Should people treated with metformin be screened for vitamin B_{12} deficiency?

Claire Holt

Article points

1. Current evidence suggests that metformin reduces the absorption of vitamin B_{12} 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 B_{12}

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Current evidence suggests a relationship between metformin treatment and vitamin B_{12} deficiency in people with diabetes. At present, these individuals do not undergo screening for vitamin B_{12} deficiency. This article discusses the health and cost implications of screening for vitamin B_{12} 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 B_{12} 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 B_{12} malabsorption might be permanent.

In controlled studies comparing metformin with placebo, metformin significantly reduced vitamin B_{12} levels (Wulffelé et al, 2003; DeFronzo and Goodman, 2005; Sahin et al, 2007). These studies were not able to demonstrate an increase in vitamin B_{12} 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 B_{12} 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 B_{12} 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 B_{12} 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 B_{12} 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 B_{12} deficiency. When comparing metformin with placebo, metformin significantly increased the risk of developing vitamin B_{12} deficiency by 7.2% (P=0.004; de Jager et al, 2010).

Current practice is to measure serum vitamin B_{12} when there are signs of neuropathy, cognitive impairment, anaemia or other clinical features suggestive of vitamin B_{12} deficiency. There are currently no national guidelines recommending screening adults with type 2 diabetes on metformin therapy for vitamin B_{12} deficiency. Vitamin B_{12} deficiency can have serious health implications if left undiagnosed and untreated. However, not all people with biochemical vitamin B_{12} deficiency will develop clinical symptoms.

Aetiology

Vitamin B_{12} (cyanocobalamin) and folate are part of the complex of water-soluble B vitamins used in the production of red blood cells. Vitamin B_{12} is required for DNA synthesis and carbohydrate metabolism. Vitamin B_{12} 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 B_{12} deficiency include megaloblastic anaemia characterised by enlarged red blood cells, neutropenia and thrombocytopenia. Vitamin B_{12} 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 B_{12} 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 B_{12} deficiency and megaloblastic anaemia. Sixty per cent of vitamin B_{12} 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 B_{12} when given large doses orally (Elia, 1998). In clinical practice, those with pernicious anaemia should be given vitamin B_{12} replacement intramuscularly (as hydroxocobalamin). Other causes of vitamin B_{12} 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 B_{12} before it can be absorbed. Medications that may affect vitamin B_{12} absorption include phenytoin, proton pump inhibitors, nitrous oxide and dihydrofolate reductase inhibitors. Vitamin B_{12} 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

Page points

1. There are currently no national guidelines recommending screening adults with type 2 diabetes on metformin therapy for vitamin B_{12} deficiency.
2. Vitamin B_{12} deficiency can have serious health implications if left undiagnosed and untreated. However, not all people with biochemical vitamin B_{12} deficiency will develop clinical symptoms.
3. Haematological features of vitamin B_{12} deficiency include megaloblastic anaemia characterised by enlarged red blood cells, neutropenia and thrombocytopenia.

Page points

1. Oral vitamin B_{12} 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 B_{12} painful, it is currently the accepted treatment for patients with proven deficiency.
2. If all people taking metformin were screened for vitamin B_{12} 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 B_{12} levels, anaemia and neurological symptoms, and evidence to suggest that detecting vitamin B_{12} deficiency early or as levels fall into the lower range improves outcomes.

question of screening metformin users for vitamin B_{12} deficiency.

1. The condition sought should be an important health problem

Vitamin B_{12} 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 B_{12} deficiency in people taking metformin. Pflipsen et al (2009) reported that taking multivitamins may reduce the incidence of vitamin B_{12} deficiency, although Reinstatler et al (2012) suggested that the amount of vitamin B_{12} 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 B_{12} orally," but also that "vitamin B_{12} 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 B_{12} 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 B_{12} 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 B_{12} supplementation.

A Cochrane review by Vidal-Alaball et al (2009), based on the findings of two randomised controlled trials, found oral vitamin B_{12} to be as effective as intramuscular vitamin B_{12} 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 B_{12} (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 B_{12} (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 B_{12} 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 B_{12} replacement include how low the B_{12} 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 B_{12} deficiency is routine practice in primary care. Practice nurses (or in some health authorities, healthcare assistants) administer intramuscular vitamin B_{12} (as hydroxocobalamin). If all people taking metformin were screened for vitamin B_{12} 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 B_{12} levels, anaemia and neurological symptoms, and evidence to suggest that detecting

vitamin B_{12} 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 B_{12} 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 B_{12} deficiency causes neuropathy. Vitamin B_{12} is used in the production of essential lipids that form myelin. When someone becomes deficient in vitamin B_{12} 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 B_{12} 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 B_{12} and folate recorded 6 months before or after entering onto the register (NICE, 2010a). Early detection and correction of vitamin B_{12} deficiency may improve cognitive function (NICE, 2009).

5. There should be a suitable test or examination

In UK laboratories, when testing for vitamin B_{12} deficiency total cobalamin levels are measured. The usual reference range of 191–663 ng/L[1] is based on the results expected from healthy individuals, of whom an estimated 5% have abnormal results. In the total vitamin B_{12} assay, not all the cobalamin is functional and the proportion of functional vitamin B_{12} varies between individuals. Therefore, some people have low vitamin B_{12} levels but, if they have high levels of functional vitamin B_{12}, 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 B_{12} levels but low levels of functional vitamin B_{12} and are more likely to develop problems. Measuring methylmelonic acid (MMA) or holotranscobalamin may give a better indication of functional vitamin B_{12} deficiency. MMA is a non-esterified fatty acid and its conversion into succinic acid is one of the metabolic pathways catalysed by a vitamin B_{12}-dependent enzyme. When vitamin B_{12} 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 B_{12} 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).

[1]Laboratory reference ranges may differ.

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 B_{12} 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 B_{12} 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 B_{12} deficiency should receive vitamin B_{12} 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

Page points

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Page points

1. The cost of oral versus intramuscular vitamin B_{12} supplementation must take into account follow-up blood tests (vitamin B_{12} levels), which do not need to be repeated with intramuscular supplementation.
2. Follow-up of abnormal vitamin B_{12} level test results would need to take into account the person's dietary intake of vitamin B_{12}, 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 B_{12} 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 B_{12} 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 B_{12} 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 B_{12} 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 B_{12} and increases the risk of deficiency. Approximately one in 10 adults with type 2 diabetes taking metformin develop vitamin B_{12} deficiency within 4.3 years of commencing therapy. However, not all people who develop biochemical vitamin B_{12} deficiency will go on to develop clinical signs of deficiency. Follow-up of abnormal vitamin B_{12} level test results would need to take into account the person's dietary intake of vitamin B_{12}, 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 B_{12} supplementation in some people who have vitamin B_{12} 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 B_{12} 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 B_{12} levels in anyone with diabetes and peripheral neuropathy, rather than assuming that this is due to diabetes. ■

Adams JF, Clark JS, Ireland JT et al (1983) Malabsorption of vitamin B_{12} and intrinsic factor secretion during biguanide therapy. *Diabetologia* **24**: 16–8

Bauman WA, Shaw S, Jayatilleke E et al (2000) Increased intake of calcium reverses vitamin B_{12} malabsorption induced by metformin. *Diabetes Care* **23**: 1227–31

Bolaman Z, Kadikoylu G, Yukselen V et al (2003) Oral versus intramuscular cobalamin treatment in megaloblastic anemia: a single-center, prospective, randomized, open-label study. *Clin Ther* **25**: 3124–34

BMJ Group and RPS Publishing (2012) *British National Formulary* 63. BMJ Group and RPS Publishing, London

Burtis CA, Ashwood ER, Bruns DE (2005) *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics* (4th edn). Elsevier Saunders, PA, USA

Crawford F, Inkster M, Kleijnen J et al (2007) Predicting foot ulcers in patients with diabetes: a systematic review and meta-analysis. *QJM* **100**: 65–86

Davis WA, Norman PE, Bruce DG et al (2006) Predictors, consequences and costs of diabetes-related lower extremity amputation complicating type 2 diabetes: the Fremantle Diabetes Study. *Diabetologia* **49**: 2634–41

DeFronzo RA, Goodman AM (1995) Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med* **333**: 541–9

de Jager J, Kooy A, Wulffelé MG et al (2010) Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B_{12} deficiency: randomised placebo controlled trial. *Br Med J* **340**: c2181

Elia M (1998) Oral or parenteral therapy for B_{12} deficiency. *Lancet* **352**: 1721–2

Fitzgerald MA (2007) Drug-induced vitamin B_{12} deficiency. *Nurse Pract* **32**: 6–7

Fujita H, Narito T, Yoshioka N et al (2003) A case of megaloblastic anemia due to vitamin B_{12} deficiency precipitated in a totally gastrectomized type II diabetic patient following the introduction of metformin therapy. *Endocr J* **50**: 483–4

"Current evidence suggests that metformin reduces the absorption of vitamin B_{12} and increases risk of deficiency. Approximately one in 10 people develop vitamin B_{12} deficiency within 4.3 years of commencing therapy."

Gilroy J, Holliday PL (1982) *Basic Neurology*. Macmillan Publishing Company, London

Hermann LS, Nilsson B, Wettre S (2004) Vitamin B_{12} status of patients treated with metformin: A cross-sectional cohort study. *Br J Diabetes Vasc Dis* **4**: 401–6

Jawa AA, Akram J, Sultan M et al (2010) Nutrition-related vitamin B_{12} deficiency in patients in Pakistan with type 2 diabetes mellitus not taking metformin. *Endocr Pract* **16**: 205–8

Kuzminski AM, Del Giacco EJ, Allen RH et al (1998) Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* **92**: 1191–8

Liu KW, Dai LK, Jean W (2006) Metformin-related vitamin B_{12} deficiency. *Age Ageing* **35**: 200–1

Miller A, Korem M, Almong R et al (2005) Vitamin B_{12}, demyelination, remyelination and repair in multiple sclerosis. *J Neurol Sci* **233**: 93–7

NHS Choices News (2010) Avandia diabetes drug suspended. Available at: http://bit.ly/bmYvcA (accessed 08.08.12)

NICE (2009) *CG87 Type 2 Diabetes – Newer Agents*. NICE, London. Available at: www.nice.org.uk/cg87 (accessed 28.06.12)

NICE (2010a) *NICE Menu of Indicators – NM09 QOF ID: DEM3*. NICE, London. Available at: http://bit.ly/LFqz9u (accessed 28.06.12)

NICE (2010b) *NICE Cost Impact Assessment: QOF Indicator for Dementia. NICE, London*. Available at: http://bit.ly/KOETeC (accessed 28.06.12)

Pflipsen MC, Oh RC, Sangull A et al (2009) The prevalence of vitamin B_{12} deficiency in patients with type 2 diabetes: a cross-sectional study. *J Am Board Fam Med* **22**: 528–34

Reinstatler L, Qi YP, Williamson RS et al (2012) Association of biochemical B_{12} deficiency with metformin therapy and vitamin B_{12} supplements: the National Health and Nutrition Examination Survey, 1999–2006. *Diabetes Care* **35**: 327–33

Sahin M, Tutuncu, NB, Ertugrul D et al (2007) Effects of metformin or rosiglitazone on serum concentrations of homocysteine, folate, and vitamin B_{12} in patients with type 2 diabetes mellitus. *J Diabetes Complications* **21**: 118–23

SIGN (2010) 116. *Management of Diabetes: A National Clinical Guideline*. SIGN, Edinburgh. Available at: http://bit.ly/MXZj23 (accessed 17.03.12)

Ting RZ, Szeto CC, Chan MH et al (2006) Risk factors of vitamin B_{12} deficiency in patients receiving metformin. *Arch Intern Med* **116**: 1975–9

Tomkin GH, Hadden DR, Weaver JA et al (1971) Vitamin-B_{12} status of patients on long-term metformin therapy. *Br Med J* **2**: 685–7

UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* **352** 854–65

Vidal-Alaball J, Butler C, Cannings-John R et al (2009) Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database of Systematic Reviews*, Issue 3. Art. No.: CD004655. DOI: 10.1002/14651858.CD004655.pub2.

Wile DJ, Toth C (2010) Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. *Diabetes Care* **33**: 156–61

Wilson, JM, Jungner G (1968) *Principles and Practice of Screening for Disease: Public Health Papers No. 34*. World Health Organization, Geneva. Available at: http://bit.ly/17Qrdg (accessed 28.06.12)

Wulffelé MG, Kooy A, Lehert P et al (2003) Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B_{12} in type 2 diabetes: a randomized, placebo-controlled trial. *J Intern Med* **254**: 455–63