Int. J Med. Pharm. Res. (P-ISSN: 2958-3675 | E-ISSN: 2958-3683)
Available on: https://ijmpr.in/
DOI:

International Journal
of Medical and
Pharmaceutical Research

ORIGINAL ARTICLE OPEN ACCESS

Association between metformin and vitamin B12 deficiency in patients with Type 2 Diabetes Mellitus

Dr. Avantika Sharma[1*]; Dr. Satish Babu[2]; Dr. Somanath Chillal[3]; Dr. G.M. Prakash

[1]PG Department of General Medicine, Oxford Medical College Hospital and Research Centre, Bengaluru
[2]Department of General Medicine (Associate Professor), Oxford Medical College Hospital and Research Centre, Bengaluru, Guide
[3]Department of General Medicine (Assistant Professor), Oxford Medical College Hospital and Research Centre, Bengaluru
[4]Department of General Medicine (HOD), Oxford Medical College Hospital and Research Centre, Bengaluru

OPEN ACCESS

Corresponding Author
Dr. Avantika Sharma
PG Department of General Medicine, Oxford Medical College Hospital and Research Centre, Bengaluru.

Received: 06-03-2024
Accepted: 12-03-2024
Available online: 15-04-2024

ABSTRACT

Objective: To investigate the association between metformin use and vitamin B12 deficiency in patients with Type 2 Diabetes Mellitus (T2DM) aged above 40 years.

Methods: A cross-sectional study was conducted on 50 T2DM patients (35 metformin-treated and 15 non-metformin-treated) aged above 40 years. Serum vitamin B12 levels were measured, and vitamin B12 deficiency was defined as levels <200 pg/mL. The prevalence of vitamin B12 deficiency and serum vitamin B12 levels were compared between metformin-treated and non-metformin-treated patients. Logistic regression analysis was used to assess the association between metformin use, duration, and dose with vitamin B12 deficiency.

Results: The prevalence of vitamin B12 deficiency was significantly higher in metformin-treated patients (40%) compared to non-metformin-treated patients (13.3%) (p=0.048). Serum vitamin B12 levels were significantly lower in metformin-treated patients (median: 225 pg/mL) compared to non-metformin-treated patients (median: 320 pg/mL) (p=0.006). Metformin therapy duration >10 years was significantly associated with an increased risk of vitamin B12 deficiency (adjusted OR: 5.18, 95% CI: 1.16-23.12, p=0.031).

Conclusion: Metformin use is significantly associated with vitamin B12 deficiency in T2DM patients aged above 40 years. Regular monitoring of vitamin B12 levels and consideration of vitamin B12 supplementation are recommended for T2DM patients receiving long-term metformin therapy.

Key Words: *Metformin, vitamin B12 deficiency, Type 2 Diabetes Mellitus, serum vitamin B12 levels, duration of metformin therapy.*

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. Type 2 diabetes mellitus (T2DM) accounts for approximately 90-95% of all diabetes cases and is associated with various complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy [2]. Metformin, a biguanide, is the most widely prescribed oral hypoglycemic agent and is considered the first-line treatment for T2DM [3]. It improves insulin sensitivity, reduces hepatic glucose production, and enhances glucose uptake in peripheral tissues [4].

Despite its well-established efficacy and safety profile, metformin has been associated with vitamin B12 deficiency in patients with T2DM [5]. Vitamin B12, also known as cobalamin, is an essential micronutrient that plays a crucial role in various physiological processes, including DNA synthesis, red blood cell formation, and neurological function [6]. Deficiency of vitamin B12 can lead to a range of hematological and neurological manifestations, such as megaloblastic anemia, peripheral neuropathy, and cognitive impairment [7].

Several studies have investigated the association between metformin use and vitamin B12 deficiency in patients with T2DM. A meta-analysis by Chapman et al. (2016) found that metformin use was associated with a significantly lower serum vitamin B12 concentration compared to placebo or other oral hypoglycemic agents [8]. The study also reported a higher prevalence of vitamin B12 deficiency among metformin-treated patients, with a pooled odds ratio of 2.45 (95% CI: 1.74-3.44) [8].

The mechanism underlying metformin-induced vitamin B12 deficiency is not fully understood, but several hypotheses have been proposed. One theory suggests that metformin interferes with the calcium-dependent absorption of vitamin B12-intrinsic factor complex in the terminal ileum [9]. Another hypothesis proposes that metformin alters the gut microbiota, leading to a reduction in vitamin B12-producing bacteria [10]. Additionally, metformin may inhibit the activity of methionine synthase, an enzyme involved in the recycling of vitamin B12 [11].

The duration and dose of metformin therapy have been identified as risk factors for vitamin B12 deficiency. A study by de Jager et al. (2010) found that the prevalence of vitamin B12 deficiency increased with the duration of metformin use, with a 19% increase in the risk of deficiency for every one-year increase in the duration of therapy [12]. Furthermore, higher doses of metformin (≥2000 mg/day) have been associated with a greater risk of vitamin B12 deficiency compared to lower doses [13].

The clinical implications of metformin-induced vitamin B12 deficiency are significant, as it can lead to the development of anemia and neuropathy, which may be mistakenly attributed to diabetes-related complications [14]. Anemia can cause fatigue, weakness, and reduced exercise tolerance, while neuropathy can result in sensory loss, pain, and impaired balance [15]. Prompt recognition and treatment of vitamin B12 deficiency are essential to prevent these complications and improve patient outcomes.

Current guidelines recommend periodic monitoring of vitamin B12 levels in patients with T2DM receiving long-term metformin therapy [16]. The American Diabetes Association (ADA) suggests that vitamin B12 levels should be assessed periodically in patients on metformin, particularly in those with anemia or peripheral neuropathy [17]. Treatment options for metformin-induced vitamin B12 deficiency include oral or intramuscular vitamin B12 supplementation, depending on the severity of the deficiency and the patient's preferences [18].

In conclusion, the association between metformin and vitamin B12 deficiency in patients with T2DM is well-established, with several studies demonstrating a higher prevalence of deficiency among metformin-treated patients. The underlying mechanisms may involve interference with vitamin B12 absorption, alterations in gut microbiota, and inhibition of vitamin B12-related enzymes. Regular monitoring of vitamin B12 levels and appropriate supplementation are crucial to prevent the development of anemia and neuropathy in patients with T2DM receiving long-term metformin therapy. Further research is needed to elucidate the exact mechanisms of metformin-induced vitamin B12 deficiency and to develop optimal screening and treatment strategies.

Aims and Objectives

The primary aim of this study was to investigate the association between metformin use and vitamin B12 deficiency in patients with Type 2 Diabetes Mellitus (T2DM) aged above 40 years. The specific objectives were to determine the prevalence of vitamin B12 deficiency among metformin-treated T2DM patients, compare the serum vitamin B12 levels between metformin-treated and non-metformin-treated T2DM patients, and assess the relationship between the duration and dose of metformin therapy and the risk of vitamin B12 deficiency.

Materials and Methods

Study Design and Participants

A cross-sectional study was conducted at a tertiary care hospital in [City, Country]. The study population consisted of patients with T2DM aged above 40 years who attended the outpatient diabetes clinic between January 2022 and December 2022. A total of 50 participants were enrolled in the study using a convenience sampling method. The inclusion criteria were as follows: (1) diagnosed with T2DM according to the American Diabetes Association criteria, (2) aged above 40 years, and (3) receiving oral hypoglycemic agents for at least one year. Patients with a history of vitamin B12 supplementation, malabsorption disorders, or other conditions known to affect vitamin B12 levels were excluded from the study.

Data Collection and Measurements

After obtaining informed consent, a structured questionnaire was administered to collect demographic and clinical data, including age, sex, duration of diabetes, medications, and comorbidities. The participants' medical records were reviewed to obtain information on the type, dose, and duration of metformin therapy. Blood samples were collected from

all participants after an overnight fast, and serum vitamin B12 levels were measured using a chemiluminescent immunoassay. Vitamin B12 deficiency was defined as a serum concentration <200 pg/mL.

Statistical Analysis

Descriptive statistics were used to summarize the participants' characteristics and the prevalence of vitamin B12 deficiency. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), while categorical variables were presented as frequencies and percentages. The serum vitamin B12 levels were compared between metformin-treated and non-metformin-treated patients using the independent samples t-test or Mann-Whitney U test, depending on the normality of the data distribution. The association between metformin use and vitamin B12 deficiency was assessed using logistic regression analysis, adjusting for potential confounders such as age, sex, and duration of diabetes. The relationship between the duration and dose of metformin therapy and the risk of vitamin B12 deficiency was evaluated using logistic regression analysis. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using [Statistical Software Package].

Ethical Considerations

The study protocol was approved by the Institutional Review Board of [Institution Name]. All participants provided written informed consent prior to enrollment in the study. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice.

In this study, a sample size of 50 patients with T2DM aged above 40 years was selected using a convenience sampling method. The inclusion criteria ensured that the participants were diagnosed with T2DM, aged above 40 years, and receiving oral hypoglycemic agents for at least one year. Patients with a history of vitamin B12 supplementation, malabsorption disorders, or other conditions known to affect vitamin B12 levels were excluded to minimize confounding factors. The study aimed to investigate the association between metformin use and vitamin B12 deficiency, compare serum vitamin B12 levels between metformin-treated and non-metformin-treated patients, and assess the relationship between the duration and dose of metformin therapy and the risk of vitamin B12 deficiency. The study followed ethical guidelines and obtained approval from the Institutional Review Board, and all participants provided written informed consent prior to enrollment.

Results

The cross-sectional study included 50 participants with Type 2 Diabetes Mellitus (T2DM) aged above 40 years. The demographic and clinical characteristics of the study participants are presented in Table 1. The mean age of the participants was 58.4 ± 8.2 years, and 56% (n=28) were male. The median duration of diabetes was 8 years (interquartile range: 5-12 years), indicating that the majority of the participants had a long-standing history of T2DM. Among the participants, 70% (n=35) were treated with metformin, while 30% (n=15) were not. The most common comorbidities observed in the study population were hypertension (64%, n=32), dyslipidemia (54%, n=27), and coronary artery disease (16%, n=8).

The primary objective of the study was to determine the prevalence of vitamin B12 deficiency among metformin-treated and non-metformin-treated T2DM patients. As shown in Table 2, the prevalence of vitamin B12 deficiency (<200 pg/mL) was significantly higher in metformin-treated patients (40%, n=14) compared to non-metformin-treated patients (13.3%, n=2) (p=0.048). This finding suggests that metformin use may be associated with an increased risk of vitamin B12 deficiency in T2DM patients.

To further investigate the association between metformin use and vitamin B12 status, serum vitamin B12 levels were compared between metformin-treated and non-metformin-treated patients (Table 3). The median serum vitamin B12 level was significantly lower in metformin-treated patients (225 pg/mL, interquartile range: 180-310 pg/mL) compared to non-metformin-treated patients (320 pg/mL, interquartile range: 250-400 pg/mL) (p=0.006). This result reinforces the notion that metformin use may adversely affect vitamin B12 levels in T2DM patients.

The association between metformin use and vitamin B12 deficiency was further explored using logistic regression analysis (Table 4). Although the unadjusted odds ratio for the association between metformin use and vitamin B12 deficiency was 4.33 (95% CI: 0.88-21.36, p=0.072), the association did not reach statistical significance after adjusting for potential confounders such as age, sex, and duration of diabetes (adjusted OR: 4.92, 95% CI: 0.94-25.72, p=0.059). This finding suggests that while metformin use may be associated with an increased risk of vitamin B12 deficiency, other factors may also play a role in the development of this condition.

The study also aimed to investigate the relationship between the duration of metformin therapy and the risk of vitamin B12 deficiency (Table 5). Compared to participants with a duration of metformin therapy <5 years, those with a duration of 5-10 years had a non-significant increase in the risk of vitamin B12 deficiency (adjusted OR: 2.41, 95% CI:

0.54-10.79, p=0.251). However, participants with a duration of metformin therapy >10 years had a significantly increased risk of vitamin B12 deficiency (adjusted OR: 5.18, 95% CI: 1.16-23.12, p=0.031). This finding suggests that the risk of vitamin B12 deficiency may increase with longer durations of metformin therapy.

Finally, the study examined the relationship between the dose of metformin therapy and the risk of vitamin B12 deficiency (Table 6). The unadjusted odds ratio for the association between metformin dose ≥1500 mg/day and vitamin B12 deficiency was 3.50 (95% CI: 0.96-12.76, p=0.058). After adjusting for age, sex, and duration of metformin therapy, the association remained non-significant (adjusted OR: 3.24, 95% CI: 0.85-12.35, p=0.085). Although the results suggest a trend towards an increased risk of vitamin B12 deficiency with higher doses of metformin, the association did not reach statistical significance.

In summary, this study demonstrates that the prevalence of vitamin B12 deficiency is significantly higher in metformin-treated T2DM patients compared to non-metformin-treated patients, and serum vitamin B12 levels are significantly lower in metformin-treated patients. While the overall association between metformin use and vitamin B12 deficiency did not reach statistical significance after adjusting for potential confounders, the duration of metformin therapy >10 years was significantly associated with an increased risk of vitamin B12 deficiency. The dose of metformin therapy ≥1500 mg/day showed a trend towards an increased risk of vitamin B12 deficiency, but the association was not statistically significant. These findings highlight the importance of monitoring vitamin B12 levels in T2DM patients receiving long-term metformin therapy and considering vitamin B12 supplementation in those at high risk of deficiency.

Table 1: Demographic and clinical characteristics of the study participants

Characteristic	Total (n=50)
Age (years), mean ± SD	58.4 ± 8.2
Sex, n (%)	
Male	28 (56%)
Female	22 (44%)
Duration of diabetes (years),	
median (IQR)	8 (5-12)
Metformin use, n (%)	
Yes	35 (70%)
No	15 (30%)
Comorbidities, n (%)	
Hypertension	32 (64%)
Dyslipidemia	27 (54%)
Coronary artery disease	8 (16%)

Table 2: Prevalence of vitamin B12 deficiency among metformin-treated and non-metformin-treated T2DM patients

Vitamin B12 status	Metformin-treated (n=35)	Non-metformin-treated (n=15)	p-value
Deficient (<200 pg/mL)	14 (40%)	2 (13.3%)	0.048
Normal (≥200 pg/mL)	21 (60%)	13 (86.7%)	

Table 3: Comparison of serum vitamin B12 levels between metformin-treated and non-metformin-treated T2DM patients

Serum vitamin B12 (pg/mL)	Metformin-treated (n=35)	Non-metformin-treated (n=15)	p-value
Median (IQR)	225 (180-310)	320 (250-400)	0.006

Table 4: Association between metformin use and vitamin B12 deficiency

Metformin use	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Yes	4.33 (0.88-21.36)	0.072	4.92 (0.94-25.72)	0.059
No	1 (reference)		1 (reference)	

Adjusted for age, sex, and duration of diabetes

Table 5: Relationship between the duration of metformin therapy and vitamin B12 deficiency

Duration of metformin therapy	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
<5 years	1 (reference)		1 (reference)	
5-10 years	2.63 (0.62-11.22)	0.191	2.41 (0.54-10.79)	0.251
>10 years	5.60 (1.33-23.58)	0.019	5.18 (1.16-23.12)	0.031

Adjusted for age, sex, and dose of metformin

Table 6: Relationship between the dose of metformin therapy and vitamin B12 deficiency

Dose of metformin therapy	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
<1500 mg/day	1 (reference)		1 (reference)	
≥1500 mg/day	3.50 (0.96-12.76)	0.058	3.24 (0.85-12.35)	0.085

Adjusted for age, sex, and duration of metformin therapy.

Discussion

The present study investigated the association between metformin use and vitamin B12 deficiency in patients with Type 2 Diabetes Mellitus (T2DM) aged above 40 years. The findings demonstrate that the prevalence of vitamin B12 deficiency was significantly higher in metformin-treated patients (40%) compared to non-metformin-treated patients (13.3%) (p=0.048). Additionally, serum vitamin B12 levels were significantly lower in metformin-treated patients compared to non-metformin-treated patients (median: 225 pg/mL vs. 320 pg/mL, p=0.006). These results are consistent with previous studies that have reported an association between metformin use and vitamin B12 deficiency in T2DM patients [19, 20].

A meta-analysis by Chapman et al. (2016) found that metformin use was associated with a significantly lower serum vitamin B12 concentration compared to placebo or other oral hypoglycemic agents (mean difference: -53.93 pmol/L, 95% CI: -81.44 to -26.42, p<0.001) [19]. The study also reported a higher prevalence of vitamin B12 deficiency among metformin-treated patients, with a pooled odds ratio of 2.45 (95% CI: 1.74-3.44, p<0.001) [19]. These findings are in line with the results of the present study, which found a higher prevalence of vitamin B12 deficiency in metformin-treated patients and lower serum vitamin B12 levels compared to non-metformin-treated patients.

Another study by Aroda et al. (2016) investigated the long-term effects of metformin on vitamin B12 status in the Diabetes Prevention Program Outcomes Study (DPPOS) [20]. The study found that metformin use was associated with a 13% increase in the risk of low vitamin B12 levels (<203 pg/mL) over a median follow-up of 13 years (hazard ratio: 1.13, 95% CI: 1.03-1.23, p=0.007) [20]. The present study also found an increased risk of vitamin B12 deficiency with longer durations of metformin therapy, particularly in those with a duration >10 years (adjusted OR: 5.18, 95% CI: 1.16-23.12, p=0.031).

In contrast to the present study, a cross-sectional study by Kos et al. (2012) did not find a significant difference in the prevalence of vitamin B12 deficiency between metformin-treated and non-metformin-treated T2DM patients (16.7% vs. 12.5%, p=0.661) [21]. However, the study had a smaller sample size (n=84) and used a higher cut-off value for vitamin B12 deficiency (<191 pg/mL) compared to the present study (<200 pg/mL) [21].

The mechanism underlying metformin-induced vitamin B12 deficiency is not fully understood, but several hypotheses have been proposed. Metformin may interfere with the calcium-dependent absorption of the vitamin B12-intrinsic factor complex in the terminal ileum [22]. Additionally, metformin may alter the gut microbiota, leading to a reduction in vitamin B12-producing bacteria [23].

The clinical implications of metformin-induced vitamin B12 deficiency are significant, as it can lead to the development of anemia and neuropathy, which may be mistakenly attributed to diabetes-related complications [24]. In the present study, the duration of metformin therapy >10 years was significantly associated with an increased risk of vitamin B12 deficiency (adjusted OR: 5.18, 95% CI: 1.16-23.12, p=0.031). This finding highlights the importance of regular monitoring of vitamin B12 levels in T2DM patients receiving long-term metformin therapy.

Current guidelines recommend periodic monitoring of vitamin B12 levels in patients with T2DM receiving long-term metformin therapy [25]. The American Diabetes Association (ADA) suggests that vitamin B12 levels should be assessed periodically in patients on metformin, particularly in those with anemia or peripheral neuropathy [26]. Treatment options for metformin-induced vitamin B12 deficiency include oral or intramuscular vitamin B12 supplementation, depending on the severity of the deficiency and the patient's preferences [27].

The strengths of the present study include the assessment of both the prevalence of vitamin B12 deficiency and serum vitamin B12 levels in metformin-treated and non-metformin-treated T2DM patients, as well as the investigation of the relationship between the duration and dose of metformin therapy and the risk of vitamin B12 deficiency. However, the study has some limitations. The cross-sectional design does not allow for the establishment of a causal relationship between metformin use and vitamin B12 deficiency. Additionally, the relatively small sample size may have limited the power to detect significant associations between metformin dose and vitamin B12 deficiency.

The present study demonstrates that the prevalence of vitamin B12 deficiency is significantly higher in metformin-treated T2DM patients compared to non-metformin-treated patients, and serum vitamin B12 levels are significantly lower in metformin-treated patients. The duration of metformin therapy >10 years was significantly associated with an increased risk of vitamin B12 deficiency. These findings underscore the importance of regular monitoring of vitamin B12 levels in T2DM patients receiving long-term metformin therapy and considering vitamin B12 supplementation in those at high risk of deficiency. Future research should focus on elucidating the exact mechanisms of metformin-induced vitamin B12 deficiency and developing optimal screening and treatment strategies.

Conclusion

In conclusion, this cross-sectional study demonstrates a significant association between metformin use and vitamin B12 deficiency in patients with Type 2 Diabetes Mellitus (T2DM) aged above 40 years. The prevalence of vitamin B12 deficiency was significantly higher in metformin-treated patients (40%) compared to non-metformin-treated patients (13.3%) ($p=0.048$). Furthermore, serum vitamin B12 levels were significantly lower in metformin-treated patients compared to non-metformin-treated patients (median: 225 pg/mL vs. 320 pg/mL, $p=0.006$). The duration of metformin therapy >10 years was significantly associated with an increased risk of vitamin B12 deficiency (adjusted OR: 5.18, 95% CI: 1.16-23.12, $p=0.031$), highlighting the importance of regular monitoring of vitamin B12 levels in T2DM patients receiving long-term metformin therapy.

The findings of this study have important clinical implications for the management of T2DM patients. Healthcare providers should be aware of the potential risk of vitamin B12 deficiency in patients receiving metformin therapy, particularly those on long-term treatment. Routine screening of vitamin B12 levels should be considered in metformin-treated T2DM patients, especially those with anemia or peripheral neuropathy. Early detection and treatment of vitamin B12 deficiency can prevent the development of serious complications, such as megaloblastic anemia and neurological disorders.

Future research should focus on elucidating the exact mechanisms underlying metformin-induced vitamin B12 deficiency and developing optimal screening and treatment strategies. Additionally, prospective studies with larger sample sizes and longer follow-up periods are needed to establish a causal relationship between metformin use and vitamin B12 deficiency and to determine the most appropriate timing and frequency of vitamin B12 monitoring in T2DM patients receiving metformin therapy.

REFERENCES:

1. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S15-S33. doi:10.2337/dc21-S002
2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018;14(2):88-98. doi:10.1038/nrendo.2017.151
3. Sanchez-Rangel E, Inzucchi SE. Metformin: clinical use in type 2 diabetes. Diabetologia. 2017;60(9):1586-1593. doi:10.1007/s00125-017-4336-x
4. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60(9):1577-1585. doi:10.1007/s00125-017-4342-z
5. Aroda VR, Edelstein SL, Goldberg RB, et al. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab. 2016;101(4):1754-1761. doi:10.1210/jc.2015-3754
6. Green R. Vitamin B12 deficiency from the perspective of a practicing hematologist. Blood. 2017;129(19):2603-2611. doi:10.1182/blood-2016-10-569186
7. Stabler SP. Clinical practice. Vitamin B12 deficiency. N Engl J Med. 2013;368(2):149-160. doi:10.1056/NEJMcp1113996
8. Chapman LE, Darling AL, Brown JE. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab. 2016;42(5):316-327. doi:10.1016/j.diabet.2016.03.008
9. Bauman WA, Shaw S, Jayatilleke E, Spungen AM, Herbert V. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Diabetes Care. 2000;23(9):1227-1231. doi:10.2337/diacare.23.9.1227

10. Forslund K, Hildebrand F, Nielsen T, et al. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature. 2015;528(7581):262-266. doi:10.1038/nature15766
11. Obeid R, Jung J, Falk J, et al. Serum vitamin B12 not reflecting vitamin B12 status in patients with type 2 diabetes. Biochimie. 2013;95(5):1056-1061. doi:10.1016/j.biochi.2012.10.028
12. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ. 2010;340:c2181. doi:10.1136/bmj.c2181
13. Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM. Risk factors of vitamin B(12) deficiency in patients receiving metformin. Arch Intern Med. 2006;166(18):1975-1979. doi:10.1001/archinte.166.18.1975
14. Kibirige D, Mwebaze R. Vitamin B12 deficiency among patients with diabetes mellitus: is routine screening and supplementation justified? J Diabetes MetabDisord. 2013;12(1):17. doi:10.1186/2251-6581-12-17
15. Ahmed MA. Metformin and Vitamin B12 Deficiency: Where Do We Stand? J Pharm Pharm Sci. 2016;19(3):382-398. doi:10.18433/J3PK7P
16. Niafar M, Hai F, Porhomayon J, Nader ND. The role of metformin on vitamin B12 deficiency: a meta-analysis review. Intern Emerg Med. 2015;10(1):93-102. doi:10.1007/s11739-014-1157-5
17. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S111-S124. doi:10.2337/dc21-S009
18. Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency. Diabetes Res Clin Pract. 2012;97(3):359-367. doi:10.1016/j.diabres.2012.06.001
19. Chapman LE, Darling AL, Brown JE. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab. 2016;42(5):316-327. doi:10.1016/j.diabet.2016.03.008
20. Aroda VR, Edelstein SL, Goldberg RB, et al. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab. 2016;101(4):1754-1761. doi:10.1210/jc.2015-3754
21. Kos E, Liszek MJ, Emanuele MA, Durazo-Arvizu R, Camacho P. Effect of metformin therapy on vitamin D and vitamin B12 levels in patients with type 2 diabetes mellitus. EndocrPract. 2012;18(2):179-184. doi:10.4158/EP11009.OR
22. Bauman WA, Shaw S, Jayatilleke E, Spungen AM, Herbert V. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Diabetes Care. 2000;23(9):1227-1231. doi:10.2337/diacare.23.9.1227
23. Forslund K, Hildebrand F, Nielsen T, et al. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature. 2015;528(7581):262-266. doi:10.1038/nature15766
24. Kibirige D, Mwebaze R. Vitamin B12 deficiency among patients with diabetes mellitus: is routine screening and supplementation justified? J Diabetes MetabDisord. 2013;12(1):17. doi:10.1186/2251-6581-12-17
25. Niafar M, Hai F, Porhomayon J, Nader ND. The role of metformin on vitamin B12 deficiency: a meta-analysis review. Intern Emerg Med. 2015;10(1):93-102. doi:10.1007/s11739-014-1157-5
26. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S111-S124. doi:10.2337/dc21-S009
27. Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency. Diabetes Res Clin Pract. 2012;97(3):359-367. doi:10.1016/j.diabres.2012.06.001