JAMA Diagnostic Test Interpretation

Interpretation of Vitamin B_{12} Status After a Roux-en-Y Gastric Bypass

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A 37-year-old woman with a history of diabetes, hypertension, obstructive sleep apnea, depression, and Roux-en-Y gastric bypass (RYGB) 16 years prior presented to an ambulatory care clinic with fatigue, loss of appetite, and hair loss. She lost 50.8 kg from the time of the procedure to presentation, her body mass index at presentation was 23, and her preoperative comorbidities were in remission. She did not have any nausea, abdominal pain, or change in bowel habits, but her periods had been more irregular over the past 2 to 3 months and, when present, lasted for 7 to 10 days. She also noted a tingling sensation in her hands and feet. She was under some financial stress after recently losing her job, and reported drinking 2 to 6 beers within a 2-hour period on the weekends. She took a gummy multivitamin sporadically and self-reported a daily total calorie intake of less than 500 kcal and less than 20 g of protein. On physical examination, although she reported having paresthesias in her fingertips and toes, her neurological examination findings were nonfocal. She exhibited bilateral flattening of the temporalis muscle and thenar eminence. Her vital signs were normal, and serum tests were ordered (**Table**).

HOW DO YOU INTERPRET THESE RESULTS?

A. This patient has iron deficiency anemia in the setting of polycystic ovarian syndrome.

B. This patient has B_{12} deficiency.

C. The patient has both iron and vitamin B_{12} deficiencies.

D. The patient has anemia of chronic disease.

Table. Patient's Laboratory Results

Test	Patient's Value	Reference Range
Vitamin B_{12}, pg/mL	149	200-910
Hemoglobin, g/dL	8.3	12.0-16.0
Hematocrit, %	28.1	37.0-47.0
Mean corpuscular volume, fL	64.2	81.0-99.0
Iron, µg/dL	13	37-145
Ferritin, ng/mL	<8	13-126
Vitamin D (25-hydroxyvitamin D), ng/mL	43	30-100
Parathyroid hormone, pg/mL	45	15-65
Thyrotropin, mIU/L	0.66	0.35-4.00
Thiamine, nmol/L	200	70-180
Vitamin A, µg/dL	40	38-98
Albumin, g/dL	4	3.3-4.8

SI conversion factors: To convert vitamin B_{12} to pmol/L, multiply by 0.7378; hemoglobin and albumin to g/L, multiply by 10.0; mean corpuscular volume to μm^3, multiply by 1.0; iron to µmol/L, multiply by 0.179; ferritin to pmol/L, multiply by 2.247; vitamin D (25-hydroxyvitamin D) to nmol/L, multiply by 2.496; parathyroid hormone to ng/L, multiply by 1.0; vitamin A to µmol/L, multiply by 0.0349.

Answer

C. The patient has both iron and vitamin B_{12} deficiencies.

The patient has B_{12} deficiency and concomitant iron deficiency anemia. From her history, this is likely secondary to nonadherence with postoperative vitamin supplementation recommendations.

Test Characteristics

Vitamin B_{12} (cobalamin) is a water-soluble vitamin, necessary for neurologic functioning, hematopoiesis, and DNA synthesis. It is obtained exclusively from animal proteins and absorbed in the ileum, facilitated by intrinsic factor.

Serum B_{12} is measured with a competitive-binding immunoenzymatic assay. Intrinsic factor conjugate and paramagnetic particles coated with monoclonal immunoglobulin G anti–intrinsic factor are added to the sample. B_{12} binds to the intrinsic factor conjugate, blocking it from binding with the paramagnetic particles. A magnetic field holds the particle-bound intrinsic factor in place while unbound materials are washed away. Finally, a chemiluminescent substrate is added and the light is measured with a luminometer. The light production is inversely proportional to the concentration of vitamin B_{12} in the sample. Sensitivity for deficiency detection is 95% at levels less than 200 pg/mL (<150 pmol/L), but specificity is limited to 50%. Serum B_{12} less than 400 pg/mL is considered suboptimal because 5% to 10% of patients with neurologic symptoms related to B_{12} insufficiency present with levels from 200 to 400 pg/mL.[1] At levels greater

than 200 pg/mL, sensitivity is reduced and can be bolstered by serum methylmalonic acid (MMA). During the Krebs cycle, B_{12} mediates the enzymatic conversion of methylmalonyl-coenzyme A to succinyl-coenzyme A; therefore, MMA levels greater than 0.75 µmol/L are suggestive of B_{12} deficiency.[2]

Neurologic symptoms, most commonly parasthesias, may be observed at serum levels as high as 280 mg/mL and often precede hematological abnormalities, such as macrocytic anemia or hypersegmented neutrophils.[3] Many individuals with paresthesias alone have nonfocal examination findings; however, common signs of deficiency include impaired vibration and pain perception as well as proprioception.[4] The Medicare midpoint reimbursement for serum B_{12} is $27.94.[5]

Application of Test Results to This Patient

Although B_{12} deficiency can cause anemia, it is unlikely in the current case. B_{12} deficiency usually causes macrocytic anemia. When combined with iron deficiency, one may expect normocytic anemia. The microcytosis, low iron, and ferritin all indicate anemia secondary to iron deficiency alone. This patient's anemia is likely secondary to menses, inadequate iron supplementation, and reduced iron absorption. Gummy vitamins commonly do not contain minerals, likely making her supplementation insufficient.

Because it takes several years of poor nutrition to deplete stores, prevalence of B_{12} deficiency after RYGB is about 20%.[2] The current patient's combination of symptomatic B_{12} deficiency, overt signs of malnutrition, and poor dietary intake indicate chronic nonadherence with nutrition and supplementation guidelines. Given that the psychiatric comorbidity for patients who undergo RYGB is 3.2 times higher than age- and sex-matched normal-weight controls,[6] clinicians should investigate secondary causes of nonadherence. The patient's malnutrition and occasional binge drinking (≥4 servings within 2 hours) overlapped with a history of financial stress and depression indicate a psychosocial etiology of nonadherence that warrants a comprehensive clinical approach.

Alternative Diagnostic Testing Approaches

Apart from MMA, serum homocysteine may be considered as an additional second-line test, although it is less specific than MMA. Homocysteine is converted into methionine via methylation from L-methylfolate, mediated by B_{12}. Therefore, it is elevated in individuals with B_{12} and folate deficiencies. Diagnostic testing for pernicious anemia could be considered, but because all patients who undergo bariatric surgery require lifelong B_{12} supplementation, it would not have changed the patient's treatment.

Patient Outcome

The patient began ingesting protein shakes containing 30 g of protein twice daily, 500 mg of calcium citrate 3 times daily, 60 mg of elemental iron twice daily, a multivitamin with minerals daily, 2000 IU of vitamin D daily, and 1000 µg of sublingual B_{12} daily, resulting in improvement of her symptoms and laboratory abnormalities, specifically her low B_{12} level and iron deficiency anemia.

Apart from active absorption via intrinsic factor, 1% of B_{12} is passively absorbed along the length of the small bowel. Therefore, daily oral or sublingual supplementation of 700 to 2000 µg is generally more than sufficient to meet daily needs (2.4 µg/d) and resolve deficiency within weeks.[7,8]

Further questioning of the patient revealed a suicide attempt 4 weeks prior to presentation. She attributed her poor appetite and dietary intake to worsening depression. The patient began intensive outpatient psychotherapy with a psychotropic regimen and began experiencing significant improvement in her mood.

Clinical Bottom Line

- Clinicians should routinely screen the nutritional status of patients who undergo bariatric surgery.
- Clinicians should evaluate and manage psychosocial etiologies of behavioral nonadherence.
- All patients who have undergone bariatric surgery require lifelong vitamin and mineral supplementation.

ARTICLE INFORMATION

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