

HYPERVITAMINOSIS B12

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HIPERVITAMINOZA B12

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ABSTRACT

Increased concentrations of vitamin B12 are the result of excessive intake of this vitamin, increased release of vitamins from hepatic depots, or elevated concentrations of transcobalamin resulting from the increased production or reduced decomposition of this molecule. The most common diseases that lead to B12 hypervitaminosis are malignancies and solid tumours. As a result of elevated concentrations, acnes emerge or exacerbate the already existing acneiform changes. Rosacea fulminant, allergic, and other anaphylactic reactions may also develop. The aim of the study was to determine the effect of increased concentrations of vitamin B12 onto human health. In a study conducted by Deneuvil and associates, the elevated B12 vitamin levels were observed in 12% of respondents. In the study by Carmel and associates, 14% of the respondents had high cobalaminemia. The results of other studies show that the prevalence of high cobalaminemia is 13%, while very high cobalaminemia is registered in 7% of cases. In the multicentric BDOSE study, the incidence of high serum cobalamin was 18%. The increased concentrations of cobalamin are most commonly caused by a disease, while disorders due to inadequate intake and overdose are much less common. As a result of B12 hypervitaminosis, acnes emerge or exacerbation of the pre-existing acneiform changes may occur. In addition to acne, other dermatological diseases (Rosacea fulminant, dermatitis) may develop as a result of hypervitaminosis, followed by allergic and anaphylactic reactions.

Key words: vitamin B12; hypervitaminosis; acne.

INTRODUCTION

This vitamin participates as a coenzyme in the reactions in which DNA is synthesized, as well as in those reactions in which methionine is produced from homocysteine (1).

The highest percentage of vitamin B12 that is required for enzymatic reactions is taken into the body through food, primarily of animal origin (offal, various types of meat, eggs, milk) (1, 2). The foodstuffs that have vitamin B12 are exclusively foodstuffs of animal origin (3). A certain percentage of vitamins are synthesized in the human body by bacteria, primarily *Escherichia coli* (1). According to the most contemporary recommendations, the daily requirements of vitamin B12 are 7 µg per day, with slightly higher demands during breastfeeding and lactation, as well as with children and the elderly (4). In

SAŽETAK

Povišene koncentracije vitamina B12 nastaju usled prekomernog unosa ovog vitamina, njegovog povećanog oslobađanja iz jetrinih depoa ili povišenih koncentracija transkobalamina koje nastaju prilikom povećane proizvodnje ili smanjene razgradnje ovog molekula. Najčešća oboljenja koja dovode do hipervitaminske B12 jesu maligne bolesti i solidni tumori. Kao posledica povišenih koncentracija nastaju akne ili dolazi do pogoršanja već postojećih akneiformnih promena. Mogu se razviti i Rosacea fulminans, alergijske i anafilaktičke reakcije. Cilj rada bio je da se utvrdi efekat povećanih koncentracija vitamina B12 na zdravlje čoveka. U studiji Deneuvila i saradnika povišene vrednosti vitamina B12 zabeležene su kod 12% ispitanika. U studiji Karmela i saradnika visoku kobalaminemiju imalo je 14% ispitanika. Rezultati drugih istraživanja pokazuju da je prevalencija visoke kobalaminemije 13%, dok se veoma visoka kobalaminemija registruje u 7% slučajeva. U multicentričnoj BDOSE studiji učestalost visokog serumskog kobalamina bila je 18%. Povećane koncentracije kobalamina najčešće nastaju kao posledica bolesti, dok su poremećaji usled neadekvatnog unosa i predoziranja znatno ređi. Kao posledica hipervitaminske B12 nastaju akne ili dolazi do pogoršanja prethodno postojećih akneiformnih promena. Osim akni, kao posledica hipervitaminske mogu se razviti i druga dermatološka oboljenja (Rosacea fulminans, dermatitis), zatim alergijske i anafilaktičke reakcije.

Ključne reči: vitamin B12; hipervitaminska; akne.

addition to participating in the synthesis of the DNA chain, Vitamin B12 participates in the metabolism of amino acids as well as in the metabolism of fatty acids. (5). It is also worth noting that vitamin B12 can be stored to some extent in the liver; although it is a water-soluble vitamin (6). High levels of serum vitamin B12 are considered to be the ones higher than 950 µg/ml (701 pmol/L) (1).

ETIOLOGY OF HYPERVITAMINOSIS B12

Elevated vitamin B12 concentrations can be a result of four different mechanisms: excessive intake of concentrated vitamin B12 through food or parenteral route; increased release of vitamin B12 from internal reservoirs (vitamin B12 depot is located in the liver); increased concentrations of transcobalamin resulting from increased production of these proteins or due to their

reduced decomposition; quantitative deficiency or decrease in transcobalamin affinity for vitamin B12 (1).

Clinically speaking, high cobalamin values are commonly associated with malignancies and solid tumours. Liver diseases (acute hepatitis, cirrhosis, cancer) lead to an increase in vitamin B12 levels in serum, because the liver is no longer able to store this vitamin (1, 5). Solid tumours cause an increase in vitamin B12 levels by increasing the synthesis of transcobalamin or haptoglobin (1). Hypervitaminosis B12 is also taken as a prognostic tumour marker. It has been noticed that people with malignant tumours and hypervitaminosis B12 have a significantly poorer prognosis and considerably shorter life expectancy than those with vitamin B12 levels within the limits of reference values (7). The increase in cobalamin values is also found in haematological diseases: chronic myeloid leukaemia, promyelocytic leukaemia, polycythaemia, and hyper-eosinophilic syndrome (1). Increased concentrations of vitamin B12 may also occur in alcoholism, renal, autoimmune and bronchopulmonary diseases (8).

Numerous other diseases may also lead to increased levels of vitamin B12. The role of the kidney in the metabolism of vitamin B12 has been known for a long time now, though not fully understood yet. Kidney failure is one of the factors that can lead to B12 hypervitaminosis. Increased concentrations are thought to be the result of the accumulation of proteins involved in the transport of vitamin B12 (9). In addition to renal failure, hypervitaminosis B12 can be detected in Gaucher's disease, systemic lupus erythematosus, and rheumatoid arthritis (1). In immune diseases and inflammatory diseases, an increase in the concentration of vitamin B12 most likely happens due to an increase in transcobalamin II during the acute phase of inflammation (10).

Vitamin B12 overdose after the application of oral supplementation or through food is extremely rare (1). Hypervitaminosis B12, which is of exogenous origin, is most commonly caused by intake of higher concentrations of vitamin B12 via vitamin supplements and complexes that contain this vitamin or parenterally. Previously, hypervitaminosis B12 was most commonly registered after the Schilling test (the test used in the vitamin B12 deficiency examination testing). Intramuscular injections of vitamin B12 were administered during this test and their inadequate dosage caused hypervitaminosis B12. Today, hypervitaminosis B12 may most often be registered as a consequence of the parenteral treatment of vitamin B12 deficiency. Numerous studies have confirmed that oral administration of vitamin B12 in the treatment of deficiency is as effective as parenteral, while venous supplementation of vitamin B12 is less and less justified (1, 7-11).

CLINICAL MANIFESTATIONS OF HYPERVITAMINOSIS B12

As a consequence of B12 hypervitaminosis, dermatological diseases are most commonly reported. There are several reports showing that hypervitaminosis B12 may lead to acne, and the use of cyanocobalamin is associated with exacerbation of the pre-existing acneiform changes (12). Such changes generally occur after a long-term intramuscular supplementation of vitamin B12 and usually disappear spontaneously upon discontinuation of therapy (12).

The mechanism of acne formation during vitamin B12 supplementation has not yet been precisely elucidated. A study that examined the impact of cobalamin on the pathogenesis of acne has found that supplementation with this vitamin had an effect on the activity of skin-borne bacteria, modulating their transcriptional activity, thereby increasing the possibility of development of the acneiform changes. Vitamin B12 administration has been found to down-regulate genes that affect vitamin B12 biosynthesis in the bacteria *Propionibacterium acnes*. It has also been determined that vitamin B12 administration stimulates synthesis of porphyrin, which is responsible for the appearance of inflammatory changes that occur together with acne (13).

Vitamin B12 overdose may also occur after oral administration of vitamin B12, although it is extremely rare. The toxic, teratogenic and carcinogenic effects of vitamin B12 have not been detected yet, even with high doses of vitamin B12 in people with pernicious anemia (14).

Doses that are 2000 to 4000% higher than therapeutic ones have also been shown to lead to dermatological complications that primarily manifest as Rosacea fulminans (15). In pernicious anemia, high doses of vitamin B12 are given for therapeutic purposes (16). In humans, about 1% of the oral dose is passively absorbed (17). Allergic and anaphylactic reactions are extremely rare and usually occur after parenteral or intramuscular administration of hydroxycobalamin and cyanocobalamin (18).

Vitamin B12 supplementation can also cause side effects that come as a result of higher concentrations of cobalt. In patients whose contact dermatitis is caused by cobalt, oral supplementation with vitamin B12 may lead to the development of numerous skin reactions such as chronic vesicular dermatitis, cheilitis and stomatitis. Foods containing cobalt in the form of cobalamin do not correlate with the systemic development of skin reactions because the concentrations found in the foods are extremely low. However, foods containing higher concentrations of cobalt in other forms may lead to the development of vesicular eczema of the hands (19).

DIAGNOSIS OF B12 HYPERVITAMINOSIS

The case history and the conduct of tests to determine the vitamin B12 concentrations in serum are important in diagnosing hypervitaminosis B12. A good medical history is particularly important in those patients who develop hypervitaminosis as a result of taking too much of the concentrated vitamin. Patients often do not pay too much attention to the supplements they use on a daily basis, which leads to over-intake of vitamins. The diagnosis of elevated levels of vitamin B12 in the body is made on the basis of specific tests which determine the concentration of this vitamin in the serum (radioisotopes, immunoassay). Routine laboratory analyses that are important in determining the vitamin B12 deficiency (blood count, reticulocyte count, peripheral blood smear, biochemical analysis) are not recommended here as no deviations can be observed (20). Skin changes may sometimes call for the histopathological examination, and swabs may be taken for analysis of acneiform changes (12, 21).

THERAPY FOR HYPERVITAMINOSIS B12

Certain studies show that the bioavailability of vitamin B12 depends on the dose administered (22). Treatment for B12 hypervitaminosis that occurred as a consequence of the over-intake of vitamins involves complete suspension of the intake of vitamins, both oral and parenteral, while the changes usually withdraw independently after a certain period of time. Skin manifestations may also require the use of corticosteroid therapy. Treatment of hypervitaminosis resulting from certain diseases requires treatment of the basic condition that has led to an increase in vitamin B12 (8). Unlike the association of elevated endogenous vitamin B12 with certain pathologies, exogenously administered vitamin B12 has almost no toxicity, even if given at supraphysiological concentrations performed by elite athletes, or to suppress cyanide poisoning (23). High doses of hydroxocobalamin achieve rapid and sustained metabolic control and improvement of certain symptoms during some psychiatric conditions, as can be seen from the case report of twenty-eight-year-old people (24).

FREQUENCY OF HYPERVITAMINOSIS B12

Although the number of studies examining the incidence of vitamin B12 elevations is low, the epidemiological data available indicate that elevated vitamin B12 levels are relatively frequently detectable. In the study by Deneuvil and associates, the elevated vitamin B12 levels were observed in 12% of respondents (25). In the study by Carmel and associates, 14% of respondents had high cobalaminemia (> 664 pmol / L) (26). The results of other studies show that the prevalence of high

cobalaminemia is 13%, while very high cobalaminemia is registered in 7% of cases (12). In the multicentric BDOSE study, the incidence of high serum cobalamin was 18% (27).

CAUSE OF HYPERVITAMINOSIS B12

The available epidemiological studies show that vitamin B12 hypervitaminosis occurs primarily as a result of certain diseases, while the data on elevated vitamin B12 levels that result from the introduction of higher concentrations into the body are unknown (12, 25, 27). Patients with diabetic neuropathy treated with 1 mg of oral methylcobalamin every day for twelve months, significantly increased plasma vitamin B12 levels. This increase in vitamin B12 levels improved all neurophysiological parameters, motor function, and significantly improved their quality of life (28). Certain studies that were conducted in Alberta, highlighted a model that would save a large amount of money within 5 years of its usage, if patients switched from intramuscular administration of vitamin B12 to oral administration of vitamin B12 (29).

VITAMIN B12 HYPOVITAMINOSIS IN ANIMALS

Certain studies indicate that a high oral dose of vitamin B12 reduces renal superoxide and reduces renal postchemical / reperfusion injury in mice. The leading cause of acute kidney injury, which is a potentially fatal syndrome characterized by a sudden decline in renal function is the ischemic-reperfusion injury. Excessive production of superoxide greatly contributes to this injury, and vitamin B12 has the function of removing superoxide. So, this study supports the finding that a high dose of vitamin B12 improves kidney function and morphology in mice with ischemic-reperfusion injury (30).

CONSEQUENCES OF VITAMIN B12 HYPERVITAMINOSIS

Increased concentrations of cobalamin are most often caused by certain diseases, while ailments that occur due to inadequate intake and overdose are much less frequent (1). The consequences of high concentrations of cobalamin are primarily manifested as skin diseases, where it comes to occurrence or aggravation of the pre-existing acneiform changes (12). In addition, Rosacea fulminans may develop as a consequence of excessive intake (15). Thus, very high oral doses of 1000-2000 μ g/d of vitamin B12 can adequately meet the recommended daily requirement of 2.4 μ g/d even in patients with impaired intrinsic factor secretion (31).

LIMITATIONS

Several studies have shown that serum vitamin B12 has limited diagnostic value as a stand-alone indicator due to its low specificity and sensitivity in detecting real vitamin B12 deficiency in tissue. If serum vitamin B12 level is low, it does not necessarily mean that this deficiency is real in other tissues and organs (31). But there are also other limitations, such as that oral vitamin B12 therapy has been shown to be an effective treatment option for patients with vitamin B12 deficiency, but only in the three studied provinces, and the program included in its form only oral (tablets) and not parenteral preparations. To ensure adequate use of limited healthcare capacity, clinicians and form committees should encourage oral vitamin B12 therapy as a clinically cost-effective therapy and the first line of choice for vitamin B deficiency (29).

CONCLUSION

Adequate daily intake of vitamin B12 is the objective of maintaining optimal levels of this vitamin in the blood. The causes of vitamin B12 hypervitaminosis can be due to increased intake of vitamin B12 supplements, but also due to the consequences of various diseases. Vitamin B12 is soluble in water, but that does not reduce the possibility of its hypervitaminosis if higher doses are taken than recommended.

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