

Should people treated with metformin be screened for vitamin B₁₂ deficiency?

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Article points

1. Current evidence suggests that metformin reduces the absorption of vitamin B₁₂ and increases the risk of deficiency.
2. The World Health Organization set out 10 principles of early disease detection to assess whether screening for a disease has health and cost benefits.
3. Formal screening programmes need to be supported by sufficient evidence and justified in health economic terms.

Key words

- Metformin
- Screening
- Supplementation
- Vitamin B₁₂

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Current evidence suggests a relationship between metformin treatment and vitamin B₁₂ deficiency in people with diabetes. At present, these individuals do not undergo screening for vitamin B₁₂ deficiency. This article discusses the health and cost implications of screening for vitamin B₁₂ deficiency in people with diabetes taking metformin, alongside the 10 principles outlined in the World Health Organization publication *Principles and Practice of Screening for Disease: Public Health Papers No. 34* (Wilson and Jungner, 1968).

Biguanides have been used in the treatment of diabetes since 1957. Metformin (the only biguanide now available) is a cheap, effective and widely used treatment for type 2 diabetes. Metformin is the most widely used oral antidiabetes drug and is recommended as first-line therapy for those with type 2 diabetes who are overweight, where diet and exercise have not achieved adequate glycaemic control (NICE, 2009; SIGN, 2010). Metformin has been shown to improve macrovascular outcomes and reduce the absolute risk of death and all-cause mortality (UK Prospective Diabetes Study Group, 1998).

For over 40 years researchers have reported the effects of metformin on vitamin B₁₂ absorption (Tomkin et al, 1971; Adams et al, 1983; Liu et al, 2006) and serum levels (Bauman et al, 2000; Hermann et al, 2004; Wile and Toth, 2010). This effect is dependent on the dose and duration of metformin

therapy (Ting et al, 2006; Wile and Toth, 2010). Adams et al (1983) warned us that the effects on vitamin B₁₂ malabsorption might be permanent.

In controlled studies comparing metformin with placebo, metformin significantly reduced vitamin B₁₂ levels (Wulffelé et al, 2003; DeFronzo and Goodman, 2005; Sahin et al, 2007). These studies were not able to demonstrate an increase in vitamin B₁₂ deficiency (i.e. a reduction of levels below the reference range). This may have been due to the short study duration and the body's natural vitamin B₁₂ stores. In 2010, de Jager et al carried out a double-blind randomised controlled trial to study the effects of metformin on the incidence of vitamin B₁₂ deficiency. Participants with type 2 diabetes receiving insulin therapy were randomised to receive, in addition, either metformin ($n=131$) or placebo ($n=146$). The study was longer than previous studies and participants

were followed up for 4.3 years. The results demonstrated that metformin significantly reduced vitamin B₁₂ levels and that the longer the therapy, the greater the reduction. In the metformin group at baseline there were three participants (1.6%) with vitamin B₁₂ deficiency and four participants (2.2%) in the placebo group. At the end of the study, 19 participants (9.9%) in the metformin group and five (2.7%) in the placebo group had vitamin B₁₂ deficiency. When comparing metformin with placebo, metformin significantly increased the risk of developing vitamin B₁₂ deficiency by 7.2% ($P=0.004$; de Jager et al, 2010).

Current practice is to measure serum vitamin B₁₂ when there are signs of neuropathy, cognitive impairment, anaemia or other clinical features suggestive of vitamin B₁₂ deficiency. There are currently no national guidelines recommending screening adults with type 2 diabetes on metformin therapy for vitamin B₁₂ deficiency. Vitamin B₁₂ deficiency can have serious health implications if left undiagnosed and untreated. However, not all people with biochemical vitamin B₁₂ deficiency will develop clinical symptoms.

Aetiology

Vitamin B₁₂ (cyanocobalamin) and folate are part of the complex of water-soluble B vitamins used in the production of red blood cells. Vitamin B₁₂ is required for DNA synthesis and carbohydrate metabolism. Vitamin B₁₂ is available from sources such as meat, dairy products, fish, shell fish and fortified cereals, and it is stored in the liver for up to a year or more (Burtis et al, 2005). Haematological features of vitamin B₁₂ deficiency include megaloblastic anaemia characterised by enlarged red blood cells, neutropenia and thrombocytopenia. Vitamin B₁₂ deficiency is also associated with dementia, peripheral neuropathy, sub-acute combined degeneration of the cord and demyelination and degeneration of the optic nerve (Gilroy and Holliday, 1982).

There are several known causes of vitamin B₁₂ deficiency. Dietary deficiency

is a common problem in some areas of the world (Jawa et al, 2010). Pernicious anaemia is an autoimmune disease in which reduced production of intrinsic factor (IF) in the stomach results in vitamin B₁₂ deficiency and megaloblastic anaemia. Sixty per cent of vitamin B₁₂ is absorbed by an active process involving IF; however, there is also a passive mechanism of absorption that is independent of IF in which uptake occurs by simple diffusion. Researchers have found that people with pernicious anaemia are able to absorb small amounts of vitamin B₁₂ when given large doses orally (Elia, 1998). In clinical practice, those with pernicious anaemia should be given vitamin B₁₂ replacement intramuscularly (as hydroxocobalamin). Other causes of vitamin B₁₂ malabsorption include diseases affecting the small bowel, such as Crohn's disease, coeliac disease, tropical sprue and conditions in which an overgrowth of bacteria colonise the bowel and ingest vitamin B₁₂ before it can be absorbed. Medications that may affect vitamin B₁₂ absorption include phenytoin, proton pump inhibitors, nitrous oxide and dihydrofolate reductase inhibitors. Vitamin B₁₂ deficiency increases with age and is more common in the elderly.

The 10 WHO principles

Back in the 1960s the World Health Organization (WHO) set out 10 principles of early disease detection to assess whether screening for a disease has health and cost benefit (Wilson and Jungner, 1968), and the principles are still relevant today. The body stated that the "object of screening for disease is to discover those among the apparently well who are in fact suffering from disease. They can then be placed under treatment." It was also noted that: "Early detection (case finding) aims at discovering and curing conditions which have already produced pathological change but which have not so far reached a stage at which medical aid is sought spontaneously."

The 10 WHO principles are reviewed below with regard to how each applies to the

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1. There are currently no national guidelines recommending screening adults with type 2 diabetes on metformin therapy for vitamin B₁₂ deficiency.
2. Vitamin B₁₂ deficiency can have serious health implications if left undiagnosed and untreated. However, not all people with biochemical vitamin B₁₂ deficiency will develop clinical symptoms.
3. Haematological features of vitamin B₁₂ deficiency include megaloblastic anaemia characterised by enlarged red blood cells, neutropenia and thrombocytopenia.

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1. Oral vitamin B₁₂ is readily available over-the-counter in chemists and health food shops in the UK at doses ranging from 1 to 1000 µg. Although most people find intramuscular injections of vitamin B₁₂ painful, it is currently the accepted treatment for patients with proven deficiency.
2. If all people taking metformin were screened for vitamin B₁₂ deficiency and a significant proportion found to need intramuscular supplementation, the NHS could face a capacity problem.
3. There is a correlation between low vitamin B₁₂ levels, anaemia and neurological symptoms, and evidence to suggest that detecting vitamin B₁₂ deficiency early or as levels fall into the lower range improves outcomes.

question of screening metformin users for vitamin B₁₂ deficiency.

1. The condition sought should be an important health problem

Vitamin B₁₂ deficiency can lead to dementia, subacute combined degeneration of the cord, demyelination, degeneration of the optic nerve and peripheral neuropathy. Peripheral neuropathy is linked to an increased risk of foot ulceration (Crawford et al, 2007), which is associated with an increased risk of amputation and death (Davis et al, 2006).

2. There should be an accepted treatment for individuals with recognised disease

Fujita et al (2003), Fitzgerald (2007) and Jawa et al (2010) suggested that oral supplementation can be effective in treating vitamin B₁₂ deficiency in people taking metformin. Pflipsen et al (2009) reported that taking multivitamins may reduce the incidence of vitamin B₁₂ deficiency, although Reinstatler et al (2012) suggested that the amount of vitamin B₁₂ in most multivitamins (6 µg) may not be enough to correct the levels in people with deficiency.

The *British National Formulary* (BMJ Group and RPS Publishing, 2012) states, "There is little place for the use of low-dose vitamin B₁₂ orally," but also that "vitamin B₁₂ in larger oral doses of 1–2 mg daily (unlicensed) may be effective." However, supplementation is generally administered intramuscularly in general practice in the UK – this may be due to the lack of evidence supporting the efficacy of oral preparations. Oral vitamin B₁₂ is readily available over-the-counter in chemists and health food shops in the UK at doses ranging from 1 to 1000 µg. Although most people find intramuscular injections of vitamin B₁₂ painful, it is currently the accepted treatment for those with proven deficiency. It would be interesting to know whether, given the choice, people would opt for oral or intramuscular vitamin B₁₂ supplementation.

A Cochrane review by Vidal-Alaball et al (2009), based on the findings of two

randomised controlled trials, found oral vitamin B₁₂ to be as effective as intramuscular vitamin B₁₂ for improving haematological and neurological outcomes.

In the first of the included studies, Bolaman et al (2003) randomised 66 people with megaloblastic anaemia to receive oral vitamin B₁₂ (1000 µg) daily for 10 days, then once per week for 4 weeks (orally or intramuscularly) in a prospective, open-label, 90-day study. In the other included study, Kuzminski et al (1998) randomised participants to receive either daily oral vitamin B₁₂ (2000 µg) for 120 days, or 1000 µg intramuscularly on days 1, 3, 7, 10, 14, 21, 30, 60 and 90.

Adherence to treatment might be higher with intramuscular vitamin B₁₂ supplementation compared with oral preparations for vulnerable groups, such as those with mental health problems, learning difficulties or dementia. Other factors that may determine the suitability of oral versus intramuscular vitamin B₁₂ replacement include how low the B₁₂ levels are, whether the individual is symptomatic or if they also have evidence of pernicious anaemia, in which case the intramuscular route is preferable. The cost of oral versus intramuscular supplementation is a consideration.

3. Facilities for diagnosis and treatment should be available

Diagnosing and treating vitamin B₁₂ deficiency is routine practice in primary care. Practice nurses (or in some health authorities, healthcare assistants) administer intramuscular vitamin B₁₂ (as hydroxocobalamin). If all people taking metformin were screened for vitamin B₁₂ deficiency and a significant proportion found to need intramuscular supplementation, the NHS could face a capacity problem.

4. There should be a recognisable latent or early symptomatic stage

There is a correlation between low vitamin B₁₂ levels, anaemia and neurological symptoms, and evidence to suggest that detecting

vitamin B₁₂ deficiency early or as levels fall into the lower range improves outcomes. In some cases, cognitive function (NICE, 2010b) and neurological symptoms (Wile and Toth, 2010) may improve. Although an improvement in peripheral neuropathy has been seen following vitamin B₁₂ replacement, in some cases once peripheral neuropathy is established it may be irreversible (Wile and Toth, 2010).

Miller et al (2005) explain the mechanism by which vitamin B₁₂ deficiency causes neuropathy. Vitamin B₁₂ is used in the production of essential lipids that form myelin. When someone becomes deficient in vitamin B₁₂ this process cannot occur, leading to demyelination, which affects the signals travelling down the nerves. The authors suggest that the body's inflammatory response to this process of demyelination increases vitamin B₁₂ uptake, which could worsen deficiency.

The Quality and Outcomes Framework introduced a new audit standard in 2011/12 to the dementia register. Payment is given for the percentage of those with a new diagnosis of dementia who have a full blood count, calcium, glucose, renal and liver function, thyroid function, serum vitamin B₁₂ and folate recorded 6 months before or after entering onto the register (NICE, 2010a). Early detection and correction of vitamin B₁₂ deficiency may improve cognitive function (NICE, 2009).

5. There should be a suitable test or examination

In UK laboratories, when testing for vitamin B₁₂ deficiency total cobalamin levels are measured. The usual reference range of 191–663 ng/L¹ is based on the results expected from healthy individuals, of whom an estimated 5% have abnormal results. In the total vitamin B₁₂ assay, not all the cobalamin is functional and the proportion of functional vitamin B₁₂ varies between individuals. Therefore, some people have low vitamin B₁₂ levels but, if they have high levels of functional vitamin B₁₂, are less likely to become anaemic or to develop problems (such as neurological symptoms) when their levels are low. Likewise, some people have normal vitamin B₁₂

levels but low levels of functional vitamin B₁₂ and are more likely to develop problems. Measuring methylmalonic acid (MMA) or holotranscobalamin may give a better indication of functional vitamin B₁₂ deficiency. MMA is a non-esterified fatty acid and its conversion into succinic acid is one of the metabolic pathways catalysed by a vitamin B₁₂-dependent enzyme. When vitamin B₁₂ is lacking this cannot occur, resulting in a build up of MMA, which is released from the cells and can then be measured. Currently, most UK laboratories do not measure MMA. Studies have shown that when vitamin B₁₂ levels fall, homocysteine levels rise (Wulffelé et al, 2003; Hermann et al, 2004; Sahin et al, 2007; Pflipsen et al, 2009; Wile and Toth, 2010).

6. The test should be acceptable to the population

Most people with diabetes are accustomed to having blood tests on a regular basis and this is generally accepted.

7. The natural history of the condition, including development from latent to declared disease, should be adequately understood

Vitamin B₁₂ levels decrease as early as 6 weeks following initiation of metformin therapy (Sahin et al, 2007) but deficiency takes longer to develop owing to the body's stores. Vitamin B₁₂ deficiency worsens with dose and duration of metformin (Ting et al, 2006; Wile and Toth, 2010).

8. There should be an agreed policy on whom to treat as patients

We may assume that all people with established biochemical vitamin B₁₂ deficiency should receive vitamin B₁₂ supplementation to avoid future clinical symptoms developing.

9. The cost of case-finding (including diagnosis and treatment of diagnosed individuals) should, as a whole, be economically balanced in relation to possible expenditure on medical care

Assessing the cost of case-finding, including diagnosis and treatment of individuals, and economically balancing this in relation to possible expenditure on medical care as a whole, is a

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¹Laboratory reference ranges may differ.

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1. The cost of oral versus intramuscular vitamin B₁₂ supplementation must take into account follow-up blood tests (vitamin B₁₂ levels), which do not need to be repeated with intramuscular supplementation.
2. Follow-up of abnormal vitamin B₁₂ level test results would need to take into account the person's dietary intake of vitamin B₁₂, current medication, and whether they have unexplained anaemia, macrocytosis, neurological symptoms, psychiatric illness, dementia or a family history of pernicious anaemia.
3. Healthcare professionals should, at the very least, remember to check vitamin B₁₂ levels in anyone with diabetes and peripheral neuropathy, rather than assuming that this is due to diabetes.

complex issue. The diagnostic test can be carried out at the same time as the annual blood test at no further inconvenience to the individual but incurs a cost in itself. The cost of oral versus intramuscular supplementation must take into account follow-up blood tests (vitamin B₁₂ levels), which do not need to be repeated with intramuscular supplementation. The cost of administering intramuscular therapy should include the use of surgery premises – intramuscular therapy is more cost-effective for a healthcare assistant to administer than a practice nurse.

10. Case-finding should be a continual process and not a “once and for all” project

As vitamin B₁₂ deficiency is more common with increasing metformin dose and duration and patient age, case-finding should be a continual process. Bauman et al (2000), Hermann et al (2004), Fitzgerald (2007), de Jager et al (2010) and Wile and Toth (2010) recommend regular serum vitamin B₁₂ measurements while on metformin therapy, and Tomkin et al (1971) suggest this should be performed annually.

Conclusion

Current evidence suggests that metformin reduces the absorption of vitamin B₁₂ and increases the risk of deficiency. Approximately one in 10 adults with type 2 diabetes taking metformin develop vitamin B₁₂ deficiency within 4.3 years of commencing therapy. However, not all people who develop biochemical vitamin B₁₂ deficiency will go on to develop clinical signs of deficiency. Follow-up of abnormal vitamin B₁₂ level test results would need to take into account the person's dietary intake of vitamin B₁₂, current medication, and whether they have unexplained anaemia, macrocytosis, neurological symptoms, psychiatric illness, dementia or a family history of pernicious anaemia. There may be a place for oral rather than intramuscular vitamin B₁₂ supplementation in some people who have vitamin B₁₂ deficiency.

Screening those at risk of deficiency might prevent pathological changes developing and harm occurring; however, formal screening programmes need to be supported by sufficient evidence and justified in health economic

terms. Further research may shed light on this discussion, such as a trial of vitamin B₁₂ replacement versus placebo in metformin users of sufficient power and duration to detect differences in the development of clinical deficiency rather than biochemical deficiency alone. Diabetes research has emphasised the need to ensure that treatments improve clinical outcomes and not just biochemical or haematological abnormalities. Rosiglitazone improving HbA_{1c} but subsequently being withdrawn owing to a link with an increased risk of heart attack and stroke (NHS Choices News, 2010) is a good example of this, emphasising the limitations of surrogate markers. In the meantime, healthcare professionals should, at the very least, remember to check vitamin B₁₂ levels in anyone with diabetes and peripheral neuropathy, rather than assuming that this is due to diabetes. ■

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