

Vitamin B₁₂ Deficiency and Metformin Use

Wendimere Reilly and Jasminka Z Ilich*

Nutrition, Food and Exercise Sciences, College of Human Sciences, Florida State University, Tallahassee, Florida 32306-1493, USA

*Corresponding author: Jasminka Z Ilich, Nutrition, Food and Exercise Sciences, College of Human Sciences, Florida State University, Tallahassee, Florida 32306-1493, USA, Tel: 850-645-7177; E-mail: jilichemst@fsu.edu

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Introduction

Vitamin B₁₂, also known as cobalamin, is a water-soluble vitamin essential for hematopoietic and neurological functions in the body. It is obtained primarily from animal sources such as meat and fish. Many breakfast cereals and nondairy beverages such as soymilk are fortified with vitamin B₁₂ [1]. When vitamin B₁₂ from animal foods enters the stomach it is protein bound and must be released by the action of pepsin in the stomach. It is then attached to R-proteins and is transported through the duodenum where it is hydrolyzed and free cobalamin is released [2]. Cobalamin requires intrinsic factor (IF) to attach to it, in order to be absorbed in the terminal ileum. This absorption process is calcium mediated and is the most probable opportunity for metformin induced vitamin B₁₂ deficiency. Adding supplemental calcium has been shown to mediate the deficiency in some cases [3] though there is not enough evidence to recommend calcium supplementation as an effective preventative measure.

Vitamin B₁₂ is an essential cofactor in the conversion of homocysteine to methionine and regeneration of folate. This is a key step in the metabolic process that leads to DNA synthesis and formation and protection of the myelin sheath. Demyelination of nerve endings can lead to peripheral neuropathy. Symptoms begin to manifest as numbness and paresthesia in the feet. This tingling feeling is caused by pressure on the nerves. If the vitamin B₁₂ deficiency is not corrected, weakness, ataxia, sphincter disturbance, and changes in mental status will follow [4].

Metformin, a drug commonly sold under the trade name glucophage, is an important prescription medication used for the management of diabetes. It is currently sold worldwide and the American Diabetic Association recommends it as a first-line treatment for the prevention of type 2 diabetes in individuals with pre-diabetes [5]. In 2010, there were over 100 million prescriptions for metformin worldwide [6] and in 2012, there were 60.4 million prescriptions dispensed in retail pharmacies in the United States [7]. Metformin increases insulin sensitivity in the liver and decreases glucose production. It is also used to treat polycystic ovarian syndrome, a disease linked to high blood glucose levels [8]. Metformin is currently being studied as a treatment for heart attack recovery [9], tuberculosis [10] and cancer prevention [6].

As early as 1971 researchers began to speculate that one of the side effects of metformin use was vitamin B₁₂ malabsorption [11]. Current research points to the effect of metformin on the calcium dependent B₁₂-intrinsic factor complex and absorption in the terminal ileum as the primary mechanism for vitamin B₁₂ depletion [3]. Although a substantial amount of research has been conducted during the past forty-five years regarding metformin and vitamin B₁₂ deficiency, screening and assessment has never been included as part of the drug protocol. Recently, two large human clinical trials have released

findings, further strengthening the evidence linking metformin use and vitamin B₁₂ depletion and thus a possible need for routine vitamin B₁₂ assessment in patients using metformin [12,13]. Our objective is to review the latest evidence about the relationship between B₁₂ status and metformin use.

The Evidence

Although regular vitamin B₁₂ screening in metformin users has been recommended for over forty-five years, the medical community still believes that there is not enough evidence for voluntary compliance. In an evaluation of records from a Maryland Veterans Affairs Clinic, it was found that in a population of 235 patients taking metformin >2 g/day for >5 years, 60% were never tested for vitamin B₁₂ status. Even those at high risk for vitamin B deficiency (>10 years of use) 46% never had vitamin B₁₂ status measured [14]. The study reported vitamin B₁₂ deficiency in 5.5% of the group, and anemia in 12%. During treatment with metformin 33 of the patients developed neuropathy but of this group 42% were still not assessed for vitamin B₁₂ status [14].

The preponderance of evidence in favor of vitamin B₁₂ screening in metformin users continues to mount. In 2010 a multi-center randomized placebo controlled trial of 390 patients conducted over four years in the Netherlands found the absolute risk of low vitamin B₁₂ concentration was 11.2% higher in the metformin group [15]. In a 2014 Korean study investigating type 2 diabetes and metformin use, 799 patients were evaluated for vitamin B₁₂ status. Vitamin B₁₂ deficiency was prevalent in 9.5% [12]. The study evaluated the correlation between vitamin B₁₂ deficiency and length of use and amount of metformin. It was found that those with the greatest risk of vitamin B₁₂ deficiency were those taking metformin for >4 years in a dose of >1 g/day [12].

Most recently, the Diabetic Prevention Program, a randomized, controlled clinical trial consisting of twenty-seven study centers funded by the NIH, released findings from a 13 year study of metformin use in pre-diabetic patients. The trial consisted of 2155 overweight subjects with impaired glucose tolerance that were placed in a placebo or metformin group and followed for 3.2 years. The researchers continued to follow those in the metformin group for an additional 9 years in an open label trial. The study found a 19% risk of low or borderline deficiency in those taking metformin for >5 years and 20% in those taking it for 13 years [13]. The researchers suggest routine testing of vitamin B₁₂ in patients being treated with metformin.

One of the earliest reported cases of vitamin B₁₂ deficiency related neuropathy in conjunction with metformin use was reported in 1995 by Dr. David S. Bell of the University of Alabama at Birmingham, School of Medicine [16]. Several studies have found higher electrophysiological markers of neuropathy in metformin users

[13,17,18] but more research is necessary. One of the limitations of the scientific research has been the validation of the neuropathy scales, as even blinded testing may still be subjective [17]. Over 60% of diabetic patients will eventually suffer some form of neuropathy [19]. Diabetic neuropathy can lead to foot ulceration and amputation. A cost-of-illness model study conducted in 2001 determined that the cost of type 2 diabetes related peripheral neuropathy and its complications has the potential to range from \$4.3-\$12.7 billion per year and could result in up to 27% of the direct medical costs of diabetes [20]. The true economic impact is far greater as this study did not include indirect costs such as travel expenses and productivity losses. Neurological issues are not specific to vitamin B₁₂ deficiency but they are present in 75% to 90% of individuals with clinically observable B₁₂ deficiency. While more research still needs to be done to determine the extent of vitamin B₁₂ deficiency induced neuropathy in diabetic patients versus high blood glucose induced neuropathy, the possibility of deficiency induced neuropathy only adds credence to the case for vitamin B₁₂ screening in those taking metformin.

Summary and Recommendations

Determining the amount of vitamin B₁₂ to correct deficiency has not been clearly defined but it is theorized that the amount of vitamin B₁₂ in typical multi-vitamin formulas is not sufficient [2] to correct deficiency. It has been suggested that an annual 1000 mcg injection could be sufficient to prevent deficiency [4]. More research is still needed and screening should still be performed, especially if there are co-factors such as polypharmacy, poor dietary intake, and malabsorptive disorders.

A serum vitamin B₁₂ test runs about \$40. To put this cost into perspective, this is similar to a one-month supply of a tricyclic antidepressant, the most common first line protocol for painful diabetic neuropathy [20]. Based on the evidence and relatively low cost of vitamin B₁₂, testing should be considered as a standard protocol for those beginning metformin drug therapy. Screening for vitamin B₁₂ status via serum B₁₂ should be conducted prior to initiation of metformin and then annually as part of standard lab work [21]. For those using the drug for long periods (>4 yrs) or higher doses (>1 g/day) and for those that are taking proton pump inhibitors (for gastric acid reflex) in conjunction with metformin or presenting with symptoms of neuropathy, more sensitive testing such as serum homocysteine and methylmalonic acid concentrations should be considered as pharmaceutical drug use has become the norm instead of the exception, it is time to become proactive in evaluating the deleterious effects that they may have on nutritional status. The registered dietitian is perhaps the most qualified to determine when and if nutrient screening is warranted after a thorough assessment that includes diet, lifestyle, health status and polypharmacy issues.

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