VITAMIN D DEFICIENCY

PATHWAY SUMMARY

Assessment
Consider vitamin D in children with the following risk factors:

- Dark skin
- Limited sun exposure
- Low dietary intake
- Chronic use of medications
- Malabsorption problems
- Obesity
- Premature birth
- Chronic renal disease or history of renal transplant
- Infants that are breastfed without vitamin D supplementation and growth is faltering
- Infants of breastfeeding mothers with dark skin or covered (minimal skin exposure) without vitamin D supplementation or low intake of foods containing vitamin D

Laboratory Study
- Request for 1,25 dihydroxyvitamin D will be intercepted by the team and the provider form letter will be sent to the ordering provider

Therapeutics
- The Children’s Hospital Colorado Vitamin D Committee recommends that all individuals, who are supplemented, take once-daily vitamin D₃ or its weekly equivalent to maintain serum 25(OH)D levels of at least 30 ng/mL.

Recommendations for follow up:
- Vitamin D levels should be rechecked after 6 to 12 weeks
- Vitamin D can be evaluated sooner if medically indicated.
- Patients with chronic illness should have their vitamin D levels checked annually
- Consider Endocrinology referral if deficiency is resistant to treatment or patient has documented rickets that is not associated with vitamin D deficiency (hypophosphatemic rickets).

Prevention
Information regarding appropriate sun exposure, the use of vitamin D supplements, and eating a diet rich in calcium and vitamin D should be made available to each patient.

Table 1. Dosing Recommendations

Frequently Asked Questions
TARGET POPULATION

Inclusion Criteria

- Patients with risk factors for low vitamin D levels

Exclusion Criteria

- Pediatric patients with chronic medical conditions which may require large doses and more frequent follow up.
- Patients with documented Rickets, that is not associated with vitamin D deficiency (hypophosphatemic)

BACKGROUND | DEFINITIONS

Vitamin D is a fat-soluble vitamin that acts as a steroid hormone. The body makes vitamin D from cholesterol through the action of the sun's UVB rays on the skin. Factors such as skin color, age, amount and time of sun exposure, and geographic location affect how much vitamin D the body makes. The primary function of vitamin D is to maintain normal blood concentrations of calcium and phosphorus, in addition to supporting bone, cardiovascular, pancreas, muscle, and brain health\textsuperscript{1}. Normal bone mineralization depends on adequate calcium and phosphate and this is maintained by vitamin D. Low vitamin D results in decreased calcium and phosphate, which leads to secondary hyperparathyroidism causing inadequate mineralization and loss of skeletal mass. When growth plates have closed, this can lead to osteomalacia; if the growth plates have not closed, rickets may develop.

RECOMMENDATION FOR SCREENING

Note: Screening for vitamin D levels should be reserved for patients with risk factors for deficiency. Universal screening of all patients is not recommended\textsuperscript{2,3}.

Consider assessing vitamin D status in children with the following risk factors:

- Dark skin\textsuperscript{1}
- Limited sun exposure, including frequent sunscreen use and cultural convention associated with covering body\textsuperscript{3}
- Low dietary intake, including vegan/macrobiotic diets or allergy/intolerance\textsuperscript{3}
- Chronic use of medications (e.g. anticonvulsants, steroids [including inhaled])\textsuperscript{2}
• Malabsorption problems (including celiac disease, cystic fibrosis, etc.)
• Obesity
• Premature birth
• Chronic renal disease or history of renal transplant
• Infants that are breastfed without vitamin D supplementation and growth is faltering
• Infants of breastfeeding mothers with dark skin or covered (minimal skin exposure) without vitamin D supplementation or low intake of foods containing vitamin D

LABORATORY STUDIES

Vitamin D levels are measured by total serum 25-hydroxyvitamin D [also referred to as 25(OH)D]. Since the development of 1,25-dihydroxyvitamin D testing, proper utilization based on clinical need has been problematic. Testing 25-hydroxyvitamin D is most useful in nutrition assessment, primarily due to its longer half-life. The circulating half-life of 1,25-dihydroxyvitamin D is relatively short, which limits utility for overall vitamin D assessment. Testing can be useful in the diagnosis of renal dysfunction in conjunction with parathyroid hormone. 1,25-dihydroxyvitamin D is elevated in sarcoidosis and primary hyperparathyroidism, and decreased in renal failure and hyperparathyroidism.

Laboratory Approval Process

Test requests for 1,25 dihydroxyvitamin D will be flagged for review by the lab and sent to the ordering provider for review.

• Laboratory team responsibility:
  o Request for 1,25 dihydroxyvitamin D will be intercepted by the team and the provider form letter will be sent to the ordering provider.
  o After the ordering provider responds with their decision, the lab team will either:
    o Send the specimen for processing
    OR
    o Cancel the request and redirect, if appropriate, to 25(OH)D testing

• The lab team will document the case and decision in their database

• Provider responsibility:
  o In the event the ordering provider does not respond within two days, the request will be sent to the on-call provider for the group.
  o The on-call provider can decide to approve the testing or redirect testing if clinically indicated

Evaluation of Laboratory Results

Vitamin D status as measured by 25(OH)D

• Deficiency = Less than 10 ng/mL
  o At risk for rickets, pathologic fractures, and non-skeletal disease
• Insufficiency = 10 to 20 ng/mL
  o At risk for bone disease including osteopenia/osteoporosis, musculoskeletal pain, and non-skeletal disease including periodontal disease
  o At risk for insufficiency = 20 to 30 ng/mL (interpretation should take into account time of year, skin color, and presence of obesity or medical condition)
  o At risk for non-skeletal disease (cardiac, oncologic)
**CLINICAL PATHWAY**

- Sufficiency = 30 to 96 ng/mL
- Toxicity = Greater than 96 ng/mL
  - Hypercalcemia
    - Gastrointestinal distress, bone pain
- Hypercalciuria
  - Kidney stones
- Hyperphosphatemia

**THERAPEUTICS**

**Recommendations for supplementation:**

These recommendations do not differentiate between the use of cholecalciferol (D₃) or ergocalciferol (D₂), as there is insufficient data to show any significant difference in absorption, particularly at therapeutic levels⁶. For patients who require large weekly doses (i.e., 50,000 International Units [IUs]) ergocalciferol (D₂) is preferred: however, it should be noted that patient insurance may require prescription and prior authorization (PAR). The American Academy of Pediatrics recommends daily dosing; however, the dosing schedule (daily versus weekly) should be individualized to minimize financial issues and treatment burden, particularly in patients with chronic illness⁶. Other considerations include the potential for vitamin D toxicity if a weekly high-dose regimen is inadvertently continued or possible loss of efficacy if the weekly dose is missed. The Children’s Hospital Colorado Vitamin D Committee recommends that all individuals, who are supplemented, take once-daily vitamin D₃ or its weekly equivalent to maintain serum 25(OH)D levels of at least 30 ng/mL.

**Table 1. Dosing Recommendations**

<table>
<thead>
<tr>
<th>25(OH)D Level</th>
<th>Daily dosing for children 0 to less than 10 years of age</th>
<th>Daily dosing for patients 10 to 18 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency: Less than 10 ng/mL</td>
<td>2000 International Units (normal weight)</td>
<td>4000 International Units (normal weight)</td>
</tr>
<tr>
<td></td>
<td>4000 International Units (obese, BMI greater than 95%)</td>
<td>8000 International Units (obese, BMI greater than 95%)</td>
</tr>
<tr>
<td>Insufficiency: 10 to 20 ng/mL</td>
<td>1000 International Units (normal weight)</td>
<td>2000 International Units (normal weight)</td>
</tr>
<tr>
<td></td>
<td>2000 International Units (obese BMI greater than 95%)</td>
<td>4000 International Units (obese, BMI greater than 95%)</td>
</tr>
<tr>
<td>At-risk-for-insufficiency: 20 to 30 ng/mL</td>
<td>400 to 800 International Units (normal weight)</td>
<td>800 International Units (normal weight)</td>
</tr>
<tr>
<td></td>
<td>1000 International Units (obese, BMI greater than 95%)</td>
<td>1000 International Units (obese, BMI greater than 95%)</td>
</tr>
</tbody>
</table>

Consider increased supplementation in patients with at-risk medical conditions (i.e., premature birth status, renal impairment, CF, malabsorption), if dark skin, or limited dietary intake.

*** Dosing amount should be inclusive of all supplements (ie. Vitamin D, multivitamin, Omega-3, etc)
Recommendations for follow up:

- Vitamin D levels should be rechecked after 6 to 12 weeks when supplementation is initiated, or with any dose change.
- Vitamin D can be evaluated sooner if medically indicated. A dose response to therapy should be evident on laboratory evaluation within 4 to 6 weeks of supplementation.
- Patients with chronic illness (CF, renal disease, etc.) should have their vitamin D levels checked annually as part of routine health maintenance, and regardless of supplementation status.
- Consider Endocrinology referral if deficiency is resistant to treatment or patient has documented rickets that is not associated with vitamin D deficiency (hypophosphatemic rickets). Children’s Hospital Colorado Endocrinology department is available for phone consultation at any time with questions or concerns (720-777-6128).

PREVENTION

Information regarding appropriate sun exposure, the use of vitamin D supplements, and eating a diet rich in calcium and vitamin D should be made available to each patient.

Prevention and maintenance measures to avoid deficiency through vitamin D supplementation are suggested as follows:

- Breast feeding infants up to 12 months old: 400 International Units/day
- Inadequate sun exposure or limited dietary intake:
  - 1 to 18 years old: 400 to 800 International Units/day
  - Adults: 800 International Units/day
- Pregnant and lactating women: 6400 International Units/day, if baby is not being supplemented to support 400 International Units recommendation in breast milk
- Obese patients: 1000 International Units/day

Patients with at-risk medical conditions (i.e. premature birth status, renal impairment, CF, malabsorption, etc), may require higher maintenance doses and more frequent follow up.

FREQUENTLY ASKED QUESTIONS

What are the forms of vitamin D?

- Cholecalciferal (vitamin D₃)
  - A naturally occurring form of vitamin D made by the skin upon sun exposure (UVB rays)
  - Found in foods and most supplements, including cod liver oil and sheep lanolin
- Calcidiol (25-hydroxyvitamin D)
  - A prehormone made directly from cholecalciferol in the liver
  - Low bio-activity, but a major circulating form in the blood stream
  - Used to measure vitamin D deficiency
- Calcitriol (1,25 dihydroxyvitamin D₃)
  - An activated form of vitamin D made from calcidiol in the kidneys and body tissue
  - Most potent steroid hormone in the body
I. Ergocalciferol (vitamin D₂)
   - Not naturally occurring in the body, made in the laboratory and used in prescription vitamin D

II. Is there a difference between the forms of Vitamin D in supplements?
   - There are two main forms of vitamin D in supplements: cholecalciferol and ergocalciferol.
   - There is no evidence of significant difference in absorption between the different forms, especially at therapeutic levels.

III. What is the controversy regarding vitamin D “sufficiency”?
   - The Institute of Medicine (IOM) and Endocrine Society recommendations disagree on the “level of sufficiency” in assessments of bone health for determining deficiency thresholds. There often isn’t a specific level above which one is protected, nor is there a level at which disease is inevitable.
   - Treating to a 25(OH)D level greater than 30 ng/mL may not produce additional benefits above treating to a level of greater than 20 ng/mL; however, the health risks of doing so appear to be minimal but therapy may be expensive for patients.

IV. Are there drug interactions that make a patient more “at risk”?
   - Corticosteroids
     - Reduce calcium absorption resulting in impaired vitamin D metabolism
   - Bile acid sequestrants (e.g. cholestyramine)
     - May impair absorption of vitamin D
     - Should be taken several hours apart
   - Orlistat
     - May impair absorption of vitamin D
     - Should be taken at least 2 hours apart
   - Phenobarbital and phenytoin: increase the hepatic metabolism of vitamin D to inactive compounds and decrease calcium absorption, which also impairs vitamin D metabolism.

V. Is there a specific time my patients should take their supplement?
   - We advise taking vitamin D supplements with the largest meal of the day to improve absorption.

VI. Should I advise my patients to get more sun?
   - Monitored sun exposure
     - Colorado is above the 31 degree latitude cut off, increasing risk of vitamin D deficiency
   - Unprotected sun exposure (UVB rays):
     - Light skin tones: 10 to 5 minutes daily on arms/legs provides 2000 to 3000 International Units
     - Darker skin: requires 5 to 6 times longer

VII. Should I screen for metabolic or underlying malabsorption if my patient is deficient?
   - Most patients do not have any other disease processes, and thus lead to unnecessary evaluation. Consider additional screening, only for patients with signs or symptoms suggesting underlying disease processes (e.g. diarrhea, frequent upper respiratory infections, or skin changes such as dry skin or hair loss).

VIII. If my patient has vitamin D deficiency, should I screen for osteoporosis?
   - Additional screening is only indicated if clinical history (bone pain, fractures, etc.) is suggestive of osteoporosis.
     - Bone density testing is expensive and very low yield.
When should I repeat laboratory evaluation after starting supplementation?

- Labs should be repeated in 6 to 12 weeks.

Does insurance typically cover supplementation?

- Insurance usually does not cover vitamin D supplementation. Very high doses (i.e. 50,000 International Units per week) may be available through prior authorization (PAR), but are not typically recommend except in cases of severe deficiency.

**PARENT AND PROVIDER EDUCATION MATERIALS**

Handouts:

- Vitamin D supplements
- Dosing chart
- Table of dietary vitamin D
Dear Provider,

Our lab received a request for 1,25 dihydroxy vitamin D for your patient, (Name, DOB). This request requires review before it will be sent for processing. Recent studies found that more than 50% of orders were placed in error, where 25-hydroxy vitamin D was the intended test to assess nutritional status.

25-hydroxy vitamin D is most useful in nutrition assessment, primarily due to its longer half-life. It is elevated with vitamin D intoxication, and decreased with malabsorption, nutritional deficiency, and in liver disease. This test is performed daily in Children's Hospital Colorado Laboratory.

The circulating half-life of 1,25 dihydroxy vitamin D is relatively short, which limits utility for overall vitamin D assessment. Testing can be useful in the diagnosis of renal dysfunction in conjunction with parathyroid hormone. 1,25-dihydroxy is elevated in sarcoidosis and primary hyperthyroidism, and decreased in renal failure and hypoparathyroidism.

There are two options for how to proceed with this test:

- We can cancel the order for 1,25 dihydroxy vitamin D and you can write an add-on communication for 25 hydroxyl vitamin D - we do not need a new order or specimen.
- Proceed with the test as you have ordered it.

Please let us know if we can be helpful and how you want to proceed. We apologize for any inconvenience if this was the test you intended.

Sincerely,

The Laboratory Team and Vitamin D Committee at Children's Hospital Colorado
REFERENCES

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