NATIONAL CLINICAL GUIDELINES

THE RECOGNITION, PREVENTION AND MANAGEMENT OF VITAMIN D DEFICIENCY IN CHILDREN AND ADULTS

Ministry of Public Health
P.O. Box 42,
Doha, Qatar
Phone: (+974)4 407 0969
Email: clinicalguidelines@moph.gov.qa

Valid From: 22nd April 2021
Date of Next Revision: 22nd April 2023

المبادئ الإرشادية السريرية لدولة قطر
NATIONAL CLINICAL GUIDELINES FOR QATAR

وزارة الصحـــــة العامـــــة
Ministry of Public Health
State of Qatar • دولـــة قطـــر

Version History

Version	Status	Date	Editor	Description
1.0	Final	22nd April 2021	Guidelines Team	Version for Publication.

Citation

Suggested citation style:

Ministry of Public Health Qatar. National Clinical Guideline: The Recognition and Management of Vitamin D Deficiency in Children and Adults (2021).

Abbreviations

The abbreviations used in this guideline are as follows:

$1,25(OH)_2D$	1,25-dihydroxycholecalciferol
25(OH)D	25-hydroxyvitamin D
AIDS	Acquired Immunodeficiency Syndrome
ALP	Alkaline Phosphatase
BMD	Bone Mineral Density
BMI	Body Mass Index
BMP	Basic Metabolic Panel
eGFR	Estimated Glomerular Filtration Rate
IM	Intramuscular
IOM	Institute of Medicine
IU	International Unit
NIH	National Institute of Health
PHPT	Primary Hyperparathyroidism
PTH	Parathyroid Hormone
U&E	Urea and Electrolytes
UEC	Urea, Electrolytes and Creatinine
VDDR	Vitamin D-Dependent Rickets
WG	Weeks of Gestation

View Pathway

Table of Contents

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 vitamin D deficiency in children and adults. The objective is to guide the appropriate assessment, investigation, diagnosis, prevention, treatment, and referral of patients presenting to provider organisations in Qatar. It is intended that the guideline will be used by healthcare professionals in both primary care and specialist settings.

1.2 Scope of the Guideline

This Guideline covers the following aspects of care:

- Prevention of Vitamin D deficiency in different patient populations.
- Diagnosis and Treatment of Vitamin D deficiency in children.
- Diagnosis and Treatment of Vitamin D deficiency in adults.
- Referral Criteria to Specialist Care.
- Specialist Management of rickets and osteomalacia.

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 based on 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. Ayham Mohammad Abdulhamid	Internal Medicine & Endocrinologist	Qatar Red Crescent Society
Dr Azza Abuelrish	Medical Officer	Qatar Petroleum
Dr Salwa Mohammed Abuyaqoub	Senior Consultant Obstetrics/Gynaecology, Chair of Obstetric, Vice Chair of Education, Residency Training Program Director, Assistant Professor	Women's Wellness and Research Center, Hamad Medical Corporation, Weill Cornell Medicine-Qatar
Haidar Abdelfattah Yousef Albustanji	Consultant Endocrinology & Internal Medicine	Ministry of Interior
Dr Noora Alhamad	Clinical Pharmacist	Sidra Medicine
Dr Sawsan Al-Obaidly	Senior Consultant, Maternal-Foetal Medicine, Assistant Professor	Hamad Medical Corporation, Weill Cornell Medicine-Qatar
Dr Ahmed Hussein Babiker	Head of Registration Section & Clinical Pharmacist	Ministry of Public Health
Dr Jobin Benjamin	Specialist Internal Medicine	Aster DM
Dr Tariq Chukir	Consultant Endocrinologist & Assistant Professor of Medicine	Weill Cornell Medicine-Qatar
Dr Vijay Ganji	Prof of Human Nutrition, College of Health Sciences, QU Health	Qatar University
Dr Mohammed Hammoudeh	Senior Consultant, Rheumatology	Hamad Medical Corporation
Dr Mohammed Samer Hamwy	Consultant Paediatrics & Internal Medicine	Al Ahli Hospital
Dr Amel Khalifa	Attending Physician, Endocrinologist	Sidra Medicine
Dr Rasha Muftah Khalifa	Senior Consultant Family Medicine, Clinical Guidelines Consultant	Primary Health Care Corp
Dr Sadriya Al Kohji	Head of Child Health & Adolescent Health, Community Medicine Consultant	Primary Health Care Corp
Ms Winnie D Panganiban	Staff Nurse	Primary Health Care Corp
Dr Abdulhak Amer Sadalla	Consultant Internal Medicine	Al Emadi Hospital
Dr Ashraf Abdel Salam	Attending Physician, Paediatrician	Sidra Medicine
Dr Esmat Swallmeh	ADEON, Medical Nursing Network	Hamad Medical Corporation

Guideline Development Group Members		
Name	**Title**	**Organisation**
Dr Mostafa Essam Tawfeek	Internal Medicine Consultant	Doha Clinic Hospital
Dr Fawziya Khedr A A Al Yafei	Consultant, Paediatric Endocrinologist	Hamad Medical Corporation
Dr Mahmoud Ali Zirie	Srenior Consultant & Head of Endocrinology, Director of National Diabetes Center	Hamad Medical Corporation

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
Dr Hani Ben Hassen Al Kilani	Senior Consultant, Executive Director for Corporate Clinical Policy and Guidelines	Hamad Medical Corporation
Prof Anthony Akobeng	Chair Clinical Practice Guidelines Committee	Sidra Medicine
Dr Alshaymaa Mohammed A. M. Al-Motawa	Consultant Family Medicine	Qatar Petroleum
Dr Basil Bashqawi	Accreditation Coordinator, Dept of Health Professions	Ministry of Public Health
Dr Abi Khalil Charbel	Associate Professor of Medicine Consultant Cardiology	Weill Cornell Medicine-Qatar
Dr Paul Dijkstra	Director of Medical Education	Aspetar
Dr Mohammed Elrishi	Senior Consultant Endocrine, Diabetes, and Internal Medicine	Al Ahli Hospital
Dr Dahlia Mustafa Hassan	Senior Consultant Family Medicine	Primary Health Care Corp
Dr Ghassan Youseph Hommos	Senior Consultant Endocrinology	Al Emadi Hospital
Dr Egon Toft	VP and Dean	College of Medicine, Qatar University

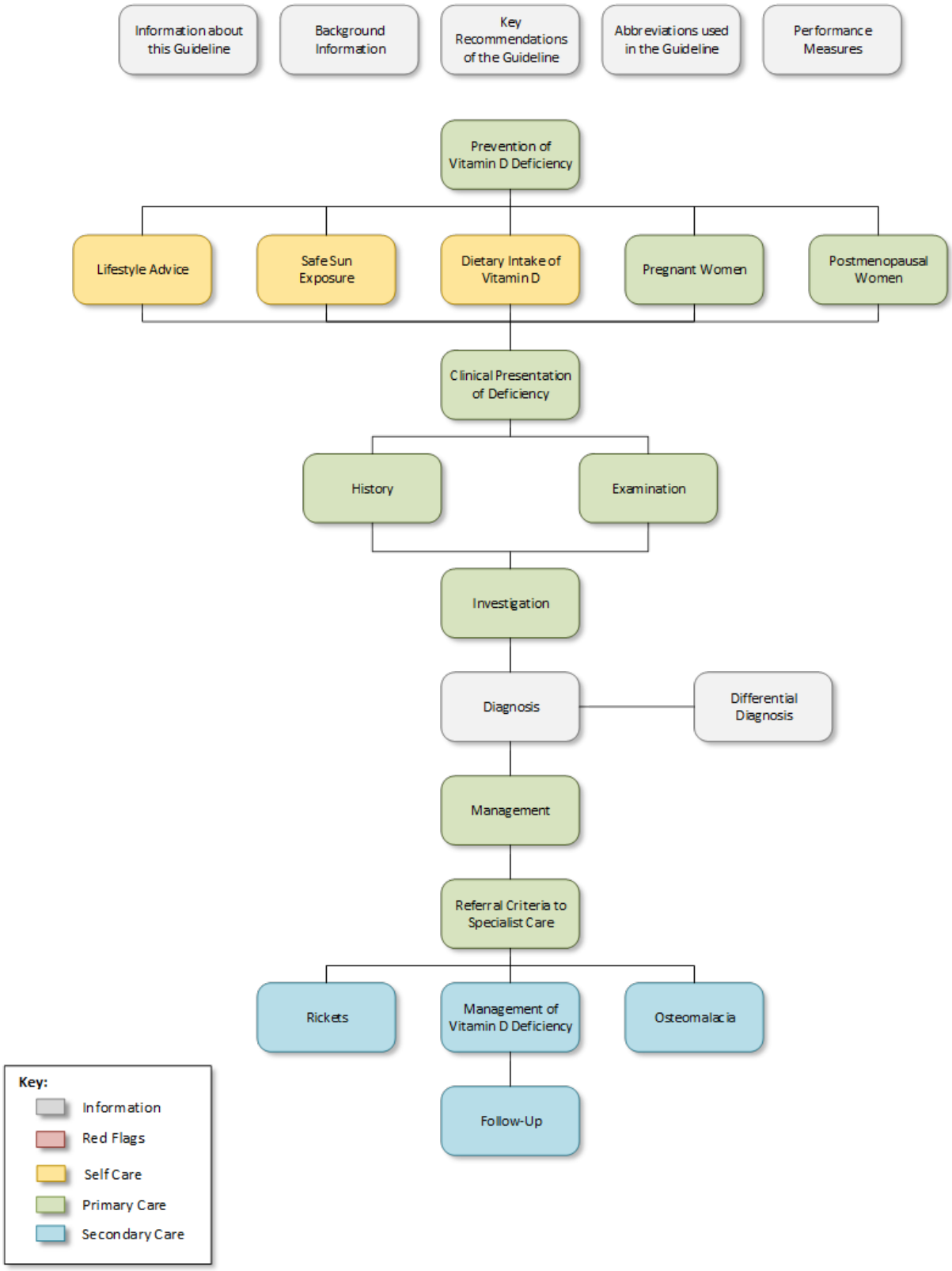
1.8 Responsibilities of Healthcare Professionals

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 Vitamin D Deficiency Pathway

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



3 Key Recommendations of the Guideline

The key recommendations of this guideline are as follows:

Prevention (*Section 5*):

- Only 10-20% daily requirement of vitamin D is derived from dietary sources [1].
- Foods rich in vitamin D are listed in *Section 5.2*.
- Note that breastmilk contains almost no vitamin D [2]. Exclusively breastfed and partially formula-fed infants must be given vitamin D supplementation [2–4] [**L1, RGA**].

Safe Sun Exposure (*Section 5.1*):

- Adequate outdoor activities with associated sun exposure are recommended [3].
    - Adults: 3 sunlight exposures per week for 10-15 minutes each from 9:00am-2:00pm are sufficient to achieve healthy vitamin D levels for most people [1].
        - It is recommended to expose one third of the body to the sun or the face and upper limbs [5,6].
        - An extended exposure in winter time may be required [2].
        - Darker skin people need extended time of sunlight exposure [1,7,8].
        - Over exposure will not add additional value to Vitamin D synthesis [9].
    - Infants and children: Non-direct and non-burning sun exposure 3 times per week for 10-15 minutes each from 9:00am-2:00pm is advised for infants >6 months old and older children with sunscreen/sunblock and protective clothing [**R-GDG**].
- Normal use of sunscreens is appropriate and does not lead to low vitamin D [2].
- When planning pregnancy, women should receive the same vitamin D supply as the general adult population (see *Table 5.3*) [10,11] [**L1, RGA**].

Prevention in Pregnant Women (*Section 5.4*):

- When pregnancy is confirmed, supplementation should be started to maintain optimal levels (see *Section 10*) [7,10] [**L1, RGA**].

Prevention in Postmenopausal Women (*Section 5.5*):

- Postmenopausal women are at greater risk for vitamin D insufficiency compared to premenopausal women.
- Those with vitamin D deficiency are also at increased risks for osteoporosis and fragility fractures[12,13].
- Screen for serum 25(OH)D status in postmenopausal women with an increased risk for low vitamin D [14] [**L1, RGA**].
- Healthy postmenopausal women >65 years old should receive 800 - 2,000 IU/day of vitamin D supplementation [**R-GDG**].
- Women with serum 25(OH)D levels <20 ng/mL (50 nmol/L) may need treatment with 4,000-10,000 IU/day to achieve adequate levels [14,15] [**L1, RGA**].
- Calcium supplementation may be considered if dietary intake of calcium is insufficient[14,16] [**L1, RGA**] to maintain intake levels of 1,000 mg/day for women aged ≤50 years [17] and 1,200-1,300 mg/day for women aged >50 years [16,17].

Recommended Dietary Intake (*Section 5.3*):
See *Section 5.3* and *Table 5.3* for recommended dietary intake levels of Vitamin D for different age groups and populations.

Investigation (*Section 9*):

- Routine blood screening for vitamin D deficiency is not recommended in healthy individuals who are not at risk and in the absence of specific clinical concerns [1,3,9,10,18–21] [**L1, RGB**].
- Evaluation of vitamin D status is justified in [3,10,19] [**L1, RGA**]:
    - Symptomatic patients with suspected vitamin D deficiency.
    - In patients at risk for vitamin D deficiency.
    - In patients with metabolic bone diseases.

Diagnosis (*Section 10*):

- **Symptomatic vitamin D deficiency** is diagnosed in patients when clinical symptoms also have a low 25(OH)D concentration value [10].
- **Non-symptomatic (subclinical) vitamin D deficiency** is diagnosed in patients with a low 25(OH)D and no clinical symptoms or signs [10].
- See *Table 10* in *Section 10* for the normal range of Vitamin D levels in different populations.

Management (*Section 11*):

- Vitamin D supplements may be initiated without investigations in breastfed infants <12 months with other risk factors (see *Section 4.4*) and symptoms/signs (see *Section 6*) [2] [**L2, RGA**].
- All other patients should receive supplements according to their vitamin D status (see *Table 11.2*) and comorbid conditions (if any).
- Once the serum 25(OH)D level exceeds 20 ng/mL, maintenance treatment is recommended (see *Section 11.2*) [1,10,19] [**L1, RGA**].
- Adequate calcium intake should be provided along with the treatment. Dietary calcium supplement is preferred over supplementary calcium intake [**R-GDG**].
- Adjuvant calcium supplements may be considered in patients with poor intake of dairy products [2,7] [**L2, RGA**].
- The interaction of Vitamin D with other drugs should be considered carefully [7,22] [**L1**].
- See *Table 11.2* for treatment regimens in different patient populations.
- Maintenance dosing should be selected for each patient individually as it is patient-specific and depends on the target level and other comorbidities that may affect its metabolism and absorption [23] [**L1, RGA**].
- Safe sun exposure (see *Section 5.1*) and healthy diet (see *Sections 5.2 and 5.3*) along with required dietary changes should supplement the pharmacological treatment [**R-GDG**].
- Once patients are on long term maintenance regimen, 25(OH)D concentration should be re-evaluated after 3-4 months and then to monitor semi-annually[16].
- All infants and individuals receiving >2,000 IU/day (>50mcg/day) vitamin D, should be monitored for calcium concentration after 1-2 months to rule out hypercalcaemia [**R-GDG**].

Referral Criteria for Specialist Care (*Section 12*):

- Refer to *Section 12* for specific criteria for referral to Specialist Care.

Specialist Management (*Section 13*):

See *Section 13.2* for detailed information on Specialist Management of Vitamin D Deficiency.
See *Section 13.3* for detailed information on the diagnosis and management of Rickets.
See *Section 13.4* for detailed information on the diagnosis and management of osteomalacia.

4 Background Information

4.1 Definition and Classification

Vitamin D is a fat-soluble steroid-related nutrient. The term "vitamin D" refers to both ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) [3,10,11,18,24].

Dietary and endogenously synthesised vitamin D in dermis are converted to 25-hydroxyvitamin D (calcidiol or 25(OH)D) in the liver. 25(OH)D is the most abundant metabolite of vitamin D [10]. Its serum concentration is a recognised biomarker of vitamin D status and is used to determine the status of vitamin D supply [3,10,11,18,22].

The circulating 25(OH)D is converted to 1,25-dihydroxyvitamin D (calcitriol or $1,25(OH)_2D$), an active (hormone) form of vitamin D [10] by 1-α hydroxylase in the kidney. $1,25(OH)_2D$ is not used as a marker of vitamin D status because of its short half-life.

Vitamin D **insufficiency** is suboptimal levels of the vitamin. It can adversely affect bone health but not severe enough to cause osteomalacia or rickets [1,25].

Vitamin D **deficiency** is defined as not having enough vitamin D that the body needs to function physiologically [11]. The diagnostic criteria and cut-off points for vitamin D deficiency are discussed below under the Diagnosis section (*Section 10*).

4.2 Aetiology

Vitamin D deficiency can result from several causes [19]:

- Decreased dietary intake and/or absorption (see *Section 5.2*).
- Inadequate sun exposure (see *Section 5.1*).
- Decreased endogenous synthesis can be seen in individuals with:
    - Chronic liver disease (e.g. cirrhosis).
    - Hypoparathyroidism.
    - Renal failure.
    - 1-alpha hydroxylase deficiency.
    - Nephrotic syndrome.
- Increased hepatic catabolism (medications which activate degradation of vitamin D are listed in *Sections 4.4 and 11.6*)
- End organ resistance (e.g. hereditary vitamin D resistant rickets).

4.3 Prevalence

Several studies estimated the prevalence of vitamin D deficiency in various groups of people living in Qatar. **These studies, however, are not population-based and findings might not reflect the actual incidence of vitamin D deficiency in the population as a whole** [26,27]. Various cut-off points were used in the publications, complicating the comparison between them.

In general, the prevalence of low vitamin D status in Qatar seems to be high. The most recent study [27] reported the prevalence rate of vitamin D deficiency (<25 nmol/L, <10 ng/mL) among individuals aged 18-65 years old attending primary healthcare facilities in Qatar in 2017 as 14.1%. The prevalence of vitamin D

insufficiency (<50 nmol/L, <20 ng/mL) in the same study was 71.4%. This means 85.5% of patients had 25(OH)D below the desired level (≥50 nmol/L, ≥20 ng/mL).

The prevalence of low vitamin D (<50 nmol/L, <20 ng/mL) among health care professionals in Qatar was similar (~86.75%, i.e. 84.4% among men and 89.1% among women) [26]. Of them, 41% of men and 64% of women had deficiency and severe deficiency (<25 nmol/L, <10 ng/mL) [26].

Another study estimated vitamin D status among patient (primarily women) of the rheumatology clinic in Doha and reported 56% of patients with rheumatic diseases had deficiency (<25 nmol/L, <10 ng/mL) [28].

Some studies reported even higher prevalence of low vitamin D status in Qatar (e.g., ~90% [26,29]). These studies defined vitamin D insufficiency as <75 nmol/L (<30 ng/mL) but these cut-off points have been reconsidered and changed recently (see *Section 10*).

A higher prevalence of vitamin D deficiency among young adults, females, Qatari nationality and individuals with higher body mass index as well as association of hypertension, cardiovascular diseases and stroke with a higher risk of severe vitamin D deficiency status have been suggested [27]. Genetic differences in vitamin D metabolism have also been reported but these did not affect the 25(OH)D levels [30].

4.4 Risk Factors

Patients from the following groups are at increased risk of vitamin D deficiency [1,2,7,9,11,18–20,22,31]:

- Premature infants.
- Exclusively breastfed infants.
- Older people (>65 years).
- Individuals with obesity.
- Vegetarians (or fish free diet).
- Patients who underwent bariatric surgery.
- Night workers.
- Individuals with inadequate UV light exposure:
    - Occlusive garments.
    - Pigmented skin, especially dark-skin complexion.
    - Institutionalised or housebound.
    - Disabled individuals.
- Individuals with bone, liver, or kidney diseases.
- Individuals with gastrointestinal disorders:
    - Certain malabsorption syndromes.
    - Short bowel syndrome.
    - Cholestyramine use.
    - Conditions that limit fat absorption.
- Individuals with certain medical conditions, e.g. with primary hyperparathyroidism (PHPT) [32].
- Individuals taking medications interfering with vitamin D metabolism (see details in *Section 11.6*):
    - Rifampicin.
    - Anticonvulsants.
    - Anti-AIDS medications.
    - Anti-fungal medications.
    - High dose glucocorticoids.
- Women with multiple, short interval pregnancies or with prolonged breast feeding without vitamin D supplementation.

4.5 Prognosis

Management of vitamin D deficiency and correction of risk factors should [18,33]:

- Restore vitamin D levels.
- Lead to an improvement of symptoms.
- Reduce the risk of complications.

If left untreated, vitamin D deficiency:

- May be associated with several common chronic diseases, including [7,11]:
  - Osteoporosis[34,35].
  - Autoimmune diseases [36,37].
  - Cardiovascular diseases [38,39].
  - Viral and bacterial respiratory tract infections (e.g., tuberculosis, influenza) [40,41].
  - Diabetes [42,43].
  - Mood disorders [44].
- Leads to inadequate bone mineralisation resulting in [1,11,18,19,33]:
  - Increased risk of bone fractures and falls.
  - Rickets.
  - Osteomalacia.

5 Prevention of Vitamin D Deficiency

5.1 Lifestyle Advice

Lifestyle advice should include information on:

Safe sun exposure

- The skin is the major source of endogenous vitamin D [1,3]. 80-90 % of vitamin D is produced via sun exposure [1].
- Adequate outdoor activities with associated sun exposure are recommended [3].
  - Adults: 3 sunlight exposures per week for 10-15 minutes each from 9:00am-2:00pm are sufficient to achieve healthy vitamin D levels for most people [1].
    - It is recommended to expose one third of the body to the sun or the face and upper limbs [5,6].
    - An extended exposure in winter time may be required [2].
    - Darker skin people need extended time of sunlight exposure [1,7,8].
    - Over exposure will not add additional value to Vitamin D synthesis [9].
  - Infants and children: Non-direct and non-burning sun exposure 3 times per week for 10-15 minutes each from 9:00am-2:00pm is advised for infants >6 months old and older children with sunscreen/sunblock and protective clothing [**R-GDG**].
- Normal use of sunscreens is appropriate and does not lead to low vitamin D [2].
- The use of hats and sunglasses is recommended [2].
- UVB radiation does not penetrate glass and cloths, i.e. indoor exposure to sunlight through a window is not beneficial for skin synthesis of vitamin D [2,45].

Healthy diet and required dietary changes

- Only 10-20% daily requirement of vitamin D is derived from dietary sources [1].
- Foods rich in vitamin D are listed below in *Section 5.2*.

Supplementation

- Encourage pregnant woman and breastfeeding mother adequate for intake of vitamin D supplementation [**R-GDG**].
- Consider vitamin D supplementation to infants or fortification of infant formulas to prevent rickets (see more details in *Section 5.4*) [2,3].
- Over-the-counter or by prescription supplements may be considered [46].
- Seasonal variation of sunlight efficacy in vitamin D synthesis must be accounted when suggesting supplementation [2,3].

5.2 Sources of Vitamin D

5.2.1 Endogenous Vitamin D Synthesis

The skin is the major source of vitamin D, which is produced as a result of skin exposure to the sun's ultraviolet light B[3].

5.2.2 Exogenous Vitamin D Sources

There are few dietary sources that contain vitamin D [1–3,9,24,31]:

- Oily fish and fish products:
  - Trout.
  - Salmon (canned 300-600 IU per 3.5 oz., fresh farmed 100 to 250 IU per 3.5 oz., fresh wild 600-1,000 IU per 3.5 oz.).
  - Mackerel (canned 250 IU per 3.5 oz.).
  - Herring.
  - Sardines (canned 300 IU per 3.5 oz.).
  - Anchovies.
  - Pilchards.
  - Tuna (canned 230 IU per3.6 oz.).
  - Fish liver oil (e.g., cod liver oil- 400 IU per teaspoon).
- Egg yolk (20 IU).
- Nuts (not very high amounts).
- Mushrooms (wild-grown mushrooms contain higher amounts of vitamin D2).
- Fortified foods:
  - Cereal (100 IU per serving).
  - Milk (100 IU per 8 oz.), yogurt, cheese, butter, etc.
  - Margarines.
  - Cooking oils.
  - Orange juice (100 IU per 8 oz.).
  - Soy, rice, almond beverages.

Note that breastmilk contains almost no vitamin D [2]. Exclusively breastfed and partially formula-fed infants must be given vitamin D supplementation [2–4] [**L1, RGA**].

5.3 Recommended Dietary Vitamin D Intake

Currently, there is lack of consensus on the optimal oral intake of vitamin D in different populations [24]. Various amounts per day have been reported by organisations.

Table 5.3 includes recommendations based on guidelines by Endocrine Society (USA) [47] and Vitamin D opinion leaders (EVIDAS) [48]. It also takes into account recommendations by GULF (UAE) [11]. Dosing depends on 25(OH)D concentrations and antecedent prophylactic management [**R-GDG**].

Patient Groups		Age	Recommendations for Daily Intake
Preterm infants		≤32 weeks gestational age	800 IU/day until a total of 1,000 IU is taken (diet + vitamin D supplements)
		33-36 weeks gestational age	400 IU/day
Children and adolescents	**Without risk factors**	<1 year	400 IU/day
		1-18 years	600 IU/day
	With risk factors	Recommended vitamin D intake is higher than for those without risk factors and depends upon the patient's risk factors and their risk of developing vitamin D deficiency. *The upper limit of safety:*	
		<1 year	*1,000 IU/day*
		1-10 years	*2,000 IU/day*
		11-17 years	*4,000 IU/day*
Adults	**Without risk factors**	18-65 years	800 – 2,000 IU/day
		>65years	800 – 2,000 IU/day
	With risk factors	Higher intake may be required, depending on the risk factor and depends upon the patient's risk factors and their risk of developing vitamin D deficiency. *The upper limit of safety:*	
		>18 years	*4,000 IU/day*
Individuals with obesity		Any age	Three times greater than the recommended dose but not exceeding the upper limits of safety.

Table 5.3: Recommended Dietary Vitamin D Intake [3,9–11,22,24,49,50].

Note:

- After bariatric surgery, patients should receive D_3 3,000 IU/day orally from all sources to maintain a 25(OH)D level of >30 ng/mL (75 nmol/L) [51] [**L1**]. Refer to the MOPH National Clinical Guideline on *Bariatric (Metabolic) Endoscopy and Surgery in Adults* [52].

5.4 Pregnant Women

When planning a pregnancy, women should receive the same vitamin D supply as the general adult population (see *Table 5.3*) [10,11] [**L1, RGA**]. When pregnancy is confirmed, supplementation should be started to maintain optimal levels (see *Section 10*) [7,10] [**L1, RGA**].

Supplementation should preferably begin in the first trimester of pregnancy [11]:

- 400 IU/day of vitamin D is recommended for all pregnant women [53,54] [**L1**]. High risk women may be advised to take at least 1,000 IU/Day [53] [**L1**].
- The 25(OH)D concentration should be monitored accordingly (see *Section 11.3*) [10,11] [**L1, RGA**].
- If the assessment of 25(OH)D concentration is not possible, vitamin D supplementation should be provided at a dose of 400 – 1,000 IU/day throughout pregnancy and lactation [**R-GDG**].
- The safe upper intake level is 4,000 IU/day [11,22,55]. Note: The active form of vitamin D does not cross the placenta.

Because vitamin D levels of neonates correlate positively with maternal 25(OH)D concentration [56,57], babies from mothers who have not taken vitamin D supplements throughout pregnancy require particular attention[1]. Breastfed infants may need to receive drops containing vitamin D from 1 month of age [1].

5.5 Postmenopausal Women

Postmenopausal women are at greater risk for vitamin D insufficiency compared to premenopausal women. Those with vitamin D deficiency are also at increased risks for osteoporosis and fragility fractures[12,13]. Supplements of both vitamin D and calcium result in increased bone mineral density throughout the skeleton [16,22] and reduce fracture rates in institutionalised older people [22].

To maintain optimal levels for vitamin D, the following are recommended:

- Screen for serum 25(OH)D status in postmenopausal women with an increased risk for low vitamin D [14] [**L1, RGA**].
- Healthy postmenopausal women >65 years old should receive 800 - 2,000 IU/day of vitamin D supplementation [**R-GDG**]. The tolerable upper intake level is 4,000 IU/day [17] [**L1**].
- Calcium supplementation may be considered if dietary intake of calcium is insufficient[14,16] [**L1, RGA**] to maintain intake levels of 1,000 mg/day for women aged ≤50 years [17] and 1,200-1,300 mg/day for women aged >50 years [16,17].

6 Clinical Presentation

6.1 Signs and Symptoms in Children

Typical clinical features of vitamin D deficiency in children include [1,2,9,19,31]:

- Poor growth.
- Delayed fontanelle closure.
- Motor delay.
- Delayed walking or a waddling gait.
- Non-specific bony or muscular pain and tenderness.
- Tender or swollen joints (e.g., the wrists or costochondral junctions).
- Skeletal deformities (bowlegs or knock knees).
- Dental abnormalities (e.g., delayed eruption of teeth or enamel hypoplasia).
- Carpopedal spasm, seizures, or irritability.
- Breathing difficulties (apnoea or stridor).
- Delayed sexual maturation.

Clinical signs of rickets are listed in *Section 13.3.2*.

6.1 Signs and Symptoms in Adults

Typical clinical features of vitamin D deficiency in adults include [1,2,19,20,31]:

- Fatigue with exercise.
- Non-specific bony pain.
- Bone discomfort or pain in low back, pelvis, lower extremities.
    - Symmetric low back pain in women.
- Low bone mineral density may result in frequent fractures.
- Proximal muscle weakness (myopathy).
- Muscular aches.
- Psychosomatic conditions such as feeling low, depression.

Laboratory features such as hypocalcaemia, hypophosphataemia, increased alkaline phosphatase (ALP), and elevated parathyroid hormone (PTH) are often a late presenting feature of vitamin D deficiency [1,58].

Note that some adult patients may be asymptomatic [10].

7 History

The following points in the history are important to elicit from the patient with suspected vitamin D deficiency [2,7]:

- Time spent outdoors.
- Type of clothing (e.g., covering).
- Dietary history including:
  - Breastfeeding/formula in infants.
  - Eating preferences and diets (e.g. vegetarian/vegan).
  - Calcium intake.
- Presence of chronic disorders.
- History of bariatric surgeries.
- Medication history.
- Previous vitamin D levels and treatments if any.
- Symptoms of low calcium including:
  - Muscle cramps.
  - Tetany.
  - Stridor.
  - Seizures (rare beyond 6–12 months of age).
- History of falls in older adults.

8 Examination

Note that majority of patients have normal findings on examination[9]. Nevertheless, if vitamin D deficiency is suspected, a thorough examination should be performed.

Check the following:

- Skin colour: people with dark skin (Fitzpatrick skin type).
- Growth parameters in children.
- Anterior fontanelle closure in children (no closure by 2 years).
- Body mass index (BMI) and/or corresponding measurements in children:
  - Refer to the National Clinical Guideline on the management of obesity in adults [59] and children [60] by MOPH.
- Dental conditions:
  - Delayed dentition in children (no teeth by 9 months, no molars by 14 months).
  - Dental problems in adults.
- Width of wrists/ankles.
- Presence of long bone deformity (e.g., genu varum/valgus - if weight bearing).
- Presence of rachitic rosary (prominent knobs of bone at the costochondral joints).

9 Investigation

Routine blood screening for vitamin D deficiency is not recommended in healthy individuals who are not at risk and in the absence of specific clinical concerns [1,3,9,10,18–21] [**L1, RGB**].

Evaluation of vitamin D status is justified in [3,10,19] [**L1, RGA**]:

- Symptomatic patients with suspected vitamin D deficiency.
- In patients at risk for vitamin D deficiency.
- In patients with metabolic bone diseases.

Consider the following investigations when clinically indicated [1,2,7,10,18–20]. The range of additional investigations should depend on a severity of vitamin D deficiency [10] and the presence of co-existing disorders (e.g. rickets) [2] [**L2, RGA**].

- 25(OH)D level.
- Full blood count.
- Inflammatory markers:
    - Erythrocyte sedimentation rate.
    - C-reactive protein.
- Phosphate.
- Magnesium.
- PTH (especially if low calcium intake).
- A basic metabolic panel (BMP) test.
- Liver function tests, including:
    - ALP.
- Bone mineral density assessment by DXA.
- Celiac disease screening.

9.1 Limitations to Current Testing Methods

The precision and accuracy of current vitamin D testing may be impacted by the following limitations [3,22,61,62]:

- Lack of assay standardisation:
    - Considerable variability among various assays and among laboratories.
    - Serum 25(OH)D does not indicate the amount of vitamin D in tissues.
- Half-life of circulating 25(OH)D is 15 hours. Half-life of circulating 1,25(OH)2D is even shorter and is influenced by parathyroid hormone, calcium, phosphate, and patient's genotype.
- Amounts of circulating 1,25(OH)2D only decrease when the deficiency is already severe.
- The normative data for 25(OH)D concentrations does not take into considerations of skin colour, sun exposure, age, geographical latitude, vitamin D dietary intake, and other critical parameters.

10 Diagnosis

The diagnosis of vitamin D deficiency is based on the determination of total plasma 25(OH)D concentrations and on the presence of symptoms:

- **Symptomatic vitamin D deficiency** is diagnosed in patients when clinical symptoms also have a low 25(OH)D concentration value [10].
- **Non-symptomatic (subclinical) vitamin D deficiency** is diagnosed in patients with a low 25(OH)D and no clinical symptoms or signs [10].

Currently, there is lack of consensus on the optimal and deficient levels of serum 25(OH)D values [3,7,11,18,19,46,61]. Various cut-off points for vitamin D deficiency have been reported by organisations.

In the present guideline, we propose using Food and Nutrition Board of Institute of Medicine (IOM), National Institute of Health (NIH) guidelines/cut-off points of serum 25(OH)D adequacy and deficiency (*Table 10*) [22].

Vitamin D status	Concentrations		Health status
	nmol/L	ng/mL	
Deficiency*	<30	<12	Can lead to rickets in infants and children and osteomalacia in adults.
Insufficiency (mild deficiency)	30-49	12-19	Generally considered inadequate for bone and overall health in healthy individuals.
Sufficient**	≥50	≥20˜	Generally considered adequate for bone and overall health in healthy individuals.
Sufficient for People with Metabolic Bone Conditions	≥75	≥30	Sufficient level for prevention of fractures in people at risk of falling.
Elevated	>125	>50 ¥	Linked to potential adverse effects.

Table 10: Serum 25(OH)D concentrations [2,9,22]**.**

* – Amounts <12.5 nmol/L may be referred as severe deficiency [2].

** – The cut-off points do not differentiate between children and adults. They are applicable for all ages and pregnancy [2]. ˜– **A level >30 ng/ml is desired to optimise the effect of vitamin D on calcium, bone, and muscles**. Also, this level is related to decreased risk for cardiometabolic diseases such as metabolic syndrome and diabetes [63]. ¥ – Amounts >100 ng/ml bring the patient to the risk of vitamin D toxicity.

10.1 Differential Diagnosis

If vitamin D deficiency is considered, consider alternative diagnoses [7,18,19,33]:

- Renal insufficiency.
- Conditions increasing ALP.
- Conditions which cause hypocalcaemia (e.g., PHPT).
- Other bone diseases (e.g. osteogenesis imperfecta, congenital syphilis, osteoporosis).
- Skeletal dysplasia (achondroplasia).
- Hyperparathyroidism.
- Nonaccidental injury.
- Fracture.
- Osteomyelitis.
- Paget's disease of the bone.

View Pathway

- Cancers:
    - Bone cancer.
    - Soft tissue sarcoma.
    - Myeloma.
- Blount disease.
- Cystic fibrosis.
- Normal variation.

11 Primary Care Management

Patients with low vitamin D should be treated to restore their levels to the normal range (refer to *Table 10*) [2,10] [**L2, RGA**].

Sufficient information about the various forms of vitamin D, over- or underdose should be provided to the patient [23] [**L2**]. Ensure that patients are not confusing cholecalciferol with other sound-alike or look-alike medications (e.g. alfacalcidol, ergocalciferol, etc.) [23].

11.1 Management of Vitamin D Deficiency

Vitamin D supplements may be initiated without investigations in breastfed infants <12 months with other risk factors (see *Section 4.4*) and symptoms/signs (see *Section 6*) [2] [**L2, RGA**].

All other patients should receive supplements according to their vitamin D status (see *Table 11.2*) and comorbid conditions (if any). Once the serum 25(OH)D level exceeds 20 ng/mL, maintenance treatment is recommended (see *Section 11.2*) [1,10,19] [**L1, RGA**].

Several forms of the vitamin are available:

- Cholecalciferol (vitamin D_3) from animal products and own skin synthesis:
  - Preferred over ergocalciferol (vitamin D_2) [64] [**L1, RGA**].
- Ergocalciferol (vitamin D_2) originates from plants and mushrooms:
  - Suitable for vegans [7].
- Calcitriol and other synthetic vitamin D analogues:
  - Rapid onset of action compared with other forms.
  - Suitable for patients with certain comorbid conditions like hypocalcaemia associated with CKD or hypoparathyroidism [19,23].
  - Refer to *Section 13.2* for details and seek specialist advice before prescribing.

Adequate calcium intake should be provided along with the treatment. Dietary calcium supplement is preferred over supplementary calcium intake [**R-GDG**]. Adjuvant calcium supplements may be considered in patients with poor intake of dairy products [2,7] [**L2, RGA**].

The interaction of Vitamin D with other drugs should be considered carefully [7,22] [**L1**].

11.2 Treatment Regimen

There available hundreds of different treatments varied by form (see *Section 11.1*), mode of delivery (oral and intramuscular (IM) injection), dose and frequency, and length of treatment regimen [46]. Vitamin D dosage and schedule mainly depend on [7]:

- Severity of deficiency.
- Age of the patient.
- Body weight.
- Need of rapid normalisation of blood levels.

Maintenance dosing should be selected for each patient individually as it is patient-specific and depends on the target level and other comorbidities that may affect its metabolism and absorption [23] [**L1, RGA**].
Safe sun exposure (see *Section 5.1*) and healthy diet (see *Sections 5.2 and 5.3*) along with required dietary changes should supplement the pharmacological treatment [**R-GDG**].

Age	Vitamin D status	Oral doses of cholecalciferol (D_3)	Notes
Preterm	**Insufficiency**	200 IU/kg /day	
	Deficiency	800 IU/day	Review after 1 month.
<3 months (term)	**Insufficiency**	400 IU/day for 3 months	
	Deficiency	1,000 IU/day daily for 3 months	
3-12 months	**Insufficiency**	400 IU/day for 3 months	
	Deficiency	2,000 IU/day for 6 weeks followed by a maintenance dose 400-1,000 IU/day.	If one-time treatment option is selected, review after 1 month and consider repeating dose.
1-18 years	**Insufficiency**	1,000-2,000 IU/day for 3 months	Review after 3 months and swich to maintenance dose.
	Deficiency	1,000-2,000 IU/day for 6 months OR 3,000–4,000 IU/day for 3 months	Review after 3 months and swich to maintenance dose.
>18 years	**Insufficiency**	800-2,000 IU/day for 3 months OR 50,000 IU twice a month	Review after 3 months and swich to maintenance dose.
	Deficiency	50,000 IU once a week for 2-3 months.	Review after 3 months and swich to maintenance dose.

Table 11.2: Treatment of low vitamin D[2,7,23,65]**.** For the upper limits of safety refer to *Table.5.3*.

11.3 Monitoring

Vitamin D levels should be rechecked after 3 months since the therapy initiation to assess response to treatment and transition to maintenance therapy [23]. Once patients are on long term maintenance regimen, 25(OH)D concentration should be re-evaluated after 3-4 months and then to monitor semi-annually [7]. Routine monitoring is generally not required [7,20] [**L1, RGB**] but is justified in the following patients [7,19,23] [**L1, RGA**]:

- With symptomatic vitamin D deficiency.
- With previous severe hypovitaminosis D.
- With persistent risk of severe hypovitaminosis D.
- With malabsorption conditions.
- With poor compliance.
- With chronic kidney disease.
- At risk for hypercalcaemia due to underlying diseases
- Taking calcitriol.
- Present with symptoms of vitamin D toxicity.

Note that vitamin D can unmask previously undiagnosed PHPT [20]. 25(OH)D level should be measured in all patients with PHPT [66]. Adjusted serum calcium may need to be checked [20] [**L1, RGA**]:

- In malabsorption patients: every 2 weeks.
- In otherwise healthy individuals:
    - After starting vitamin D supplementation; or
    - 1 month after completing the loading regimen.

11.4 Vitamin D Overtreatment

Toxicity due to overtreatment is rarely noted but possible, especially with highly concentrated vitamin D preparations [2,19]. Signs of acute vitamin D toxicity include [19,22,23,31]:

- Confusion.
- Fatigue.
- Headache.
- Irritability.
- Metallic taste.
- Pancreatitis.
- Polyuria.
- Polydipsia.
- Muscle weakness.
- Nausea.
- Vomiting.
- Constipation.
- Dehydration.
- Decreased appetite, weight loss, and anorexia.
- Increased blood pressure.
- Hypercalcaemia or hypercalciuria.
- Calcification of soft tissues.
- Kidney stones.

Chronic intoxication (e.g., inappropriate long-term self-administration) results in hypercalcaemia and hypercalciuria [24] leading to:

- Bone pain [19].
- Nephrotoxicity [22,23].
- Nephrolithiasis [22,23].
- Nephrocalcinosis [19,31].
- Vascular calcinosis [31].
- Hyperphosphataemia [23].
- Cardiac arrhythmias [22].

All infants and individuals receiving >2,000 IU/day (>50mcg/day) of vitamin D should be counselled about the clinical signs of hypercalcemia. Calcium level should be checked in patients with suspected hypercalcemia [**R-GDG**]. Appropriate management is required [67]. Symptoms of intoxication may still be observed for several months after the drug discontinuation [23].

11.5 Special Precautions and Warnings

In patients with the following, vitamin D supplementation should be used with caution and levels should be monitored closely [18,20,31,68,69] [**L1, RGC**]:

- Granulomatous diseases (e.g., sarcoidosis).
- Hypercalcaemia or hypercalciuria.
- Metastatic bone disease.
- Metastatic calcification.
- Williams syndrome.
- PHPT [**R-GDG**].

NB: Cholecalciferol should be used with caution in pregnancy [23] [**L2, RGC**].

View Pathway

11.6 Drug Interaction

The following medications should be revised by a healthcare specialist before prescribing as they can affect vitamin D absorption and metabolism [1,7,9,18,20]:

- Anticonvulsants.
- Antiepileptic drugs:
    - Barbiturates (e.g. phenobarbital).
    - Phenytoin.
- Corticosteroids.
- Statins [70–72].
- Cardiac glycosides.
- Antimicrobials:
    - Rifampicin.
    - Isoniazid.
    - Hydroxychloroquine.
- Immunosuppressive agents:
    - Cyclosporine.
    - Tacrolimus.
- Chemotherapeutic agents.
- Highly active antiretroviral agents.
- Histamine H2-receptor antagonists.
- Anti-fungal medications:
    - Ketoconazole.
    - Miconazole.
- Bile acid sequestrants:
    - Cholestyramine.
- Lipase inhibitors:
    - Orlistat.
- Ion exchange resins:
    - Cholestyramine.
- Laxatives:
    - Paraffin oil.

Thiazide diuretics (e.g. bendroflumethiazide) should be taken with caution as their interaction with vitamin D may induce side effects [7,18] [**L1, RGC**].

View Pathway

12 Referral Criteria to Specialist Care

Refer to secondary care in the following situations [2,9,20] [**L1**]:

- Atypical biochemistry (e.g., abnormal serum calcium).
- Atypical clinical manifestations or biochemistry.
- Children with elevated levels of serum alkaline phosphatase (ALP):
    - >500 IU/L in neonates.
    - >1,000 IU/L in children up to 9 years of age.
- Children on anticonvulsants or antiretroviral or chronic glucocorticoids.
- Deficiency due to malabsorption including history of bariatric surgery.
- Failure to respond to treatment after 3 months.
- Family history of sever rickets (parents, sibling).
- Focal bone pain.
- Infants with symptoms/signs.
- Liver disease.
- Lymphoma.
- Metastatic cancer.
- Nutritional rickets.
- No response to high dose supplements.
- Nonspecific symptoms.
- Parathyroid disorders.
- Renal stones.
- Renal failure (failure of kidney hydroxylation of 25(OH)D3 to form the active form) [**R-GDG**].
- Sarcoidosis.
- Short stature and skeletal deformity.
- Suspected rickets.
- Tuberculosis.
- Unexplained deficiency.
- Unexplained weight loss.

View Pathway

13 Specialist Management

13.1 Multidisciplinary Team Management

A multidisciplinary assessment may be required in patients with low vitamin D and co-morbid conditions.

13.2 Management of Vitamin D Deficiency in Special Populations

Other forms of vitamin D may also be considered for the management of low vitamin D in patients with co-morbid conditions (see *Table 13.2*).

Patient Group	Treatment	Notes
Persistent vitamin D deficiency	Calcidol or calcitriol	Higher doses of daily vitamin D.
Elderly	Combined calcium and vitamin D preparations*.	Consider the joint formulary for mobile, frail, elderly individuals who are housebound or care home patients. Postmenopausal women with serum 25(OH)D levels <20 ng/mL (50 nmol/L) may need treatment with 4,000-10,000 IU/day to achieve adequate levels [14,15].
Obesity	Cholecalciferol, ergocalciferol, or calcifediol.	Three times greater than the recommended dose may be needed. If desired levels are not achieved with oral supplementations of D2 or D3, calcitriol or IM injections should be considered.
Bariatric surgery	Cholecalciferol 3,000-6,000 IU/day PO. OR Ergocalciferol 50,000 IU PO 1-3 times per week.	If desired levels are not achieved with oral supplementations of D2 or D3, calcitriol or IM injections should be considered.
Malabsorption	Ergocalciferol 300,000 IU by IM injection. Review 3 months after the first injection and repeat if required. OR Calcitriol (in patients with fat malabsorption). OR Alfacalcidiol.	High doses of vitamin D are usually required. If desired levels are not achieved with oral supplementations of D_2 or D_3, calcitriol or/and injectable formulations of vitamin D should be considered.
Chronic liver disease	Ergocalciferol 300,000 IU by IM injection. Review after 3 months after the first injection and repeat if required. OR Calcifediol or calcitriol (in patients with a severe liver disease).	

Congenital abnormalities of the hepatic 25-hydroxylase enzyme	Calcitriol. OR Alfacalcidiol.	
Renal abnormalities	Cholecalciferol. OR Ergocalciferol. OR Calcitriol. OR Alfacalcidiol in adults 1 mcg/day initially, maintenance dose: 0.25-1 mcg/day.	Activated vitamin D metabolites may be considered. Alfacalcidiol is used in patients with severe renal impairment requiring vitamin D therapy. The dose should be adjusted to avoid hypercalcaemia.
Hypoparathyroidism	Calcitriol is typically started at 0.25 mcg twice daily, with weekly titrations to achieve a low-normal serum calcium.	Alfacalcidiol may also be considered.
Secondary/tertiary hyperparathyroidism	Cholecalciferol, ergocalciferol, calcitriol or alfacalcidol.	

Table 13.2: Treatment of low vitamin D in special populations [7,10,20,22–24,51,73,74].
* - Avoid long-term regimen of combined calcium and vitamin D preparations in other patients.

Regular blood tests should be performed in patients with chronic kidney disease [23] [**L2, RGA**]:

- Serum 25(OH)D level.
- Serum/urine calcium.
- Serum phosphate.

13.3 Rickets

13.3.1 Classification

Rickets is characterised by a defect in mineralisation of cartilages and the widening of the epiphyseal plates [75,76]. It can be classified as:

- Nutritional rickets due to [75]:
  - Vitamin D deficiency is the most common cause (see details below).
  - Calcium deficiency (calcipenic rickets).
  - Phosphorus deficiency (phosphopenic rickets).
- Genetic disorders [75,77]:
  - Vitamin D-dependent rickets (VDDR):
    - VDDR type 1: inability to fully activate calciferols.
    - VDDR types 2a and 2b: resistance to $1,25(OH)_2D$.
    - VDDR type 3: excessive inactivation of vitamin D metabolites.
  - Congenital hypophosphataemic rickets:
    - FGF-23-dependent hypophosphataemic rickets.
    - FGF-23-independent hypophosphataemic rickets.
- Drug-induced rickets [75].
- Rickets secondary to liver diseases [75].

13.3.2 Diagnosis

Clinical manifestations of rickets depend on the underlying aetiology, severity, and duration of the disease. These may include [9,18,75]:

- Skull modifications:
  - Craniotabes (in infants >3 months of age).
  - Frontal bossing.
  - Wide fontanels.
- Chest alterations:
  - Ricketic rosary.
  - Costo-chondral junction (pigeon chest, Harrison groove).
- Extremities:
  - Deformities of upper limb deformities in crawling infants:
    - Wrist widening.
  - Deformities of lower limbs deformities in walking children:
    - Bowlegs.
    - Knock knees.
    - Knees and ankles swelling.
  - Limb fractures.
- Spinal column deformities:
  - Scoliosis.
  - Lordosis.
  - Kyphosis.
- Gait disturbance.
- Growth retardation.
- Bone softening, tenderness, and pain.
- Contracted pelvis.
- Hypotonia.
- Proximal myopathy.

Children with clinically suspected rickets should undergo a full evaluation to confirm the diagnosis, including biochemical tests and imaging (see *Section 9*).

13.3.2 Management

Treatment includes early intensive (see *Table 13.3*) and late maintenance phase (see *Section 5*).

Consider additional supplementation with calcium and phosphate during vitamin D treatment when required [2] [**L2**]:

- Adult patients should consume total calcium of at least 1,000 mg/day (for ages 19-70 years) to 1,200 mg/day (for women of ages 51-70 years and for all adults ≥71 years). Higher calcium doses (up to 4 g/day) may be necessary in patients with malabsorption [78].
- In children calcium intake should be maintained at ~1,000 mg/day (30-75 mg/kg/day of elemental calcium in three divided doses) [78].
- Once vitamin D supplementation is reduced to 400 IU/day with normal PTH and 25(OH) D levels, calcium supplementation may be ceased [78].

Age	Regimen	
	Single-dose therapy (Stoss Therapy)*	Multiple doses of vitamin D
<1 Month	N/A	1,000 IU/day for 2-3 months
1-12 Months	100,000-300,000 IU once orally (preferred) or IM OR 50,000 IU of D_2 or D_3 once weekly for 6 weeks followed by a maintenance dose 400-600 IU/day	2,000-5,000 IU/day for at least 3 months
> 12 Months		5,000 IU/day for 2-3 months

Table 13.3: Treatment of rickets due to nutritional deficiency of vitamin D [9,75,79]**.**
* - Consider in patients with low medication compliance.

The following parameters should be monitored throughout the treatment [75]:

- Serum calcium.
- Phosphate.
- ALP.
- 25(OH)D level.
- Random measurements of urine calcium to creatinine ratio.

Consider referral to an endocrinologist if children presenting with clinical rickets, abnormal serum calcium, or vitamin D deficiency do not respond to high dose supplements [2] [**L2**]. Severe persistent osseous abnormalities may be treated surgically [75].

13.4 Osteomalacia

Osteomalacia is a defect in the mineralisation of the bone matrix [75,76].

13.4.1 Diagnosis

Signs and symptoms of osteomalacia are non-specific [76] and resemble those of rickets in children[22]. These may include [33,76]:

- Proximal muscle weakness and wasting.
- Myalgias and arthralgias.
- Muscle spasms.
- Altered or "waddling" gait.
- Aching bone pain (lower spine, pelvis, or lower extremities) aggravated by activity and weight-bearing.
- Symmetric lower back pain.
- Decreased bone mass and bone density.
- Spinal, limb, or pelvic deformities (long-term osteomalacia).
- Increased falls.
- Hypocalcaemic seizures or tetany.

There is no single laboratory test specific for osteomalacia [76]. Basic abnormalities include low vitamin D level along with hypocalcaemia and/or hypophosphataemia and elevated alkaline phosphatase level [76]. Detailed evaluation of clinical and family history along with laboratory investigations are required for proper diagnosis.

View Pathway

13.4.2 Management

Treatment should focus on reversing the underlying disorder and correction of vitamin D and electrolyte deficiencies [76].

Consider the following regimen [76] [**L2, RGA**]:

- 50,000 IU of vitamin D2 or D3 orally once/week for 6-8 weeks followed by 800 IU of vitamin D3 daily.
    - During treatment, patients should also take at least 1,000 mg of calcium per day. If the goal is not met with dietary calcium, consider additional supplements.
    - If hypercalcaemia or hypercalciuria is present, the dose can be adjusted to prevent excessive vitamin D dosing.

14 Follow-Up

After treatment for vitamin D deficiency, follow-up laboratory testing is important [9,23]. Nursing staff perform follow-up consultations to confirm:

- Patient compliance.
- Response to treatment.
- Therapeutic effectiveness, i.e. that normal levels of vitamin D are sustained on maintenance dosage.

Serum vitamin D levels could be reassessed after 3 months of vitamin D supplementation [23].
In patients at risk of persistently low 25(OH)D level, retesting is appropriate after 8-12 weeks [7] [**L1, RGA**].

The same laboratory should be used for follow-up of serum 25(OH)D assays [11] [**L2**].

Following treatment, the person will require lifestyle changes (see *Section 5.1*) in addition to daily supplement to maintain optimum vitamin D levels [18,33] [**L1, RGA**].

15 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.

16 Performance Measures

A list of potential performance measures is given below in *Table 16.*

Measure Ref	Numerator	Denominator
VITD01	The number of patients in the denominator who were prescribed vitamin D supplements.	The number of patients with serum 25(OH)D level <30 nmol/L (<12 ng/mL).
VITD02	The number of patients in the denominator who reached serum 25(OH)D level ≥50 nmol/L (≥20 ng/mL) in 3 months after initiation of treatment.	The number of patients with serum 25(OH)D level <30 nmol/L (<12 ng/mL) who received treatment with vitamin D supplements.
VITD03	The number of patients in the denominator who got prescription of supplement dose of vitamin D.	The number of individuals who attended primary/secondary clinics and was not diagnosed to have vitamin D deficiency.

Table 16: Performance Measures.

17 References

1. Government of Dubai & Dubai Health Authority (DHA). Management of Vitamin D Deficiency in Children and Adults. (2017).
2. The Royal Children's Hospital Melbourne. Clinical Practice Guidelines: Vitamin D deficiency. *The Royal Children's Hospital Melbourne* https://www.rch.org.au/clinicalguide/guideline_index/Vitamin_D_deficiency/ (2020).
3. Grossman, Z. *et al.* Vitamin D in European children—statement from the European Academy of Paediatrics (EAP). *Eur J Pediatr* **176**, 829–831 (2017).
4. Armstrong, C. AAP Doubles Recommended Vitamin D Intake in Children. *AFP* **80**, 196 (2009).
5. Pearce, S. H. & Cheetham, T. D. Diagnosis and management of vitamin D deficiency. *BMJ* **340**, b5664–b5664 (2010).
6. Dawodu, A., Kochiyil, J. & Altaye, M. Pilot study of sunlight exposure and vitamin D status in Arab women of childbearing age. *EMHJ - Eastern Mediterranean Health Journal, 17 (7), 570-574, 2011* (2011).
7. Cesareo, R. *et al.* Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE) Position Statement: Clinical Management of Vitamin D Deficiency in Adults. *Nutrients* **10**, (2018).
8. Clemens, T. L., Adams, J. S., Henderson, S. L. & Holick, M. F. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. *Lancet* **1**, 74–76 (1982).
9. Primary Health Care Corporation (PHCC). *Clinical Practice Guidelines for the Management of Vitamin D Deficiency in Children and Adolescence. Lst updated: 2018*. 1–11 (2016).
10. Rusińska, A. *et al.* Vitamin D Supplementation Guidelines for General Population and Groups at Risk of Vitamin D Deficiency in Poland—Recommendations of the Polish Society of Pediatric Endocrinology and Diabetes and the Expert Panel With Participation of National Specialist Consultants and Representatives of Scientific Societies—2018 Update. *Front Endocrinol (Lausanne)* **9**, (2018).
11. Haq, A., Wimalawansa, S. J., Pludowski, P. & Anouti, F. A. Clinical practice guidelines for vitamin D in the United Arab Emirates. *The Journal of Steroid Biochemistry and Molecular Biology* **175**, 4–11 (2018).
12. Bilezikian, J. P. Primary Hyperparathyroidism. *J Clin Endocrinol Metab* **103**, 3993–4004 (2018).
13. Lerchbaum, E. Vitamin D and menopause--a narrative review. *Maturitas* **79**, 3–7 (2014).
14. Pérez-López, F. R. *et al.* EMAS position statement: Vitamin D and postmenopausal health. *Maturitas* **71**, 83–88 (2012).
15. Tayem, Y., Alotaibi, R., Hozayen, R. & Hassan, A. Therapeutic regimens for vitamin D deficiency in postmenopausal women: a systematic review. *Prz Menopauzalny* **18**, 57–62 (2019).
16. Malabanan, A. O. & Holick, M. F. Vitamin D and bone health in postmenopausal women. *J Womens Health (Larchmt)* **12**, 151–156 (2003).
17. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Dietary Reference Intakes for Calcium and Vitamin D*. (National Academies Press (US), 2011).
18. National Institute for Health and Care Excellence (NICE). *Vitamin D deficiency in children. Last reviewed in 2020.* (NICE, 2020).
19. Sizar, O., Khare, S., Goyal, A., Bansal, P. & Givler, A. Vitamin D Deficiency. in *StatPearls* (StatPearls Publishing, 2020).
20. Cowan, A., Pugh, R. & McCaughey, A. *Treatment of Vitamin D Deficiency in Adults*. 1–6 https://mm.wirral.nhs.uk/document_uploads/guidelines/Vitamin%20D%20Guidelines%20for%20Adults%20v2.pdf (2017).
21. National Institute for Health and Care Excellence (NICE). *Vitamin D: supplement use in specific population groups. Public health guideline [PH56]. Last updated in 2017*. (NICE, 2014).
22. National Institutes of Health (NIH) & Office of Dietary Supplements. Dietary supplement fact sheet: vitamin D. https://ods.od.nih.gov/factsheets/Vitamind-HealthProfessional/ (2020).
23. Al-Hashimi, N. & Abraham, S. Cholecalciferol. in *StatPearls* (StatPearls Publishing, 2020).
24. Pludowski, P. *et al.* Vitamin D supplementation guidelines. *The Journal of Steroid Biochemistry and Molecular Biology* **175**, 125–135 (2018).
25. Thompson, R. M. *et al.* Vitamin D Insufficiency and Fracture Risk in Urban Children. *J Pediatr Orthop* **37**, 368–373 (2017).

26. Mahdy, S. M. *et al.* Vitamin D status in health care professionals in Qatar. *Saudi Medical Journal* **31**, 74–77 (2010).
27. Zainel, A.-J. A. L., Qotba, H., Al Nuaimi, A. & Syed, M. Vitamin D status among adults (18–65 years old) attending primary healthcare centres in Qatar: a cross-sectional analysis of the Electronic Medical Records for the year 2017. *BMJ Open* **9**, e029334 (2019).
28. Siam, A. R. *et al.* Vitamin D Defficiency in Rheumatology Clinic Practice in Qatar. *Qatar Medical Journal* **2006**, 17 (2006).
29. Badawi, A., Arora, P., Sadoun, E., Al-Thani, A.-A. & Thani, M. H. A. Prevalence of vitamin D insufficiency in Qatar: a systematic review. *Journal of Public Health Research* 7.
30. Dakroury, Y. *et al.* Association of Differing Qatari Genotypes with Vitamin D Metabolites. *International Journal of Endocrinology* **2020**, 1–6 (2020).
31. Bordelon, P., Ghetu, M. V. & Langan, R. C. Recognition and Management of Vitamin D Deficiency. *AFP* **80**, 841–846 (2009).
32. Marcocci, C., Bollerslev, J., Khan, A. A. & Shoback, D. M. Medical management of primary hyperparathyroidism: proceedings of the fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. *J Clin Endocrinol Metab* **99**, 3607–3618 (2014).
33. National Institute for Health and Care Excellence (NICE). *Vitamin D deficiency in adults - treatment and prevention. Last revised in 2020.* (NICE, 2020).
34. Hill, T. R. & Aspray, T. J. The role of vitamin D in maintaining bone health in older people. *Ther Adv Musculoskelet Dis* **9**, 89–95 (2017).
35. Christodoulou, S., Goula, T., Ververidis, A. & Drosos, G. Vitamin D and Bone Disease. *Biomed Res Int* **2013**, (2013).
36. Marques, C. D. L., Dantas, A. T., Fragoso, T. S. & Duarte, Â. L. B. P. The importance of vitamin D levels in autoimmune diseases. *Rev. Bras. Reumatol.* **50**, 67–80 (2010).
37. Arnson, Y., Amital, H. & Shoenfeld, Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. *Ann Rheum Dis* **66**, 1137–1142 (2007).
38. Judd, S. E. & Tangpricha, V. Vitamin D Deficiency and Risk for Cardiovascular Disease. *Am J Med Sci* **338**, 40–44 (2009).
39. Kheiri, B. *et al.* Vitamin D deficiency and risk of cardiovascular diseases: a narrative review. *Clin Hypertens* **24**, (2018).
40. Zisi, D., Challa, A. & Makis, A. The association between vitamin D status and infectious diseases of the respiratory system in infancy and childhood. *Hormones (Athens)* **18**, 353–363 (2019).
41. Gunville, C. F., Mourani, P. M. & Ginde, A. A. The Role of Vitamin D in Prevention and Treatment of Infection. *Inflamm Allergy Drug Targets* **12**, 239–245 (2013).
42. Berridge, M. J. Vitamin D deficiency and diabetes. *Biochem J* **474**, 1321–1332 (2017).
43. Szymczak-Pajor, I. & Śliwińska, A. Analysis of Association between Vitamin D Deficiency and Insulin Resistance. *Nutrients* **11**, (2019).
44. Murphy, P. K. & Wagner, C. L. Vitamin D and Mood Disorders Among Women: An Integrative Review. *Journal of Midwifery & Women's Health* **53**, 440–446 (2008).
45. Hossein-nezhad, A. & Holick, M. F. Vitamin D for Health: A Global Perspective. *Mayo Clin Proc* **88**, 720–755 (2013).
46. Rockwell, M., Kraak, V., Hulver, M. & Epling, J. Clinical Management of Low Vitamin D: A Scoping Review of Physicians' Practices. *Nutrients* **10**, (2018).
47. Holick, M. F. *et al.* Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* **96**, 1911–1930 (2011).
48. Pludowski, P. *et al.* Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe — recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. *Endokrynologia Polska* **64**, 319–327 (2013).
49. Braegger, C. *et al.* Vitamin D in the Healthy European Paediatric Population. *Journal of Pediatric Gastroenterology and Nutrition* **56**, 692–701 (2013).
50. European Food Safety Authority (EFSA). EFSA Panel on Dietetic Products NaACAScientific opinion on the tolerable upper intake level of vitamin D. *EFSA J* 10:45 (2012).
51. Mechanick, J. I. *et al.* Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American

Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Surg Obes Relat Dis* **9**, 159–191 (2013).
52. Ministry of Public Health (MOPH) Qatar. Bariatric Endoscopy and Surgery in Adults. (2019).
53. Vitamin D in Pregnancy. Scientific Impact Paper No. 43. (2014).
54. National Institute for Health and Care Excellence (NICE). *Vitamin D: increasing supplement use in at-risk groups. PH56.* (NICE, 2014).
55. Wagner, C. L., Hollis, B. W., Kotsa, K., Fakhoury, H. & Karras, S. N. Vitamin D administration during pregnancy as prevention for pregnancy, neonatal and postnatal complications. *Rev Endocr Metab Disord* **18**, 307–322 (2017).
56. Al Emadi, S. & Hammoudeh, M. Vitamin D study in pregnant women and their babies. *Qatar Medical Journal* **2013**, 7 (2013).
57. Kazemi, A., Sharifi, F., Jafari, N. & Mousavinasab, N. High prevalence of vitamin D deficiency among pregnant women and their newborns in an Iranian population. *J Womens Health (Larchmt)* **18**, 835–839 (2009).
58. Al-Daghri, N. M. *et al.* Vitamin D Status and its correlation with Parathyroid Hormone level among population in Riyadh, Saudi Arabia. *Journal of King Saud University - Science* **32**, 2016–2019 (2020).
59. Ministry of Public Health (MOPH) Qatar. The Management of Obesity in Adults. Last updated: 2019. (2016).
60. Ministry of Public Health (MOPH) Qatar. National Clinical Guideline: The Management of Obesity in Children. (2019).
61. Mimouni, F. B. Vitamin D Status in Growing Children: Should We Routinely Screen for Vitamin D Adequacy? *Journal of Pediatric Gastroenterology and Nutrition* **51**, S121–S122 (2010).
62. Jones, K. S. *et al.* 25(OH)D2 Half-Life Is Shorter Than 25(OH)D3 Half-Life and Is Influenced by DBP Concentration and Genotype. *J Clin Endocrinol Metab* **99**, 3373–3381 (2014).
63. Ganji, V., Tangpricha, V. & Zhang, X. Serum Vitamin D Concentration ≥75 nmol/L Is Related to Decreased Cardiometabolic and Inflammatory Biomarkers, Metabolic Syndrome, and Diabetes; and Increased Cardiorespiratory Fitness in US Adults. *Nutrients* **12**, (2020).
64. Tripkovic, L. *et al.* Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. *Am J Clin Nutr* **95**, 1357–1364 (2012).
65. McDermott, M. T. *Endocrine secrets*. (2020).
66. Eastell, R. *et al.* Diagnosis of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop. *The Journal of Clinical Endocrinology & Metabolism* **99**, 3570–3579 (2014).
67. Asif, A. & Farooq, N. Vitamin D Toxicity. in *StatPearls* (StatPearls Publishing, 2020).
68. Ralph, A. P. Vitamin D Supplementation in Patients with Tuberculosis. *AFP* **82**, 577 (2010).
69. Altundag, O. *et al.* Calcium and vitamin D supplementation during bisphosphonate administration may increase osteoclastic activity in patients with bone metastasis. *Med Hypotheses* **63**, 1010–1013 (2004).
70. Schwartz, J. B. Effects of vitamin D supplementation in atorvastatin-treated patients: a new drug interaction with an unexpected consequence. *Clin Pharmacol Ther* **85**, 198–203 (2009).
71. Bhattacharyya, S., Bhattacharyya, K. & Maitra, A. Possible mechanisms of interaction between statins and vitamin D. *QJM: An International Journal of Medicine* **105**, 487–491 (2012).
72. Robien, K., Oppeneer, S. J., Kelly, J. A. & Hamilton-Reeves, J. M. Drug-vitamin D interactions: A systematic review of the literature. *Nutr Clin Pract* **28**, 194–208 (2013).
73. National Institute for Health and Care Excellence (NICE). *Chronic kidney disease in adults: assessment and management. Clinical guideline [CG182]. Last updated: 2015*. (NICE, 2014).
74. British Medical Association, Royal Pharmaceutical Society of Great Britain & Joint Formulary Committee (Great Britain). *BNF 76*. (2018).
75. Dahash, B. A. & Sankararaman, S. Rickets. in *StatPearls* (StatPearls Publishing, 2020).
76. Zimmerman, L. & McKeon, B. Osteomalacia. in *StatPearls* (StatPearls Publishing, 2020).
77. Levine, M. A. Diagnosis and Management of Vitamin D Dependent Rickets. *Front Pediatr* **8**, (2020).
78. Sahay, M. & Sahay, R. Rickets–vitamin D deficiency and dependency. *Indian J Endocrinol Metab* **16**, 164–176 (2012).
79. Özkan, B. Nutritional Rickets. *J Clin Res Pediatr Endocrinol* **2**, 137–143 (2010).

Appendix: Detailed Description of the Literature Search

A systematic search for existing literature on the low back pain was performed in the period November 1st – December 13th, 2020. Review of additional literature based on GDG request was performed in the period March 17th – April 26th.

The search for clinical practice guidelines on low back pain diagnosis and/or management was performed in the *PubMed* database and websites of relevant organisations and societies including the *The National Osteoporosis Society (NOS), The Endocrine Society, American Society for Bone and Mineral Research (ASBMR), The European Calcified Tissue Society (ECTS)* and other. The present guideline is primarily based on National Institute of Health (NIH) guidelines, Endocrine Society (USA) and Vitamin D opinion leaders (EVIDAS). It also takes into account recommendations by GULF (UAE) guidelines and is supplemented with other relevant studies.

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. Information published on medical websites and drug prescribing information sheets were found via Google search engine.

The included publications were identified using the term “vitamin D” and specified with the following terms in combinations:

Management, causes, risk factors, aetiology, prevalence, prognosis, presentation, symptoms, screening, differential diagnosis, screening, lifestyle, sunbathing, sunscreen, pregnant, postmenopausal, elderly, pharmacological treatment/pharmacotherapy, primary/secondary care, referral criteria, multidisciplinary, calcium, supplementation, prevention, treatment, monitoring, overtreatment, toxicity, rickets, osteomalacia, medication(s), drug(s), source, interaction, safety limit/dose, follow-up.

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

View Pathway

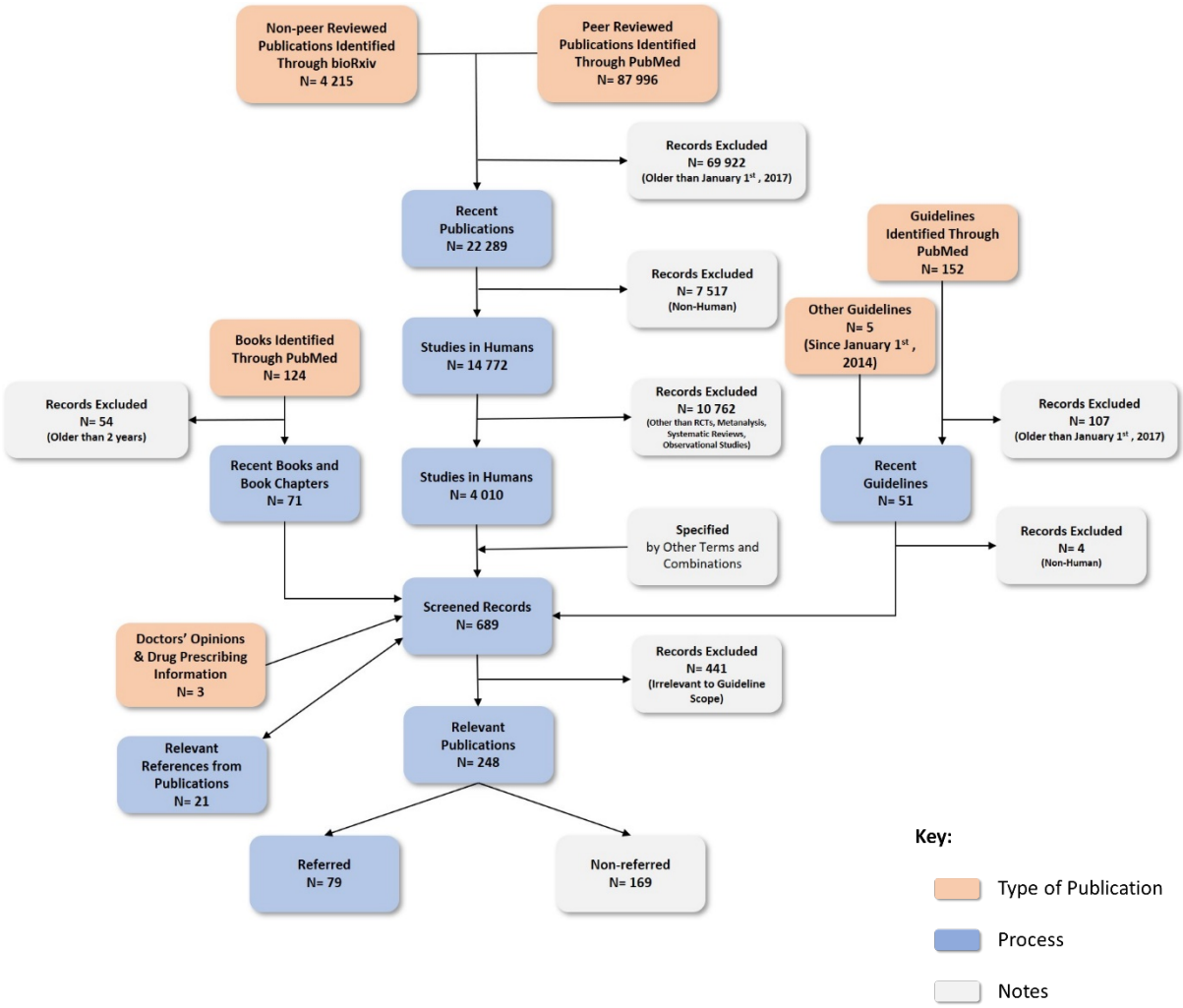


Fig A.1: Literature search results and application of exclusion criteria.

Acknowledgements

The following individuals are recognised for their contribution to the successful development of the National Clinical Guideline.

MOPH National Clinical Guidelines Team:

- **Ms Huda Amer Al-Katheeri**, *Director of Strategic Planning & Performance Dept, MOPH*.
- **Dr Nawal Al Tamimi,** *Head of Healthcare Quality & Patient Safety Dept, MOPH.*
- **Dr Rasha Bushra Nusr**, *Quality Improvement Senior Specialist, MOPH.*
- **Dr Rasmeh Ali Salameh Al Huneiti**, *Guideline & Standardisation Specialist, MOPH.*
- **Dr Bushra Saeed**, *Quality Improvement Coordinator, MOPH.*
- **Dr Mehmood Syed,** *Project Clinical Lead.*
- **Dr Samuel Abegunde,** *Physician Executive.*
- **Dr Natalia Siomava,** *Senior Medical Writer.*
- **Ms Rouba Hoteit,** *Medical Writer.*

Please use the following email address to provide feedback on this guideline:
clinicalguidelines@moph.gov.qa