NATIONAL CLINICAL GUIDELINES

THE DIAGNOSIS & MANAGEMENT OF HYPOTHYROIDISM IN ADULTS

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المبادئ الإرشادية السريرية لدولة قطر
NATIONAL CLINICAL GUIDELINES FOR QATAR

وزارة الصحـــــة العامـــــة
Ministry of Public Health
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Version History

Version	Status	Date	Editor	Description
1.0	Final	14th December 2016	Guidelines Team	Final version for publication.
1.1	Final	19th March 2017	Guidelines Team	Minor updates to Section 2.
2.0	Final	19th September 2019	Guidelines Team	Updated Version for Publication.

Citation

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Ministry of Public Health Qatar. National Clinical Guideline: The Diagnosis and Management of Hypothyroidism in Adults (2019).

Abbreviations

The abbreviations used in this guideline are as follows:

Anti-TPO-Ab	Anti-thyroid peroxidase antibodies
FT3	Free tri-iodothyronine
FT4	Free thyroxine
L-T4	Levothyroxine
T3	Tri-iodothyronine
T4	Thyroxine (tetra-iodothyronine)
TFT	Thyroid function tests
TSH	Thyroid-Stimulating Hormone

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1 Information About This Guideline

1.1 Objective and Purpose of the Guideline

The purpose of this guideline is to define the appropriate diagnosis and management of hypothyroidism in adults. The objective is to reduce inappropriate investigation, prescribing and referral of patients presenting to provider organisations in Qatar. It is intended that the guideline will be used primarily by physicians in outpatient settings.

1.2 Scope of the Guideline

Aspects of care covered in this guideline include:

- Causes and clinical features of hypothyroidism in adults aged over 18 years, including:
    - Clinical assessment of hypothyroidism.
    - Use of thyroid function tests for diagnosis.
    - Management of hypothyroidism.
    - Consideration of myxoedema coma.

Aspects of care not covered in this guideline include:

- Assessment and management of thyroid disorders in children.
- Assessment and management of thyroid disorders in the elderly (aged over 65 years).
- Assessment and management of thyroid disorders in women planning or during pregnancy, or in the postpartum period.
- Management of thyroid cancer.

1.3 Editorial Approach

This guideline document has been developed and issued by the Ministry of Public Health of Qatar (MOPH), through a process which aligns with international best practice in guideline development and localisation. The guideline will be reviewed on a regular basis and updated to incorporate comments and feedback from stakeholders across Qatar.

The editorial methodology, used to develop this guideline, has involved the following critical steps:

- Extensive literature search for well reputed published evidence relating to the topic.
- Critical appraisal of the literature.
- Development of a draft summary guideline.
- Review of the summary guideline with a Guideline Development Group, comprised of practising healthcare professionals, subject matter experts and patient representatives, from across Qatar.
- Independent review of the guideline by the National Clinical Guidelines & Pathways Committee, appointed by the MOPH, from amongst stakeholder organisations across Qatar.

Whilst the MOPH has sponsored the development of the guideline, the MOPH has not influenced the specific recommendations made within it.

1.4 Sources of Evidence

The professional literature published in the English language has been systematically queried using specially developed, customised, and tested search strings. Search strategies are developed to allow efficient yet comprehensive analysis of relevant publications for a given topic and to maximise retrieval of articles with certain desired characteristics pertinent to a guideline.

For each guideline, all retrieved publications have been individually reviewed by a clinical editor and assessed in terms of quality, utility, and relevance. Preference is given to publications that:

1. Are designed with rigorous scientific methodology.
2. Are published in higher-quality journals (i.e. journals that are read and cited most often within their field).
3. Address an aspect of specific importance to the guideline in question.

Further information about the literature search and appraisal process is included in the appendix.

1.5 Evidence Grading and Recommendations

Recommendations made within this guideline are supported by evidence from the medical literature and where possible the most authoritative sources have been used in the development of this guideline. In order to provide insight into the evidence basis for each recommendation, the following evidence hierarchy has been used to grade the level of authoritativeness of the evidence used, where recommendations have been made within this guideline.

Where the recommendations of international guidelines have been adopted, the evidence grading is assigned to the underlying evidence used by the international guideline. Where more than one source has been cited, the evidence grading relates to the highest level of evidence cited:

- **Level 1 (L1):**
  - Meta-analyses.
  - Randomised controlled trials with meta-analysis.
  - Randomised controlled trials.
  - Systematic reviews.

- **Level 2 (L2):**
  - Observational studies, examples include:
    - Cohort studies with statistical adjustment for potential confounders.
    - Cohort studies without adjustment.
    - Case series with historical or literature controls.
    - Uncontrolled case series.
  - Statements in published articles or textbooks.

- **Level 3 (L3):**
  - Expert opinion.
  - Unpublished data, examples include:
    - Large database analyses.
    - Written protocols or outcomes reports from large practices.

In order to give additional insight into the reasoning underlying certain recommendations and the strength of recommendation, the following recommendation grading has been used, where recommendations are made:

- **Recommendation Grade A (RGA):** Evidence demonstrates at least moderate certainty of at least moderate net benefit.
- **Recommendation Grade B (RGB):** Evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended.
- **Recommendation Grade C (RGC):** Evidence demonstrates potential harm that outweighs benefit; additional research is recommended.
- **Recommendation of the GDG (R-GDG):** Recommended best practice on the basis of the clinical experience of the Guideline Development Group members.

1.6 Guideline Development Group Members

The following table lists members of the Guideline Development Group (GDG) nominated by their respective organisations and the Clinical Governance Group. The GDG members have reviewed and provided feedback on the draft guideline relating to the topic. Each member has completed a declaration of conflicts of interest, which has been reviewed and retained by the MOPH.

Guideline Development Group Members		
Name	**Title**	**Organisation**
Dr Ahmad Mostafah Abdel Wahhab	Senior Specialist Family Medicine & Trainer	Primary Health Care Corp
Dr Abdelsalam Mohd Al Bashir	Consultant Family Medicine	Primary Health Care Corp
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Dr Nabeel Isseh	Consultant Endocrinology	Al Ahli Hospital
Dr Arif Mahmood	Consultant Family Medicine	Qatar Petroleum
Dr Usama Mia	Consultant Family Medicine	Qatar Petroleum
Dr Rana Marwan Nakchou	Consultant Endocrinology	Ministry of Interior Clinics
Dr Mohamed Salem Nasralla Saleh	Specialist Family Medicine	Primary Health Care Corp
Dr Mahmoud Zirie	Senior Consultant Endocrinology	Hamad Medical Corp

1.7 National Clinical Guidelines & Pathways Committee Members

The following table lists members of the National Clinical Guidelines & Pathways Committee (NCGPC), appointed by the MOPH. The NCGPC members have reviewed and provided their feedback and approval of the guideline document. Each member has completed a declaration of conflicts of interest, which has been reviewed and retained by the MOPH.

National Clinical Guidelines & Pathways Committee (NCGPC) Members		
Name	**Title**	**Organisation**
Ms Huda Amer Al-Katheeri	Chair of the NCGPC, Director of Strategic Planning & Performance Department	Ministry of Public Health
Shk Dr Mohammed Hamad J. Al Thani	Co-Chair of the NCGPC, Director of Public Health	Ministry of Public Health
Prof Anthony Akobeng	Chair Clinical Practice Guidelines Committee	Sidra Medicine
Dr Maryam Ibrahim Al-Heidous	Registration coordinator, QCHP	Ministry of Public Health
Dr Alshaymaa Mohammed A. M. Al-Motawa	Consultant Family Medicine	Qatar Petroleum
Dr Abi Khalil Charbel	Associate Professor of Medicine Consultant Cardiology	Weill Cornell Medicine-Qatar
Dr Paul Dijkstra	Director of Medical Education	Aspetar
Dr Mohamed Elrishi	Consultant Endocrinology and Internal Medicine	Al Ahli Hospital
Dr Dahlia Mustafa Hassan	Consultant Family Medicine	Primary Health Care Corp
Dr Ghassan Youseph Hommos	Consultant Endocrinology	Al Emadi Hospital
Dr Chris Kenny	Executive Director Clinical and Service Development, Office of the Chief Medical Officer	Hamad Medical Corporation
Dr Egon Toft	VP and Dean of College of Medicine	College of Medicine, Qatar University

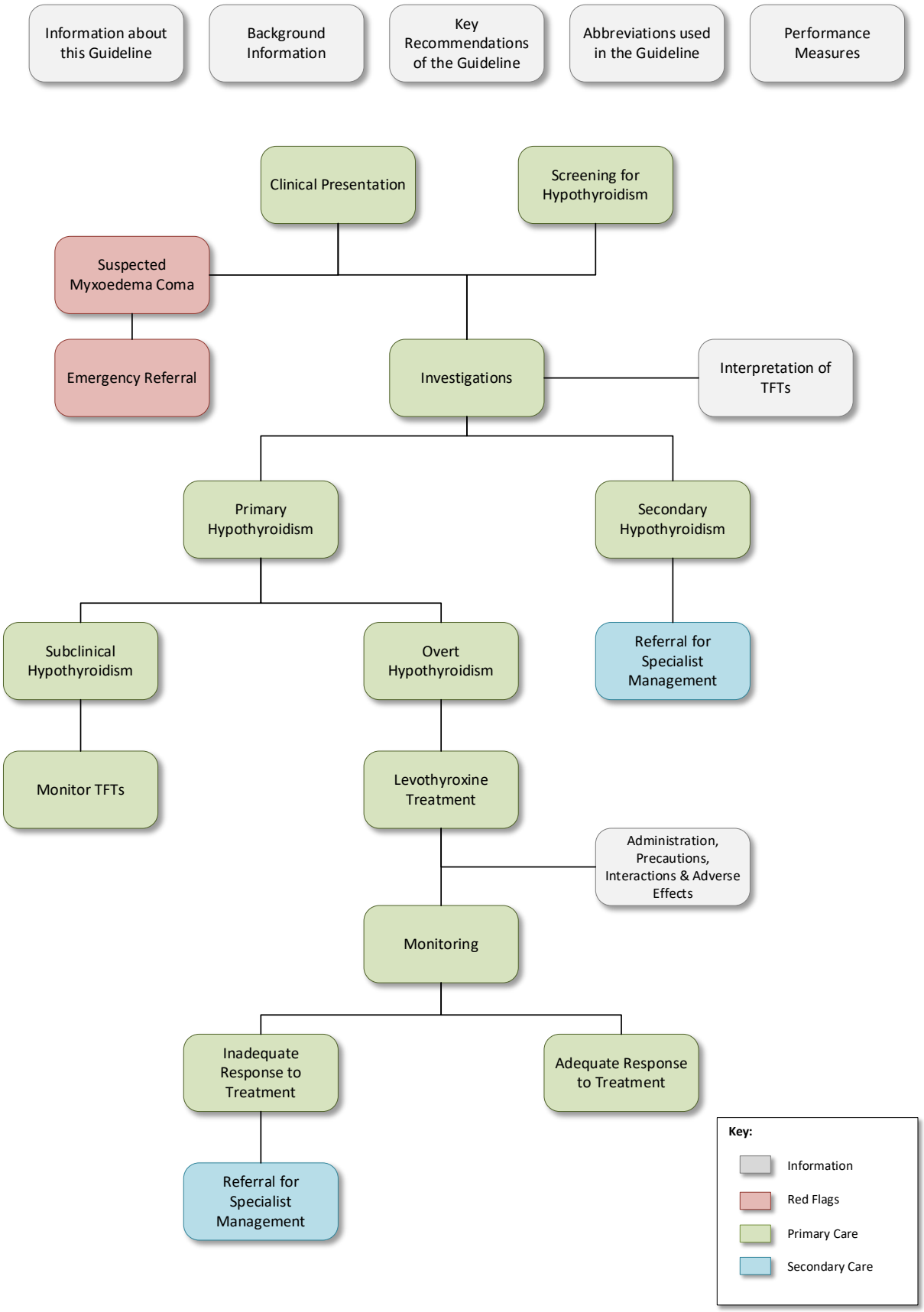
1.8 Responsibilities of Healthcare Professionals

This guideline has been issued by the MOPH to define how care should be provided in Qatar. It is based upon a comprehensive assessment of the evidence as well as its applicability to the national context of Qatar. Healthcare professionals are expected to take this guidance into account when exercising their clinical judgement in the care of patients presenting to them.

The guidance does not override individual professional responsibility to take decisions which are appropriate to the circumstances of the patient concerned. Such decisions should be made in consultation with the patient, their guardians, or carers and should consider the individual risks and benefits of any intervention that is contemplated in the patient's care.

2 Hypothyroidism Pathway

Click on a box below to see the relevant page of the Pathway.



3 Key Recommendations of the Guideline

The key recommendations of this guideline are:

Investigations:

- Universal screening for hypothyroidism in a healthy adult population is not warranted [1] [**L2, RGA**].
- Targeted testing, using TSH, is recommended for selected patient groups [1,2][**L2, RGA**].
- It is essential that thyroid function is tested biochemically alongside a careful clinical assessment of the individual patient [1][**L2, RGA**].
- Serum total T3 or assessment of serum FT3 should not routinely be performed to diagnose hypothyroidism [2][**L2, RGA**].
- Repetition of a positive test result for anti-thyroid peroxidase antibodies, is not routinely recommended [**R-GDG**].

Treatment:

- Treat all patients with overt hypothyroidism with levothyroxine[1–3] [**L1, RGA**].
- Routine levothyroxine treatment is not recommended in patients with subclinical hypothyroidism[1,2,4,5] [**L1, RGA**].
- Secondary hypothyroidism should be managed by endocrine specialists in the same way as all other diseases of the pituitary gland[1–3] [**L3**].
- The optimal dose of levothyroxine for long-term therapy should be titrated against the results of thyroid function tests together with clinical findings[1,2,6] [**L2, RGA**].
- Start at a lower dose and titrate with smaller increments in older patients and those with cardiac disease[7] [**RGA**].
- The use of T3 alone or in combination with T4 should be reserved for use by endocrine specialists, in individual patients [**R-GDG**].
- Avoid thyroid hormone excess to prevent the adverse effects of iatrogenic thyrotoxicosis (including atrial fibrillation or osteoporosis)[6] [**L1, RGA**].

Monitoring:

- The use of TSH alone is adequate for most patients on replacement therapy, once they are stable and compliant [1,2].
- Assessment of serum FT4, in addition to TSH, may be considered when monitoring levothyroxine therapy[2] [**L1, RGA**].
- Symptoms alone lack sensitivity and specificity and therefore are not recommended for judging adequacy of replacement in the absence of biochemical assessment[6] [**L2, RGA**].
- Use FT4 rather than TSH as a therapeutic end point for treatment of secondary hypothyroidism, aiming for titration to the upper third of the normal range [**R-GDG**].
- Women of reproductive age being treated for hypothyroidism, should have their dose maintained at a level to keep TSH between 1.5 - 2.5 mIU/L [**R-GDG**].

Suspected Myxoedema Coma:

- Patients with suspected myxoedema coma should be admitted to an intensive care unit for vigorous pulmonary and cardiovascular support[8] [**L3**].
- If myxoedema coma is suspected, it is essential that treatment is initiated immediately without awaiting confirmation of the diagnosis[9] [**L2**].

4 Background Information

4.1 Definition and Classification

Hypothyroidism is defined as a failure of the thyroid gland to produce sufficient amounts of thyroid hormones to meet the metabolic demands of the organism.

Hypothyroidism may be classified on the basis of the level of endocrine dysfunction[2] (see *Section 8.2*) :

- Primary hypothyroidism (caused by dysfunction of the thyroid gland):
  - Overt hypothyroidism.
  - Subclinical hypothyroidism.
- Secondary (central) hypothyroidism (caused by dysfunction of the pituitary or hypothalamus).

4.2 Aetiology

Causes of primary hypothyroidism include[1–3,10,11]:

- Iodine deficiency is the most common cause worldwide.
- In iodine-sufficient communities, the cause is most commonly either:
  - Chronic autoimmune disease:
    - Increases in frequency with age, female gender and is more common in people with other autoimmune diseases and those with a family history of thyroid disease or goitre.
    - Chronic Autoimmune disease can be sub-classified as:
      - Atrophic autoimmune thyroiditis; or
      - Goitrous autoimmune thyroiditis (Hashimoto's thyroiditis).
  - Secondary to treatment for hyperthyroidism, e.g. radioiodine or surgical treatment, may account for up to one-third of cases of hypothyroidism.
- Other causes include:
  - Thyroid cancer.
  - External beam radiation for non-thyroid head and neck malignancies.
  - Drug-induced primary hypothyroidism.
  - Congenital hypothyroidism.
  - Subacute thyroiditis (may be transient).
  - Peripheral thyroid hormone resistance (extremely rare).

Causes of secondary (central) hypothyroidism include[2]:

- Tumour.
- Radiation.
- Surgery.
- Trauma (especially road traffic accidents).
- Sheehan's syndrome (postpartum pituitary necrosis).
- Inflammatory or infiltrative diseases.
- Drug induced secondary hypothyroidism.

4.3 Prevalence

Data on the incidence and prevalence of hypothyroidism in Qatar is presently lacking, however a 2016 systematic review of thyroid disorders in the Arab world, reported that the prevalence of hypothyroidism

ranged from 6.18% in Libya to 47.34% in Makkah, Saudi Arabia[12]. This compares with a prevalence of hypothyroidism in the UK of 2% [13]. In the US, the prevalence of hypothyroidism (TSH > 4.5 mIU/L) in the general population is 3.7% [14].

4.4 Complications

Complications of untreated hypothyroidism include[8,15–18]:

- Hyperlipidaemia.
- Hypertension.
- Atrial fibrillation.
- Cardiovascular disease.
- Neuropsychiatric symptoms.
- Reduced bone mineral density and fractures.
- Myxoedema coma (see *Section 6.1*)
- Glaucoma.

4.5 Associated conditions

There is an increased frequency of other disorders in this population, e.g.[2,8,15,19–22]:

- Type 1 diabetes:
    - Up to 30% of women with type 1 diabetes may have thyroid disease.
- Pernicious anaemia.
- Chronic anaemia.
- Primary adrenal failure (Addison's disease).
- Myasthenia gravis.
- Coeliac disease.
- Rheumatoid arthritis.
- Systemic lupus erythematosus.
- Migraine.

5 Clinical Presentation

The symptoms and signs of hypothyroidism are the same in primary and central hypothyroidism[23]. The symptoms of hypothyroidism can be relatively non-specific and may be considered to result from a slowdown of metabolic processes and tissue accumulation of glycosaminoglycans[1,2,18,24,25].

Symptoms include[1,2,18,24,25]:

- Dry skin.
- Tiredness and sleepiness.
- Weakness.
- Muscle cramps.
- Feeling cold.
- Poor memory and concentration.
- Constipation.
- Weight gain with poor appetite.
- Shortness of breath.
- Hair loss.
- Voice changes – hoarse or deep voice.
- Menstrual irregularities which may include: menorrhagia, oligomenorrhoea or amenorrhoea.
- Decreased libido or subfertility.
- Recurrent miscarriage.
- Numbness.
- Deafness.
- Low mood or depression.
- Snoring.
- Poor balance.

Signs may include[1,2,24]:

- Diastolic hypertension.
- Dry, coarse skin and hair.
- Yellow skin due to carotene accumulation.
- Cold peripheries.
- Non-pitting peripheral oedema.
- Ascites.
- Pleural and pericardial effusions.
- Altered facial appearance.
- Diffuse alopecia.
- Bradycardia.
- Delayed relaxation of tendon reflexes.
- Carpal tunnel syndrome.
- Sleep apnoea.
- Rarely: ataxia, cognitive impairment, psychosis or steroid responsive encephalopathy.

6 Alarm Features

6.1 Suspected Myxoedema Coma

Myxoedema coma[8,9]:

- Contrary to the name of the condition, many patients are not comatose and may not have myxoedema (non-pitting oedema).
- Mainly occurs in patients over 60 years.
- Mortality remains high at 50% even with intensive treatment.
- Patients with suspected myxoedema coma should be admitted to an intensive care unit for vigorous pulmonary and cardiovascular support [8][**L3**].
- When myxoedema coma is suspected, it is essential that treatment is initiated immediately without awaiting confirmation of the diagnosis [9][**L2**].

Typical features of myxoedema coma include[8,9]:

- The usual features of hypothyroidism, as well as:
    - Hypoventilation.
    - Hypothermia.
    - Bradycardia.
    - Blood pressure changes.
    - Deteriorating mental state – including a confused agitated state ('myxoedema madness').

Patients will generally have a history of signs and symptoms of hypothyroidism – possibly previously undiagnosed or poorly adherent to treatment. However, there is usually a precipitating factor, e.g.[8,9]:

- Chest infection.
- Heart failure.
- Stroke.
- Blood loss.
- Exposure to cold.
- Drugs that depress respiration.

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7 Screening for Hypothyroidism

Universal screening for hypothyroidism in a healthy adult population is not warranted[1] [**L1, RGA**].

Targeted testing for hypothyroidism is recommended for the patient groups outlined below. Initial measurement should be with TSH (except where stated otherwise)[1–3,18,23,25–27] [**L2, RGA**]:

- Family history of thyroid disease or goitre.
- Abnormal thyroid examination, including goitre.
- Autoimmune disease, e.g.:
    - Type 1 diabetes - annual monitoring is recommended.
    - Pernicious anaemia.
    - Systemic lupus erythematosus.
- Atrial fibrillation.
- Dyslipidaemia.
- Hyponatraemia.
- Personal history of recurrent miscarriage:
    - Consider measuring TSH and anti-thyroid peroxidase antibodies (Anti-TPO-Ab).
- Radioactive iodine or surgery for hyperthyroidism:
    - Measure TSH with FT4 at 4-8 weeks post-treatment, then every 3 months for up to 1 year, and every 6-12 months thereafter with TSH alone.
- Amiodarone:
    - Measure TSH with FT4, at baseline and every 3-6 months thereafter.
    - If amiodarone is stopped, monitoring should continue every 3-6 months for a further 12 months.
- Lithium:
    - Measure TSH with FT4 before commencing treatment and after 3 months of treatment. If test results remain normal, monitor every 6-12 months thereafter.
- Previous neck irradiation or surgery involving the thyroid gland for head and neck cancer, including lymphoma:
    - Annual monitoring is recommended.
- Down's or Turner's syndrome:
    - Annual monitoring is recommended.
- Psychiatric disorders.
- Depression and anxiety.
- Patients with cognitive impairment.
- Women with irregular menstrual periods and men with reduced potency (frequent in secondary hypothyroidism).
- Post-partum women with a family history of thyroid dysfunction or goitre.

8 Investigations

8.1 Blood Tests for Hypothyroidism

8.1.1 Thyroid Function Tests

Thyroid function tests (TFTs) for primary hypothyroidism[1,2] [**L2, RGA**]:

- It is essential that thyroid function is tested biochemically alongside a careful clinical assessment of the individual patient.
- Clinical symptoms and/or signs alone are insufficient to make a diagnosis of hypothyroidism.
- Testing must include measurement of the levels of TSH and FT4 in serum.

In patients with secondary (central) hypothyroidism, assessment of FT4 and TSH, should be performed to diagnose hypothyroidism, with FT4 to guide treatment thereafter[1,2] [**L2, RGA**]:

NB: Serum total T3 or assessment of serum FT3 should not routinely be performed to diagnose hypothyroidism[2] [**L2, RGA**].

8.1.2 Anti-Thyroid Peroxidase Antibodies

Measurement of anti-thyroid peroxidase antibodies (Anti-TPO Ab) is of clinical use in the following circumstances[1]:

- In the diagnosis of autoimmune thyroid disorders e.g., in patients with subclinical hypothyroidism or a goitre.
- The patient is at risk of autoimmune thyroid disorders.
- The patient is at risk of hypothyroidism during treatment with interferon alpha, interleukin-2, lithium or amiodarone therapy.

Repetition of a positive test is not routinely recommended [**R-GDG**].

8.2 Interpretation of Blood Test Results

The diagnosis of hypothyroidism requires abnormal TFT results[1,2]:

- A low serum FT4 serves to establish a diagnosis of hypothyroidism:
    - Primary hypothyroidism – serum TSH is elevated, and FT4 is either low or normal.
    - Secondary (central) hypothyroidism – serum TSH is either low, normal or slightly elevated and FT4 is low.

Primary hypothyroidism may be further subclassified as:

- Overt primary hypothyroidism[1]:
    - Is diagnosed by a serum Thyroid-Stimulating Hormone (TSH) concentration above the normal reference range (usually above 10 mIU/L); and a low serum free thyroxine (FT4) concentration.
    - Clinical features of hypothyroidism may either be present or absent.

- Subclinical primary hypothyroidism[1,2]:
    - Serum TSH is elevated (but usually less than10 mIU/L), together with a normal serum FT4.
    - Confirm 6-12 weeks after the initial results in order to exclude transient causes of a raised TSH.

- Subclinical hypothyroid patients who are also Anti-TPO Ab positive are more likely to have higher serum TSH and are more likely to develop overt hypothyroidism.
- It can progress to overt hypothyroidism, particularly if anti-thyroid peroxidase antibody (Anti-TPO Ab) positive.

Primary hypothyroidism may be excluded if[1,2]:

- The serum TSH is within the reference range; and
- The patient is not taking any medication known to affect TSH.
- Secondary hypothyroidism may still be considered if the clinical picture is suggestive, as TSH alone is not a reliable test for detecting thyroid dysfunction arising from hypothalamic-pituitary dysfunction.

Note:

- Physicians are advised to tolerate mild elevation in TSH levels in people over 80 years old[11].

8.2.1 Pitfalls of Interpreting Thyroid Function Tests

Difficulty in interpreting thyroid function tests may be encountered in the following conditions[1,2,16,18]:

- Pregnancy.
- Non-thyroidal illness.
- Certain medications (e.g. heparin, phenytoin, frusemide, carbamazepine, salicylates, amiodarone, corticosteroids).
- Familial binding protein abnormalities.
- Thyroid hormone resistance syndromes.

9 Management

9.1 Primary Hypothyroidism

9.1.1 Overt Hypothyroidism

Treat all patients with overt hypothyroidism with levothyroxine [1–3][**L1, RGA**] (see *Section 9.3*).

9.1.2 Subclinical Hypothyroidism

Levothyroxine treatment is not routinely recommended in patients with subclinical hypothyroidism[5] [**L1, RGA**].

Levothyroxine therapy may be considered in the following patient groups[5]:

- Women planning or at risk of becoming pregnant.
- Patients with very high TSH levels of >20mIU/L with normal T4 levels.
- Young adults age <30 years.
- Patients already taking thyroid hormones.

In patients in whom treatment is not indicated, monitor with a review of the patient and repeat TFTs every 6-12 months[1].

9.2 Secondary Hypothyroidism

Secondary hypothyroidism should be managed by endocrine specialists in the same way as all other diseases of the pituitary gland[1–3] [**L1**].

9.3 Levothyroxine Treatment

Levothyroxine (L-T4) treatment[1,2,6]:

- Should aim to render the patient euthyroid.
- Should be considered in case of TSH 5–10 mIU/L on 2 assays associated with either clinical symptomatology or presence of anti-TPO antibodies[28].
- Adequacy of therapy should be determined both by clinical and biochemical assessment.
- Under-treatment and over-treatment should be avoided due to their detrimental health effects [**RGC**].
- The optimal dose of levothyroxine for long-term therapy should be titrated against the results of thyroid function tests together with clinical findings[1,2,6] [**L2, RGA**] and may begin at 1–1.6mcg/kg/day[28] [**L2, RGA**].
- Start at a lower dose of 25 mcg/day and titrate with smaller increments in patients over 65 years old and those with cardiac disease[7] [**RGA, R-GDG**].

The evidence does not support using levothyroxine with liothyronine (T3) combinations to treat hypothyroidism[2,11] [**L1, RGB**]. T3 alone or in combination with T4 should be reserved for use by endocrine specialists, in individual patients [**R-GDG**].

The following are not recommended in the management of hypothyroidism[1,2,6] [**L2, RGC**]:

- Routine T3 monotherapy.
- Thyroid extracts.
- Iodine-containing preparations.
- Dietary supplementation, including other iodine-containing functional foods, should not be used in the management of hypothyroidism in iodine-sufficient areas.
- Nutraceuticals or other over-the-counter preparations.

9.3.1 Administration

Administer levothyroxine on an empty stomach (30-60 minutes before breakfast or >2 hours after dinner)[7]:

- Should be stored properly as per product instructions and not taken with substances or medications that interfere with its absorption[2] [**L1, RGA**].
- Tablets:
    - May be crushed into 5 to 10 mL of water and drunk immediately.
    - Should be taken with a full glass of water if swallowing the tablet as the whole.
    - See *Section 9.3.3* for medication that may interfere with L-T4 absorption and metabolism.
- Gel capsules:
    - Should not be crushed or cut.
    - Can be used as a suppository.
- Solution:
    - Can be drunk undiluted or diluted in water.
    - Liquid form is recommended over tablet form in patients with malabsorption and gastric disorders[16,29] [**L1, RGA**].

When deciding on a starting dose of levothyroxine, consider the following patient factors[6,7] [**L1, RGA**]:

- Age.
- Pregnancy status.
- General clinical context, including the presence of cardiac disease.
- Weight.
- Lean body mass.
- Aetiology of hypothyroidism.
- Degree of TSH elevation.
- Serum TSH goal – appropriate to the clinical situation.

9.3.2 Precautions

Patients with adrenal insufficiency should start corticosteroid therapy before starting levothyroxine[2] [**L1, RGA**]. Slower dose titration is recommended in patients[2]:

- Aged over 50 years; or
- With cardiovascular disorders, particularly ischaemic heart disease or arrhythmias.

Levothyroxine treatment can increase blood glucose levels in patients with diabetes, although this is rarely clinically significant. The dose of glucose-lowering drugs may need to be adjusted.

Levothyroxine is contraindicated in individuals with[7] [**L2, RGC**]:

- Uncorrected adrenal insufficiency.
- Acute myocardial infarction.
- Acute myocarditis.
- Pan-carditis.
- Active heart arrhythmias.

- Hyperthyroidism or thyrotoxicosis.

9.3.3 Interactions

Some drugs modify thyroid status whilst others produce abnormal thyroid function test results in otherwise euthyroid subjects. In general, serum TSH is less affected by medication than thyroid hormones, although glucocorticoids and dopamine in high doses inhibit TSH release[1].

Certain drugs and dietary agents will impair the absorption of levothyroxine from the intestine or increase renal clearance. Patients on levothyroxine therapy should be advised to take their levothyroxine at least 4 hours apart from these medications and dietary agents[1].

Common agents that interfere with absorption of levothyroxine therapy[2,16,30]:

- Ferrous sulphate.
- Calcium salts.
- Proton pump inhibitors.
- H2 receptor antagonists.
- Ciprofloxacin.
- Orlistat.

Dietary factors that may affect absorption of levothyroxine[2,16]:

- Ingestion of medication with a meal.
- Grapefruit juice.
- Espresso coffee.
- High fibre diet.
- Soybean formula (infants).
- Soy.

Common agents that increase the clearance of levothyroxine[2]:

- Phenobarbital.
- Primidone.
- Phenytoin.
- Carbamazepine.
- Oxcarbazepine.
- Rifampin.
- Growth hormone.
- Sertraline.
- Tyrosine kinase inhibitors.
- Quetiapine.
- Stavudine.
- Nevirapine.

Additional monitoring may also be required in patients taking oral hormonal contraceptives and hormone replacement therapy[30].

9.3.4 Adverse Effects

Perceived allergy or intolerance to levothyroxine can be managed by changing the dose or product, including consideration of gel capsules and liquid form[6,16] [**L2, RGB**]. In selected cases, a consultation with an allergist may be appropriate[7].

Avoid thyroid hormone excess to prevent the adverse effects of iatrogenic thyrotoxicosis (including atrial fibrillation or osteoporosis)[6] [**L1, RGA**].

Note:

- Escalated doses of levothyroxine and extended treatment increase the risk for prolonged exposure to supratherapeutic doses of the drug, which increase the chances of adverse outcomes[31] [**L2, RGC**].

9.3.5 Monitoring

The minimum period to achieve stable concentrations after a change in dose of levothyroxine is 6-8 weeks and thyroid function tests should not normally be requested before this period has elapsed[7,30].

Monitoring of Thyroid Function[1,2,7]:

- Check TSH levels:
    - 6-8 weeks after initiating treatment.
    - 6-8 weeks after dose changes.
    - 6-8 weeks after initiation of drugs that decrease the bioavailability, or alter the metabolic disposition, of the levothyroxine dose.
- Assessment of serum FT4, in addition to TSH, may be considered when monitoring levothyroxine therapy[2] [**L1, RGA**].
- The use of TSH alone is adequate for most patients on replacement therapy, once they are stable and compliant.

Symptoms alone lack sensitivity and specificity and therefore are not recommended for judging adequacy of replacement in the absence of biochemical assessment[6] [**L2, RGA**]:

- Symptoms should be considered in the context of serum TSH values, relevant comorbidities and other potential causes[6] [**L2, RGA**].
- In patients in whom levothyroxine dose requirements are much higher than expected, consider evaluation for gastrointestinal disorders, including[6,16] [**L1, RGA**]:
    - Helicobacter pylori–related gastritis.
    - Atrophic gastritis.
    - Coeliac disease.
    - Lactose intolerance.
    - Inflammatory bowel disease.
- If such disorders are detected and effectively treated, re-evaluation of thyroid function and levothyroxine dosage is recommended.

Therapeutic endpoints in the treatment of hypothyroidism[1,2]:

- The most reliable therapeutic endpoint for the treatment of primary hypothyroidism is the serum TSH value rather than FT4 or T3 levels.
- Use FT4 rather than TSH as a therapeutic end point for treatment of secondary hypothyroidism, aiming for titration to the upper third of the normal range [**R-GDG**].

Women of reproductive age being treated for hypothyroidism, should have their dose maintained at a level to keep TSH between 1.5 - 2.5 mIU/L [**R-GDG**].

9.3.6 Response to Treatment

When a sufficient dose of levothyroxine lowers the TSH to within the reference range, patients will usually recover from the symptoms of hypothyroidism.

5–10% of levothyroxine-treated hypothyroid patients with normal serum TSH, will have persistent symptoms which cannot be explained by the disease and levothyroxine therapy [30]. Patients with continuing symptoms after appropriate levothyroxine treatment should therefore be further investigated to diagnose and treat the cause[1,6] [**L2**].

Poor compliance with levothyroxine therapy or suboptimal treatment may also result in persistent symptoms [1,2,6] and can be identified by the seemingly anomalous combination of a raised TSH and a normal FT4 [1].

Causes of an abnormal TSH other than thyroid disorders must also be excluded, including[1]:

- Pregnancy.
- Non-thyroidal illnesses.
- Drug treatment.
- Assay interference.
- Following an episode of thyroiditis.
- Early weeks of levothyroxine therapy.

Recent data indicate that treatment with levothyroxine in older persons with subclinical hypothyroidism may provide no symptomatic benefits[32] [**L1, RGB**].

Careful patient monitoring is recommended when the brand or source of prescribed levothyroxine has changed[33] [**L2, RGA**]. Inter-brand and inter-source differences in efficacy of the medication may be present[33].

View Pathway

10 Referral for Specialist Management

Consultation with an endocrine specialist is recommended in the following situations[2,8,34–36]:

- Children and infants.
- Pregnancy.
- Elderly patients (aged over 65 years).
- Patients in whom it is difficult to render and maintain a euthyroid state.
- Cardiac disease.
- Presence of goitre, nodule, or other structural changes in the thyroid gland.
- Presence of other endocrine disease such as adrenal and pituitary disorders.
- Unusual constellation of TFT results.
- Congenital hypothyroidism.
- Medication-induced hypothyroidism, e.g. amiodarone, lithium, alpha-interferon, interleukin-2.
- Thyroiditis causing hypothyroidism, e.g. postpartum thyroiditis and subacute thyroiditis.
- Emergent evaluation or management of myxoedema coma (i.e., hypothyroidism, altered mental status, respiratory insufficiency, and hypothermia).

11 Key Considerations for Patient Preferences

Patient preferences refer to patient perspectives, beliefs, expectations, and goals for health and life, and to the steps employed by individuals in assessing the potential benefits, harms, costs, and limitations of the management options in relation to one another. Patients may have preferences when it comes to defining their problems, identifying the range of management options and selecting or ranking the outcomes used to compare these options.

It is important for healthcare professionals to develop an understanding of the patient as an individual and the unique way in which each person experiences a condition and its impact on their life.

The following recommendations are therefore made for physicians and other healthcare professionals regarding general principles of patient care in Qatar:

- **Respect Patients:** Treat patients with respect, kindness, dignity, courtesy and honesty. Ensure that the environment is conducive to discussion and that the patient's privacy is respected, particularly when discussing sensitive, personal issues. Ask the patient how they wish to be addressed and ensure that their choice is respected and used.

- **Maintain Confidentiality:** Respect the patient's right to confidentiality and avoid disclosing or sharing patients' information without their informed consent. In this context, students and anyone not directly involved in the delivery of care should first be introduced to the patient before starting consultations or meetings, and let the patient decide if they want them to stay.

- **Clarify Third-Party Involvement:** Clarify with the patient at the first point of contact whether and how they like their partner, family members or carers to be involved in key decisions about their care or management and review this regularly. If the patient agrees, share information with their partner, family members or carers.

- **Obtain Informed Consent:** Obtain and document informed consent from patients, in accordance with MOPH policy and guidance.

- **Encourage Shared Decision Making:** Ensure that patients are involved in decision making about their own care, or their dependent's care, and that factors that could impact the patient's participation in their own consultation and care including physical or learning disabilities, sight, speech or hearing impairments and problems with understanding, reading or speaking English are addressed.

- **Disclose Medical Errors:** Disclose errors when they occur and show empathy to patients.

- **Ensure Effective Communication:** Explore ways to improve communication including using pictures, symbols or involving an interpreter or family members. Avoid using medical jargon. Use words the patient will understand and confirm understanding by asking questions.

- **Ensure Continuity of Care:** Provide clear and timely sharing of patient information between healthcare professionals especially at the point of any transitions in care.

12 Performance Measures

A list of performance measures is given in the table below. Healthcare organisations are encouraged to monitor service performance using the indicator definitions below.

Number	Numerator	Denominator
HTH01	Number of patients with TFTs recorded in the preceding 12 months.	All adult patients with a recorded diagnosis of hypothyroidism.
HTH02	Number of patients with normal TSH levels six month after starting treatment.	All patients with a recorded diagnosis of hypothyroidism in whom levothyroxine treatment has commenced.
HTH03	Number of patients who were offered repeat TFTs 6-8 weeks after the initiation of the treatment.	All patients diagnosed with hypothyroidism who received treatment with levothyroxine.
HTH04	Number of patients referred to an endocrinologist.	All adult patients with a recorded diagnosis of hypothyroidism.

Table 12.1: Performance Measures.

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Appendix: Detailed Description of the Literature Search

A systematic search for existing literature on hypothyroidism was performed in the period April 14th-16th, 2019.

The search for clinical practice guidelines on dementia diagnosis and/or management was performed in the *PubMed* database and websites of relevant organisations and societies including the *Thyroid* UK, the *British Thyroid Foundation*, and the *American Thyroid Association*.

Peer-reviewed scientific publications were found in PubMed and via *Google Scholar* Internet search engine. Non-peer reviewed studies were identified in *bioRxiv*. Books were checked on PubMed. Personal opinions of healthcare professionals, information published on medical websites, and drug prescribing information sheets were found via Google search engine.

The included publications were identified using the term "hypothyroidism" and specified with the following terms in combinations:

Levothyroxin, thyroxine, prevalence, associated condition, celiac/heart disease.

The date limit for the search was set up as March 19th, 2017 based on the last update of the present guideline.

Figure A.1 on the next page demonstrates graphically the results of the search and application of exclusion criteria.

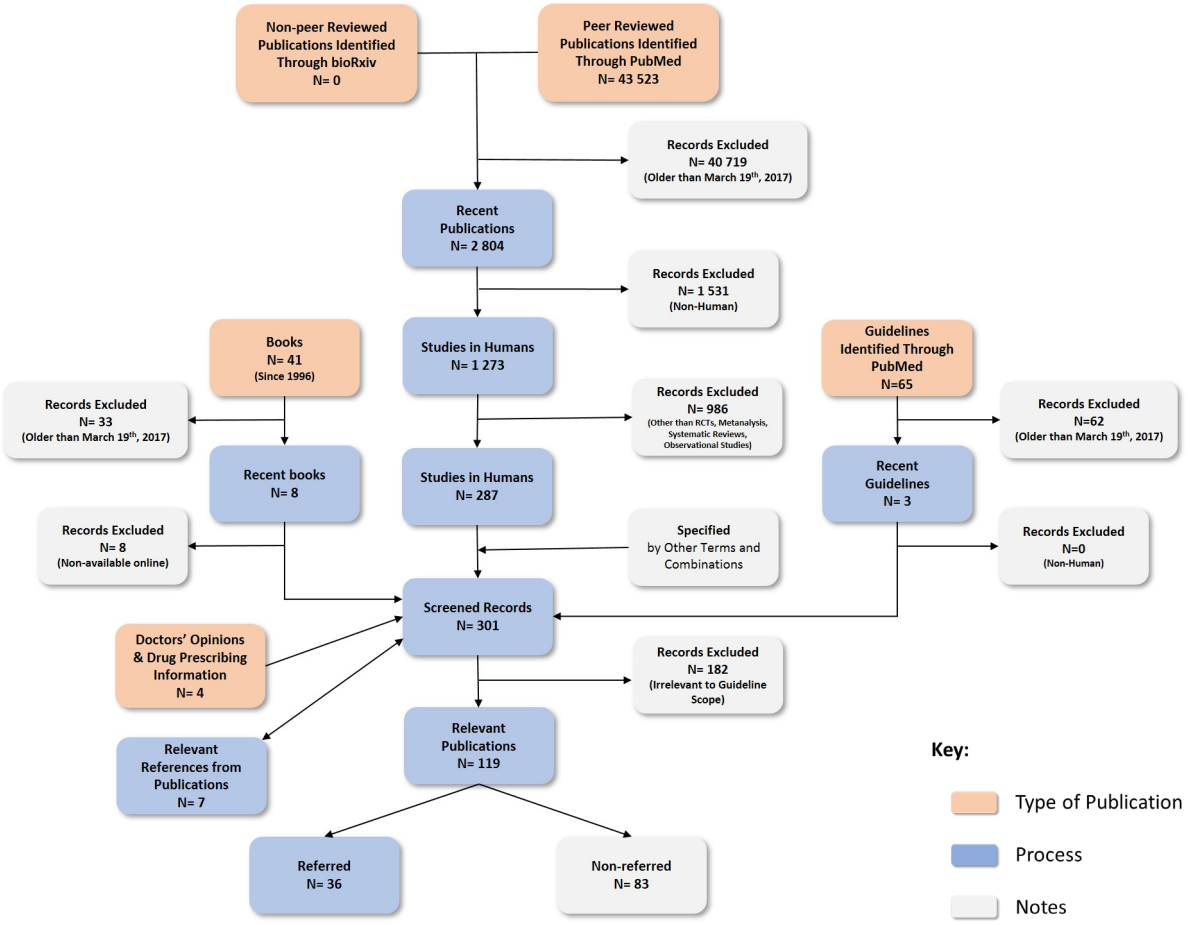

Fig A.1: Literature search results and application of exclusion criteria.

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