Which supplementation methods are effective for metformin-induced vitamin B12 deficiency?

This systematic review confirms that supplementation with vitamin B12 in people with type 2 diabetes and metformin-induced deficiency is effective to prevent and treat B12 deficiency, although the impact of supplementation on existing neuropathy varied between studies. The studies included in the review demonstrate that both oral and parenteral supplementation can increase B12 levels and decrease serum homocysteine. Proposed pathways for development of metformin-associated B12 deficiency are explored as well as the impact on haematological and neurological pathways. Oral or sublingual methylcobalamin is recommended as the most effective, cost-effective and convenient method for supplementation in those requiring treatment. The authors call for more high-quality studies exploring optimal delivery methods and consideration of supplementation rather than periodic testing in those treated long-term with metformin to be discussed more widely in guidelines. This review provides useful information as we implement the MHRA guidance from June 2022 on identifying and managing metformin-induced B12 deficiency.

Pam Brown
GP in Swansea

Vitamin B12 deficiency in those taking metformin has been known about since at least 1969; however, it has recently been identified to be more common than previously thought, prompting reviews of the existing literature and exploration of the most appropriate management options.

In this systematic review, Pratama and colleagues highlight the paucity of studies specifically in those with metformin-induced B12 deficiency and the lack of guidance on best approaches to supplementation for treatment or prevention. The article provides a helpful review of key papers exploring the mechanisms and timeframes of metformin-induced B12 deficiency, which can help us in the implementation of the MHRA guidance issued in June 2022.

Metformin may decrease intrinsic factor secretion from parietal cells, interfere with the calcium-dependent binding of the resulting intrinsic factor and B12 complex to receptors on the ileal lining, and change small intestinal motility, resulting in decreased B12 absorption. Metformin may also increase liver accumulation of B12, meaning it is less available, and it may alter reabsorption of bile acids, disrupting the enterohepatic circulation of B12. As well as causing B12 deficiency, an increase in methylmalonic acid occurs, which is thought to result in loss of myelin in the peripheral nerves and, consequently, neuropathy, which may be symptomatic as early as 2 years into metformin treatment.

There is around a 2.5-fold increase in B12 deficiency incidence in those treated with metformin, and this may occur as early as 3 months, although hepatic stores of vitamin B12 may take 5 years or more to deplete (Bell, 2022). In a previous randomised, placebo-controlled trial, de Jager et al (2010) added metformin 850 mg three times daily to insulin therapy (a higher metformin dose than is usually now used) and demonstrated a number needed to harm of just under 14 for development of B12 deficiency over the 4.3 years of the trial. Other studies have also confirmed that B12 deficiency increases with long-term use and is dose-dependent.

The authors express concern that there is not yet clear guidance on supplementation

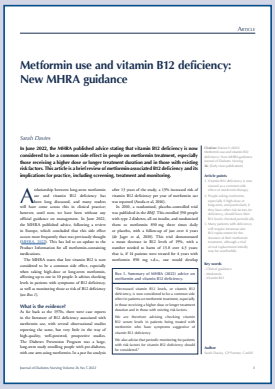
Citation: Brown P (2022) Diabetes Distilled: Which supplementation methods are effective for metformin-induced vitamin B12 deficiency? *Diabetes & Primary Care* **24**: 163–4

Further reading

Metformin and reduced vitamin B12 levels: new advice for monitoring patients at risk

Decreased vitamin B12 levels, or vitamin B12 deficiency, is now considered to be a common side effect in patients on metformin treatment, especially in those receiving a higher dose or longer treatment duration and in those with existing risk factors. We are therefore advising checking vitamin B12 serum levels in patients being treated with metformin who have symptoms suggestive of vitamin B12 deficiency. We also advise that periodic monitoring for patients with risk factors for vitamin B12 deficiency should be considered.

Metformin and reduced vitamin B12 levels: MHRA Drug Safety Update


Article

Metformin use and vitamin B12 deficiency: New MHRA guidance

Sarah Davies

In June 2022, the MHRA published advice stating that vitamin B12 deficiency is now considered to be a common side effect in people on metformin treatment, especially those receiving a higher dose or longer treatment duration and in those with existing risk factors. This article is a brief review of metformin-associated B12 deficiency and its implications for practice, including screening, treatment and monitoring.

A relationship between long-term metformin use and vitamin B12 deficiency has been well established in research and practice will have come across this in clinical practice; however, until now, we have been without any official guidance on management. In June 2022, the MHRA published advice, following a review of evidence, that vitamin B12 deficiency is now a common side effect in people on metformin therapy (MHRA 2022). This has led to an update to the Product Information for all metformin-containing medications.

The MHRA states that low vitamin B12 is now considered to be a common side effect, especially in those receiving a higher dose or longer treatment, affecting up to one in 10 people. It advises checking levels in patients with symptoms of B12 deficiency, as well as monitoring those at risk of B12 deficiency (see Box 1).

What is the evidence?

As far back as the 1970s, there were case reports in the literature of B12 deficiency associated with metformin use, with several observational studies reporting the same, but very little in the way of high-quality, well-powered, prospective studies. One of the studies mentioned by the MHRA was a long-term study enrolling people with pre-diabetes with one arm using metformin. In a post-hoc analysis after 15 years of the study, a 15% increased risk of vitamin B12 deficiency per year of metformin use was observed (Bell et al, 2022).

In 2010, a randomised, placebo-controlled trial was published in the *BMJ*. This enrolled 390 people with type 2 diabetes, off to on metformin, and randomised them to metformin 850 mg three times daily versus placebo, with a follow-up of 4 years (de Jager et al, 2010). This trial demonstrated a mean decrease in B12 levels of 19%, with a number needed to harm of 15.8 over 4.3 years, that is, if 16 patients were treated for 4 years with metformin 850 mg, t.d.s., one would develop

Box 1. Summary of MHRA (2022) advice on monitoring and treatment B12 deficiency

- Decreased vitamin B12 levels, or vitamin B12 deficiency, is now considered to be a common side effect in patients on metformin treatment, especially in those receiving a higher dose or longer treatment duration and in those with existing risk factors.
- We are therefore advising checking vitamin B12 serum levels in patients being treated with metformin who have symptoms suggestive of vitamin B12 deficiency.
- We also advise that periodic monitoring for patients with risk factors for vitamin B12 deficiency should be considered.

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Brief review of metformin-associated B12 deficiency and its implications for practice

route and methods, and they discuss studies exploring this. A 1 mg intramuscular injection of hydroxocobalamin every 3 months is the commonest option in both studies and practice, and is recommended by NICE (2022a) in its guidance on management of B12 deficiency. Methylcobalamin is an active form of B12 which can be taken orally or sublingually, is retained longer in the body and has been studied for treatment of peripheral neuropathy. If oral therapy is trialled, check B12 levels at 8–12 weeks. Studies in this systematic review support B12 supplementation for the treatment or prevention of metformin-induced deficiency and neuropathy, demonstrating increased levels of B12 and decreased serum homocysteine with supplementation.

MHRA guidance

Metformin remains the first-line treatment option for most people with type 2 diabetes, including in the recently published ADA/EASD Consensus Report (Davies et al, 2022) and in the NICE (2022b) NG28 advice on type 2 diabetes management.

The MHRA (2022) recently issued guidance on the increased risk of vitamin B12 deficiency in people treated with metformin, highlighting increased risks with higher metformin doses, longer treatment duration and in patients with risk factors for B12 deficiency, including the following:

- Existing low B12 levels.
- People at risk of decreased absorption (elderly, inflammatory bowel disease, gastric resection or autoimmune conditions).
- Strict vegan and some vegetarian diets.
- Medications known to decrease B12 absorption (proton pump inhibitors, colchicine).

Clinicians are encouraged to test B12 levels in those presenting with anaemia or neuropathy, and to consider testing periodically in those with risk factors for deficiency. Those with low B12 may be asymptomatic, have symptoms of anaemia or neuropathy, or have glossitis, mouth ulcers, mental disturbances (depression, irritability, cognitive impairment). It is recommended that metformin treatment should continue while the B12 deficiency is corrected, in view of the drug's known benefits in type 2 diabetes and its central role in treatment guidelines. ■

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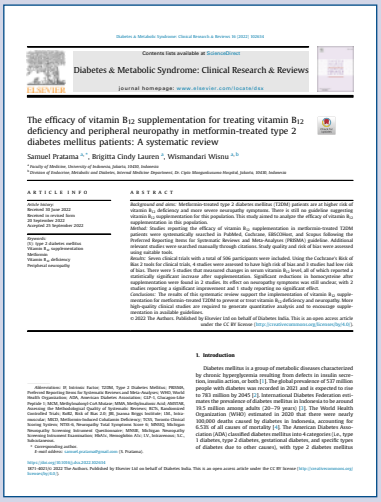
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The efficacy of vitamin B_{12} supplementation for treating vitamin B_{12} deficiency and peripheral neuropathy in metformin-treated type 2 diabetes mellitus patients: A systematic review

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ABSTRACT

Background and aims: Metformin-treated type 2 diabetes mellitus (T2DM) patients are at higher risk of vitamin B_{12} deficiency and more severe neuropathy symptoms. There is still no guideline suggesting vitamin B_{12} supplementation for this population. This study aimed to analyze the efficacy of vitamin B_{12} supplementation in this population.

Methods: Studies on the efficacy of vitamin B_{12} supplementation in metformin-treated T2DM patients were systematically searched in PubMed, Cochrane, EBSCOHost, and Scopus following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Additional relevant studies were searched manually through citations. Study quality and risk of bias were assessed using suitable tools.

Results: Seven clinical trials with a total of 506 participants were included. Using the Cochrane's Risk of Bias 2 tools for clinical trials, 4 studies were assessed to have high risk of bias and 3 studies had low risk of bias. Vitamin B_{12} serum levels were significantly increased in 5 studies, and 3 studies showed statistically significant increase after supplementation. Significant reductions in homocysteine after supplementation were found in 2 studies. Its effect on neuropathy symptoms was still unclear, with 2 studies reporting a significant improvement and 1 study reporting no significant effect.

Conclusion: The results of this systematic review support the implementation of vitamin B_{12} supplementation for metformin-treated T2DM to prevent or treat vitamin B_{12} deficiency and neuropathy. More high-quality clinical studies are required to generate quantitative analysis and to encourage supplementation in a suitable population.

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1. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. The global prevalence of 537 million people with diabetes was recorded in 2021 and is expected to rise to 783 million by 2045 [2]. International Diabetes Federation estimates the prevalence of diabetes mellitus in Indonesia to be around 19.5 million among adults (20–79 years) [3]. The World Health Organization (WHO) estimated in 2020 that there were nearly 100,000 deaths caused by diabetes in Indonesia, accounting for 6.53% of all causes of mortality [4]. The American Diabetes Association (ADA) classified diabetes mellitus into 4 categories (i.e., type 1 diabetes, type 2 diabetes, gestational diabetes, and specific types of diabetes due to other causes), with type 2 diabetes mellitus

Click here to read the systematic review in full