VITAMIN B_{12} DEFICIENCY –

THE IMPORTANCE OF TESTING AND DIAGNOSING

Nearly **1 in 6 Americans** may be vitamin B_{12} deficient[1]

IT'S IMPORTANT FOR HEALTHCARE PROFESSIONALS TO RECOGNIZE VITAMIN B_{12} DEFICIENCY

Adequate levels of vitamin B_{12} are essential for the body to function properly. This important nutrient helps keep the body's nerve and blood cells healthy, and it's used in the formation of the genetic material in the DNA of all cells.[1]

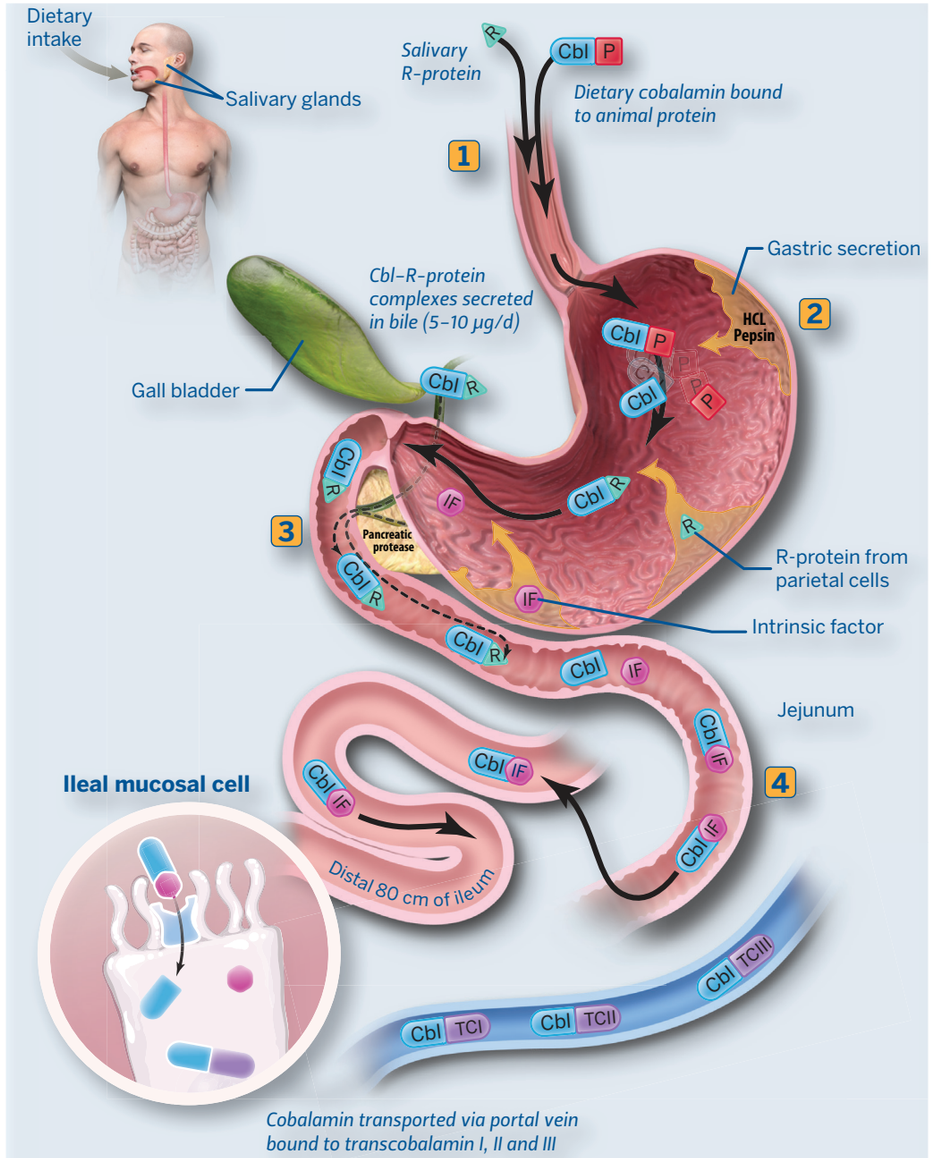
WHAT CAN CAUSE VITAMIN B_{12} DEFICIENCY?

The process of vitamin B_{12} absorption is complicated, requiring several steps to allow complete absorption by the body. Defects in any one of these steps may result in lower absorption of vitamin B_{12} and, ultimately, deficiency.[2]

A significant amount of vitamin B_{12} is stored in the liver.[3,4] If neither dietary intake nor liver stores are sufficient to meet the body's needs, a person becomes vitamin B_{12} deficient.[4]

DEFECTS IN VITAMIN B_{12}

DIGESTION AND ABSORPTION[4]



Adapted from Andrès E, et al. *CMAJ*. 2004;171(3):251-259.

1. Vitamin B_{12} enters the body in food. It travels from the mouth through the esophagus into the stomach, where it is cleaved from its binding protein by acid and pepsin.[2]
2. In the stomach, it binds to R factor, which is produced in the saliva and stomach.[2]
3. The complex of vitamin B_{12} and R factor travels to the duodenum. Here, vitamin B_{12} is cleaved from the R factor by pancreatic proteases and binds to intrinsic factor, also produced in the stomach.[2]
4. This compound then travels to the ileum, where it binds to a receptor called cobalamin, and is absorbed through the ileal mucosa.[2]

CAUSES OF VITAMIN B_{12} DEFICIENCY

RISK FACTORS THAT CAN LEAD TO VITAMIN B_{12} DEFICIENCY[5]:

- Celiac disease[6,7]
- Alcohol abuse
- Strict vegetarian or vegan diet
- Long-term use of certain medications such as metformin and proton pump inhibitors
- Immune system disorders[8]
- HIV infection[8]
- Crohn's disease
- Atrophic gastritis
- Gastric surgery
- Hypothyroidism[9]

SYMPTOMS OF VITAMIN B_{12} DEFICIENCY ARE NON-SPECIFIC

Symptoms may include[1,10]:

- Diarrhea or constipation
- Fatigue, muscle weakness[10,11]
- Loss of appetite
- Pale skin[11]
- Memory loss[10]
- Shortness of breath[11]
- Swollen, red tongue[10]
- Numbness and tingling of hands and feet
- Confusion or change in mental status
- Loss of balance

Some patients have biochemical evidence of vitamin B_{12} deficiency without apparent symptoms.[12]

THAT IS WHY IT IS IMPORTANT TO TEST FOR VITAMIN B_{12} DEFICIENCY

Thus, blood level testing is an important first step to determine if a patient has a deficiency of vitamin B_{12}. Normal serum concentrations of vitamin B_{12} range from 200 to 900 picograms per milliliter (pg/mL).[13] If levels drop below this range, patients may experience the clinical symptoms of vitamin B_{12} deficiency, or they may be asymptomatic.[12]

ARE BLOOD TESTS SUFFICIENT?

If a patient has low serum levels of vitamin B_{12} and is symptomatic, no further testing is needed. For others, additional testing using several different methodologies can enable providers to make a confident diagnosis. Three additional modalities for identifying vitamin B_{12} deficiency are tests for serum homocysteine, methylmalonic acid (MMA), and folic acid levels.[14]

HOMOCYSTEINE

Homocysteine is an amino acid that produces methionine. A deficiency in vitamin B_{12} results in accumulation of homocysteine. Thus, in the setting of vitamin B_{12} deficiency, patients would be expected to have elevated homocysteine levels.[14] Typically, laboratories report normal homocysteine levels ranging between 4 and 15 micromoles/liter (µmol/L). Measurements above 15 are considered high.[15]

METHYLMALONIC ACID (MMA)

MMA is a substance that is produced by the body in very small amounts. MMA is needed for energy production and metabolism. In one metabolic process, vitamin B_{12} enables conversion of a form of MMA to succinyl coenzyme A. When not enough vitamin B_{12} is available, the body's MMA level begins to rise. Measuring MMA in the blood or urine allows physicians to detect early vitamin B_{12} deficiency. MMA is considered a sensitive indicator of vitamin B_{12} deficiency. This test is understood to be more specific than homocysteine. Thus, MMA is the confirmatory test of choice for vitamin B_{12} deficiency.[16]

FOLIC ACID

It's important to check folic acid levels, as high levels of folic acid may mask vitamin B_{12} deficiency or result in elevated levels of homocysteine.[14,17]

INDICATIONS

- Vitamin B_{12} maintenance therapy in adult patients with pernicious anemia who are in remission following intramuscular vitamin B_{12} therapy and who have no nervous system involvement
- Treatment of adult patients with dietary, drug-induced, or malabsorption-related vitamin B_{12} deficiency not due to pernicious anemia
- Prevention of vitamin B_{12} deficiency in adult patients with vitamin B_{12} requirements in excess of normal

Limitations of Use

- NASCOBAL® should not be used for the vitamin B_{12} absorption test (Schilling test).
- In patients with correctible or temporary causes of vitamin B_{12} deficiency, the benefit of continued long-term use of NASCOBAL® following adequate correction of vitamin B_{12} deficiency and underlying disease has not been established.
- The effectiveness of NASCOBAL® in patients with active symptoms of nasal congestion, allergic rhinitis or upper respiratory infection has not been determined. Treatment with NASCOBAL® should be deferred until symptoms have subsided.

Please see Important Safety Information on page 7.
Please click here for full Prescribing Information.

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray

THE FIRST FDA-APPROVED PRESCRIPTION

VITAMIN B_{12} NASAL SPRAY

CLINICALLY PROVEN TO HAVE INCREASED VITAMIN B_{12} LEVELS FROM THE FIRST DOSE[18]

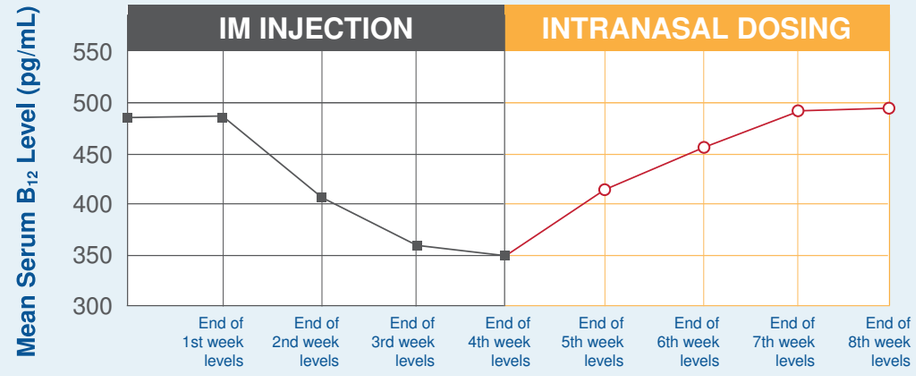
- Achieved mean peak serum vitamin B_{12} concentration within 1.5 hours[18]*
- Reached mean peak concentration of 1021 pg/mL[18]*
- At 72 hours, mean serum vitamin B_{12} level was increased by 46% above baseline[18]*

*In 21 healthy volunteers under fasting conditions, a single 500-mcg dose of NASCOBAL® was given and monitored for 3 days. Data are based on baseline-uncorrected serum vitamin B_{12} levels.[18]

INTRANASAL ADMINISTRATION HAS MAINTAINED

HEALTHY VITAMIN B_{12} LEVELS

Serum vitamin B_{12} levels in patients with pernicious anemia[19]



- Once-a-week intranasal dosing maintained higher serum vitamin B_{12} levels than 1 intramuscular vitamin B_{12} injection after 28 days

In 24 patients with a history of pernicious anemia, a single-dose cyanocobalamin 100 mcg/mL intramuscular (IM) injection was given and monitored for 28 days, followed by 4 once-weekly doses of intranasal (IN) vitamin B_{12} gel 500 mcg/0.1 mL. Mean baseline serum vitamin B_{12} prior to IN dosing = 351.4 pg/mL, and at day 28 = 480.7 pg/mL.[19]

In a separate study, bioavailability of vitamin B_{12} nasal spray was 10% less than vitamin B_{12} nasal gel. Clinical significance is unknown.[3]

HOW TO USE
NASCOBAL® NASAL SPRAY

CONVENIENT, ONCE-WEEKLY DOSING REGIMEN

Self-administered: 1 spray, 1 nostril, 1x a week[3]

Product shown may not be actual size.

NASCOBAL® Nasal Spray should be administered at least one hour before or one hour after ingestion of hot foods or liquids.

Dose adjustments may be required.

AN AFFORDABLE TREATMENT
FOR VITAMIN B_{12} DEFICIENCY

ELIGIBLE PATIENTS MAY GET NASCOBAL® FOR AS LITTLE AS $0 PER MONTH*

*Patients may redeem this offer ONLY when accompanied by a valid prescription. Offer is valid up to a maximum benefit of $150. Offer is not valid for patients whose prescriptions are reimbursed in whole or in part under Medicaid, Medicare, Medigap, VA, DoD, TRICARE, or any other federal or state programs (such as medical assistance programs) or where otherwise prohibited by law. Offer is not valid in VT or where prohibited in whole or in part. This offer may be amended or ended at any time without notice.

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IMPORTANT SAFETY INFORMATION
FOR NASCOBAL® NASAL SPRAY

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Limitations of Use

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IMPORTANT SAFETY INFORMATION FOR NASCOBAL® NASAL SPRAY

NASCOBAL® is contraindicated in patients with sensitivity to cobalt, vitamin B_{12}, or any component of the medication. Anaphylactic shock and death have been reported with parenteral forms of vitamin B_{12}. Consider administering an intradermal test dose of parenteral vitamin B_{12} to patients suspected of cyanocobalamin hypersensitivity prior to starting NASCOBAL®.

Patients with Leber's disease who were treated with vitamin B_{12} suffered severe and swift optic atrophy. NASCOBAL® is not recommended for use in patients with Leber's optic atrophy.

Doses of vitamin B_{12} exceeding 10 mcg daily may produce hematologic response in patients with folate-deficient megaloblastic anemia, and may therefore mask a previously unrecognized folate deficiency. NASCOBAL® is not a substitute for folic acid. Assess both vitamin B_{12} and folate levels prior to initiating therapy with NASCOBAL®.

Hypokalemia, thrombocytosis and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B_{12}. Serum potassium levels and platelet count should be monitored.

Please see additional Important Safety Information on next page.

Please click here for full Prescribing Information.

NASCOBAL®
(Cyanocobalamin, USP) Nasal Spray

IMPORTANT SAFETY INFORMATION FOR NASCOBAL® NASAL SPRAY

IMPORTANT SAFETY INFORMATION FOR NASCOBAL® NASAL SPRAY (continued)

Treatment with vitamin B_{12} may unmask signs of polycythemia vera. Patients exhibiting clinical or hematologic response consistent with polycythemia vera should be referred for further evaluation.

Hematocrit, reticulocyte count, vitamin B_{12}, folate and iron levels should be obtained prior to treatment. Consider the potential for concomitant drugs to interfere with vitamin B_{12} and folate diagnostic blood assays. Vitamin B_{12} and peripheral blood counts must be monitored initially at one month after the start of treatment, and then at intervals of 3 to 6 months. If a patient is not properly maintained with NASCOBAL®, consider alternative therapy.

If NASCOBAL® is used concomitantly with chloramphenicol, monitor for reduced efficacy and, if needed, consider an alternative therapy.

The limited available data on NASCOBAL® in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes.

The most common adverse reactions (≥4%) were infection, headache, glossitis, paresthesia, asthenia, nausea and rhinitis.

Please click here for full Prescribing Information.

References: 1. National Institutes of Health, Office of Dietary Supplements. Vitamin B12 fact sheet for consumers. https://ods.od.nih.gov/pdf/factsheets/VitaminB12-Consumer.pdf. Updated July 7, 2021. Accessed August 17, 2023. **2.** Headstrom PD, Rulyak SJ, Lee SD. Prevalence of and risk factors for vitamin B12 deficiency in patients with Crohn's disease. *Inflamm Bowel Dis*. 2008;14(2):217-223. **3.** NASCOBAL® [prescribing information]. Chestnut Ridge, NY: Par Pharmaceutical Companies. **4.** Andrès E, Loukili NH, Noel E, et al. Vitamin B12 (cobalamin) deficiency in elderly patients. *CMAJ*. 2004;171(3):251-259. **5.** Langan RC, Zawistoski KJ. Update on vitamin B12 deficiency. *Am Fam Physician*. 2011;83(12):1425-1430. **6.** Dahele A, Ghosh S. Vitamin B12 deficiency in untreated celiac disease. *Am J Gastroenterol*. 2001;96(3):745-750. **7.** Wierdsma NJ, van Bokhorst-de van der Schueren MAE, Berkenpas M, Mulder CJJ, van Bodegraven AA. Vitamin and mineral deficiencies are highly prevalent in newly diagnosed celiac disease patients. *Nutrients*. 2013;5(10):3975-3992. **8.** Vitamin B12 deficiency: anemia. Johns Hopkins Medicine website. https://www.hopkinsmedicine.org/health/conditions-and-diseases/vitamin-b12-deficiency-anemia. Accessed August 17, 2023. **9.** Collins AB, Pawlak R. Prevalence of vitamin B-12 deficiency among patients with thyroid dysfunction. *Asia Pac J Clin Nutr*. 2016;25(2):221-226. **10.** Vitamin B12-deficiency anemia. National Heart, Lung, and Blood Institute website. https://www.nhlbi.nih.gov/health/anemia/vitamin-b12-deficiency-anemia. Accessed August 17, 2023. **11.** Vitamin deficiency anemia. Mayo Clinic website. https://www.mayoclinic.org/diseases-conditions/vitamin-deficiency-anemia/symptoms-causes/syc-20355025. Accessed August 17, 2023. **12.** Carmel R. How I treat cobalamin (vitamin B12) deficiency. *Blood*. 2008;112(6):2214-2221. **13.** Herbert V. Staging vitamin B-12 (cobalamin) status in vegetarians. *Am J Clin Nutr*. 1994;59(5 suppl):1213S-1222S. **14.** Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. *Arch Intern Med*. 1999;159(12):1289-1298. **15.** Wedro B. Homocysteine blood test. eMedicineHealth website. https://www.emedicinehealth.com/homocysteine/article_em.htm. Updated February 6, 2020. Accessed August 17, 2023. **16.** Methylmalonic acid test (MMA). Testing.com website. https://www.testing.com/tests/methylmalonic-acid/. Updated November 9, 2021. Accessed August 17, 2023. **17.** Selhub J, Morris MS, Jacques PF, Rosenberg IH. Folate-vitamin B-12 interaction in relation to cognitive impairment, anemia, and biochemical indicators of vitamin B-12 deficiency. *Am J Clin Nutr*. 2009;89(2):702S-706S. **18.** Data on File. DOF-NS-02. Endo Pharmaceuticals Inc.; 2016. **19.** Data on File. DOF-NS-01. Endo Pharmaceuticals Inc.; 2015.

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