

# Pseudo-dementia caused by metformin-induced vitamin B12 deficiency

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## Summary

Metformin is the most widely used oral insulin-sensitizing agent. There is a significant association between long-term metformin therapy and an increased prevalence of vitamin B12 deficiency. Vitamin B12 deficiency is one of the causes of pseudo-dementia. This paper presents a rare case of pseudo-dementia in a 60-year-old Caucasian woman caused by vitamin B12 deficiency induced by the use of metformin, a vegetarian diet, and smoking. In diabetics with cognitive disorders who are on biguanide therapy, it is necessary to determine the level of vitamin B12 in the serum in order to rule out possible pseudo-dementia and to avoid possible hematological and neurological disorders. Unfortunately, vitamin B12 deficiency remains frequently unrecognized in those patients.

**Keywords:** Metformin; Vitamin B12 deficiency; Diabetes Mellitus Type 2; Dementia

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## INTRODUCTION

Metformin is the most widely used oral insulin-sensitizing agent. There is a significant association between long-term metformin therapy and an increased prevalence of vitamin B12 deficiency (Infante et al., 2021). Vitamin B12 deficiency can lead to a number of clinical consequences that include hematologic abnormalities (e.g., megaloblastic anemia), subacute combined degeneration, polyneuropathy, and cognitive impairment.

The case of a 60-year-old woman who developed pseudo-dementia as a result of metformin-induced vitamin B12 deficiency will be presented in this report.

## CASE PRESENTATION

A 60-year-old Caucasian woman comes for a neurological examination accompanied by her husband due to occasional confusion and forgetfulness, behavioral change, irritability, emotional lability, and a history of repeated falls and postural dizziness. The patient had a milder form of COVID-19 with anosmia, hypogeusia, and 7-day subfebrility six months ago. For the last 5 years, the patient has been treated for diabetes mellitus type 2 (T2DM) with metformin at a dose of 850 mg twice a day. She has been a vegetarian for the past 10 years. The patient is a smoker and has denied alcohol consumption and illicit drug use. At admission, she was depressed, bradyphrenic, disoriented in time, and had dyscalculia

and impaired short-term memory. Her Mini-Mental State Examination (MMSE) score was 24/30. She denied any hallucinations. The patient's blood pressure was 120/80 mmHg, her pulse was 80 beats per minute, and she was afebrile. The function of the cranial nerves was normal. There were no meningeal signs or motor deficits in her hands. The myotatic reflexes in the hands were normal. Tinel's sign was positive bilaterally. Hypoesthesia is evident on both hands in the median nerve innervation area. She also did not have any motor deficits in her legs. Patellar reflexes are symmetrical and of medium intensity; Achilles tendon reflexes are bilaterally attenuated. Babinski's sign was negative. The sensory exam showed impaired sensation of pain, temperature, light touch, position sense, vibration, and discriminative sensations on both lower legs. She performed hand coordination tests without dysmetria. The patient was unstable in the Romberg position with a wide-based ataxic gait. She did not have bladder or bowel incontinence. Mild cognitive impairment (MCI), bilateral carpal tunnel syndrome, and diabetic polyneuropathy were recognized, and additional checks were recommended.

Laboratory results indicate macrocytic anemia (RBC  $3.8 \times 10^{12}/L$ ; norm. 4.34-5.72; Hb 110 g/L; norm. 138-175; MCV 108 fL; norm. 83.0-97.2), reduced values of vitamin B12 (60 pmol/L; norm. 138-652), while the level of folic acid in the serum is at the lower limit of normal (7.0 nmol/L; norm. 7.0-46.4). The patient's thyroid-stimulating hormone (TSH), liver enzymes, iron studies, serum protein electrophoresis, anti-tissue transglutaminase antibodies, anti-intrinsic factor antibodies, carcinoembryonic antigen, carbohydrate antigen 19-9, carbohydrate

antigen 125, carbohydrate antigen 15-3, and alpha-feto-protein were all within normal limits. Her hemoglobin A1c was 9%. Magnetic resonance imaging (MRI) of the brain showed mild cerebral atrophy, and MRI of the cervical and thoracic spine was normal. The findings of chest radiography, computed tomography (CT) of the abdomen and pelvis, gastroscopy, and colonoscopy are also correct. Nerve conduction studies indicate moderate bilateral carpal tunnel syndrome and moderate distal sensorimotor polyneuropathy in the legs.

Considering the above, substitution therapy was started with intramuscular administration of vitamin B12 according to the following scheme: first week, 1000 mcg i.m./day, then 1000 mcg i.m. weekly for a month, then 1000 mcg i.m. 1x a month, with folic acid tablets of 5 mg once in the morning.

The patient's laboratory findings and neuropsychiatric status completely improved after 6 months of a diabetic diet, insulin therapy, and vitamin B12 and folic acid substitution.

## DISCUSSION

In this paper, I report the first case of reversible pseudo-dementia in an adult diabetic, vegetarian, and smoker due to metformin-induced vitamin B12 deficiency. Pseudo-dementia is a condition where mental cognition can be temporarily decreased. The most common causes of pseudo-dementia are megaloblastic anemia due to vitamin B12 or folic acid deficiency, hypothyroidism, syphilis, HIV infection, chronic subdural hematoma, frontal lobe brain tumor, normotensive hydrocephalus, post-COVID-19 syndrome, and depression (Alexander & Stuss, 2000; Brigić et al., 2021; Dobie, 2002; Gavrilov et al., 2019; Ho & Nicholl, 2013; Ishikawa et al., 2002; Nath et al., 2008; Włodarczyk et al., 2017). To rule out the existence of possible causes of pseudo-dementia, it is necessary to do an extensive workup that includes a complete blood count, the level of vitamin B12 and folic acid in the serum, TSH, testing for syphilis and HIV, a CT or MRI of the brain, and a psychiatrist's examination. This search algorithm can be used to identify disorders that can be effectively treated both conservatively or surgically. Metformin, a biguanide oral antihyperglycemic drug, is used as a first-line treatment for T2DM (Chaudhary & Kulkarni, 2024). It is the most prescribed oral antidiabetic worldwide; it first became available in the U.K. in 1958 and entered the Canadian market in 1971, but it has been available in the U.S. only since 1995 (Moore et al., 2013). Metformin has significantly improved the

prognosis of diabetic patients by improving insulin sensitivity and protection against vascular complications (Bailey & Turner, 1996). Berchtold et al. (1969) first reported a possible effect of metformin on vitamin B12 status. Vitamin B12 is a water-soluble vitamin that is mainly obtained from animal-sourced foods and acts as a cofactor for enzymes that play a critical role in DNA synthesis and neuroprotection, signal neurotransmission, myelin sheath synthesis, and erythropoiesis (Infante et al., 2021; Smith et al., 2018). Long-term use of metformin may result in vitamin B12 deficiency due to absorption inhibition, bacterial overgrowth, changes in small intestine motility, and intrinsic factor levels (Khattar et al., 2016). Metformin helps bacteria gather B12 from the environment by increasing the expression of B12 transporter genes in an RcdA-dependent manner.

This may theoretically reduce the B12 supply to T2DM patients taking the drug over time (Yao et al., 2023). In this case, vitamin B12 deficiency is most likely a result of altered intestinal motility caused by diabetic autonomic polyneuropathy and reduced vitamin B12 absorption within the small intestine due to a vegetarian diet and metformin therapy. The rate of vitamin B12 deficiency in patients taking metformin is about 30% (Tomkin et al., 1971). The results of several clinical studies have shown that metformin decreased serum vitamin B12 levels by 14%, 22%, and 30% (Bauman et al., 2000; DeFronzo & Goodman, 1995; Wulffélé et al., 2003). Deficiency of vitamin B12 is more significant with long-term use of higher doses of metformin (Khattar et al., 2016; Ting et al., 2006). Apart from the use of metformin, a vegetarian diet and cigarette smoking are also risk factors for the development of vitamin B12 deficiency. A vegetarian diet implies a reduced intake of vitamin B12, and smoking leads to increased excretion of vitamin B12 in the urine (Linnell et al., 1968; Pawlak et al., 2013).

In this case, the patient was a smoker, and vitamin B12 deficiency is particularly common in smokers with T2DM who've been taking metformin (Khan et al., 2017). Gastric acid promotes the conversion of pepsinogen to pepsin, which releases vitamin B12 from food proteins. A lack of gastric acid due to prolonged use of proton pump inhibitors or H2-receptor antagonists will also reduce vitamin B12 concentrations (Miller, 2018). Low serum vitamin B12 levels are associated with neurodegenerative diseases (e.g., Alzheimer's disease and Parkinson's disease) and cognitive impairment (Moore et al., 2012). Munshi et al. (2006) have found that older adults with poor diabetes control have cognitive impairment. Low vitamin B12 levels may cause silent brain injury through oxidative stress, resulting in calcium influx

and apoptosis (Jatoi et al., 2020). Vitamin B12 deficiency is only one of the possible causes of cognitive impairment in patients with T2DM. Other risk factors include atherosclerosis, cerebral microangiopathy, and oxidative stress as a consequence of glucose toxicity (Biessels et al., 2006).

In the presented case, sensorimotor polyneuropathy and consequent sensory ataxia are caused by diabetes and vitamin B12 deficiency. Porter et al. (2019) found that metformin use was associated with cognitive dysfunction and vitamin B12 and B6 deficiency. Ellis et al. (1982) found that lack of vitamin B6 due to insufficient intake was linked to carpal tunnel syndrome. Although its effectiveness is controversial, vitamin B6 is often used as a conservative and adjunct therapy in the treatment of carpal tunnel syndrome (Ryan-Harshman & Aldoori, 2007). In this case, carpal tunnel syndrome is most probably triggered by diabetes and perhaps also by vitamin B6 deficiency (this test was not performed), since vitamin B12 deficiency is not a risk factor for the development of this compressive mononeuropathy of the median nerve. Laroussi et al. (2024) reported a rare case of acute-onset reversible dementia with seizures due to metformin-induced vitamin B12 deficiency. It is well known that the use of combined hormonal contraceptives associated with smoking and obesity increases the risk of stroke (Lima et al., 2017). Similar to the previous observation, in the presented case it was shown that the use of

metformin, smoking, and a vegetarian diet increases the risk of vitamin B12 deficiency and consequent cognitive impairment.

## CONCLUSION

In diabetics with cognitive disorders who are on biguanide therapy, especially if they are vegetarians and smokers, it is necessary to determine the level of vitamin B12 in the serum in order to rule out possible pseudo-dementia. The level of vitamin B12 in the serum should be periodically controlled, even in asymptomatic diabetics who have been taking biguanides for a long time, and prophylactic administration of vitamin B12 would be recommended in order to avoid possible hematological and neurological disorders. Unfortunately, vitamin B12 deficiency remains frequently unrecognized in those patients.

**Ethical Considerations:** Does this study include human subjects? YES

Authors confirmed the compliance with all relevant ethical regulations.

**Conflict of interest:** No conflict of interest.

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