Starship Clinical Guidelines
developed by clinicians at Starship Child Health

Vitamin D deficiency - investigation and management

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Within this Document

- Guideline exclusions
- Identification of 'at risk' groups
- Classification of vitamin D status
- Target vitamin D level
- Clinical features of vitamin D deficiency
- Principles of treatment
- Management of children at risk of vitamin D deficiency
- Management of children with clinical vitamin D deficiency
- Treatment monitoring
- Available forms of vitamin D in New Zealand
- Symptomatic vitamin D deficiency with hypocalcaemia, hypophosphataemia and elevated PTH (parathyroid hormone)
- Symptomatic hypocalcaemia
- Vitamin D toxicity
- Primary prevention
- Prevalence
- Vitamin D and sun exposure
- Vitamin D and diet
- Information for Families

Related Documents

Hypocalcaemia

Guideline exclusions

This guideline does **not** cover:

- Supplementation for pregnant women or lactating mothers - please refer to the Ministry of Health Companion Statement on vitamin D and Sun Exposure in Pregnancy and Infancy in New Zealand [5]
- Vitamin D therapy in symptomatic hypocalcaemic neonates or babies <3 months of age - please consult Paediatric Endocrinology Service for advice

- Children with renal impairment - dosing may need adjustment - please consult Paediatric Renal Service for advice.

Identification of 'at risk' groups

Vitamin D is important across all age groups for bone health and metabolism. There is increasing evidence for its role in immune modulation and its anti-inflammatory properties.

Many individuals have multiple risk factors for vitamin D deficiency, including:

- Winter and Spring seasons (exacerbated by more southern latitude)
- Darker skin pigmentation
- Prolonged exclusive breastfeeding
- Being born to a vitamin D deficient mother (more common in dark-skinned, veiled, recent migrant mothers)
- Reduced sun exposure
    - Veiled or modest clothing
    - Active avoidance of sun exposure
    - Chronic illness or disability that prevents regular sun exposure
- Malabsorption syndromes (e.g. Coeliac disease, pancreatic insufficiency)
- Chronic liver or renal disease
- Use of drugs that affect vitamin D synthesis or degradation (eg. Rifampicin, some anticonvulsants)

Classification of vitamin D status

- Sufficiency: > 50 nmol/L
- Biochemical insufficiency: 30 - 50 nmol/L
- Deficiency: < 30 nmol/L

Target vitamin D level

The current recommended lower limit for serum 25(OH)D = **50nmol/L**. This defines normal vitamin D status and is the level required for optimal calcium metabolism.[6,7] Emerging data from studies in adults examining the relationship between vitamin D status and other health outcomes suggest that 25(OH)D levels of >75nmol/L may be optimal (Nowson CA *Med J Aust* 2012; 196: 686-687.)

Clinical features of vitamin D deficiency

Vitamin D deficiency is most commonly asymptomatic. However, severe vitamin D deficiency may manifest as rickets with the below clinical features:

Bony Signs

- Swelling of wrists and ankles
- Leg deformities (genu varum or valgum)
- Rachitic rosary in the chest wall (enlarged costochondral joints)
- Delayed tooth eruption (no incisors by aged 10 months, no molars by age 18 months)
- Craniotabes (softening of skull bones)
- Delayed closure of anterior fontanelle
- Frontal bossing
- Minimal trauma fractures

Non-Bony Signs

- Delayed gross motor development
- Poor linear growth
- Raised intracranial pressure
- Dilated cardiomyopathy
- Symptoms of hypocalcaemia - tetany, stridor, seizure

Radiological features

- Splaying, fraying and cupping of metaphyses
- Osteopenia

Principles of treatment

Treatment choice should be balanced by the following considerations:

- safety of treatment
- adherence considerations, i.e. infrequent higher ("STOSS") dosing or daily lower dosing
- medications that are available and funded in New Zealand

Management of children at risk of vitamin D deficiency

Children at risk of vitamin D deficiency but without symptoms or signs generally do not need blood tests and can just commence supplementation.

Prophylaxis - for those at risk of vitamin D deficiency	
Age	**Recommended treatment**
< 12 months	400 IU daily (Vitadol C 0.3ml = 10 drops daily) Advise breastfeeding mother to be checked by her GP for low vitamin D and treated as well
1-2 years	Consider annual high dose treatment in Autumn (eg April) 150,000 IU as single dose (3 x 1.25mg capsules* - caps can be opened and mixed with oil or food)
2-5 years	Consider annual high dose treatment in Autumn (eg April) 300,000 IU as single dose (6 x 1.25mg capsules* - caps can be opened and mixed with oil or food)
> 5 years	Consider annual high dose treatment in Autumn (eg April) 600,000 IU as single dose (12 x 1.25mg capsules* - caps can be opened and mixed with oil or food)
*1.25mg capsule = Vitamin D3 brand capsule, contains soya oil	

Management of children with clinical vitamin D deficiency

Clinical suspicion of vitamin D deficiency	Clinical suspicion of severe vitamin D deficiency (eg rickets)

Blood serum levels: - Calcium - Phosphate - Alkaline phosphatase (ALP) - 25(OH)D	Blood serum levels: - Calcium - Phosphate - Alkaline phosphatase (ALP) - 25(OH)D - Parathyroid hormone (PTH) - Urea - Creatinine - Sodium - Potassium X-ray wrists
Patients with renal disease may need dosing adjustment - consult with Paediatric Renal team	

Treatment of vitamin D deficiency			
Age	**Indication**	**Recommended treatment†**	**Alternative treatment††**
All ages	All ages 25(OH) Vit D <50 nmol/L PLUS Hypocalcaemia OR Hypophosphataemia OR Raised PTH	Alfacalcidol 1 drop/kg/day max 10 drops (One-Alpha liquid 2mcg/ml) PLUS Calcium supplementation 40-80mg/kg/day elemental calcium in 4 divided doses (Calsource Ca 1000 effervescent tablets - each tablet contains 1000mg elemental calcium. Dissolve 1 tablet in 10ml water to give 100mg/ml) Once Calcium and phosphate normalised give high dose treatment as below once >3 months old	
	25(OH) Vit D <50 nmol/L **PLUS** **symptomatic hypocalcaemia**	Hypocalcaemia guideline	
< 3 months	25(OH) Vit D = 30-50 nmol/L Normal serum Calcium Normal serum Phosphate	400 IU daily (Vitadol C 0.3ml = 10 drops daily) for 3 months	

Treatment of vitamin D deficiency			
	25(OH)D <30 nmol/L Normal serum Calcium Normal serum Phosphate	2000 IU daily (1.25mg capsule* - mix contents of one capsule with 10ml soya oil and give 0.4ml daily)	
3 months - 2 years	25(OH)D <50 nmol/L Normal serum Calcium Normal serum Phosphate	High dose treatment 150,000 IU as single dose (3 x 1.25mg capsules* - caps can be opened and mixed with oil or food)	2000 IU daily (1.25mg capsule* - mix contents of one capsule* with 10ml soya oil and give 0.4ml daily)
2-5 years	25(OH)D <50 nmol/L Normal serum Calcium Normal serum Phosphate	High dose treatment 300,000 IU as single dose (6 x 1.25mg capsules* - caps can be opened and mixed with oil or food)	2000 IU daily (1.25mg capsule* - mix contents of one capsule* with 10ml soya oil and give 0.4ml daily)
> 5 years	25(OH)D <50 nmol/L Normal serum Calcium Normal serum Phosphate	High dose treatment 600,000 IU as single dose (12 x 1.25mg capsules* - caps can be opened and mixed with oil or food)	2000 IU daily (1.25mg capsule* - mix contents of one capsule* with 10ml soya oil and give 0.4ml daily)
† Recommended treatment is based on a combination of international consensus recommendations combined with local experience with use of high dose regimes			
†† Alternative treatment can be considered as an alternative to high dose regime. This is based on international consensus and relies on good adherence to daily dosing			
* 1.25mg capsule = Vitamin D3 brand capsule, contains soya oil			

Treatment monitoring

3 months after STOSS therapy recheck the following to ensure adequate response:

- Serum 25(OH)D
- Serum calcium, phosphate and ALP

Children who do not respond to high dose vitamin D therapy require specialist review.

Annual testing of at risk children or those previously treated for Vitamin D deficiency is controversial. Biochemical testing is more expensive than empiric treatment regimes.[8]

If ongoing risk factors are present and behavioural change (i.e. adequate sun exposure and dietary change) has not been possible then a pragmatic approach is recommended.

Empiric treatment options include:

- Annual STOSS therapy at the start of each autumn season (simple dosing used locally over long term increases vitamin D levels over winter when sun exposure is lowest)
- Monthly STOSS therapy
- Daily dosing (follows international guidance, however concerns about long term adherence)

Available forms of vitamin D in New Zealand

There are a number of over the counter vitamin D preparations available as either capsules, drops, oral sprays or sublingual preparations. These come predominantly as either as 1000 IU capsules/sprays or 200 IU/0.5ml solutions, or 400IU/drop. None are funded but offer smaller dosages without other Vitamins. Adherence can be a problem with daily lower dose vitamin D supplementation. A larger loading dose of cholecalciferol improves adherence and is funded.

Intermittent high dose therapy is known as STOSS therapy. Starship Endocrinology recommends this for children with symptomatic deficiency. STOSS therapy will provide a 'supraphysiologic' dose that is redistributed into fat and will provide 2-3 month stores of vitamin D. Timing of initiation of STOSS therapy will depend on initial serum calcium and phosphate levels as per table above.

Daily dosing may be considered for either the prevention of vitamin D deficiency or in asymptomatic vitamin D deficiency in a child where compliance with daily therapy can be assured. Note the recommended dietary allowance of Vitamin D is 600IU from 1 to 18 years of age including pregnancy. From birth to 12 months adequate vitamin D intake is 400IU daily.

Fully funded formulations

Vitadol C	(0.3ml = 400IU Vitamin D) Preparation contains Vitamin A,C and D **0.3ml is the maximum prescribed dose** higher doses will exceed the maximum safe dose for the accompanying vitamin A in the preparation.
Cholecalciferol capsule	1 tab/capsule = 50,000 IU Vitamin D3 = 1.25mg Note: **these capsules contain soya oil. They must not be prescribed for children known to have a peanut or soya allergy unless under the supervision of the Paediatric Endocrinology Service**
Alfacalcidol	Drops 2mcg/ml - 1 drop contains approximately 0.1mcg Vit D3 analogue
Note: 1 mcg of vitamin D = 40 IU of vitamin D	

Symptomatic vitamin D deficiency with hypocalcaemia, hypophosphataemia and elevated PTH (parathyroid hormone)

Intermittent high dose vitamin D therapy (STOSS therapy) while serum PTH is elevated may cause hypervitaminosis D and severe hypercalcaemia.

In rare cases children with very elevated serum PTH levels given high dose vitamin D therapy may develop very rapid changes in bone metabolism leading to severe hypocalcaemia.

Normalise serum calcium and phosphate levels PRIOR to starting high dose Vitamin D therapy.

1. Use a step-wise approach as per table above
2. Recheck serum calcium, phosphate and ALP after one month. Once the phosphate is normal this indicates PTH is likely to be normal
3. STOSS therapy can then be initiated as above.

Symptomatic hypocalcaemia

Severe vitamin D deficiency may present with symptomatic hypocalcaemia.

For management of severe symptomatic hypocalcaemia refer to the Starship Clinical Guideline on **hypocalcaemia**.

Please note: Hypocalcaemia is most commonly seen in infants of mothers who were also vitamin D deficient throughout their pregnancy. Advise mother to have vitamin D levels checked too through their GP.

Vitamin D toxicity

Vitamin D toxicity is uncommon but can occur due to excessive supplementation and has been seen in doses between 40,000-560,000IU/kg. [9] It may also occur if an individual has prescribed vitamin D supplements and then also obtains over the counter supplements with high levels of Vitamin D such as cod liver oil.

The main effects of vitamin D toxicity are due to the hypercalcaemia it produces.

Signs and symptoms of hypercalcaemia
Constipation Abdominal pain and vomiting Bony pain Renal calculi +/- renal impairment Fatigue/behaviour changes Headaches Growth restriction in children Polydipsia Cardiac arrhythmias (rare)

If vitamin D toxicity is suspected then urgent serum calcium, phosphate, and renal function should be ordered. The serum 25(OH)D concentration should also be checked but this is not urgent as it is the serum calcium level that will dictate any specific treatment required.

Vitamin D toxicity is treated by cessation of all vitamin D containing supplements, reducing calcium intake and treatment of severe hypercalcaemia. If severe symptomatic hypercalcaemia (e.g. Serum calcium> 3.0 mmol/L) is present, then inpatient therapy will be required.

These children should be discussed with the Paediatric Endocrinology team acutely

Primary prevention

Exclusively breastfed infants

Breast milk contains very low levels of Vitamin D - approximately 25 IU/l even in mothers who are Vitamin D replete.[6] Pregnant and breastfeeding mothers are at risk of vitamin D deficiency. As maternal Vitamin D status determines Vitamin D at birth and during early infancy (for breastfed infants) this also places their infants at high risk.[10]

The Australasian Paediatric Endocrine Group, the American Academy of Paediatrics, the Canadian Paediatric Society and the UK Chief Medical Officers all recommend routine supplementation of exclusively breastfed infants with other risk factors for low vitamin D levels (e.g. dark skin pigmentation, maternal risk factors for vitamin D deficiency etc.) for at least the first year of life.

400 IU vitamin D daily is recommended, available as Vitadol C 0.3mls daily (fully funded) from birth:

- Prescribe to at risk neonates discharged from SCBU/NICU, the postnatal wards or at the 6 week Well Child check.

Other opportunities to prescribe:

- At risk infants discharged from paediatric wards after admission with other acute presentations
- Through communication to GP in any routine correspondence from clinics/wards etc

Infant formula is fortified with vitamin D at 5mcg/L (200IU/L). Therefore routine supplementation of formula-fed babies is not recommended until they are consuming less than 500ml formula per day.

A recent Otago study has demonstrated that giving mothers 100,000 IU of cholecalciferol will result in a significant rise in infant Vitamin D levels with breastfeeding. This may prove to be another method of preventing vitamin D deficiency in at risk groups during pregnancy (Wheeler et al. *J Nutr. 2016* Aug 24. pii: jn236679.)

At risk, asymptomatic children

For asymptomatic children with multiple risk factors for vitamin D deficiency, our current recommendation is to check baseline serum 25(OH)D level, serum calcium and phosphate to confirm deficiency BEFORE the initiation of intermittent high dose vitamin D therapy (STOSS therapy).

Repeated vitamin D testing is more expensive than pragmatic empiric treatment regimes in a child with ongoing multiple risk factors for vitamin D deficiency as it is most likely that the serum testing will just confirm clinical suspicion of a low vitamin D level. (see Treatment monitoring).

Some children at very high risk may need high dose vitamin D supplementation more often than annually. If suspected then serum 25(OH)D concentration should be measured to guide prescribing.

Some recently arrived migrant children with known risk factors for deficiency may have normal vitamin D status on arrival to NZ. These children should have their vitamin D level re-checked at the end of their first NZ winter.[6]

Prevalence

In 2002 a study of the nutritional status of a random ethnically stratified sample of 413 Auckland children aged 6-23 months found:

- Vitamin D deficiency present in 10% (defined by a serum 25-hydroxy-Vitamin D concentration [25(OH)D] <27.5nmol/L, the 25(OH)D concentration that defines a child as being at risk of rickets)
- Risk of vitamin D deficiency 7 times higher in children whose vitamin D status was determined during winter versus summer.
- Prevalence of vitamin D deficiency varied with ethnicity: Pacific 24%, Maori 11%, European 3% and Other Ethnic Groups 16% .[1,2]

In a recently published study of vitamin D status of exclusively breastfed infants in Auckland aged 2-3 months, 24% were vitamin D deficient (25(OH)D <27.5nmol/L).[3] A group at particular risk of symptomatic deficiency presenting to Starship Children's hospital are Indian children from vegan families.[4] .

Vitamin D and sun exposure

Exposure of the skin to ultraviolet B (UVB) from sunlight is the main source of Vitamin D synthesis for most people. It is estimated to provide over 90% of Vitamin D in humans.[11]

The ability to synthesise adequate Vitamin D depends on skin colour, timing and amount of sun exposure as well as seasonal changes in UVB levels, cloud cover and the latitude of place of residence.

There are no specific paediatric data available as to the amount of sun exposure required for different skin types to synthesise adequate Vitamin D. Therefore it is not possible to make a single recommendation for amount of sun exposure required that would suit all children.

All prescriptions for Vitamin D therapy must be accompanied by appropriate education with regards to safe sun exposure.

See the Ministry of Health documents:

- **Ministry of Health consensus statement on Vitamin D and Sun exposure in New Zealand**. [11]
- **Companion Statement on Vitamin D and Sun Exposure in Pregnancy and Infancy in New Zealand**

More detailed information regarding sun exposure for individual skin types (from adult data) can be found in the Australasian Paediatric Endocrine Group consensus statement 2013. [6]

Vitamin D and diet

Recommended Daily Intake (RDI)[4]:

0-12 months	400 IU
1-18 years and in pregnant or lactating women	600 IU

Less than 10% of the body's Vitamin D requirements are obtained from dietary sources.

The best dietary source of Vitamin D is oily fish (e.g. Salmon, mackerel) and fish liver oils. Other dietary sources include: egg yolks, beef, Portobello and Shiitake mushrooms (which also make their Vitamin D from sunlight) and fortified milk.

Ensure adequate calcium intake in children's diets for bone health and wellbeing. See the attached pdf leaflet for parents on **Calcium**.

Information for Families

The Ministry of Health has produced a patient information leaflet about Vitamin D and sun exposure. This is available in 10 languages and can be downloaded by accessing the following link **http://www.health.govt.nz/your-health/pregnancy-and-kids/first-year/helpful-advice-during-first-year/vitamin-d-and-your-baby**

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