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Commentary

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Supraphysiological vitamin B12 serum concentrations without supplementation: the pitfalls of interpretation

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Serum vitamin B12 (cobalamin) concentrations are usually measured in order to detect a deficiency. However, in routine laboratory practice serum vitamin B12 (B12) levels are more often above than below normal.[1] Supraphysiological serum B12 levels may result from high dose supplementation, more often, however, they are due to increased levels of the sequestered form of the vitamin.[2] The most commonly used assay for serum B12[3] measures both the free vitamin and the fraction bound to carrier proteins (holohaptocorrin or transcobalamin) or immunoglobulins.[1] Therefore total serum B12 concentrations may not always reflect intracellular B12 levels, additionally a functional deficiency of the vitamin could be obscured, which still cannot be detected by an established gold standard. Recent publications have suggested the estimation of at least one additional biomarker (holotranscobalamin, homocysteine or methylmalonic acid) in this situation.[3]

Besides the difficulties of a precise measurement of serum B12 concentrations, the various pathophysiological causes of elevated B12 levels create further pitfalls. High B12 concentrations due to high levels of immunoglobulin-(transcobalamin)-B12 complexes may be due to excessive levels of the vitamin, increased levels of its transport proteins[1] or related to autoimmune or haematological disorders.[4] The estimated prevalence of immunoglobulin complexes causing or contributing to elevated serum B12 concentrations ranges between 8% and 25%.[1,4] Immune-sequestered B12 cannot enter cells and therefore is not biologically active. However, in case reports patients with high levels of immune-sequestered B12 did not show distinctive features of B12 deficiency, thereby suggesting normal concentrations of free B12.[1] Indeed, normal serum B12 levels were detected after precipitation of the immunoglobulins.[4] Furthermore, the presence of autoantibodies against B12 is not associated with a resistance to supplemented B12.[1] However, the development of antibodies against B12 or B12-binding proteins should be further investigated, in particular with regard to the underlying aetiology.

High or supraphysiological serum B12 levels without supplementation have been associated with many pathological conditions including renal failure, haematological disorders, cancer, and hepatic or autoimmune diseases.[4,5] All conditions may show elevated concentrations of B12 transport proteins. In addition, in liver disease there may be an increased release of B12 due to hepatic cytolysis and/or reduced B12 clearance.[1] Thus, a high or supraphysiological serum B12 concentration without supplementation could be useful as diagnostic marker for a severe underlying disease.[2,5]

Furthermore, very high serum B12 levels may be of prognostic significance. High levels have been frequently reported in critically ill patients[5] and were associated with higher mortality.[6] In studies on palliative cancer patients, the combination of both elevated serum levels of B12 and of c-reactive protein (CRP) was a negative prognostic factor, as it was associated with reduced survival.[7]

Elevated serum B12 levels may also be associated with a functional deficiency of the vitamin. Functional deficiency has been described despite high B12 concentrations and is due to a failure of cellular uptake or intracellular processing, trafficking or utilization.[3,5] Cellular uptake is reduced due to pathological increases of B12-binding proteins other than transcobalamin II,[5] or to formation of immunoglobulin-B12-complexes.[1] It is still unknown, whether B12 should be supplemented in these conditions.

Recent findings in diseases associated with oxidative stress have revealed that intracellular oxidative stress results in local functional B12 deficiency.[8] Insufficient intracellular processing of B12 due to oxidative stress has been reported in diabetes mellitus or in Alzheimer's disease,[9,10] where it has been postulated to be a significant pathophysiological factor.[9] Intracellular reduction of the central cobalt atom is essential for the formation of the metabolically active forms of B12. This process requires

reduced glutathione and the hydroquinone form of flavin adenine dinucleotide (FADH2), it is therefore compromised by oxidative stress.[9] In such conditions treatment with glutathione and/or vitamin C, a key physiological regenerator of intracellular glutathione, may provide therapeutic benefit. This warrants further investigation.

B12 as a key co-factor in metabolic methylation is involved in several vital biological processes. Therefore, supplementation is important for rapid restoration of the B12 status, which is indicated by low serum levels. However, also normal or supraphysiological B12 levels should be carefully assessed in the context of the individual state of health. Supraphysiological levels may even serve as a new important diagnostic marker in serious conditions unrelated to the individual patient's B12 status. Valid alternative markers and gold standard determination methods are therefore urgently needed.

In conclusion, more research is required, particularly with the aim of acquiring data that would allow improved diagnostic guidelines on the interpretation of high serum B12 levels.

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