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# Metformin and Vitamin B12: Not always a straightforward relationship

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## Abstract

Metformin is a near ubiquitous treatment for type 2 diabetes. Several studies point to the association between a reduction in vitamin B 12 levels and the use of metformin. Particular attention also needs to be focused upon patients who are considered to have peripheral neuropathy and authoritative guidelines suggest that screening for vitamin B12 deficiency should be undertaken in those taking metformin, especially if peripheral neuropathy if suspected. This is a review of the current understanding of the relationship between metformin and vitamin b12 intended to help primary care clinicians to better manage those patients who take the medication.

**Keywords**. Metformin, Vitamin B12, Diabetes Mellitus, Screening.

**ملخص البحث**

**الميتفورمين هو علاج شبه منتشر لمرض السكري من النوع 2. تشير العديد من الدراسات إلى الارتباط بين انخفاض مستويات فيتامين ب 12 واستخدام الميتفورمين. يجب أيضًا التركيز بشكل خاص على المرضى الذين يُعتبرون مصابين باعتلال الأعصاب المحيطية وتشير الإرشادات الرسمية إلى أنه يجب إجراء فحص لنقص فيتامين ب 12 في أولئك الذين يتناولون الميتفورمين ، خاصةً إذا كان الاعتلال العصبي المحيطي مشتبهًا فيه. هذه مراجعة للفهم الحالي للعلاقة بين الميتفورمين وفيتامين ب 12 تهدف إلى مساعدة أطباء الرعاية الأولية على إدارة هؤلاء المرضى الذين يتناولون الدواء بشكل أفضل.**

**الكلمات المفتاحية : ميتفورمين ، فيتامين ب 12 ، داء السكري ، فحص.**

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## Introduction

According to the 2019 International Diabetes Federation (IDF) Diabetes Atlas, the global diabetes prevalence is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 (Saeedi et al., 2019).

The combined prevalence of diabetes in the Middle East is high (14.6%), with Kuwait, Saudi Arabia, and UAE having the highest prevalence of diabetes (Kalan Farmanfarma et al., 2020). The levels of the condition are projected to rise in Oman, from 15.2% in 2020 to 23.8% in 2050 (Awad, S. F., Al-Mawali, A., et al.,2020).

Out of Jordan's total health expenditure, 19.0% in 1990, 21.1% in 2020, it is forecast that 25.2% will be spent on type 2 diabetes mellitus in 2050 (Awad, S. F., Huangfu, P., et al., 2020). There is also considerable effort to prevent people becoming diabetic. For instance, the Middle East's largest diabetes research project, the Qatar Diabetes Prevention Programme (QDPP), will re-start recruitment of subjects in early 2021 (The Peninsula, 2020).

Despite the advances that have been made in the understanding of diabetes and the variety of therapeutic options available, metformin has been a decades old option, and remains the recommended first-line treatment for most patients with type 2 diabetes mellitus (Liu et al., 2014).

However, long-term use of metformin may be associated with biochemical vitamin B12 deficiency and it is recommended that periodic measurement of vitamin B12 levels in metformin-treated patients is undertaken, especially in those with anemia or peripheral neuropathy (Diabetes Care, 2020).

## Metformin

Metformin's history is a long one and originated as a constituent of many herbal remedies. The Ebers Papyrus, written in 1500 B.C.E. records its use in Egypt (Witters, 2001) and in 1918, Galega officinalis (goat's rue), rich in guanidine, was shown to lower blood glucose (Bailey, 2017).

Metformin is thought to work by disrupting the mitochondria, reducing adenosine triphosphate production and increasing adenosine monophosphate concentrations (Pernicova & Korbonits, 2014 cited in Miller, 2018) or inhibiting cell respiration by modulating respiratory chain complex 1 (Hajjar et al., 2013). It is now used for patients with prediabetes, gestational diabetes, and polycystic ovarian syndrome (Romero et al., 2018).

Vitamin B12 deficiency in patients taking metformin was first described by in 1969 (Berchtold et al., 1969).

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Since that time, the association between metformin and vitamin B12 has been explored through a variety of studies. vitamin $B_{12}$ therapy in patients in the Middle East and Far East, with a recent analysis from five teaching hospitals in Jordan, indicating that vitamin B12 was the second most common injectable therapy after insulin (Al-Azayzih et al., 2017, as cited in Elhadd et al., 2018).

Assessing metformin users for vitamin B12 is endorsed in the 2018 American Diabetes Association Clinical Practice Recommendations and the 2017 ADA diabetic neuropathy statement recommends patients with diabetic neuropathy to be checked for the deficiency, to exclude a treatable cause of neuropathy (Pop-Busui et al., 2016).

**What is vitamin B12:**

Vitamin B12 is a water-soluble vitamin which exists in several forms and contain cobalt and are referred to as "cobalamins." (Office of Dietary Supplements - Vitamin B12, 2021). Vitamin B12 can only be synthesized by microorganisms and humans are entirely dependent on dietary sources of vitamin B12 (Schjonsby, 1989). It is found in meat, fish, dairy products, and fortified cereals (Linder, Tamboue and Clements, 2016). Fruit and vegetables lack vitamin B12 unless they are contaminated with vitamin B12 producing bacteria (Miller, 2018). The average daily intake is about 3 nmol, and the physiological needs are 0.4 to 0.8 nmol (Schjonsby, 1989).

**How is it absorbed?**

After ingestion, vitamin B12 is separated from food by the action of gastric acid and then connects to intrinsic factor produced by the stomach's parietal cells (Linder, Tamboue and Clements, 2016). Vitamin B12 in fortified foods and dietary supplements is already in free form and can bind to intrinsic factor without the need for gastric acid. Between 1–5% of "free" vitamin B12 is absorbed by passive diffusion from the oral cavity or nasal mucosa to the colic mucosa (Lane and Rojas-Fernandez, 2002 cited in Andrès et al., 2018).

The intrinsic factor–vitamin B12 complex proceeds to the ileum, then binds with the intrinsic factor–vitamin B-12 receptor complex consisting of 2 proteins, cubilin and amnionless (Miller, 2018). The binding is calcium dependent, and it enters the cell by receptor-mediated endocytosis. In the ileal cell, vitamin B12 is separated from intrinsic factor and exported out of the cell. 80-94% of vitamin B12 is bound to haptocorrin as holohaptocorrin and the remaining vitamin B12 is bound to transcobalamin as holotranscobalamin (Hunt et al., 2014). Holohaptocorrin delivers vitamin B-12 only to the liver and holotranscobalamin delivers vitamin B-12 to all the tissues of the body (Miller, 2018).

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Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications ( MECSJ )
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## The role of vitamin B12:

Vitamin B12 is required for DNA synthesis, normal neurological function and red blood cell formation (Office of Dietary Supplements - Vitamin B12, 2021). Methylcobalamin and 5-deoxyadenosylcobalamin are the forms of vitamin B12 that are active in human metabolism (Rietsema, 2014).

Intracellular conversion of vitamin B12 to two active coenzymes, adenosylcobalamin in mitochondria and methylcobalamin in the cytoplasm, is necessary for the homeostasis of methylmalonic acid and homocysteine, respectively (Hunt et al., 2014).

Methylcobalamin is involved in the transfer of methyl groups from the folate derivative 5-methyltetrahydrofolate to the sulfur amino acid homocysteine to produce methionine in a cytosolic reaction catalyzed by the enzyme methionine synthase. When the adequate amount of vitamin B12 is lacking, homocysteine accumulates (Miller, 2018).

Adenosylcobalamin is a cofactor for the enzyme methylmalonyl CoA mutase which catalyzes the mitochondrial conversion of methylmalonyl CoA to succinyl CoA. Inadequate levels of vitamin B12 causes methylmalonyl CoA to accumulate and be converted to form methylmalonic acid (Miller, 2018).

## Vitamin B12 deficiency.

There are a variety of identified risk factors for vitamin B12 deficiency, including genetic causes such as the autosomal recessive transcobalamin II deficiency; the autoimmune disease pernicious anemia; nutritional conditions such as veganism; surgical resection of the stomach or terminal ileum, and medications such as histamine H2 blockers, proton pump inhibitors and metformin (Langan & Goodbred, 2017).

The symptoms and signs can be non-specific, especially in the early stages (Sukumar & Saravanan, 2019). Clinical manifestations of deficiency include of fatigue and glossitis (Hunt et al., 2014), megaloblastic anemia (Bender, 2003), and neurologic disease such as peripheral neuropathy (McCombe & McLeod, 1984), neurodegeneration of the spinal cord (Fenton et al., 2011) and cognitive deficits (Osimani et al., 2005).

An estimated 20% of patients with neurological signs do not manifest anaemia (Quadros, 2010 cited in Hunt et al., 2014). Furthermore, the hepatic storage of vitamin B12 can delay clinical manifestations for up to 10 years after the onset of deficiency (Carmel, 2000, as cited in Langan & Goodbred, 2017).

A serum vitamin B12 level less than 148 pmol/L (200 ng/L) is considered sensitive enough to diagnose 97% of patients with vitamin B12 deficiency, but there is no consensus if this indicates clinically significant serum vitamin B12 deficiency (Hunt et al., 2014).

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications ( MECSJ )
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www.mecsj.com/

Furthermore, evidence suggests that serum vitamin B12 concentrations might not accurately reflect intracellular concentrations (Hunt et al., 2014). Measuring both circulating serum vitamin B12 levels and a functional biomarker, such as methylmalonic acid (MMA), is considered preferable to either alone (Yetley et al., 2011).

**Metformin and vitamin B12**

Since the observation of Berchtold et al. associating vitamin B12 and metformin use (Berchtold et al., 1969), various mechanisms for vitamin B12 deficiency have been proposed. These mechanisms include delays glucose absorption, influences on small bowel motility and on bacterial overgrowth (Caspary & Creutzfeldt, 1971, cited in Liu et al., 2014). More recently, it is considered that metformin binds to the B12-cubulin complex altering the membrane potential and competitively repels the divalent calcium ions, preventing calcium dependent uptake of vitamin B12 by cells (Gilligan, 2002, p. 484).

Since the association between vitamin B12 deficiency and metformin was almost sixty years ago (Berchtold et al., 1969), other researchers (Tomkin et al., 1971) found that 21 (30%) of 71 diabetes patients receiving long-term metformin treatment (mean dose was1.97 g; mean duration was 4.6 y) exhibited malabsorption of radiolabeled vitamin B12. The vitamin B-12 absorption normalized within 5 to 28 days in 6 of 7 patients who were taken off metformin.

Analysis of NHANES survey revealed that 13.1% of diabetes patients treated with metformin had low vitamin B12 levels (150-220 pg/ml) in comparison to 6.2% who were not taking metformin. Vitamin B12 levels less than 150 pg/ml occurred in 5.6% of those taking metformin as opposed to 2.2% not receiving metformin (Rietsema, 2014).

Several other studies have suggested an association between metformin use and vitamin B12. Chapman et al 2016 review of 26 papers, showed that in 10 out of 17 observational studies showed statistically significantly lower levels of vitamin B12 in patients on metformin than those who were not on metformin. A meta-analysis performed on four trials showed a statistically significant overall mean reduction of vitamin B12 after 6 weeks to 3 months of use (Chapman et al., 2016).

Similarly, in a study of elderly patients in long term care institutions, the prevalence of vitamin B12 deficiency in diabetic patients taking metformin was 53.2% compared with 31% ($P < 0.001$) of diabetic patients who did not take metformin and 33.3% ($P < 0.001$) of those without diabetes. Prevalence of vitamin B 12 deficiency among those taking metformin ≥1500 mg/day for more than 2 years was 75.9% and was more than 2 times that of patients taking metformin less than 1500 mg/day for 2 or fewer years (35.3%) (Wong et al., 2018).

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Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications ( MECSJ )
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However, in a cross-sectional study among 550 type 2 diabetes patients using metformin (mean daily dose 1,306 mg; mean duration 64 months) conducted in four primary care centers in the Netherlands, duration of metformin use was not associated with cobalamin concentrations after multivariable adjustment (Beulens et al., 2014).

**Peripheral neuropathy**

The American Diabetes Association guidelines recommend periodic testing of vitamin B12 in metformin-treated patients, especially in those with peripheral neuropathy (Diabetes Care, 2020). Peripheral neuropathy been estimated that the population prevalence is 2.4% rising with age to 8% (Martyn & Hughes, 1997, p. 311). There are a variety of causes, and diabetes mellitus is one of the commonest. Peripheral neuropathy is the most common complication of diabetes mellitus, possibly developing in up to 50% of patients (Tesfaye et al., 2010, cited in Ahmed et al., 2017).

Fifty years ago, a three-month study of 402 patients attending a diabetic clinic screened for evidence of neurological complications detected 87 (21.6%) to have peripheral neuropathy, and, of those, 7 (8%) were found to have unsuspected vitamin B12 deficiency. It was reported that treatment with hydroxycobalamin improved dramatically the neurological state of 5 of those patients (Khan et al., 1969).

In an Indian based study comparing the prevalence of vitamin B12 deficiency and peripheral neuropathy in patients with Type 2 diabetes mellitus treated with or without metformin, the mean serum B12 levels was significantly lower in metformin exposed; mean neuropathy score was significantly higher in metformin exposed group and significant negative correlation between cumulative metformin dose and vitamin B12 level (Singh et al., 2013).

In contrast, a study based in Qatar, the prevalence of vitamin B12 deficiency was lower in those taking metformin compared to those who did not. However, those with vitamin B12 deficiency had a comparable prevalence and severity of sensory neuropathy and painful neuropathy to those without vitamin B12 deficiency (Elhadd et al., 2018).

Although it is nearly impossible to clinically distinguish neuropathy caused by vitamin B12 deficiency from diabetic neuropathy, neuropathy should still be closely monitored, since early diagnosis and treatment improve prognosis (Kim et al., 2019).

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications ( MECSJ )
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www.mecsj.com/

## Controversy

In a study of vitamin B12 status in women with polycystic ovary syndrome treated with metformin (1.5-2.5 g per day) or placebo for six months, showed a decline in serum vitamin B12, no reduction in the physiological active part of vitamin B12 bound to transcobalamin (holotranscobalamin) or increase in methylmalonic acid. Instead, the non-functional part of circulating cobalamin bound to haptocorrin declined (Kim et al., 2019). It was argued that vitamin B12- dependent reactions function well in large numbers of metformin-treated patients despite low serum B12 (Obeid, 2014). However, Ahmad et al argued that six-month period of metformin use in a study did not seem to be sufficient to deplete vitamin B12 stores and consequently result in elevated MMA or homocysteine levels (Ahmed et al., 2017).

Similarly, one follow-up study showed that using 850 mg/day metformin (compared with insulin) over a mean of 3.4 years in 390 patients with type 2 diabetes lowered plasma B12, but homocysteine was not significantly higher than the insulin group (de Jager et al., 2010). Metformin was associated with a slight increase of 5% in homocysteine levels, and Ahmad et al suggests that the p value at 0.09 may indicate a borderline significant trend. Furthermore, they highlight that trial's authors attributed the non-significance to the relatively low numbers of patients with vitamin B12 deficiency, and they expected the homocysteine levels to show further increases with a longer treatment duration.

## Treatment

Oral and nasal routes have been suggested as other ways for vitamin B12 administration (Andrès et al., 2018), utilizing what has been termed "medicine's best kept secret." (Graham et al., 2007). In a study of comparing the effectiveness of oral versus intramuscular vitamin B12 in patients aged ≥65 years with vitamin B12 deficiency, oral administration was no less effective than IM administration at 8 weeks. Although differences were found between administration routes at week 52 (Sanz-Cuesta et al., 2020).

Guidelines from the British Society for Haematology recommend intramuscular injections of hydroxocobalamin - the frequency and duration depending on whether neurological deficits are present or not (Devalia et al., 2014). However, the British guidelines acknowledge that high dose oral cyanocobalamin (1–2 grams) is licensed for use in several countries outside the UK.

The British Society for Haematology does not recommend retesting vitamin B12 levels after treatment has been initiated, and no guidelines address the optimal interval for screening high-risk patients (Langan & Goodbred, 2017).

Treatment with vitamin B12 results in the production of new erythrocytes, causing an intracellular influx of potassium. This could lead to severe hypokalemia, so adequate monitoring and appropriate treatment is required (Hunt et al., 2014).

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Issue (40),2021
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www.mecsj.com/

## Screening for Vitamin B12 deficiency in patients taking metformin

In 1971, Tomkin et al advised annual screening for megaloblastic anaemia in patients on long-term metformin treatment. Recent American Diabetes Association (ADA) guidelines recommend periodic testing of vitamin B12 in metformin-treated patients, especially in those with peripheral neuropathy and anemia (Diabetes Care, 2020). Others have suggested that screening may be warranted in patients with one or more risk factors, such as gastric or small intestine resections, inflammatory bowel disease, use of proton pump inhibitors or histamine H2 blockers for more than 12 months, vegans or strict vegetarians, and adults older than 75 years (Langan & Goodbred, 2017).

## Conclusion

Metformin is almost a ubiquitous medication used in the treatment of type 2 diabetes mellitus. There is evidence from several studies that metformin is associated with low serum vitamin B12 levels. Vitamin B12 is required by humans for a variety of important cellular processes to maintain health. The detection of clinically significant vitamin B12 levels is not straightforward. There are conflicting reports as to whether metformin causes a disruption of the cellular function of vitamin B12. The conventional view is that patients who are taking high doses of metformin or for relatively long duration are at risk of vitamin B12 deficiency. Periodic testing of vitamin B12 in metformin-treated patients, especially in those with peripheral neuropathy and anemia, is recommended. When tests are undertaken to detect vitamin B12, there needs to be an understanding of the physiology of vitamin B12 uptake, carriage, and utilization in the body. Treatment for vitamin B12 deficiency usually involves the intramuscular administration of vitamin B12, the frequency and duration contingent on whether a neurological deficit exists or not.

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