3 months, alone or with combination of cyclosporine at 5 mg/kg body weight per day for 12 months. Combination therapy was associated with significantly better ocular outcome and lower rate of recurrences of GO.[467 (Level I)] In another trial, prednisolone alone was better that cyclosporine alone, but the combination therapy had the best response.[468 (Level I)] The most common adverse events related to cyclosporine are dose-dependent liver and renal toxicities as well as gingival hyperplasia.[467 (Level I)]

Rituximab: There are conflicting data with rituximab, which works by its effect in modulating and depleting B cell action, on GO. One small randomised controlled trial in patients with active, moderate-to–severe GO showed that rituximab (2000 mg and 500 mg) compared to IV GC (7.5g) significantly inactivated GO (100% versus 69%, p<0.04). There was no disease reactivation with rituximab compared with 31% with IV GC group (p=0.043).[469 (Level I)] In another small prospective, randomised, double-masked, placebo-controlled study, rituximab offered no additional benefits over placebo in patients with active, moderate-to–severe GO.[470 (Level I)]

Watchful monitoring may be indicated in some patients after GC treatment or withdrawal. Orbital vascular congestion can mimic active GO with eyelid and conjunctival redness and oedema. For patients with orbital vascular congestion, orbital decompression can be considered.[471 (Level II)]

> **Recommendation**
>
> - We recommend shared decision-making when selecting a second-line therapy in patients with moderate-to–severe GO

9.5.4 Sight-Threatening Active Graves' Ophthalmopathy

Sight-threatening GO includes dysthyroid optic neuropathy (DON), severe corneal exposure (large epithelial and/or stromal defect), corneal breakdown, and eyeball subluxation. Recent development of choroidal folds can cause metamorphopsia and should be addressed urgently too.[441, 443 (Level I)]

Very high doses of intravenous GCs (500–1000 mg of methylprednisolone) for 3 consecutive days or on alternate days during the first week are recommended for DON. This can be repeated after a week. If the response to very high doses of GC is poor, then urgent decompression surgery should be considered.[472-473 (Level II)] The predictors of poor response are presence of disc swelling at diagnosis and persistent active disease at 2 weeks post very high dose of IV GCs.[473 (Level II)]

Severe corneal exposure should be treated aggressively with medical therapy or with more invasive surgical treatment in order to prevent corneal breakdown.[441 (Level I)]

Recommendation

- Dysthyroid optic neuropathy should be treated immediately with very high doses of intravenous GCs (500–1000 mg methylprednisolone) for 3 consecutive days or on alternate days during the first week. The doses should be repeated in the second week. If the response is absent or poor, urgent orbital decompression should be done

9.5.5 Moderate-to–Severe And Inactive Graves' Ophthalmopathy

Assessment to confirm inactivity of GO is important and at times can be challenging. If in doubt, watchful monitoring over a period of time is needed. Rehabilitative surgery should be done after the disease has been inactive for 6 months.[443] (Level II) Different degrees and types or surgical intervention may be needed depending on the amount of disfigurement and/or dysfunction that persists in the post-inflammatory phase.

There are multiple options for rehabilitative surgeries.

1. *Decompression surgery*: Minimally invasive approach is preferred. Decompressing surgery aims to reduce intraocular pressure by enlarging the bony orbit with different degrees of extension of medial/lateral orbital walls or removal of the orbital floor. Fat excision via the inferolateral or inferomedial extraconal compartments is another alternative. Orbital decompression can reduce exophthalmos, periorbital puffiness, and lid retraction as well as reduce the intraocular pressure and thereby relieve retro-orbital pain. This procedure can also improve strabismus and cure postural visual obscuration in patients with orbital and optic nerve microvasculopathy. Potential complications of orbital decompression are new onset/worsening strabismus and globe dystopia.[474(Level II)]

2. *Strabismus/squint surgery*: It aims to restore fusion in primary position avoiding diplopia in downward gaze and to correct residual incomitances.[475(Level II)]

3. *Eyelid surgery*: Medical therapies such as alpha-blocker eye drops or post-ganglia adrenergic blockers are not very effective or limited by side effects. Botulinum injection is effective but transient. There are many approaches to lid retraction surgeries (from mild to severe degree of upper lid retraction), such as sutureless mullerectomy, transconjuctival free en block recession of the levator palpebrae superioris muscle and conjunctiva, or transcutaneous blepharotomy.[474,476(Level II)]

4. Cosmetic periorbital surgeries in GO are not different from those used for the ageing-related face.[474(Level II)]

If more than one surgical procedure is needed, the sequence should be orbital decompression followed by squint surgery, and lastly lid surgery.[474 (Level II)]

Recommendation

• *Elective rehabilitative surgery* should be offered to patients with GO after the disease has been inactive for at least 6 months and when GO is associated with significant impact on visual function or quality of life. Patients should be referred to specialised centres with specialised surgeons able to tailor to the specific need of the individual patient

9.5.6 Radioactive Iodine Therapy and Graves' Ophthalmopathy

Radioactive iodine confers a small but definite risk of worsening pre-existing GO or development of new GO.[449, 477-479 (Level I)] Studies have shown that glucocorticoids given concurrently may prevent worsening of GO in patients with mild active eye disease.[449 (Level I)] There is insufficient evidence for prophylaxis glucocorticoids in nonsmokers with no clinical evidence of GO who are going for RAI therapy.[449 (Level I)]

Antithyroid drugs and thyroidectomy are the preferred treatment options for hyperthyroidism in patients with active, moderate-to–severe or sight-threatening GO as compared to RAI therapy.[449, 478, 4 (Level II)] In patients with significant but inactive GO, RAI therapy can be given without glucocorticoids prophylaxis (Table 16).[4 (Level III)]

Table 16: Recommendation for RAI with or without glucocorticoids (Adapted from [4 [Level III]])

	RAI without glucocorticoids	**RAI with oral glucocorticoids**
No GO, nonsmoker	Recommend	Recommend against
No GO, smoker	Insufficient data to recommend for and against	Insufficient data to recommend for and against
GO present, active, and mild, risk factors[a] absent	Acceptable[b]	Acceptable[b]
GO present, active, and mild, risk factors[a] present	Recommend against	Recommend
GO present, active, and moderate-to–severe or sight threatening	Recommend against	Recommend against
GO present, inactive	Recommend	Recommend against

[a]Risk factors are high TRab, smoking, active and progressive GO over the preceding 3 months.
[b]The decision to use concurrent glucocorticoids should be made after considering the risk–benefit ratio for each patient. Glucocorticoids reduce the risk of GO deterioration in the presence of risk factors. However, glucocorticoid can potentially worsen diabetes, hypertension, osteoporosis and psychiatric illness as well as increase the risk of infection.

The dose of prednisolone for GO prophylaxis is 0.4–0.5 mg/kg per day, starting 1–3 days after RAI therapy in patients with mild-to–moderate GO, continued for 1 month then tapered over the next 2 months.[442, 449, 478 (Level I)] In a prospective randomised study, 15% of radioiodine group developed or had worsening of GO 2–6 months after radioiodine therapy; no patient in the radioiodine and prednisolone group had progression of GO.[449 (Level I)] A retrospective study has shown that a lower dose of 0.2–0.3 mg/kg per day of prednisolone for a total of 6 weeks can be used in patients with milder GO or in those who have no GO prior to RAI therapy but have significant risk factors for GO.[479-480 (Level II)]

Recommendations

- In patients with active, moderate-to–severe GO or sight-threatening GO, surgery or antithyroid drugs are preferred treatment options
- Oral prednisolone prophylaxis of 0.4–0.5 mg/kg per day for a total of 3 months is recommended in patients with mild-to–moderate GO who are undergoing radioiodine therapy
- Lower dose of oral prednisolone prophylaxis of 0.2–0.3 mg/kg per day can be used in patients with milder GO or who have risk factors for GO

Figure 10: Management of Graves' Ophthalmopathy (GO).[443 (Level II)]
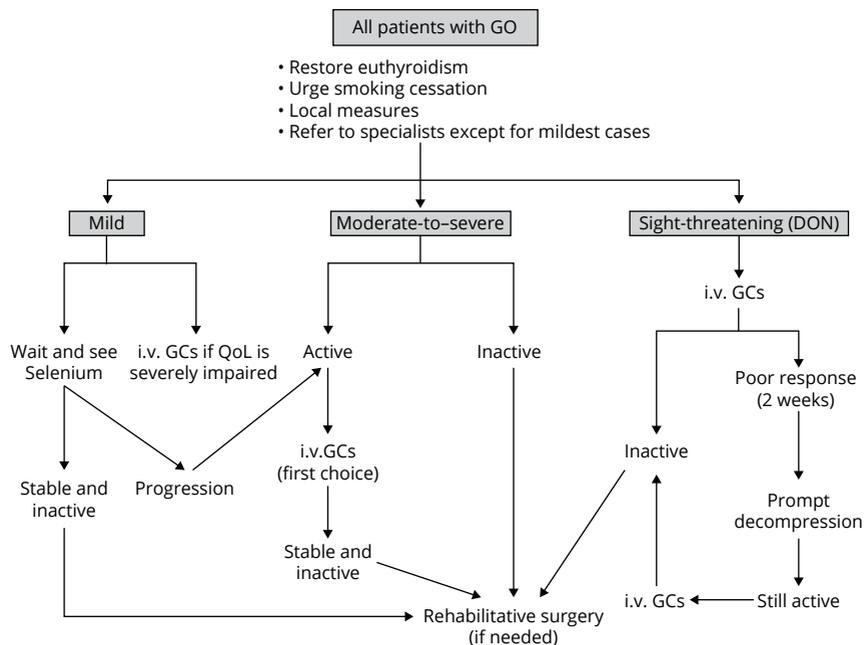
10. IMPLEMENTING THE GUIDELINES

Implementation of CPG is important as it helps in providing quality healthcare services based on best available evidence applied to local scenario and expertise. Various factors and resource implications should be considered for the success of the uptake in the CPG recommendations.

10.1 FACILITATING AND LIMITING FACTORS

The existing facilitating factors in implementing the recommendations in the CPG are:

• Availability of CPG to healthcare providers (hard copies and soft copies)
• Regular conferences and updates on management of thyroid disorders involving professional societies or bodies (Malaysian Endocrine and Metabolic Society, Family Medicine Specialist Association, Academy of Family Physician Malaysia, etc.)
• Public awareness on thyroid disease during World Thyroid Day, etc.

The existing limiting factors in implementing the recommendations in the CPG are:

• Different levels of care and wide variation in practice due to expertise, facilities, and financial constraints
• Lack of awareness among people with high risk of developing thyroid disease

10.2 POTENTIAL RESOURCE IMPLICATIONS

To implement the CPG, there must be dedicated efforts to:

• Ensure widespread distribution of CPG to healthcare providers
• Provide regular training to healthcare providers via effective seminars and workshops
• Involve multidisciplinary team at all levels of healthcare

To assist in the implementation of the CPG, the following are proposed as clinical audit indicators for quality management:

$$\text{Euthyroid hyper/hypothyroidism (target > 80\%)} = \frac{\text{No. of patients with euthyroid hyper/hypothyroidism}}{\text{Total no. of patients with hyper/hypothyroidism}} \times 100\%$$

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Appendix 1

CLINICAL QUESTIONS

1. What is the epidemiology of thyroid disorders in Malaysia?
2. What are the causes of hyperthyroidism?
3. How to diagnose hyperthyroidism?
4. How to treat hyperthyroidism?
5. How to treat Graves' hyperthyroidism?
6. How should overt hyperthyroidism due to TMNG or TA be managed?
7. How to monitor treatment of hyperthyroidism?
8. When to refer patients with hyperthyroidism?
9. What is the prevalence of subclinical hyperthyroidism?
10. What is the aetiology of subclinical hyperthyroidism?
11. What is the natural history of disease for subclinical hyperthyroidism?
12. What is the significance of subclinical hyperthyroidism?
13. What are the benefits of treatment of subclinical hyperthyroidism?
14. What is the treatment approach in patients with low TSH levels?
15. What is the treatment of subclinical hyperthyroidism?
16. What are the clinical and biochemical goals for levothyroxine replacement in primary hypothyroidism?
17. Are clinical parameters such as cold sensitivity and dry skin useful by themselves for assessing the adequacy of levothyroxine replacement in primary hypothyroidism?
18. How should levothyroxine administration be timed with respect to meals and beverages in order to maintain maximum, consistent absorption?
19. Are there medications and supplements that should not be co-administered with levothyroxine in order to avoid impaired absorption?
20. Are there gastrointestinal conditions that should be considered when a patient's levothyroxine dose is much higher than expected?
21. What medications may alter a patient's levothyroxine requirement by affecting either metabolism or binding to transport proteins?
22. What factors determine the levothyroxine dose required by a hypothyroid patient for reaching the appropriate serum TSH goal?
23. What is the best approach to initiating and adjusting levothyroxine therapy?
24. What are the potentially deleterious effects of excessive levothyroxine?
25. What are the potentially deleterious effects of inadequate levothyroxine?

26. What is the appropriate management of perceived allergy to the constituents of levothyroxine or intolerance to levothyroxine?

27. How should levothyroxine therapy be managed in individuals who have elevated TSH values due to non-adherence?

28. What biochemical goals should be employed for levothyroxine replacement in patients with secondary hypothyroidism?

29. What approach should be adopted in patients treated for hypothyroidism who have normal serum TSH values but still have unresolved symptoms?

30. Is there an unmet need in l-t4–treated patients with hypothyroidism?

31. Is there a biological rationale for persistent complaints in l-T4–treated hypothyroid patients?

32. When should endocrinologists be involved in the care of patients with hypothyroidism?

33. In hospitalised but not critically ill patients in whom levothyroxine replacement is instituted or increased, should the therapeutic goal be normalisation of serum TSH?

34. In hospitalised but not critically ill patients treated with levothyroxine replacement, what formulation and route of administration are recommended?

35. In hospitalised but not critically ill patients about to be treated with levothyroxine, should the possibility of adrenal insufficiency be excluded?

36. What are the causes of subclinical hypothyroidism?

37. How to diagnose subclinical hypothyroidism?

38. What are the complications of subclinical hypothyroidism?

39. How common are thyroid nodules and nontoxic goitre?

40. What are the clinical presentation/features of thyroid nodules and nontoxic goitre?

41. When to perform thyroid ultrasonography?

42. How to describe ultrasound findings?

43. How to select nodules for FNAB?

44. When to do other investigations for thyroid nodules?

45. How to manage benign nontoxic and nodular goitre?

46. How is thyroid storm diagnosed?

47. What is the antithyroid drug of choice in thyroid storm?

48. Are rectal antithyroid drugs useful?

49. What is the role of beta-adrenergic receptor antagonists?

50. What is the role of corticosteroids?

51. What is the role of inorganic iodide?

52. What is the role of lithium/cholecystographic agents?
53. What is the role of plasma exchange?
54. What is the role of other supportive therapy?
55. What is the role of early definitive therapy and prevention?
56. How is myxoedema coma diagnosed?
57. What are the complications of myxoedema coma?
58. What are the best treatment modalities for myxoedema coma?
59. How should patients with myxoedema coma be monitored?
60. How is pre-/perioperative hyperthyroidism best treated/risk minimised?
61. Is there a need to treat subclinical hyperthyroid disease preoperatively?
62. Is there a role for universal screening for hypothyroidism preoperatively?
63. What are the potential intra- and postoperative complications of untreated hypothyroidism?
64. How should perioperative hypothyroidism be managed?
65. How is subacute thyroiditis diagnosed?
66. How should subacute thyroiditis be managed?
67. What is the dosage of steroid used to treat subacute thyroiditis?
68. How long should patients with subacute thyroiditis be followed up?
69. How is acute thyroiditis diagnosed?
70. How should acute thyroiditis be managed?
71. What is the definition of maternal overt/subclinical hypothyroidism (OH/SCHypo)?
72. What are the common causes of maternal hypothyroidism?
73. Is maternal OH/ SCHypo associated with adverse maternal/foetal outcomes?
74. What is the impact of TPO Ab positivity on euthyroid women or women with SCHypo in pregnancy?
75. Does treatment with levothyroxine (LT4) improve adverse outcomes associated with maternal OH/ SCHypo?
76. Does treatment with LT4 Improve adverse outcomes associated with TPO Ab positivity?
77. What is the TSH goal if LT4 is given at preconception, during pregnancy and postpartum?
78. What is the LT4 requirement during pregnancy and postpartum? How should it be monitored?
79. Who should be screened for maternal hypothyroidism?
80. What is the prevalence of hyperthyroidism in pregnancy?
81. What is the definition of maternal hyperthyroidism?

82.   What are the common causes of hyperthyroidism in pregnancy?

83.   How to differentiate gestational transient thyrotoxicosis (GTT) from Graves' Disease?

84.   How to manage gestational transient thyrotoxicosis (GTT)?

85.   What are the complications of hyperthyroidism in pregnancy?

86.   How to manage Graves' Disease prior to conception?

87.   How to manage Graves' Disease during pregnancy?

88.   How to monitor patients with Graves' Disease on ATD in pregnancy?

89.   What is the role of TSH Receptor Antibody (TRAb) assays in pregnancy?

90.   Should additional foetal ultrasound monitoring for growth, heart rate and goitre be performed?

91.   How to manage thyrotoxicosis patients who are breastfeeding?

92.   What is postpartum thyroiditis and what is its natural history?

93.   What is the aetiology of postpartum thyroiditis?

94.   How to differentiate postpartum thyroiditis from Graves' Disease and what are the investigations?

95.   What is the management of postpartum thyroiditis?

96.   When to monitor patients with postpartum thyroiditis?

97.   Is postpartum thyroiditis associated with postpartum depression?

98.   What is the prevalence of Hashimoto Thyroiditis in children and adolescents?

99.   What are the clinical features of Hashimoto Thyroiditis in children and adolescents?

100. What is the natural history of Hashimoto Thyroiditis in children and adolescents?

101. How to diagnose and investigate Hashimoto Thyroiditis in children and adolescents?

102. What is the pattern of thyroid function in Hashimoto Thyroiditis in children and adolescents?

103. What is the treatment of hypothyroidism secondary to Hashimoto Thyroiditis in children and adolescents?

104. What is the treatment of non-goitrous euthyroid Hashimoto's Thyroiditis?

105. What is the treatment of euthyroid Hashimoto's Thyroiditis with goitre?

106. What is the risk of hypothyroidism in Turner Syndrome?

107. When to screen for hypothyroidism in Turner Syndrome?

108. What is the risk of hypothyroidism in Down Syndrome?

109. When to screen for hypothyroidism in Down Syndrome?

110. How to treat hypothyroidism in Down Syndrome?

111. What is the risk of hypothyroidism in Klinefelter Syndrome?

112. When to screen for hypothyroidism in Klinefelter Syndrome?

113. What is the risk of hypothyroidism in Prader–Willi Syndrome?

114. When to screen for hypothyroidism in Prader–Willi Syndrome?

115. How to treat and monitor hypothyroidism in Prader–Willi Syndrome?

116. How is Graves' Disease diagnosed in children and adolescents?

117. How should Graves' Disease be managed in children and adolescents?

118. How should children with Graves' Disease on ATD be monitored?

119. When is definitive therapy indicated?

120. What are the clinical considerations for RAI therapy?

121. What are the clinical considerations for thyroidectomy?

122. What are the features of overt hyperthyroidism in the elderly?

123. How should overt hyperthyroidism in the elderly be treated?

124. What are the risks of subclinical hyperthyroidism in the elderly?

125. Should subclinical hyperthyroidism in the elderly be treated?

126. How should subclinical hyperthyroidism in the elderly be treated?

127. How should overt hypothyroidism in the elderly be treated?

128. What are the risks of subclinical hypothyroidism in the elderly?

129. Should subclinical hypothyroidism in the elderly be treated?

130. How should subclinical hypothyroidism in the elderly be treated?

131. What are the thyroid abnormalities caused by amiodarone?

132. What are the mechanisms of amiodarone-induced thyrotoxicosis (AIT) and how to diagnose them?

133. How should amiodarone-induced thyrotoxicosis (AIT) be managed?

134. How should amiodarone-induced hypothyroidism (AIH) be managed?

135.   What are the drugs that cause thyroid disorder and what is the management?

136. What is the incidence of GO in Malaysia?

137. What is the definition of GO?

138. How is the assessment of activity and severity?

139. When to refer to ophthalmologist and endocrinologist?

140. What is the treatment of GO?

Appendix 2

During the final editing stage before this CPG is published, the Development Committee is made aware of 2 publications in 2019 which necessitate changes in recommendations. The updated, revised section is as below;

7.1.3 Is Maternal OH/SCHypo Associated With Adverse Maternal/ Foetal Outcomes?

Maternal OH has consistently been shown to be associated with adverse pregnancy outcomes, including pregnancy loss, pre-eclampsia, low birth weight (LBW), intrauterine growth restriction (IUGR) and impaired foetal neurocognitive development.[237 (Level II); 238 (Level II); 239 (Level II)] A prospective cohort study in India demonstrated more than seven times increased risk of intrauterine death while another prospective cohort study in China demonstrated more than thirteen times increased risk of foetal loss among pregnant women with OH compared to the euthyroid control.[237 (Level II); 238 (Level II)]

The associations between maternal SCHypo and adverse pregnancy outcomes have been less robust than maternal OH. This is partly due to the variable TSH cut-offs used in different studies and many studies did not take into account the influence of thyroid autoimmunity (TAI) or thyroid peroxidase antibody (TPO Ab) positivity on the outcome.[240 (Level II); 241 (Level II); 242 (Level II)] The adverse outcomes that were most consistently reported to be associated with maternal SCHypo included pregnancy loss and preterm delivery.[243 (Level II); 244 (Level II); 245 (Level II); 246 (Level II); Consortium on Thyroid and Pregnancy 2019 (Level II)]* Van den Boogard E *et al*. also reported an increased risk of pre-eclampsia among pregnant women with SCHypo while Chan *et al*. reported increased risk of placental abruption and breech presentation and Maraka *et al*. reported increased risk of premature ruptured of membrane (PROM) and placental abruption in their respective meta-analyses.[243 (Level II); 244 (Level II); 245 (Level II)] The association between impaired intellectual development in the offspring with maternal SCHypo has been shown to be present in some studies but absent in others.[247 (Level II); 238 (Level II); 248 (Level II)]

The association between maternal SCHypo and adverse pregnancy outcomes were often exacerbated by the presence of TPO Ab.[249 (Level II); 250 (Level II); 251 (Level II); 252 (Level II); 246 (Level II)] In a prospective cohort study involving 5971 singleton pregnancies, the association between maternal SCHypo and preterm delivery was lost after exclusion of women with TPO Ab positivity or co-morbidities. However, those with high TSH (defined as >4.04 mIU/L) and positive TPO Ab was found to have more than three times increased risk of preterm delivery.[250 (Level II)] A prospective cohort study in China showed that the increased risk of miscarriage occurred at a lower TSH threshold among the pregnant women with concomitant SCHypo and TAI at 2.5 mIU/L compared to 5.2 mIU/L for women with isolated SCHypo without TAI.[251 (Level II)] Similarly, a meta-analysis on nine cohort studies comparing the prevalence of miscarriage among pregnant women with SCHypo to the euthyroid pregnant women showed that the presence of TAI

increased the risk of miscarriage by 2.5 times among pregnant women with SCHypo compared to isolated SCH without TAI.[246 (Level II)]

Summary

- Maternal OH has been consistently shown to be associated with adverse pregnancy outcomes, including pregnancy loss, pre-eclampsia, preterm delivery, LBW, IUGR and impaired foetal neurocognitive development.
- The adverse outcomes that were most consistently reported to be associated with maternal SCHypo include pregnancy loss and preterm delivery.
- These associations were dependent on the maternal TPO Ab status with a lower TSH threshold (TSH at or above 2.5 mIU/L) among the TPO Ab positive women versus a higher TSH threshold (TSH >5 mIU/L) among the TPO Ab negative women.

7.1.4 What Is the Impact of TPO Ab Positivity on Euthyroid Women or Women With Subclinical Hypothyroidism in Pregnancy?

The presence of TAI has been consistently shown to be associated with pregnancy loss and preterm delivery independent of maternal thyroid function in various meta analyses.[243 (Level II); 253 (Level II); 254 (Level II); Consortium on Thyroid and Pregnancy 2019 (Level II)*]

Most studies defined the presence of TAI by TPO Ab positivity while others defined it as TPO and or thyroglobulin (Tg) Ab positivity. The risk was exacerbated in the presence of maternal TSH of more than 2.5 mIU/L.[251 (Level II)] The association between TPO Ab positivity and recurrent miscarriages was less robust with only two studies reporting an association.[255 (Level II); 243 (Level II)] Lower intellectual development scores of offspring have also been shown to be associated with TPO Ab positivity in two retrospective cohort studies but the evidence is weak.[247 (Level II); 256 (Level II)] A meta-analysis of 38 studies examining clinical significance of TAI before conception and in early pregnancy also showed an increased risk of sub-fertility and postpartum thyroiditis.[243 (Level II)]

Summary

- The presence of TAI is associated with pregnancy loss and preterm delivery independent of maternal thyroid function. This is predominantly driven by the presence of TPO Ab positivity.
- The risk was exacerbated in the presence of maternal TSH of >2.5 mIU/L.

7.1.5 Does Treatment With Levothyroxine (LT4) Improve Adverse Outcomes Associated With Maternal Overt/Subclinical Hypothyroidism?

Levothyroxine treatment for pregnant women with OH is highly recommended, although no prospective randomised control trial (RCT) has been conducted to prove its benefits. This is because of the numerous serious adverse maternal and

foetal outcomes associated with OH that have been demonstrated previously. It would be unethical to withhold treatment in this population to perform an RCT. LT4 replacement in pregnancy is particularly essential in the first 18 to 20 weeks of gestation where foetal thyroid hormones depends largely on the placental transfer of maternal thyroxine.

For maternal SCHypo, the benefits of LT4 treatment are not as clear-cut as OH. While there have been many studies that demonstrated the associations of maternal SCHypo with adverse pregnancy outcomes, especially pregnancy loss and preterm delivery, only a small number of studies demonstrated the benefits of LT4 treatment in this population. A prospective, non-randomised open-labelled study on maternal SCHypo demonstrated that the increased risk of spontaneous abortion among SCHypo patients not given LT4 treatment compared to controls with normal TSH was eliminated with LT4 treatment.[257 (Level II)] A retrospective study on the United States national cohort demonstrated significant risk reduction in pregnancy loss with LT4 treatment among pregnant women with SCHypo when the serum TSH was improved to less than 4.0 mIU/L.[258 (Level II)] Similarly, a meta-analysis of nine cohort studies showed normalisation of an increased miscarriage risk associated with maternal SCHypo upon LT4 treatment compared to that of euthyroid women.[246 (Level II)] A recent randomised controlled trial showed that LT4 treatment reduced the risk of preterm delivery among a group of TPO Ab negative women with TSH above 4 mIU/L.[259 (Level I)] However, no study has specifically assessed whether the presence of TPO Ab positivity will lower the serum TSH threshold in obtaining risk reduction on miscarriage and preterm delivery.

Two RCTs examining the effect of LT4 replacement in maternal SCHypo or isolated hypothyroxinaemia had failed to show any benefits in the improvement of IQ scores in the offspring.[260 (Level I); 261 (Level I)]

Recommendations

- Pregnant women with OH should be treated with LT4
- For maternal SCHypo, LT4 treatment should be considered in the following situations to reduce the risk of miscarriage and preterm delivery:
  a) pregnant women with negative TPOAb:
     – LT4 is recommended if TSH is >10 mIU/L
     – LT4 may be considered if TSH is above the pregnancy specific reference range or 4.0 mIU/L
  b) pregnant women with positive TPOAb:
     – LT4 is recommended if TSH is above the pregnancy specific reference range or 4.0 mIU/L
     – LT4 may be considered if TSH is >2.5 mIU/L
- LT4 treatment is not indicated to improve the IQ scores of offsprings to mothers with SCHypo

7.1.6 Does Treatment With LT4 Improve Adverse Outcomes Associated With TPO Ab Positivity?

While TPO Ab positivity has been shown to be associated with pregnancy loss and preterm delivery independent of maternal thyroid status, the benefits of LT4 replacement in reducing the risk of adverse pregnancy outcomes among TPO Ab positive women has yet to be established. The first prospective randomised controlled trial looking at the effect of LT4 treatment among euthyroid women with TAI showed significant risk reduction in miscarriage and preterm delivery with LT4 treatment.[262 (Level I)] However, a relatively high TSH cut-off of 4.4 mIU/L was used to define euthyroid in that study. Results from subsequent retrospective studies have yielded mixed results.[263 (Level II);264 (Level II)] Another recent RCT demonstrated significant risk reduction in preterm delivery but not miscarriage rate among a group of TPO Ab positive women without overt thyroid dysfunction.[265 (Level I)] However, the benefits were predominantly driven by those with TSH of 4 mIU/L and above. The TABLET trial also failed to show any benefits in improving live birth rates among euthyroid women with positive TPO Ab associated with history of miscarriage or infertility despite being commenced on LT4 before conception.[Dhillon-Smith 2019]*

The evidence available to date is therefore insufficient to recommend routine LT4 treatment in euthyroid pregnant women with positive TPO Ab.

Recommendations

- There is insufficient evidence to recommend routine LT4 treatment in euthyroid women with positive TPO Ab in pregnancy.

7.1.9 Who Should Be Screened for Maternal Hypothyroidism?

Recommendations

- The current level of evidence does not support universal screening for maternal hypothyroidism
- TSH testing should be performed for women who are trying to conceive or as soon as pregnancy is confirmed if the following risk factors are present:
  i.   History of thyroid dysfunction
  ii.   Goitre
  iii. Known thyroid antibody positivity
  iv.   Age at or above 30 years
  v.   Type 1 diabetes or other autoimmune disorders
  vi.   History of recurrent pregnancy loss or preterm delivery
  vii. Infertility
  viii. History of thyroid surgery or head and neck radiation

    ix.   Morbid obesity

    x.   Use of lithium or amiodarone

    xi.   Recent administration of iodinated radiologic contrast

    xii.   Residing in area of moderate to severe iodine deficiency

    xiii.   Family history of thyroid disorders

    xiv.   Two or more prior pregnancies

References
1.   The consortium on thyroid and pregnancy—study group on preterm birth. Association of thyroid function test abnormalities and thyroid autoimmunity with preterm birth: A systematic review and meta-analysis. *JAMA*. 2019;322 (7):632–41.
2.   Dhillon-Smith RK, Middleton LJ, Sunner KK, *et al*. Levothyroxine in women with thyroid peroxidase antibodies before conception. *New Eng J Med*. 2019;380:1316–25.

7.2.7 How to Manage Graves' Disease Prior to Conception?

.... Patients who are of childbearing potential and are still on carbimazole, should use effective contraception.[Drug Safety Update.......]

Reference
1.   Drug Safety Update, Medicines and Healthcare products Regulatory Agency (MHRA) Newsletter, volume 12, issue 7: February 2019: 2

LIST OF ABBREVIATIONS

Ab	Antibody
AIH	Amiodarone Induced Hypothyroidism
AIT	Amiodarone Induced Thyrotoxicosis
AITD	Autoimmune Thyroid Disease
ATA	American Thyroid Association
ATDs	Antithyroid Drugs
BWPS	Burch-Wartofsky Point Scale
CHADS$_2$	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke [double weight]
CMZ	Carbimazole
CRP	C-Reactive Protein
ESR	Erythrocyte Sedimentation Rate
ETA	European Thyroid Association
FFP	Fresh Frozen Plasma
FNAB	Fine Needle Aspiration Biopsy
fT3	free T3
fT4	free T4
GD	Graves' Disease
GO	Graves Ophthalmopathy
GTT	Gestational Transient Thyrotoxicosis
hCG	Human Chorionic Gonadotrophin
HLA	Human Leucocyte Antigen
ICI	Immune Checkpoint Inhibitor
IFN	Interferon
IL-2	Interleukin-2
JTA	Japan Thyroid Association
KS	Klinefelter Syndrome
LT4	Levothyroxine
MMI	Methimazole
NK	Natural Killer
NSAID	Non-Steroidal Anti-Inflammatory Drug
OH	Overt Hypothyroidism
PPT	Post Partum Thyroiditis
PTU	Propylthiouracil
PWS	Prader Willi Syndrome
SCHyper	Subclinical Hyperthyroidism
SCHypo	Subclinical Hypothyroidism
SLE	Systemic Lupus Erythematosus
TFTs	Thyroid Function Tests
TK	Tyrosine Kinase Inhibitor
TMNG	Toxic Multinodular Goitre
TA	Toxic Adenoma
T3	Tri-iodothyronine
T4	Thyroxine
TgAb	Thyroglobulin Antibody

TPE	Total Plasma Exchange
TPO	Thyroid Peroxidase Antibody
TRAb	Thyroid Receptor Antibody
TS	Turner Syndrome
TSH	Thyroid Stimulating Hormone
TS1	Thyroid Storm 1
TS2	Thyroid Storm 2
TT4	Total T4
RAI	Radioactive Iodine
US	Ultrasonography

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DISCLOSURE STATEMENT

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