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Assessment of cobalamin status

FROM THE LABORATORY

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Cobalamin is needed for normal cell metabolism, but a deficiency in the vitamin can be difficult to diagnose. There is currently no consensus on how to define biochemical cobalamin deficiency, particularly in a subclinical form.

Cobalamin (vitamin B12) is produced by soil bacteria, and the main dietary sources are meat, fish, shellfish, eggs, milk and dairy products. A normal diet provides 5–7 µg cobalamin per day, a vegetarian diet with eggs and dairy products provides <0.5 µg, while a vegan diet provides no cobalamin. A daily intake of between 4 and 7 µg is associated with adequate cobalamin status in young adults. Cobalamin levels in breastmilk depend on the mother's status and are usually high in the first few weeks following birth, but subsequently decrease (1).

The incidence of cobalamin deficiency varies according to the definition and is reported to be between 2.5 % and 26 % (1). The incidence of moderate cobalamin deficiency is high in pregnant women (2) and exclusively breastfed infants (1). Moderate cobalamin deficiency in infants is associated with developmental delays (3), and it has been proposed that cobalamin status be included in neonatal screening (4).

The majority of the vitamin is actively absorbed in the terminal ileum, but 0.5–4 % is absorbed passively. The release of cobalamin from dietary protein requires low gastric pH. Following release, cobalamin binds to the transport protein haptocorrin. The binding must be degraded by pancreatic enzymes prior to absorption. Active absorption in the terminal ileum requires binding to intrinsic factor, which is produced in the stomach. The risk of cobalamin deficiency increases with disease or use of medication that affects secretion of gastric acid or pancreatic enzymes, production and function of intrinsic factor or the terminal ileum.

Together with folate, cobalamin is required to convert homocysteine to methionine, which is the body's primary methyl group donor. Homocysteine levels rise if there is a deficiency of cobalamin or folate. Cobalamin is also a cofactor in the conversion of methylmalonyl-coenzyme A to succinyl-coenzyme A. Cobalamin deficiency leads to elevated methylmalonic acid levels.

Assessment of cobalamin status

Measurement of serum cobalamin is recommended as the primary assessment of cobalamin status, but the levels may vary according to the measurement method and also be affected by haptocorrin levels (1).

In case of doubt, it may be appropriate to analyse levels of the metabolic markers homocysteine and methylmalonic acid. In adults, homocysteine is primarily a folate marker, while methylmalonic acid is primarily a cobalamin marker. In patients with cobalamin deficiency, levels of methylmalonic acid rise, but interpretation can be difficult since both markers vary with age and sex and increase in impaired renal function (1).

The majority of cobalamin in blood is bound to haptocorrin, while around 20 % is bound to the functionally active protein transcobalamin. Analysis of holotranscobalamin measures cobalamin bound to transcobalamin, but is of debatable value (1).

Haptocorrin levels may be genetically low and also decrease during pregnancy and with the use of medications containing oestrogen (contraceptive pills and postmenopausal oestrogen replacement). These patients have low serum cobalamin levels, but normal levels of homocysteine and methylmalonic acid (1).

Hepatic disease, myeloproliferative disease and cancer can increase haptocorrin levels and lead to high serum cobalamin levels (> 800 pmol/l) (1). Therefore, it is recommended that new onset of high serum cobalamin levels not due to supplementation should be investigated (5).

What is an adequate cobalamin status?

Studies have demonstrated increased DNA damage and hypomethylation at serum cobalamin levels <300 pmol/l (6). Patients with levels lower than this should receive dietary advice and potentially cobalamin supplementation, unless the low levels are suspected to be false due to low haptocorrin levels (1).

Both homocysteine and methylmalonic acid levels are considerably reduced and difficult to interpret in pregnant women. Serum cobalamin levels of > 275 pmol/l are recommended in week 18 of pregnancy to ensure adequate cobalamin status in the infant (2).

Levels of methylmalonic acid are often high in children below the age of 5 years irrespective of cobalamin status, and use of these levels is not recommended for assessment of cobalamin status. In this age group, homocysteine is a cobalamin marker, and plasma levels > 6.5 µmol/l are indicative of cobalamin deficiency (3).

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