Vitamin B12 deficiency is a common problem in older people, presenting as a macrocytic anaemia. The prevalence of low levels of folate and vitamin B12 increases as people age. Over 20% of older Australians have low vitamin B12 levels.

Adequate treatment is essential as vitamin B12 is necessary for the development of red blood cells, normal growth and nervous system maintenance. Vitamin B12 deficiency causes anaemia, fatigue, mood disturbance and other neuropsychiatric and neurological complications.

Vitamin B12 deficiency has also been linked with an increased risk of myocardial infarction and stroke. Decreases in folate and vitamin B12 concentrations may result in an increase in homocysteine concentrations, an independent risk factor for cardiovascular disease.

Absorption
Vitamin B12 or cyanocobalamin is a water-soluble vitamin tightly bound to dietary proteins. The absorption is almost entirely dependent upon intrinsic factor, a glycoprotein secreted by the parietal cells in the stomach.

Gastrointestinal absorption of dietary vitamin B12 is a complex process. Hydrochloric acid and pepsin release the vitamin from proteins in the gut where it binds with salivary proteins. After alteration by pancreatic enzymes, cyanocobalamin is bound to intrinsic factor in the upper gastrointestinal tract where it forms a complex that is absorbed in the terminal ileum. The ileum is the final section of the small intestine.

Vitamin B12 is stored in the liver.

Causes
Reduced dietary intake is the most common cause of vitamin B12 deficiency. Vegetarians and vegans are at higher risk of vitamin B12 deficiency. Foods derived from animals such as meat, milk, eggs, fish, oysters and shellfish are the major dietary sources of vitamin B12.

The most common, non-dietary cause of vitamin B12 deficiency is pernicious anaemia. In pernicious anaemia, which is usually an autoimmune disease, autoantibodies directed against intrinsic factor or parietal cells themselves lead to an intrinsic factor deficiency, malabsorption of vitamin B12, and subsequent megaloblastic anaemia.

Other reasons may be due to malabsorption, increased requirements in pregnancy, and decreased utilisation caused by certain enzyme deficiencies. It may also be a consequence of obesity surgery.

Food-cobalamin malabsorption appears to be due to an inability to absorb protein-bound cobalamin without gastric abnormalities such as partial gastrectomy, or vagotomy. This absorption inability may be related to impaired release of cobalamin from its binding proteins, especially in patients with acid or pepsin deficiency. Therefore, food-cobalamin malabsorption is common among patients with atrophic gastritis (whether or not they also have Helicobacter pylori infection) or reduced acid secretion.

Malabsorption occurs with total or partial gastrectomy, and ileal disease or resection. Vitamin B12 deficiency commonly occurs with malabsorption syndromes such as Crohn’s disease and coeliac disease.

Vitamin B12 deficiency can also occur as a result of malabsorption due to bacterial overgrowth.

Medication-related causes
Proton pump inhibitors (omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole) reduce acid secretion and are used for the treatment of peptic ulcers, gastroesophageal reflux, dyspepsia and heartburn. Long-term use of high doses can lead to a deficiency of vitamin B12. Deficiency may develop after three to four years use. Proton pump inhibitors should be regularly reviewed for ongoing need, and a trial of lower doses or intermittent therapy where appropriate.

continued over
Metformin is an effective hypoglycaemic agent considered as first line therapy in people with type 2 diabetes. It is associated with less weight gain than other oral therapy, and has substantial evidence for decreased hypoglycaemia, myocardial infarction, stroke and death.

Higher dose and longer duration of metformin use increases the risk for vitamin B12 deficiency in people with diabetes. Metformin treatment has also been associated with decreased folate concentration.

Metformin may disrupt the absorption of vitamin B12 and intrinsic factor in the ileum. Increased calcium intake can reverse this effect.

**Signs and symptoms**

Vitamin B12 deficiency should be suspected in the following circumstances and warrants further investigation:

- Unexplained anaemia
- Unexplained neurological or psychiatric features
- Gastrointestinal problems such as sore tongue, anorexia, diarrhoea
- Prolonged use of certain medications

The consequences of clinically important decreases in vitamin B12, such as macrocytic anaemia, neuropathy and mental changes, can be profound. Specific signs and symptoms of vitamin B12 deficiency include:

- Neurologic – difficulty walking, loss of vibratory sense, impaired sense of touch, peripheral neuropathy
- Psychiatric – irritability, personality changes, depression, psychosis, mild memory impairment
- Cardiovascular – possible increased risk of myocardial infarction and stroke, palpitations
- anorexia, mild weight loss diarrhoea, atrophic glossitis
- Urologic – difficulty in urination
- Dyspnoea
- Vertigo
- Tinnitus

Giving folic acid supplements to a person deficient in vitamin B12 without B12 supplementation can lead to an irreversible exacerbation in neurological features.

**Prevention**

Strict vegetarians are at higher risk of developing B12 deficiency because of low intake of animal-source foods. Thus, it is necessary to use plant sources of vitamin B12 to prevent vegetarians from developing a deficiency. These include soybeans, mushrooms and B12 fortified foods such as cereals.

Routine monitoring of vitamin B12 levels should be considered in people prescribed regular proton pump inhibitors and metformin.

**Treatment**

Most patients with vitamin B12 deficiency require maintenance therapy for life. Replacement therapy may be either oral or by intramuscular injection.

The injectable forms include:

- Cyanocobalamin 10mg/mL
- Hydroxocobalamin 1000mcg/mL *(Hydroxo-B12, Neo-B12)*

If vitamin B12 deficiency is associated with severe anaemia or neurological symptoms, high dose IM injections are required. Initial treatment involves a dose of IM 1000 micrograms on alternate days for one to two weeks, followed by either IM 1000 micrograms of cyanocobalamin once a month or IM 1000 micrograms of hydroxocobalamin every 2 to 3 months. IM hydroxocobalamin produces a greater and more sustained increase in serum vitamin B12 than does the same dose of cyanocobalamin. IM administration is recommended for malabsorption of vitamin B12.

After the first injection, malaise usually improves within 2 days while the blood count peaks at about 7 days. Serum iron falls after 1 to 2 days in some patients, and they may need iron supplements. Potassium supplements may also be needed. The haemoglobin concentration normally increases by about 10 g/L per week. The neuropathy improves slowly with therapy but some patients will have residual defects.

Oral cyanocobalamin in doses of 50 to 200 micrograms daily given between meals is appropriate for dietary deficiency.

**References**

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