Section: General Medicine

Original Research Article

EFFICACY OF ORAL VERSUS INTRANASAL METHYLCOBALAMIN IN TYPE-2 DIABETES PATIENTS ON METFORMIN – A COMPARATIVE STUDY

Varun Raghavan[1], Adarsh Yatheesh[1], Jashir Kunnath[1], Venkatesh Bhat K[1]

[1]Assistant Professor, Department of General Medicine, Malabar Medical College Hospital & Research Centre, Modakkalur, Kerala, India

Received : 22/01/2023
Received in revised form : 19/02/2024
Accepted : 03/03/2024

Keywords:
Diabetes, metformin, methylcobalamin, nasal spray, NASO B12, B12 deficiency.

Corresponding Author:
Dr. Venkatesh Bhat K,
Email: venkateshbhat8@gmail.com

DOI: 10.47009/jamp.2024.6.2.96

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (2); 444-448

Abstract

Background: Long-term use of metformin may develop vitamin B12 deficiency in patients with diabetes. Oral supplementation of methylcobalamin is the mainstay of treatment to correct the individuals with deficiency. Oral therapy has several issues in respect to absorption, optimum therapeutic concentrations and treatment course. This study aimed to compare the effectiveness of nasal spray of methylcobalamin (NASO B12) and oral methylcobalamin tablets for treating vitamin B12 deficiency in diabetic patients receiving metformin. **Materials and Methods:** A Randomised, parallel group, open label, comparative study was conducted. A total of n=90 study subjects were assigned to two groups: Group-1 received NASO B12 nasal spray (methylcobalamin 250 µg/spray) in each nostril every alternate day for a total of seven doses and Group-2 received oral tablets of methylcobalamin 1500 µg/dose daily single dose for a total of seven doses. The primary study outcome was measuring plasma vitamin B12 levels at baseline, day 7 and 14. **Result:** Study subjects who received NASO B12 spray has significantly achieved vitamin B12 levels of >400 pg/mL which was about 82% on day 7 and 90% on day 14. No single study participant has achieved on day 7 and day 14 with oral methylcobalamin tablets. NASO B12 treated group showed exponential increase trend of plasma vitamin B12 levels on day 7 and day 14 i.e., 492.68 pg/mL and 578.18 pg/mL respectively (P<0.0001). Whereas, subjects treated with oral methylcobalamin tablets showed slight increase of plasma vitamin B12 levels on day 7 and day 14 i.e., 184.26 pg/mL and 192.89 pg/mL. Study drugs were well tolerated by study subjects throughout the study period. **Conclusion:** Nasal Methylcobalamin 250 µg/spray (NASO B12) showed superior absorption, better optimum plasma vitamin B12 levels and well tolerated when compared with oral B12 tablets and can be implemented as an effective alternative to correct metformin induced vitamin B12 deficiency.

INTRODUCTION

Vitamin B12 is important for several functions such as DNA synthesis, red blood cell formation and neurologic function.[1] It also plays a key role in the metabolism of fat and carbohydrates.[2,3] Among the various clinical manifestations of vitamin B12 deficiency are the implied effects of depletion on multiple systems, with their severity varying greatly. These clinical manifestations are heterogeneous, but they also depend on the grading and the duration of the Vitamin B12 deficiency. Fatigue and anaemia are the results of mild deficiency having values that indicate vitamin B12 deficiency but presenting with no neurological symptoms.[4]

Moderate deficiency of B12 may include obvious macrocytic anaemia, glossitis, along with some mild or minor neurological manifestations like distal sensory impairment. Severe deficiency of Vitamin B12 is leads to bone marrow suppression, neurological features and the increased risk of cardiomyopathy. In spite of these features, it is crucial to know that the clinical symptoms of such deficiency can even occur without anaemia or low plasma vitamin B12 levels. In such cases, treatment should be started as early as possible.[5,6]

The wide spectrum of etiology of vitamin B12 deficiency includes malabsorption-related causes such as autoimmune gastritis (pernicious anaemia), celiac disease, inflammatory bowel disease, surgical gastrectomy, gastric bypass and ileal resection. It can also occur less commonly owing to the nutritional habits of people (strict vegan diet followers, breastfed infants born to vegan mothers having decreased

ISSN (O): 2687-5365; ISSN (P): 2753-6556

dietary intake of animal products), due to drug interference (metformin, proton pump inhibitors, drug-affected purine, and pyrimidine synthesis), inherited disorders affecting intrinsic factor (IF) and similarly, other inherited disorders including methylmalonic acidaemia and transcobalamin II deficiency nitrous oxide abuse, Diphyllobothrium latum infection, and pancreatic insufficiency.[7,8]

Metformin is the most frequently prescribed first-line therapeutic drug for type 2 diabetes. Also, it is one of a few antihyperglycemic drugs beneficial in reducing cardiovascular morbidity and mortality, known to be a major cause of death in type 2 diabetes patients.[9] Mode of action of metformin is to induce vitamin B12 malabsorption, which may lead to increased risk for causing vitamin B12 deficiency, which is otherwise a clinically important and treatable condition. Almost an average of 6–30% of patients could show vitamin B12 deficiency due to metformin usage according to reports.[10,11]

As per the UK MHRA, decreased vitamin B12 levels or vitamin B12 deficiency, are now taken as common side effects in metformin therapy with greater incidence in those patients who are receiving a higher dose or longer treatment duration and also coexisting with risk factors. Therefore, it has laid down new advice to monitor vitamin B12 plasma levels in metformin-taking patients having symptoms of vitamin B12 deficiency.[12]

To overcome the limitations and disadvantages of the oral and intramuscular formulations of vitamin B12, a nasal spray of methylcobalamin (NASO B12; methylcobalamin 250 µg/spray) has been developed by Troikaa Pharmaceuticals Limited and has recently been approved for the treatment of vitamin B12 deficiency. NASO B12 has been demonstrated to be rapidly absorbed as well as being highly effective in the treatment of vitamin B12 deficiency. This rapid increase in the level of vitamin B12 caused by NASO B12 has led to a steady increase in the haemoglobin levels. The absorption of vitamin B12 from NASO B12 bypasses the gastrointestinal tract which is a major factor in the proposed mechanisms of metformin-induced vitamin B12 deficiency and occurs from the nasal epithelium, further hypothesizing that NASO B12 will be more effective in the treatment of vitamin B12 deficiency, as opposed to oral methylcobalamin in patients on metformin therapy.[13–16]

Hence, the present study aimed at comparing the efficacy and safety of NASO B12 with oral methylcobalamin tablets in treating the deficiency of vitamin B12 in patients on metformin therapy for the management of type 2 diabetes mellitus.

MATERIALS AND METHODS

Study drugs: The drugs used in this study are: methylcobalamin (250 µg/spray) nasal spray (NASO B12; manufactured and marketed by Troikaa Pharmaceuticals Ltd., Ahmedabad, India) and methylcobalamin 1500 µg oral tablet (Meconerve® 1500 from Micro Labs Ltd).

Study design: It was a prospective, randomized, parallel-group, comparative, open-label study which was conducted at Department of General Medicine, Malabar Medical College Hospital & Research Centre, Modakkalur, Kerala, India between September 2023 and January 2024. A total of ninety (n=90) type 2 diabetes mellitus patients on metformin for greater than or equal to 4 months with vitamin B12 deficiency were registered in this study and after that, they were randomized equally into two groups. As per the randomization procedure, Group 1 was assigned to the new methylcobalamin nasal spray (NASO B12) and Group 2 was assigned to methylcobalamin oral tablet for the treatment of vitamin B12 deficiency for a designated time period of 15 days.

Study population

Patient eligibility: This study included Diabetic individuals of either sex (age >18 years; non-pregnant females) on metformin therapy (≥ 1000 mg/day) for more than 4 months and who have vitamin B12 level <210 pg/mL (155 pmol/L). Patients with any known hypersensitivity or allergies to cobalt and/or vitamin B12 or any component of the study medication, suffering from any significant nasal pathology/chronic nasal symptoms/nasal allergies/upper respiratory tract infections, usage of any nasal medication/device, suffering from a known severe renal impairment or renal failure, or on treatment with drugs interfering with the vitamin B12 assay were taken out from the study. In addition to this, patients having participated in any clinical trial within the last 30 days at the time of screening and had any disorder that in the knowledge of investigator would disrupt study participation or affect study outcome were also excluded.

Study procedure: Eligible patients were explained about the study in detail and a written consent was taken from the interested participants before the procedure. A screening was done to confirm their eligibility as per the inclusion and exclusion criteria among these patients. The positively screened patients thus enrolled, were subjected to receive either of the allotted study treatments. First dose of the treatment was taken in the presence of the investigator in order to ensure the apt dosage method and the remaining doses were told to be self-administered at home. The patients assigned to Group 1 took a commercially available formulation of methylcobalamin (250 µg/ spray) nasal spray (NASO B12) in each nostril every alternate day for a total of seven doses during the study period (a total of 3,500 µg of methylcobalamin per patient) and the other patients, assigned to oral methylcobalamin tablets (Group 2), received a single daily dose of commercially available 1500 µg methylcobalamin tablets, for a total of seven doses during the study period (a total of 10,500 µg of methylcobalamin per patient). Fixed-dose combinations and nutritional/dietary supplements containing any form

ISSN (O): 2687-5365; ISSN (P): 2753-6556

of vitamin B12 were not allowed to be used within the study period. The assessment of efficacy of the procedure was done by measuring plasma vitamin B12 levels, assessed at baseline, day 7, and day 14. Safety in the procedure was estimated by recording the number and severity of adverse events which were reported by the patient at any given time during the study.

Outcomes: The primary outcome was the number of patients with normalized plasma vitamin B12 levels (≥400 pg/mL) at 7 and 14 days while the secondary outcomes were the mean plasma vitamin B12 levels (pg/mL) and the number of adverse events.

Statistical analysis: Student's unpaired t test was employed to compare the plasma vitamin B12 levels between the study groups. Chi-square test was used to compare the difference between gender among study groups. One way ANOVA was used to compare the statistical significance within and between the groups at baseline, day 7, and day 14.

RESULTS

Subject demographics and disposition: Study flow diagram was shown in [Figure 1]. A total of 300 study subjects were assessed for eligibility, out of that 210 subjects were excluded for various reasons. Finally, ninety subjects were selected and randomized into two groups with 45 subjects each. All the 45 subjects in each group completed the entire study period without any lost to follow-up. At last, a total of 90 subjects (45 in each group) were completed the study and analysed the data for statistical analysis. Baseline demographic details of the study populations was showed in [Table 1].

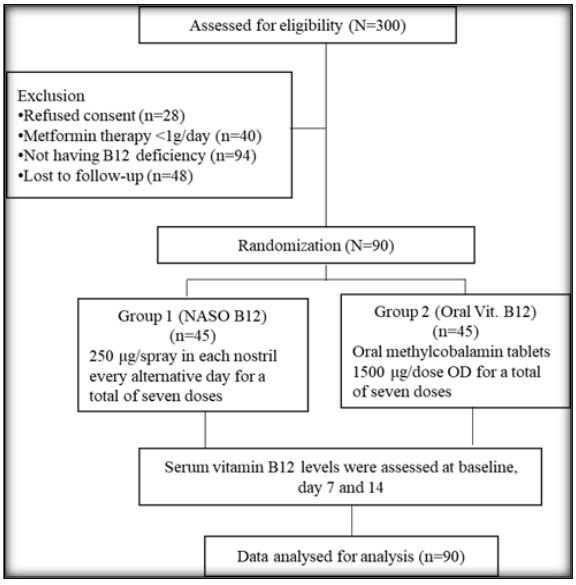


Figure 1: Study flow diagram

Efficacy outcomes: Percentage of patients achieving > 400 pg/mL B12 levels on day 7 and 14 among study groups was showed in Figure 2. Study subjects who received NASO B12 spray has significantly achieved vitamin B12 levels of >400 pg/mL which was about 82% on day 7 (study participants has completed only 3 doses of NASO B12 spray). Around 90% of study subjects achieved plasma vitamin B12 levels of ≥400 pg/mL on day 14 of NASO B12 spray therapy (study participants has completed all seven doses). Study participants who received oral methylcobalamin tablets daily for seven doses, no single patient has achieved plasma vitamin B12 levels of ≥400 pg/mL on day 7 and day 14.

Mean plasma B12 levels at baseline, day 7 and 14 among study groups was shown in Figure 3. The baseline mean±SD plasma vitamin B12 levels in the subjects of group 1 (NASO B12 group) was 132.86±22.58 and group 2 (oral methylcobalamin group) was 135.01±23.11 There was no statistically significant difference in baseline plasma vitamin B12 levels among treatment groups. NASO B12 treated group showed exponential increase trend of plasma vitamin B12 levels on day 7 and day 14 i.e., 492.68 pg/mL and 578.18 pg/mL respectively. Whereas, subjects treated with oral methylcobalamin tablets showed slight increase of plasma vitamin B12 levels on day 7 and day 14 i.e., 184.26 pg/mL and 192.89 pg/mL. Mean plasma vitamin B12 levels at baseline, day 7 and day 14 showed statistically significant (P<0.0001) with NASO B12 spray therapy, whereas oral methylcobalamin therapy not showed statistically significant.

Thus, absorption of vitamin B12 is significantly higher by NASO B12 when compared with methylcobalamin tablets. Metformin induced vitamin B12 deficiency was well corrected with NASO B12 nasal spray in 7 days (three doses) and increased optimum therapeutic levels was further maintained by next three doses. Subjects with both the treatment groups are well tolerated the study drugs and there were no clinically significant adverse events were reported throughout the study period.

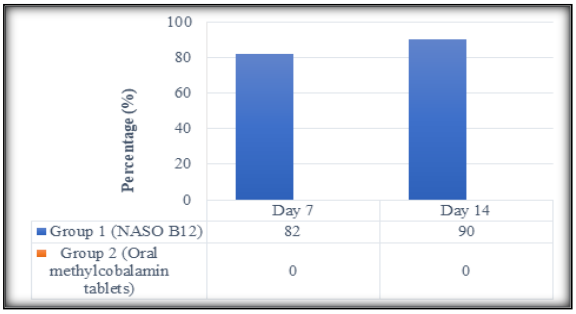
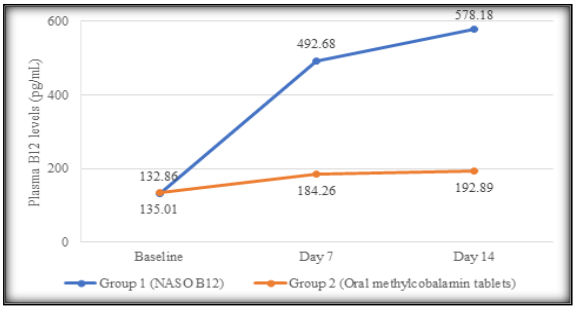


Figure 2: Percentage of patients achieving > 400 pg/mL B12 levels on day 7 and 14 among study groups



ISSN (O): 2687-5365; ISSN (P): 2753-6556

Figure 3: Mean plasma B12 levels at baseline, day 7 and 14 among study groups

Table 1: Baseline demographic details and plasma B12 levels

Variable	Group 1 (NASO B12)	Group 2 (Oral methylcobalamin tablets)	P-Value
n	45	45	
Age in years (Mean±SD)	48.34±6.18	49.14±6.76	0.55
Range	41-55	42-57	
Gender			
Female, n (%)	25 (55.6)	23 (51.1)	0.67
Male, n (%)	20 (44.4)	22 (48.9)	
Race	South Indian	South Indian	-
Baseline plasma B12 levels (pg/mL) (Mean±SD)	132.86±22.58	135.01±23.11	0.65

DISCUSSION

Absorption of vitamin B12 by the oral route is highly variable, therefore tablets of vitamin B12 don't elicit a predictable increase of vitamin B12 in the body in spite of being given in long-term.[17] Hence, vitamin B12 injections are the mainstay focus for treating the deficiency of vitamin B12. However, these injections are very painful and the patient has to frequently visit to the hospital to take the doses. Therefore, owing to these issues, the patient compliance is a major problem with oral and parenteral formulations of vitamin B12.[14]

Metformin therapy in diabetic patients has been associated with vitamin B12 deficiency. Several mechanisms in the intestine have also been proposed to be linked to the inhibition of absorption of vitamin B12 due to the effect of metformin.[11,18,19] NASO B12 is a painless, reliable, and easy-to-administer alternative to oral and parenteral formulations of vitamin B12. NASO B12 assures rapid, consistent, predictable, and dependable absorption as opposed to oral vitamin B12 therapy. NASO B12 can be self-administered by all patients including those who have swallowing difficulties, nausea or vomiting, or absorption issues such as pernicious anemia, post-bariatric surgery, or malabsorption thus ensuring high compliance. In comparison to injectable vitamin B12 therapy, NASO B12 is pain-free, is self-administered, costs less, and doesn't require multiple patient visits to the clinics. Its safety and efficacy have been elicited in two clinical studies, the results of which have proved that NASO B12 is rapidly absorbed and corrects the vitamin B12 deficiency rapidly being safe and easily tolerated.[13–15]

The present study compared the efficacy of NASO B12 and oral supplementation of vitamin B12 in treating the vitamin B12 deficiency in type 2 diabetes mellitus patients taking metformin. According to our knowledge, this is the first comparative study of the efficacy of nasal vitamin B12 therapy and oral vitamin B12 therapy in type 2 diabetes mellitus patients on metformin, having vitamin B12 deficiency. NASO B12 has been demonstrated to treat vitamin B12 deficiency in only seven doses administered on alternate days whereas oral therapy has been recommended for daily dosing.[13,15] Therefore, this study was focused on comparing the efficacy of seven daily doses of 1500 µg tablets and seven doses of NASO B12 (500 µg every alternate day) in treating the vitamin B12 deficiency.

Recently, the American Academy of Family Physicians has redefined the normal, low-normal, and low values of plasma vitamin B12 levels to be ≥ 400, 150–399, and <150 pg/mL, respectively. In accordance with the above recommendation, the normal levels of plasma vitamin B12 in the study was found to be ≥ 400 pg/mL.[20]

No adverse events were reported in the study, and both NASO B12 and vitamin B12 oral tablets were well tolerated by the patients. Proper patient counselling results in far better patient acceptance and compliance, was suitably noted. Sometimes there occurs an outflow of the red-coloured drug solution from the nose after administration of NASO B12. It is advisable to counsel the patients that they should not be concerned about the red-coloured fluid, which is the extra drug, naturally red in colour. Additionally, patients hesitant in taking nasal formulations should be made aware that the only other option is vitamin B12 injections and they are painful. Hot foods may cause nasal secretions and therefore, a resulting loss of medication; so the patients should be advised to administer NASO B12 nasal spray at least 30 min before and after taking hot foods or liquids.

In a prospective, multicentric, clinical study, Seth et al,[13] found that in vitamin B12-deficient patients, seven doses of NASO B12 on alternate days corrected the vitamin B12 levels, and weekly maintenance therapy of NASO B12 500 µg/dose for 4 weeks was able to maintain the levels (>200 pg/mL). Further, NASO B12 was well-tolerated throughout the treatment period.

Patients on metformin therapy receiving NASO B12 should also be instructed that they will require weekly intranasal administration of NASO B12 spray in each nostril after correction of vitamin B12 deficiency for the rest of their lives and no compliance to this instruction, will lead to the return of anaemia and in the development of incapacitating and irreversible damage to spinal cord nerves. The patients should also be warned about the dangers of taking folic acid in place of vitamin B12, because the former may prevent anaemia but cause the uninhibited progression of subacute combined degeneration of the spinal cord.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

As a result, NASO B12 is found to be effective in treating the deficiency of vitamin B12 in type 2 diabetes mellitus patients receiving metformin therapy. However, our study does have some limitations. Clinical symptoms and haematological parameters which could have justified the improvements in vitamin B12 levels by NASO B12 prior to and after the treatment were not studied. Further studies in this regard can be done to confirm the long-term safety of nasal formulation.

CONCLUSION

Nasal Methylcobalamin 250 µg/spray (NASO B12) showed superior absorption, better optimum plasma vitamin B12 levels and well tolerated when compared with oral B12 tablets and can be implemented as an effective alternative to correct metformin induced vitamin B12 deficiency. Therefore, NASO B12 is highly effective to reverse the vitamin B12 deficiency in type 2 diabetes patients who are on metformin therapy would be a one of the best novel and advanced treatment remedies in the future to overcome the drawbacks of oral and other parenteral preparations.

Acknowledgements

The authors are thankful to the Nursing team and supporting staff of department of General Medicine, Malabar Medical College Hospital & Research Centre, Modakkalur, Kerala, India and to the volunteers for their participation in the study.

REFERENCES

1. O'Leary F, Samman S. Vitamin B12 in Health and Disease. Nutrients. 2010 Mar 5;2(3):299–316.
2. Lyon P, Strippoli V, Fang B, Cimmino L. B Vitamins and One-Carbon Metabolism: Implications in Human Health and Disease. Nutrients. 2020 Sep 19;12(9):2867.
3. Boachie J, Adaikalakoteswari A, Samavat J, Saravanan P. Low Vitamin B12 and Lipid Metabolism: Evidence from Pre-Clinical and Clinical Studies. Nutrients. 2020 Jun 29;12(7):1925.
4. Wolffenbuttel BHR, Wouters HJCM, Heiner-Fokkema MR, van der Klauw MM. The Many Faces of Cobalamin (Vitamin B12) Deficiency. Mayo Clin Proc Innov Qual Outcomes. 2019 May 27;3(2):200–14.
5. Shipton MJ, Thachil J. Vitamin B12 deficiency – A 21st century perspective. Clin Med. 2015 Apr;15(2):145–50.
6. Green R. Vitamin B12 deficiency from the perspective of a practicing hematologist. Blood. 2017 May 11;129(19):2603–11.
7. Azzini E, Raguzzini A, Polito A. A Brief Review on Vitamin B12 Deficiency Looking at Some Case Study Reports in Adults. Int J Mol Sci. 2021 Sep 7;22(18):9694.
8. Chaparro CM, Suchdev PS. Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries. Ann N Y Acad Sci. 2019 Aug;1450(1):15–31.
9. Dutta S, Shah RB, Singhal S, Dutta SB, Bansal S, Sinha S, et al. Metformin: A Review of Potential Mechanism and Therapeutic Utility Beyond Diabetes. Drug Des Devel Ther. 2023 Jun 26;17:1907–32.
10. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley GP. 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. 2012 Feb;35(2):327–33.
11. Kim JS, Ko SH, Baeg MK, Han KD. A simple screening score to predict diabetes in cancer patients: A Korean nationwide population-based cohort study. Medicine (Baltimore). 2019 Dec;98(51):e18354.
12. GOV.UK [Internet]. [cited 2024 Mar 26]. Metformin and reduced vitamin B12 levels: new advice for monitoring patients at risk. Available from: https://www.gov.uk/drug-safety-update/metformin-and-reduced-vitamin-b12-levels-new-advice-for-monitoring-patients-at-risk
13. Seth T, V S, D B, S M, A A, P P, et al. Rapid and Safe Correction of Vitamin B12 Deficiency using Novel Methylcobalamin Nasal Spray. Int J Endocrinol Metab Disord. 2021 Jan 1;7.
14. H D, V A, A M, KR P. Novel Methylcobalamin Nasal Spray versus Intramuscular Injection: A Randomized, Crossover Comparative Bioavailability Study. Int J Endocrinol Metab Disord. 2021 Jan 1;7.
15. Farookh S, Jayanti C, Geetha A. Comparison of the efficacy of oral methylcobalamin tablets vs. nasal spray (NASO B12) in diabetic patients on metformin therapy. J Diabetol. 2022 Jan 1;13:347.
16. Andrès E, Zulfiqar AA, Serraj K, Vogel T, Kaltenbach G. Systematic Review and Pragmatic Clinical Approach to Oral and Nasal Vitamin B12 (Cobalamin) Treatment in Patients with Vitamin B12 Deficiency Related to Gastrointestinal Disorders. J Clin Med. 2018 Sep 26;7(10):304.
17. Verma D, Chandra J, Kumar P, Shukla S, Sengupta S. Efficacy of oral methylcobalamin in treatment of vitamin B12 deficiency anemia in children. Pediatr Blood Cancer. 2017 Dec;64(12).
18. Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin B12 deficiency: An association to bear in mind. World J Diabetes. 2021 Jul 15;12(7):916–31.
19. Kim J, Ahn CW, Fang S, Lee HS, Park JS. Association between metformin dose and vitamin B12 deficiency in patients with type 2 diabetes. Medicine (Baltimore). 2019 Nov 15;98(46):e17918.
20. Vitamin B12 Deficiency: Recognition and Management | AAFP [Internet]. [cited 2024 Mar 26]. Available from: https://www.aafp.org/pubs/afp/issues/2017/0915/p384.html

ISSN (O): 2687-5365; ISSN (P): 2753-6556