Interhospital Endocrine Conference

Vitamin B12 deficiency

Total body stores are 2-5 mg, of which half is stored in the liver.

The recommended daily intake is 2 mcg/d in adults

Vitamin B-12 is highly conserved through the enterohepatic circulation

malabsorption develops after 2-5 years (ie: post bariatric surgery)

dietary inadequacy develops after 10-20 years (for example; vegetarians)

Vitamin B-12 deficiency

less than 200 pg/mL – most likely

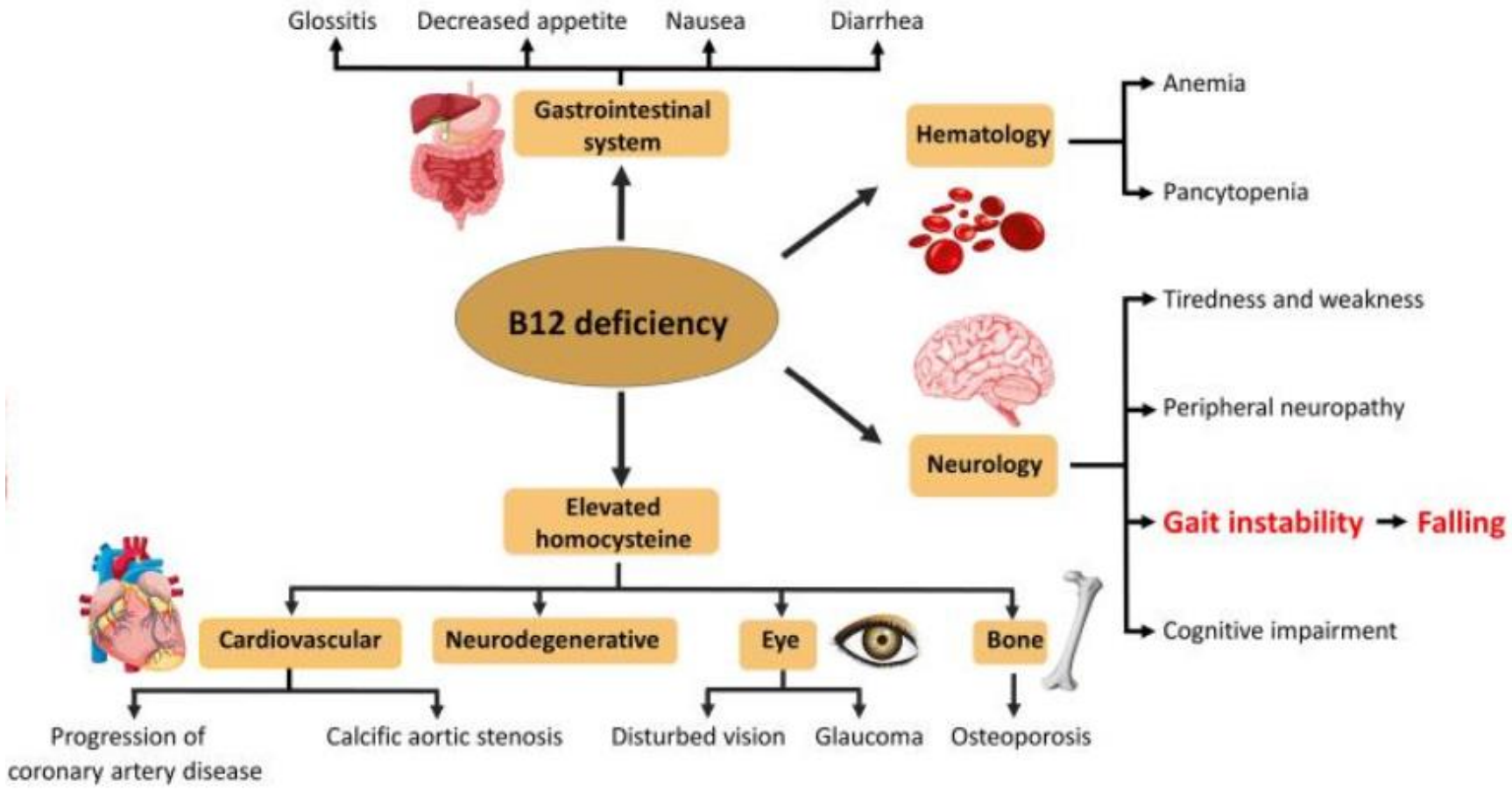
200-300 pg/mL- possibly

Risk factors for B12 deficiency

- Conditions associated with reduced vitamin B12 absorption
  - Elderly people
  - Gastrointestinal disorders such as total or partial gastrectomy, Crohn's disease and other bowel inflammatory disorders
  - Autoimmune conditions
- Diets with reduced sources of vitamin B12 (strict vegan and some vegetarian diets)
- Concomitant medication known to impair vitamin B12 absorption

  Metformin
- Genetic predisposition to vitamin B12 deficiency
  - Intrinsic factor receptor deficiency (Imerslund-Gräsbeck syndrome)
  - Transcobalamin II deficiency

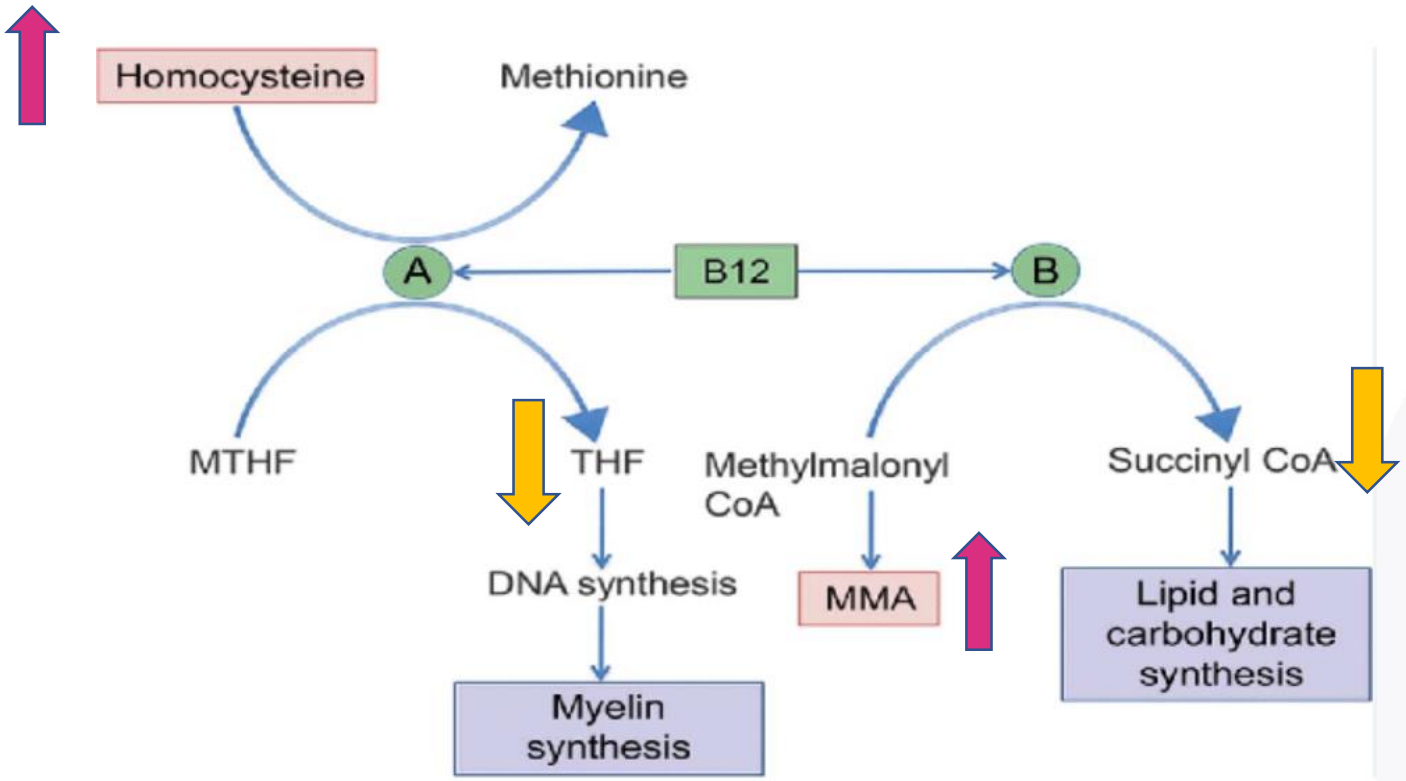
Clinical manifestations of vitamin B12 deficiency

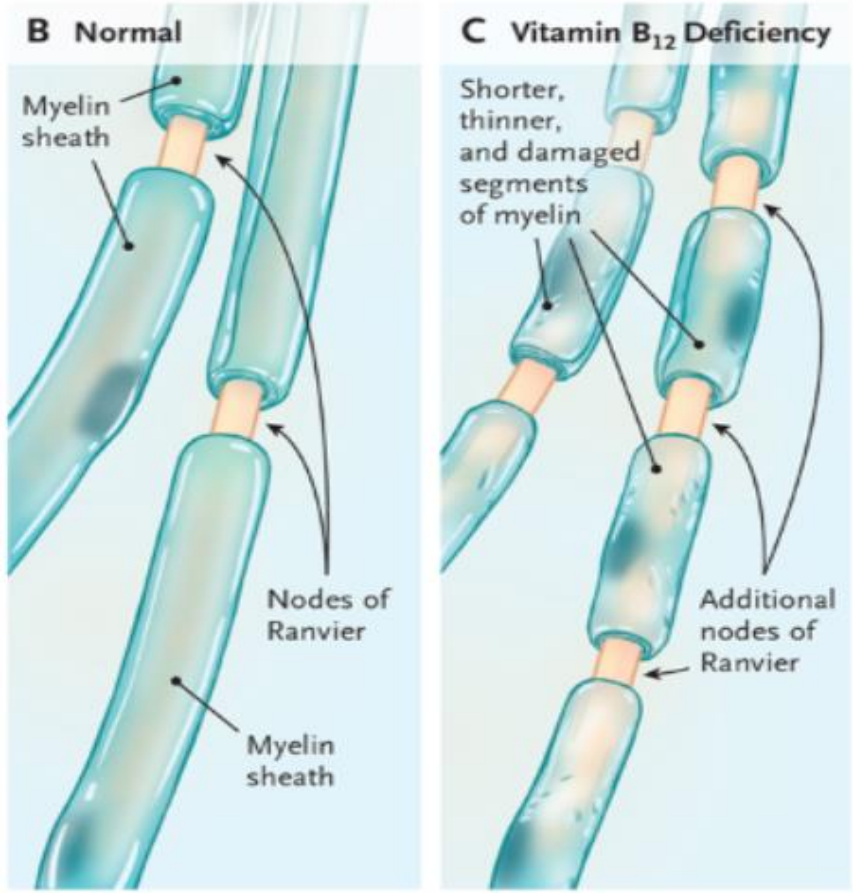


Subacute combined degeneration of spinal cord

Thewjitcharoen Y et al, JCEM Case Rep. 2024 Apr 15;2(4):luae029

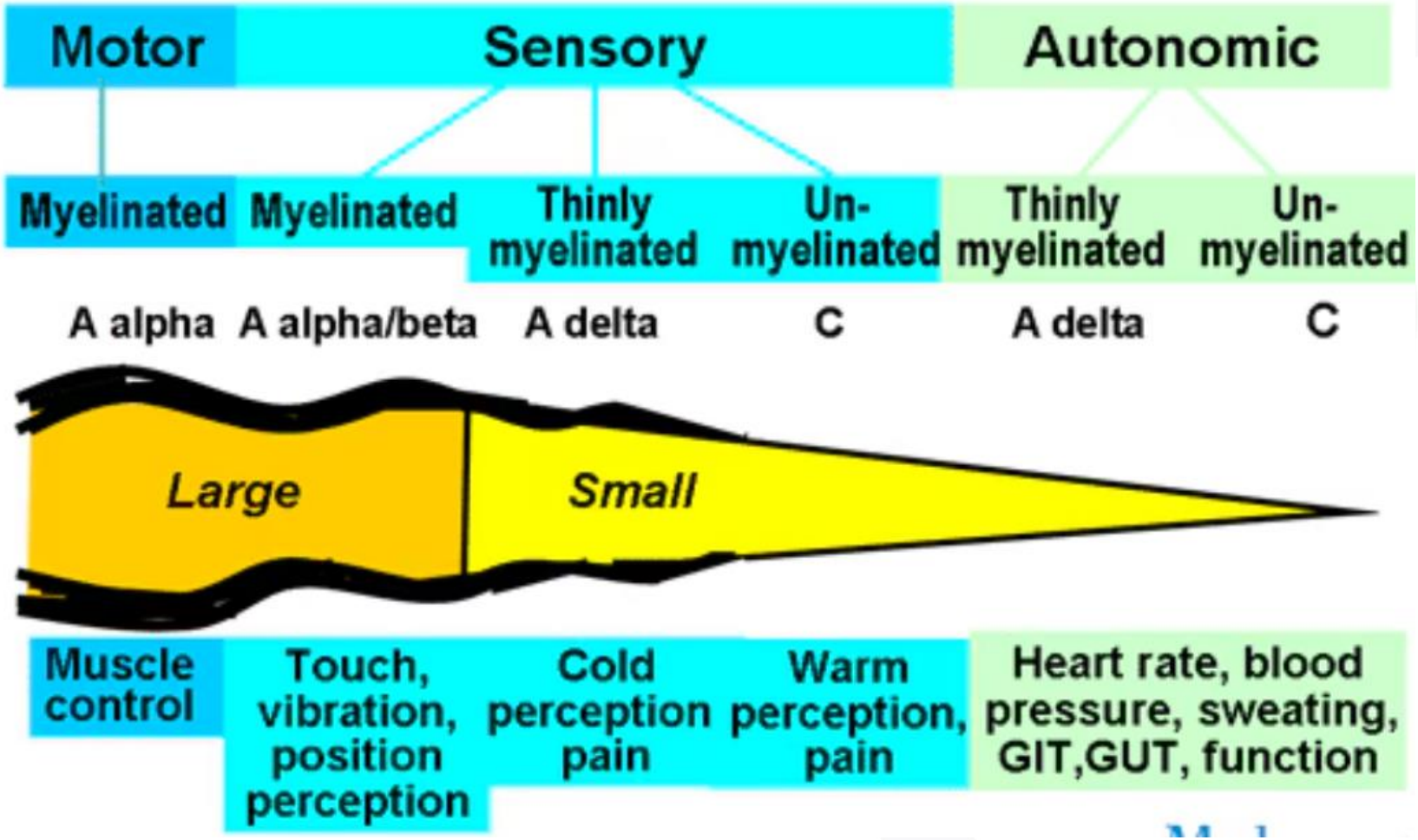
B12 and neuropathy





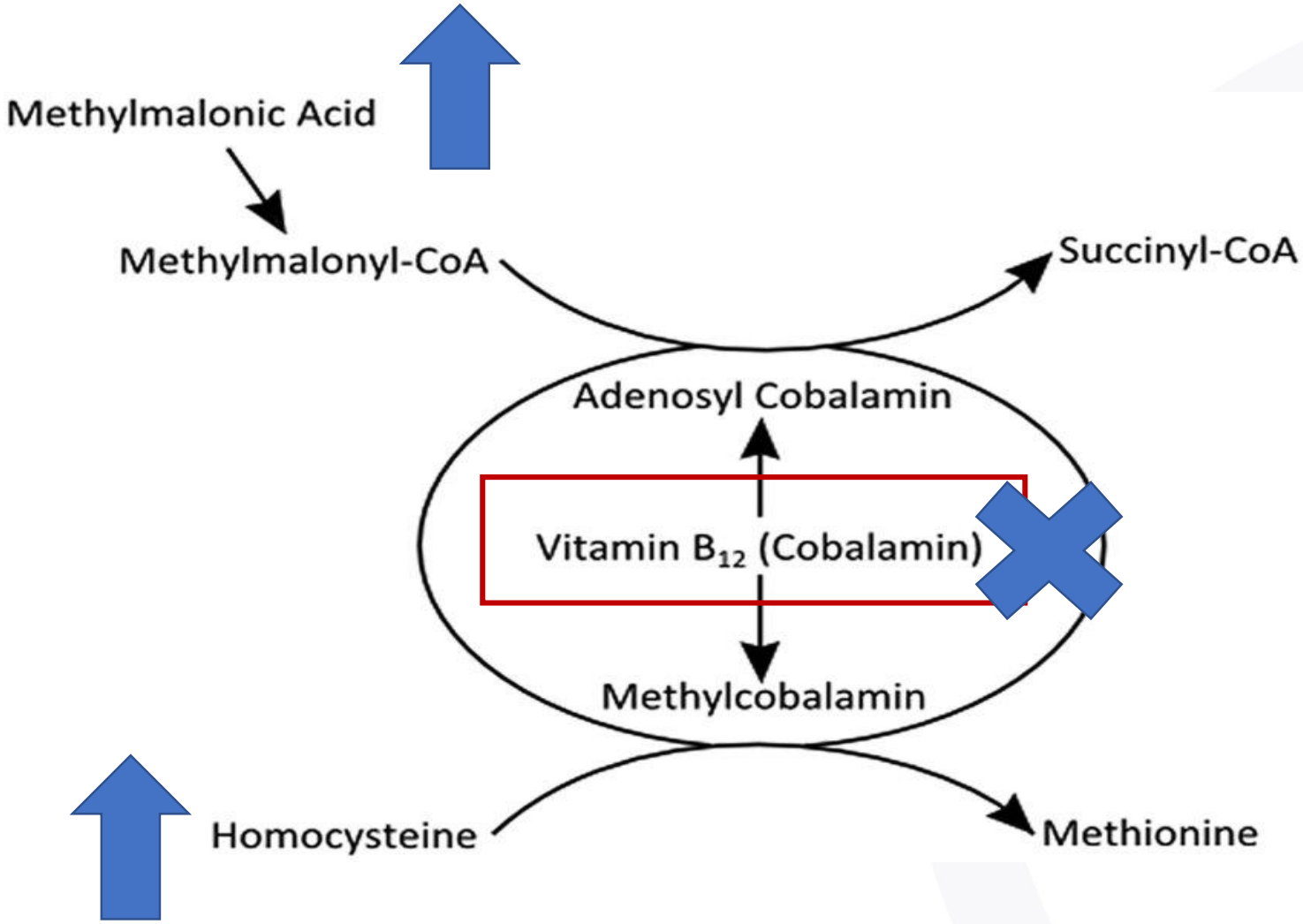
MTHF: 5,10-methylenetetrahydrofolate
THF : Tetrahydrofolate methionine
MMA : Methylmalonic acid

Peripheral neuropathy



Vinik Al, et al. Nat Clin Pract Endocrinol Metab. 2006 May;2(5):269-81.

Vitamin B12 pathway



Pract Neurol 2015;15:207–209.

BRITISH MEDICAL JOURNAL 19 JUNE 1971

Vitamin-B_{12} Status of Patients on Long-term Metformin Therapy

G. H. TOMKIN, D. R. HADDEN, J. A. WEAVER, D. A. D. MONTGOMERY

Summary

Vitamin-B_{12} malabsorption has been found in 21 (30%) of 71 diabetic patients taking long-term metformin therapy in addition to dietary management. The patients with evidence of B_{12} malabsorption had significantly lower haemoglobin levels (and significantly higher serum folic acid levels) than those with normal B_{12} absorption. Steatorrhoea was found in only one patient. Stopping metformin therapy resulted in reversion of B_{12} absorption to normal in most patients examined. Four patients with B_{12} malabsorption were found to have pathologically low serum B_{12} levels. The causes and implications of these findings are discussed and it is concluded that all patients on long-term metformin therapy should have annual serum B_{12} estimations.

Megaloblastic anaemia due to vitamin B_{12} malabsorption associated with long-term metformin treatment

Metformin has been used extensively in treating maturity-onset diabetes. It has few side effects, but it inhibits active vitamin B_{12} absorption in the distal ileum. Annual serum vitamin B_{12} measurements are therefore advisable in patients on long-term treatment.[1 2] So far no other case of vitamin B_{12}-deficient megaloblastic anaemia due to metformin therapy has been reported.

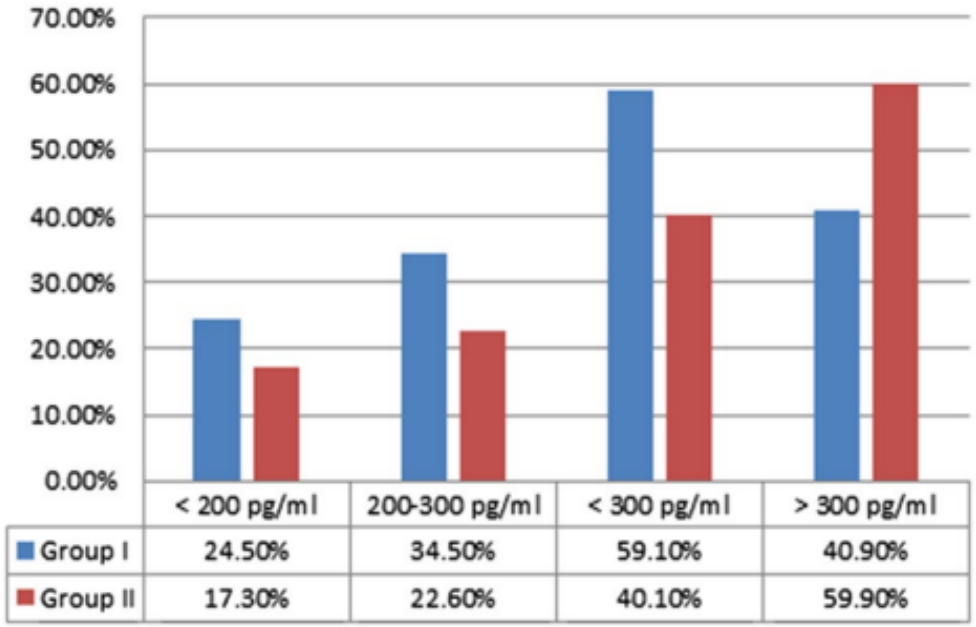
Br Med J. 1971 Jun 19;2(5763):685-7.
Br Med J. 1980 May 17;280(6225):1214-5.

ORIGINAL ARTICLE

Metformin Usage Index and assessment of vitamin B12 deficiency among metformin and non-metformin users with type 2 diabetes mellitus

Channabasappa Shivaprasad[1] · Kolla Gautham[1] · Barure Ramdas[1] · Kolli S. Gopaldatta[1] · Krishnamurthy Nishchitha[1]

- 2887 patients with T2D
- January 2018 and November 2019
- Categorized into two groups matched for age, mean duration of diabetes, and BMI
  - Metformin users
  - Non-metformin users
- Vitamin B12 levels were compared between the 2 groups



	< 200 pg/ml	200-300 pg/ml	< 300 pg/ml	> 300 pg/ml
Group I	24.50%	34.50%	59.10%	40.90%
Group II	17.30%	22.60%	40.10%	59.90%

Metformin

Non-Metformin

B12 deficiency

Acta Diabetol. 2020;57(9):1073-1080.

Clinical Trial/Experimental Study

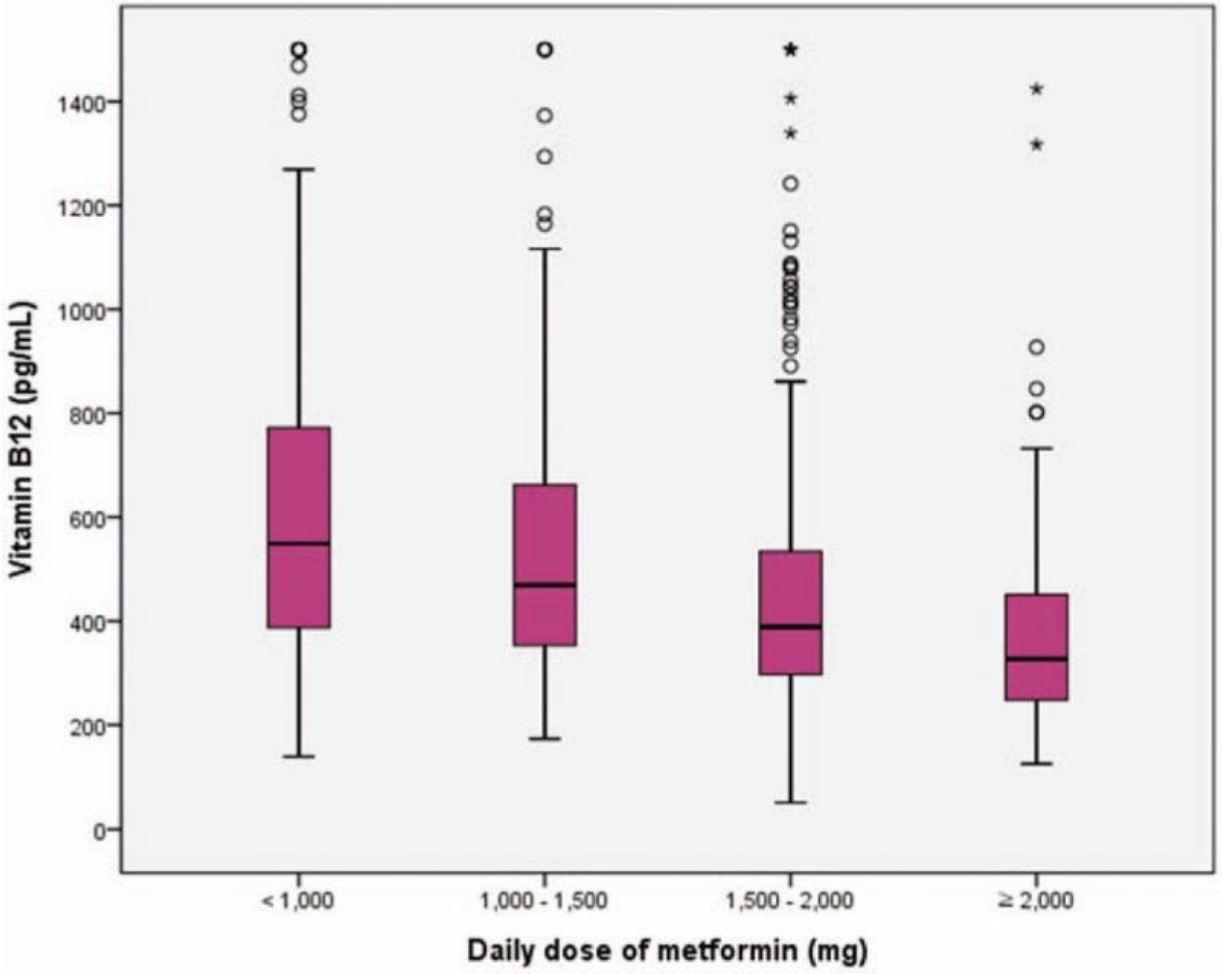
Medicine®

OPEN

Association between metformin dose and vitamin B12 deficiency in patients with type 2 diabetes

Jiwoon Kim, MD[a], Chul Woo Ahn, MD, PhD[b], Sungsoon Fang, PhD[c], Hye Sun Lee, PhD[d], Jong Suk Park, MD, PhD[b,*]

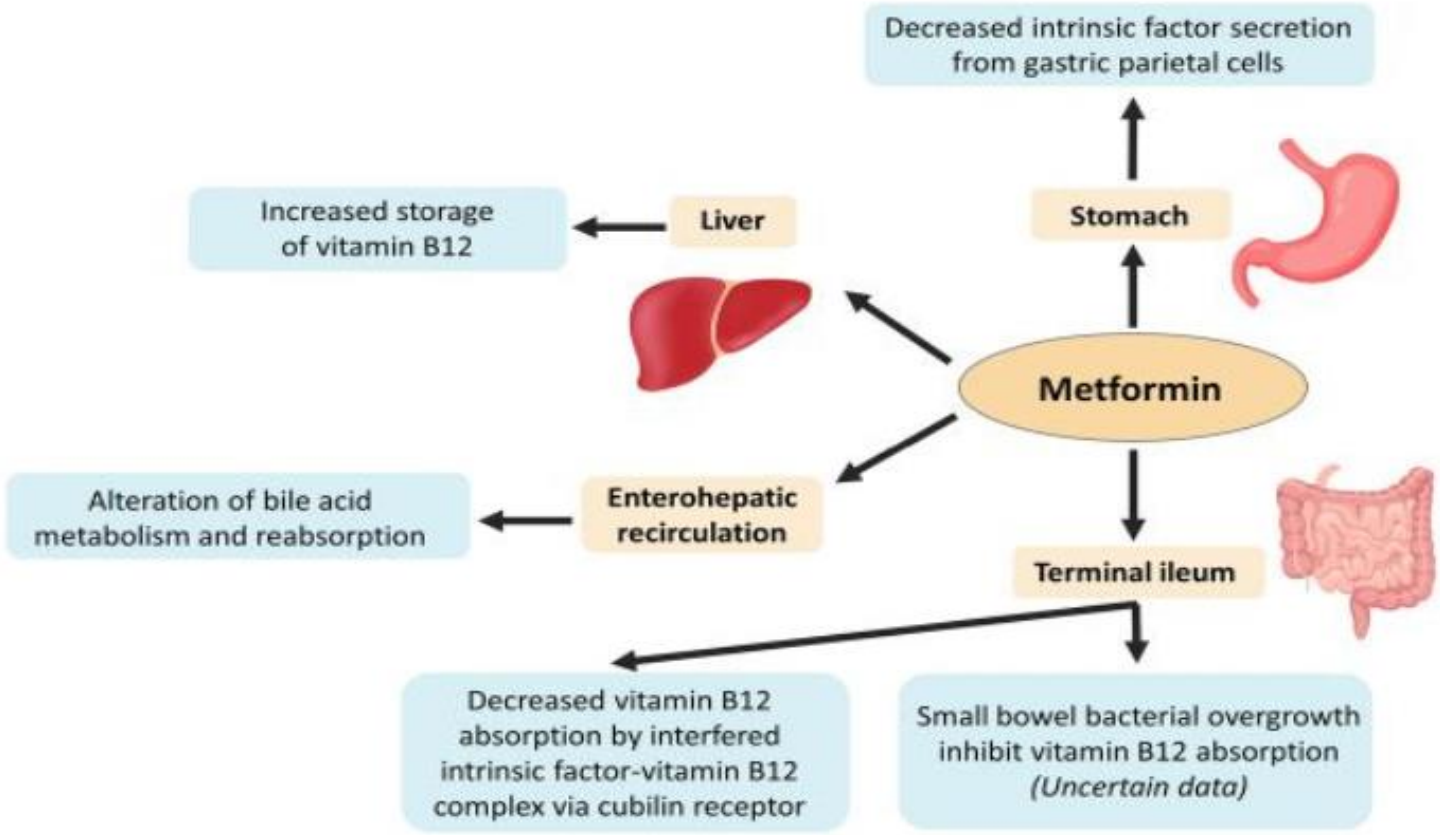
Dose-related



- cross-sectional study included 1111 patients with type 2 diabetes
- metformin for at least 6 months
- Serum vitamin B12 deficiency occurred in 22.2% of patients

Kim J, et al. Medicine (Baltimore). 2019 Nov;98(46):e17918.

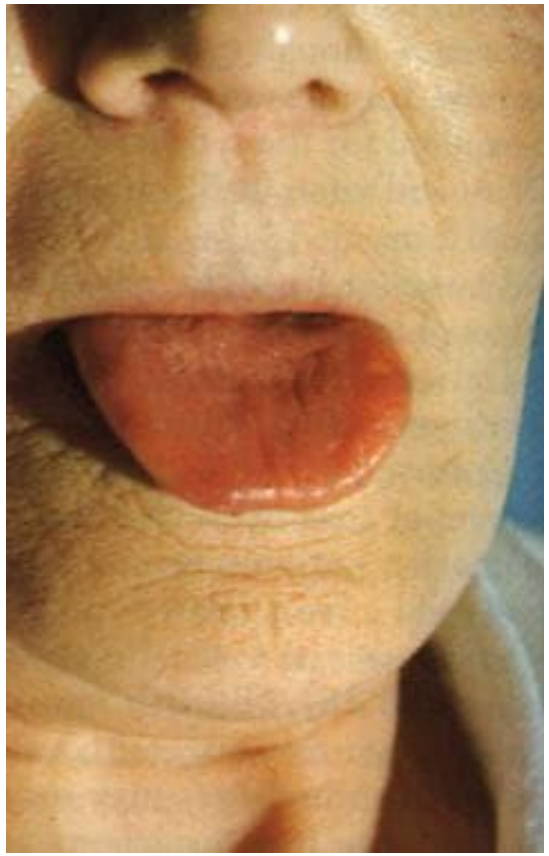
Postulated mechanism of metformin-associated vitamin B12 deficiency

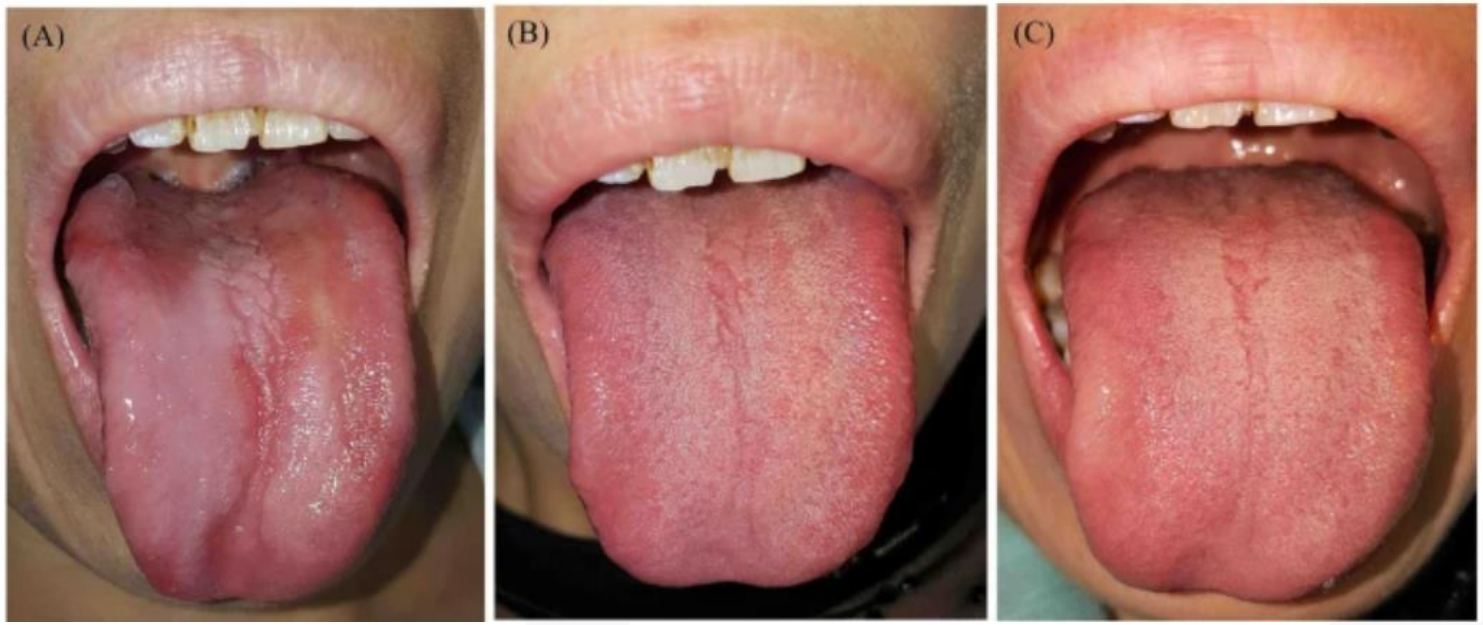


Thewjitcharoen Y et al, JCEM Case Rep. 2024 Apr 15;2(4):luae029

B12 deficiency and glossitis

- lemon-yellow pallor with raw beef tongue lacking filiform papillae



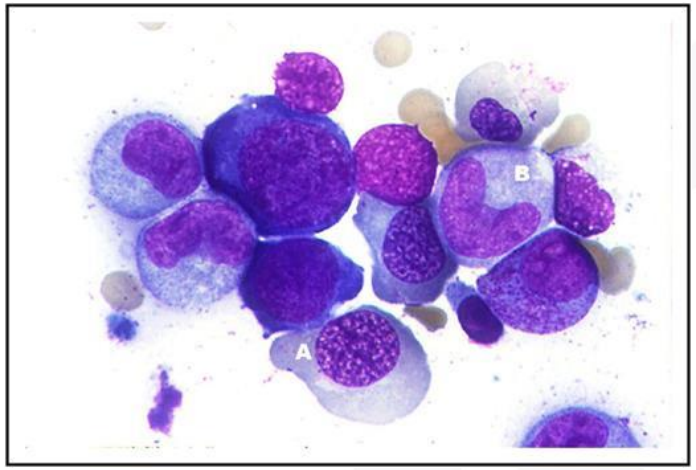


Serum levels of vitamin B12 were 94 ng/L and 1 month after treatment

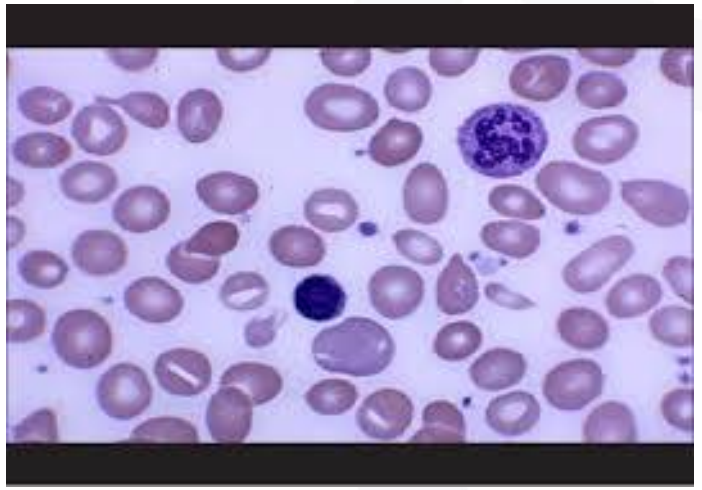
Chen GY, et al. BMC Oral Health. 2022 Oct 28;22(1):456.

Hematologic system and B12 deficiency

- Megaloblastic anemia
- Leukopenia and thrombocytopenia, leading to pancytopenia (rare)
- Hypersegmented neutrophil



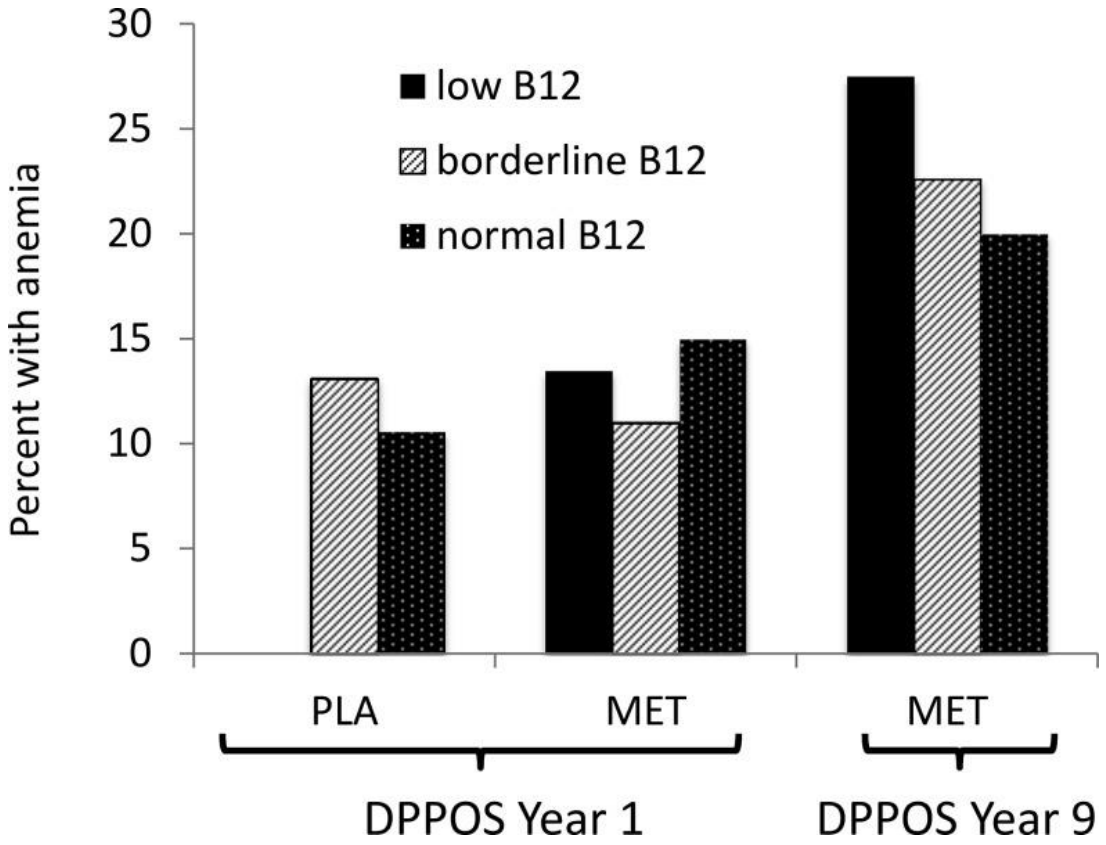
Megaloblastic change, variegated finely granular chromatin (“salt-and-pepper” appearance)



Hypersegmented neutrophil
Macrocytes
nucleated RBCs

Blood 2017; 129 (19): 2603–2611.
Cleveland Clinic Journal of Medicine January 2022, 89 (1) 8-9.

Anemia and B12 deficiency



5 years
after metformin therapy

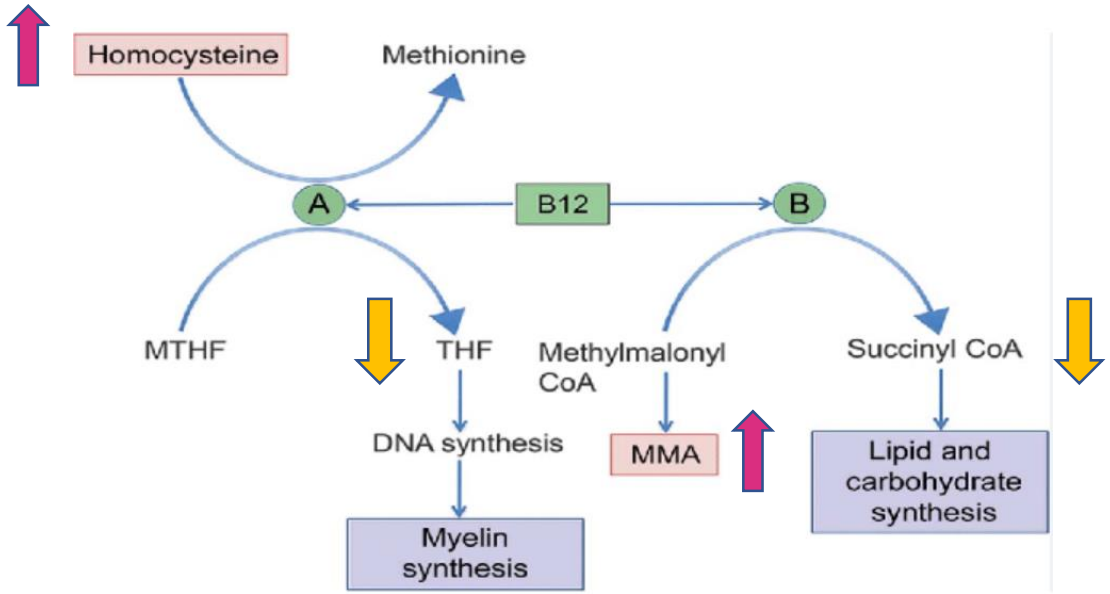
13 years
after metformin therapy

- Prevalence of anemia in B12 deficiency approximately 27%
- vitamin B12 deficiency was seen even in the **absence of anemia**

Aroda VR, et al.J Clin Endocrinol Metab. 2016 Apr;101(4):1754-61.

Hematologic system and B12 deficiency

- Hyperhomocysteinemia may lead to a prothrombotic state



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THF : Tetrahydrofolate methionine
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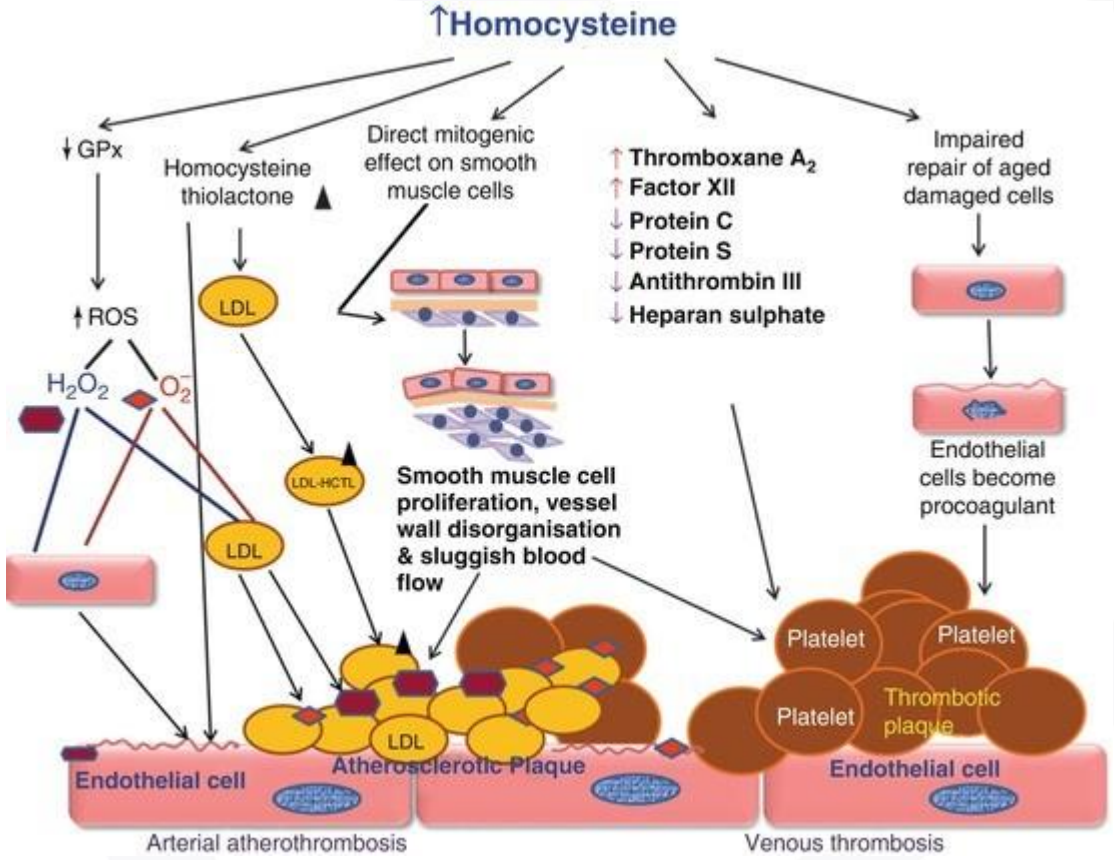
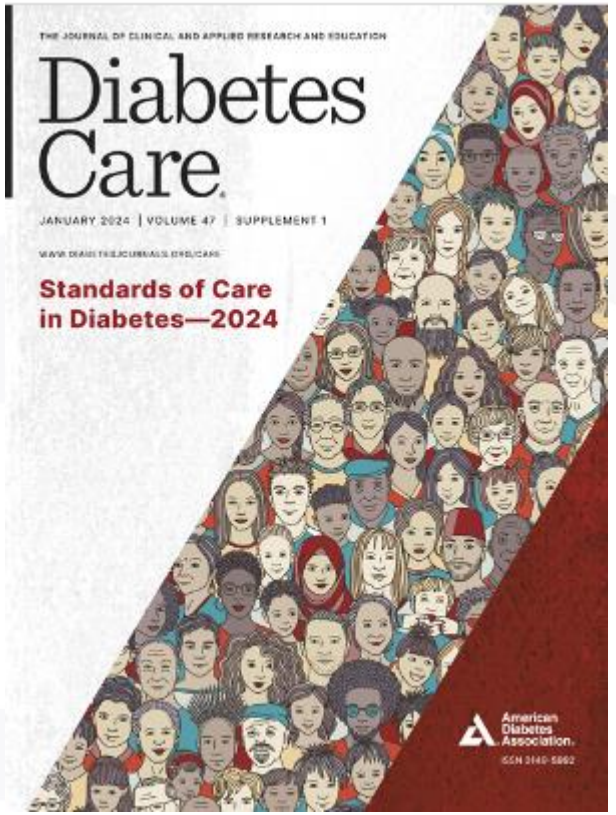


Zhou L, et al. Clin Biochem. 2023 Aug;118:110591.
Bhargava, S. (2018). The Clinical Application of Homocysteine. Springer, Singapore. https://doi.org/10.1007/978-981-10-7632-9_3

3. Prevention or Delay of Diabetes and Associated Comorbidities: *Standards of Care in Diabetes—2024*

Diabetes Care 2024;47(Suppl. 1):S43–S51 | https://doi.org/10.2337/dc24-S003



Section 9, "Pharmacologic Approaches to Glycemic Treatment," for more details). The effect of metformin on vitamin B12 increases with time (98), with a higher risk for vitamin B12 deficiency (<150 pmol/L) noted at 4–5 years. A person who has been on metformin for more than 4 years or is at risk for vitamin B12 deficiency for other reasons (e.g., vegan, previous gastric/small bowel surgery) should be monitored for vitamin B12 deficiency annually (99).

Diabetes Care 2024;47(Suppl. 1):S43–S51

Take Home Messages

- B12 deficiency can present with many clinical manifestations.
- Risk factors for B12 deficiency include being elderly, having gastrointestinal disorders, autoimmune conditions, specific diets, certain medications, and genetic predisposition.
- Periodic monitoring of vitamin B12 should be performed for patients with type 2 diabetes mellitus treated with metformin, especially if associated with anemia or peripheral diabetic polyneuropathy.
- vitamin B12 deficiency was seen even in the absence of anemia
- The risk of vitamin B12 deficiency increases with a higher dosage of metformin (>1000 mg/day) and a longer duration of therapy (more than 4 years).

เทพรารินทร์
ศูนย์เบาหวาน ไทรอยด์ และต่อมไร้ท่อ
Service Education Research