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Metformin-Associated Vitamin B12 Deficiency: An Underrecognized Complication

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Abstract

Metformin-associated vitamin B12 deficiency is a well-established side effect, especially in patients taking higher doses of metformin or who have existing risk factors. Severe deficiency causes a wide range of systemic disorders. Gait instability, which leads to frequent falling, is usually an underrecognized side effect. Older patients are more likely to develop chronic subdural hematoma even with minor trauma. We present a case of 84-year-old man with type 2 diabetes mellitus with acute-on-chronic subdural hematoma from frequent falls. Metformin therapy at dose of 1700 mg/day was given for more than 25 years. He had been in his usual state of health until 10 months ago when he began to have frequent fallings and fatigue. Physical examination in this admission revealed new-onset impaired vibratory sensation and proprioception in both feet and positive Romberg test. Subsequent evaluations demonstrated undetectable plasma vitamin B12 level and elevated plasma homocysteine. Improvement in neurological symptoms occurred within 1 week of vitamin B12 replacement and surgical hematoma evacuation. This case highlights the importance of awareness and periodic monitoring of vitamin B12 status among older patients taking metformin.

Key Words: metformin, vitamin B12, deficiency, subdural hematoma, gait instability

Abbreviations: PPI, proton pump inhibitors; MCV, mean corpuscular volume; MMA, methylmalonic acid; WBC, white blood cell.

Introduction

Vitamin B12 deficiency associated with prolonged metformin therapy has been known since the 1970s [1] but it is still an underrecognized condition. Periodic monitoring of vitamin B12 levels in patients treated with metformin has been recommended by the American Diabetes Association Standards of Medical Care in Diabetes since 2017 [2] and the Medicines and Healthcare products Regulatory Agency guidance in the United Kingdom since 2022 [3]. Annual plasma vitamin B12 measurement is recommended for all patients receiving metformin because many cases of vitamin B12 deficiency are overlooked or sometimes even misdiagnosed due to its wide range of clinical manifestations, including hematological, gastrointestinal, psychiatric, and neurological disorders [4, 5]. In people with borderline vitamin B12 levels (defined by plasma vitamin B12 levels between 190 and 407 pg/mL [140-300 pmol/L]), elevated plasma methylmalonic acid (MMA) and/or homocysteine levels may aid in establishing a possible diagnosis of deficiency [6].

A variety of disorders are associated with vitamin B12 deficiency, because vitamin B12 serves as an important cofactor in various biochemical reactions. Many cases of vitamin B12 deficiency are overlooked or misdiagnosed, especially in patients with nonclassical manifestations such as mild anemia without macrocytosis, neuropsychiatric manifestations, and symptoms of frailty [5]. It has been reported that less than 20% of people with low plasma vitamin B12 levels have macrocytic anemia [7] and that there is poor correlation between levels and symptoms [8, 9]. Recent studies showed that vitamin B12 deficiency has been linked with falling and functional decline in older populations [5, 10]. Here, we present a case of metformin-associated vitamin B12 deficiency as a potential cause of recurrent chronic subdural hematoma.

Case Presentation

An 84-year-old Thai man with well-controlled type 2 diabetes mellitus presented with dizziness and fatigue for 2 weeks. He denied fever, headache, diplopia, visual changes, nausea, vomiting, weight loss, numbness or paresthesia, or alterations in consciousness. He had been in his usual state of health until 10 months ago when he began to have frequent falls and fatigue but did not report any recent trauma. At that time, computed tomography (CT) of the brain was performed to investigate the possibility of posttraumatic brain injury. Chronic subdural hematoma at left fronto-parietal area was found as shown in Fig. 1A. In view of the small lesion and the unwillingness to undergo surgical evacuation, the patient was managed conservatively. His past medical history included essential hypertension, dyslipidemia, moderate nonproliferative diabetic retinopathy, severe aortic stenosis with history of syncope, and single-vessel coronary artery disease. He had been diagnosed with type 2 diabetes mellitus at the age of 57 years and had been well-controlled without insulin in the past 20 years. His latest glycated hemoglobin was 5.7%
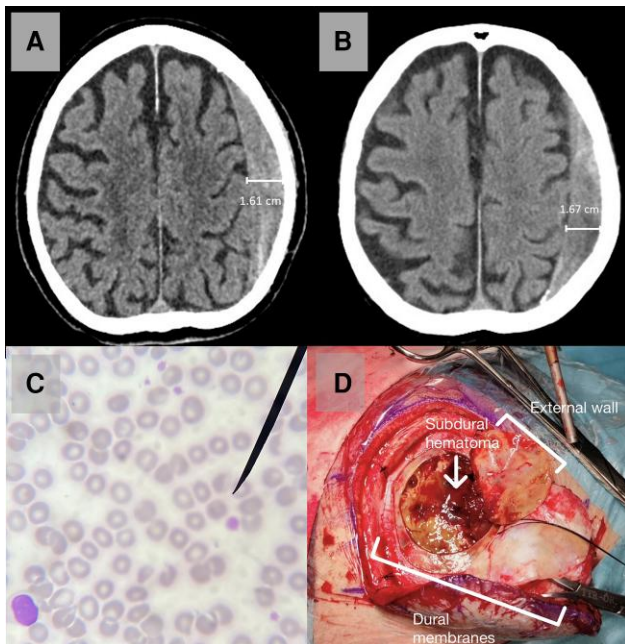
Figure 1. A, Computed tomography (CT) brain at 10 months earlier revealed a crescent-shaped hypodensity mass with a slight hyperdensity representing trace of acute hemorrhage in chronic subdural hematoma, no midline shift or other evidence for brain herniation; B, CT brain in this admission showed enlargement of subdural hematoma at left frontal and parietal convexities, representing worsening acute-on-chronic subdural hematoma; C, peripheral blood smear showed normocytic normochromic red blood cells and thrombocytopenia; D, intraoperative craniotomy revealed the intact inner membrane of multistage subdural hematoma.

(39 mmol/mol) with metformin and linagliptin. Metformin at dose of 1700 mg/day had been given for more than 25 years. Three years ago, a comprehensive foot examination was normal. Six months ago, transcatheter aortic valve implantation (TAVI) was done with left anterior descending artery percutaneous coronary intervention with drug-eluting stent implantation. On admission, his additional medications included linagliptin 5 mg/day, amlodipine 10 mg/day, valsartan 80 mg/day, simvastatin 20 mg/day, aspirin 81 mg/day, clopidogrel 75 mg/day, and pantoprazole 20 mg/day. There had been no changes to any of his medications, and no new drug was given. The patient did not take any vitamin supplements.

The patient was a retired business owner and lived with his family in Bangkok. He had a 40-pack-year smoking history but had stopped 20 years ago. He did not drink alcohol or use other substances. There was no known family history of autoimmune disease. He had a normal diet with no dietary restrictions, and there was no history of unintentional weight loss.

Physical examination showed stable vital signs without orthostatic blood pressure changes. He had a flat affect but was oriented to time, place, and person. Examination of the lungs revealed no adventitious sounds; his heart rhythm was regular and without murmur. No rashes or petechiae were seen. The neurologic examination showed normal muscle tone and strength. Deep tendon reflexes were normal and without clonus. Normal sensation to pinprick was obtained in both arms and legs. The temperature sensations by touching the patient's skin with the tuning fork were normal. A 10-g monofilament testing in both feet was also normal. There were no signs of cranial nerve involvement. The patient was

able to touch the tip of his nose with his index finger when his eyes were open but was unable to do so with eyes closed. Notably, vibratory sensation and proprioception at big toes were impaired in both feet but preserved in both hands. His gait was unsteady, and the Romberg test was positive. Sensory ataxia from lesion in the dorsal columns of the spinal cord was suspected.

Diagnostic Assessment

Computed tomography of the brain revealed an acute-on-chronic subdural hematoma in the same area with a 1.3-cm midline shift (Fig. 1B). On initial laboratory workup, a hematological screen showed a hemoglobin level of 12.8 g/dL, white blood cell (WBC) 4250 cell/mm^3, platelets 126 000/mm^3, and mean corpuscular volume (MCV) of 93.5 fL; the peripheral smear showed normocytic normochromic red blood cells and mild thrombocytopenia (Fig. 1C). No hypersegmented neutrophils, basophilic striping, or Howell-Jolly Bodies were found. When the present complete blood count was compared with the previous results, mild normocytic anemia was found as shown in Table 1. Partial thromboplastin time, international normalized ratio, liver function tests, calcium, magnesium, phosphorus, and iron values were normal.

His new-onset peripheral neuropathy, gait instability, history of prolonged metformin use, and laboratory results raised suspicion for vitamin B12 deficiency. Results of further testing revealed plasma vitamin B12 level was less than 50 pg/mL (< 37 pmol/L) (reference range, 197-771 pg/mL; 145-569 pmol/L), elevated plasma homocysteine level at 5.1 mg/L (37.7 μmol/L) (reference range, 0-2.0 mg/L; 0-15 μmol/L), and normal plasma folate level 7.3 ng/mL (16.6 nmol/L) (reference range, 4.5-32.2 ng/mL; 10.2-73.2 nmol/L). Plasma MMA was not performed. All findings were consistent with metformin-associated vitamin B12 deficiency.

Treatment

Intramuscular injection of 1000 μg of cyanocobalamin daily for 1 week, followed by weekly injections were given. Metformin was discontinued during hospitalization. Surgical evacuation of the subdural hematoma was performed (Fig. 1D) after withholding antiplatelet agents for 2 weeks. No significant bleeding perioperatively was observed and the patient subsequently recovered well.

Outcome and Follow-Up

On subsequent follow-up, the patient showed improvement of his gait and dizziness but continued to have some degree of impaired vibratory sensation and proprioception. One month later, his A1C was 6.7% (50 mmol/mol) with glimepiride 1 mg/day and linagliptin 5 mg/day. Complete blood count showed hemoglobin of 13.8 g/dL, MCV of 95.9 fL, WBC 6120 cell/mm^3, and platelets 255 000/mm^3. Monthly intramuscular injection of 1000 μg of cyanocobalamin planned for at least 6 months followed by oral administration of cyanocobalamin 1000 μg daily.

Discussion

The prevalence of metformin-associated vitamin B12 deficiency has been reported to be 2% to 30%, varying with race, baseline of studied patients, and cutoff levels of plasma

Table 1. Laboratory data at admission compared with previous results

Variable	Reference ranges	On initial evaluation	6 months prior to this admission	12 months prior to this admission	36 months prior to this admission
Hemoglobin	13.5-16.5 g/dL (8.4-10.2 mmol/L)	**12.8 g/dL (7.9 mmol/L)**	**12.0 g/dL (7.5 mmol/L)**	**12.8 g/dL (7.9 mmol/L)**	14.2 g/dL (8.8 mmol/L)
Hematocrit	41.0-50.0% (0.41-0.50 decimal fraction)	**36.4% (0.36 decimal fraction)**	**33.9% (0.33 decimal fraction)**	**36.1% (0.36 decimal fraction)**	41.1% (0.41 decimal fraction)
MCV	80-100 fL (80-100 µm3)	93.5 fL (93.5 µm3)	91.5 fL (91.5 µm3)	89.5 fL (89.5 µm3)	91.6 fL (91.6 µm3)
White cell count	4500-10 000 cells/mm^3 (4.5-10.0 cells*10^9/L)	**4250 cells/mm^3 (4.25 cells*10^9/L)**	6500 cells/mm^3 (6.5 cells*10^9/L)	6080 cells/mm^3 (6.08 cells*10^9/L)	8440 cells/mm^3 (8.44 cells*10^9/L)
Platelet count	150 000-400 000 per µL (150 000-400 000 cells*10^9/)	**126 000 per µL (126 000 cells*10^9/L)**	255 000 per µL (255 000 cells*10^9/L)	220 000 per µL (220 000 cells*10^9/L)	228 000 per µL (228 000 cells*10^9/L)
Sodium	135-145 mEq/L (135-145 mmol/L)	**133 mEq/L (133 mmol/L)**	138 mEq/L (138 mmol/L)	139 mEq/L (139 mmol/L)	140 mEq/L (140 mmol/L)
Potassium	3.5-5.0 mEq/L (3.5-5.0 mmol/L)	**3.3 mEq/L (3.3 mmol/L)**	4.0 mEq/L (4.0 mmol/L)	4.3 mEq/L (4.3 mmol/L)	4.2 mEq/L (4.2 mmol/L)
Chloride	98-108 mEq/L (98-108 mmol/L)	**95 mEq/L (95 mmol/L)**	100 mEq/L (100 mmol/L)	99 mEq/L (99 mmol/L)	102 mEq/L (102 mmol/L)
Carbon dioxide	23-32 mEq/L (23-32 mmol/L)	26 mEq/L (26 mmol/L)	25 mEq/L (25 mmol/L)	25 mEq/L (25 mmol/L)	24 mEq/L (24 mmol/L)
Urea nitrogen	8-25 mg/dL (2.9-8.9 mmol/L)	10 mg/dL (3.6 mmol/L)	10 mg/dL (3.6 mmol/L)	9 mg/dL (3.2 mmol/L)	12 mg/dL (4.3 mmol/L)
Creatinine	0.6-1.5 mg/dL (53-133 µmol/L)	0.9 mg/dL (80 µmol/L)	0.8 mg/dL (71 µmol/L)	0.8 mg/dL (71 µmol/L)	0.9 mg/dL (80 µmol/L)
Glycated hemoglobin	4.8-5.9% (29-41 mmol/mol)	5.7% (39 mmol/mol)	5.9% (41 mmol/mol)	5.8% (40 mmol/mol)	5.9% (41 mmol/mol)
Plasma B12 level	197-771 pg/mL (145-569 pmol/L)	**< 50 pg/mL (< 37 pmol/L)**	-	-	-
Plasma folate level	4.5-32.2 ng/mL (10.2-73.2 nmol/L)	7.3 ng/mL (16.6 nmol/L)	-	-	-
Plasma homocysteine level	0-2.0 mg/L (0-15 µmol/L)	**5.1 mg/L (37.7 µmol/L)**	-	-	-

Values outside the reference levels are shown in bold font. Values in parentheses are International System of Units (SI).

vitamin B12 [11-15]. To date, there is no consensus about the exact definition of vitamin B12 deficiency and varying cutoff values lead to underestimating or overestimating the incidence of vitamin B12 deficiency. In general, serum vitamin B12 levels can be interpreted as follows: if level > 300 pg/mL (221 pmol/L), B12 deficiency is unlikely; level 200 to 300 pg/mL (148 to 221 pmol/L), B12 deficiency is possible; level <200 pg/mL (148 pmol/L), B12 deficiency is highly suggested [4]. On this basis, biochemical vitamin B12 deficiency was defined as serum B12 < 300 pg/mL (221 pmol/L). A meta-analysis of the published literature showed that plasma vitamin B12 level is reduced by 77 pg/mL (57 pmol/L) after 4 months of metformin use [13]. Following 5 years with metformin 1700 mg/day, the Diabetes Prevention Program Outcomes Study showed that 22.2% of recruited patients had serum B12 levels < 300 pg/mL (221 pmol/L), 5.4% had serum B12 levels < 200 pg/mL (148 pmol/L), and only 1 patient (0.1%) had serum B12 level < 100 pg/mL (74 pmol/L) [12]. It should be noted that total plasma vitamin B12 measurements are performed in the clinical laboratory with competitive binding luminescence assays. Their results may not always accurately reflect the actual vitamin B12 store. Vitamin B12 is involved in the activity of methylmalonyl-CoA mutase and the pathway for intracellular methionine synthase. Increase in MMA and homocysteine levels could be used as biochemical indicators to establish vitamin B12 deficiency, especially in people with borderline vitamin B12 [5]. The risk of metformin-associated vitamin B12 deficiency increases with higher metformin dose (daily dosage ≥ 1500 mg), longer treatment duration (duration ≥ 4 years), and in patients with risk factors for vitamin B12 deficiency [5]. It has been suggested that a person who has been on metformin for more than 4 years or is at risk for vitamin B12 deficiency should be monitored for vitamin B12 deficiency annually [2].

The mechanism of this adverse effect has not been elucidated, but the most likely accepted hypothesis is that metformin interferes with calcium-dependent membrane action responsible for vitamin B12-intrinsic factor (IF) absorption in the terminal ileum [16]. Stores of vitamin B12 in the body can last approximately 2 to 5 years without being replenished, and replacement stores from a parenteral route of B12 could fully saturate the B12 pool within 1 month [9]. Proton pump inhibitors (PPI) and histamine 2 receptor antagonists (H2RA) may lead to malabsorption of vitamin B12 [17]. In our case, advanced age, comparatively lower consumption of meat, prolonged use of metformin for almost 3 decades, lack of multivitamin supplements, and concomitant PPI after dual antiplatelet therapy would confer a higher risk of vitamin B12 deficiency.
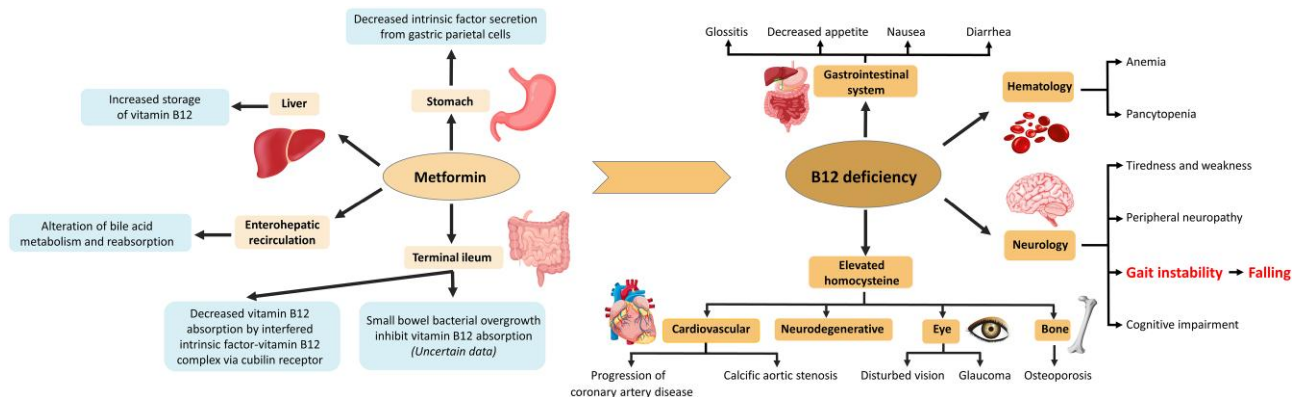
Figure 2. Postulated mechanism of metformin-associated vitamin B12 deficiency and spectrums of clinical manifestations.

Patients with vitamin B12 deficiency can have a wide range of hematological, gastrointestinal, psychiatric, and neurological disorders, as shown in Fig. 2. The most prevalent symptoms are neurologic manifestations, such as paresthesia in hands and feet, muscle cramps, dizziness, cognitive disturbances, ataxia, fatigue, and depression [4]. A previous study revealed that 30% of patients with anemia due to vitamin B12 deficiency had normal MCV [18]. On the other hand, older patients often have cardiovascular comorbidities for which antiplatelet and anticoagulant medications are prescribed, further contributing to the increased occurrence of chronic subdural hematoma. Up to 50% of patients show no history of direct head trauma [19]. Therefore, vitamin B12 deficiency should be included as one of differential diagnosis in patients who present with gait instability, frailty syndrome, or cognitive decline. Deficiency of vitamin B12 also contributes to hyperhomocysteinemia which promotes both arterial and venous thrombosis. Recent studies showed that an increase in homocysteine is related with formation and worsening of calcified aortic valves [20].

In conclusion, our case highlights the importance of an awareness of vitamin B12 deficiency among older patients on prolonged metformin therapy who present with gait instability and frequent falls. The dose and duration of metformin use correlates with the risk of vitamin B12 deficiency. Periodic measurement of vitamin B12 level for metformin-treated individuals should be considered.

Learning Points

- Metformin-associated vitamin B12 deficiency is underrecognized, especially in high-risk patients with preexisting risk factors, such as older age, higher metformin dose, longer treatment duration, and concomitant use of PPI.
- Patients with vitamin B12 deficiency can be asymptomatic or they can present atypically with anemia without macrocytosis, new-onset or worsening neuropathy, or gait instability leading to frequent falls. A high index of suspicion in patients with relevant risk factors is warranted.
- Periodic measurement of vitamin B12 level for metformin-treated individuals should be considered. The plasma B12 level above 300 pg/mL (221 pmol/L) should be targeted to achieve a normal status of vitamin B12 while taking metformin therapy.
- For patients with symptomatic B12 deficiency, effective replacement therapy should lead to normal complete

blood count within a few months of treatment, while improvement in neurological symptoms begins very quickly within 1 month of initiation of therapy.

Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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