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CURRENT TOPIC

# Metformin and Vitamin $B_{12}$ Deficiency – What is the Evidence?

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## Abstract

The widespread adoption of metformin as a primary therapeutic agent for type 2 diabetes has prompted inquiries into its potential impact on vitamin $B_{12}$ (cobalamin) levels and subsequent deficiency. This study aimed to elucidate this complex relationship and enhance the care provided to patients undergoing metformin treatment. A comprehensive search of meta-analyses, systematic reviews, randomised controlled trials and guidelines published between January 2010 and September 2021 was conducted. MeSH terms 'metformin' and 'vitamin $B_{12}$,' along with corresponding DeCS terms, guided the search. Varied recommendations from different scientific associations underscore the need for regular monitoring of vitamin $B_{12}$ levels in patients undergoing long-term metformin therapy. Different durations of metformin exposure, spanning from 6 weeks to 48 months, were associated with decreased vitamin $B_{12}$ concentrations. Observed decreases in $B_{12}$ concentrations ranged from 7.7 to 65.8 pmol/L, with percentage reductions ranging from 6.3 % to over 35 %. The evidence highlights a dosage-dependent correlation between higher metformin doses and an increased prevalence of $B_{12}$ deficiency. The results obtained highlight the association between metformin and $B_{12}$ deficiency. The prevalence of $B_{12}$ deficiency under metformin is of a greater magnitude than the one declared on the Summary of Product Characteristics approved by the medicine regulatory agencies. Thus, clinicians should be aware of this possible side effect when prescribing metformin, in order to prevent, monitor and treat if present.

**Key words:** Metformin; Vitamin $B_{12}$; Diabetes mellitus.

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## Introduction

The World Health Organization (WHO) estimates that approximately 463 million adults had diabetes in 2019, a number which is expected to increase to 700 million by 2045. Type 2 diabetes, characterised by insulin resistance and impaired glucose regulation, is associated with family history, sedentary lifestyle and obesity.[1]

The diabetes treatment involves a multifactorial risk-reduction strategy, that includes pharmacological treatment. Metformin is generally one of the first-line therapy options due to its favourable safety profile, glucose-lowering efficacy and potential cardiovascular benefits. However, questions about its potential side effects have arisen, since emerging evidence suggests that metformin may interfere with the absorption of vitamin $B_{12}$ (cobalamin) by affecting the gastrointestinal tract and intrinsic factor secretion, altering gut microbiota and increasing renal excretion of vitamin $B_{12}$.[2] This emphasises the need for monitoring of $B_{12}$ levels in long-term metformin users due to potential deficiency-related complications.

As vitamin $B_{12}$ deficiency is associated with a spectrum of clinical manifestations, including anaemia, neuropathy and cognitive impairments, a comprehensive review of the current literature is imperative to elucidate the nature and extent of the association between metformin use and vitamin $B_{12}$ deficiency.[3–6]

By synthesising available research findings, this review aimed to assess the current state of knowledge regarding the relationship between these two factors, thus informing clinical practice and guiding future research directions in the realm of diabetes management and patient well-being.

## Methods

The authors used the PICO approach outlined by O'Connor et al to perform this evidence-based review, which acronym enables the review questioned to be performed in terms of the population (P), intervention (I), comparator (C) and outcome (O).

The population included adults of both sexes medicated with metformin, due to the diagnosis of diabetes, pre-diabetes or polycystic ovarian syndrome. The therapeutic intervention consisted of comparing the use of metformin with placebo, another drug or not taking medication. The primary outcome was vitamin $B_{12}$ deficiency.

The authors excluded articles with paediatric populations, patients with prior gastrointestinal surgery, intrinsic factor deficiency, inflammatory bowel disease or celiac disease. The exclusion criteria also included duplicated articles, opinion articles and articles that were not consonant with the objective of the review. Thus, the Medical Subject Headings (MeSH) words selected from the Pubmed's MeSH Database were 'metformin' and 'vitamin $B_{12}$'. These MeSH words were used to search for synopses, guidelines, meta-analyses, systematic reviews and original papers, published between January 2010 and September 2021 in the databases *MEDLINE, National Guideline Clearinghouse, National Institute for Health Care and Excellence, Canadian Medical Association Practice Guidelines InfoBase, TRIP Database, the Cochrane Library, DARE, Bandolier* and *Index de Revistas Médicas Portuguesas* in English and Portuguese.

The strength of recommendation taxonomy (SORT) scale, from the American Academy of Family Physicians, was used to determine the level of evidence and strength of recommendation.

Results were standardised for comparison, converting time variables to months and vitamin $B_{12}$ concentrations to pmol/L.

## Results

The initial search identified a total of 85 results, of which 74 were obtained after removing duplicates. Of these, 46 were excluded after reading the title, 8 after reading the abstract and 3 after reading the full article. The results are summarised in Table 1.

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend routine vitamin $B_{12}$ monitoring for long-term metformin users, without specifying exposure times or metformin doses. The Endocrine Society (ES), American Association of Clinical Endocrinology (AACE) and American College of Endocrinology (ACE) suggest assessing $B_{12}$ levels for those with neuropathy symptoms.[2, 22-24]

The International Society of Nephrology (ISN) advises $B_{12}$ evaluation after 4 years of metformin use or in high-risk individuals (eg, patients with malabsorption syndrome or reduced dietary intake [vegans]).[25] Furthermore, the Canadian Diabetes Association (CDA) suggests periodic $B_{12}$ measurements in metformin users or individuals with signs or symptoms of deficiency (such as impaired proprioception or peripheral neuropathy).[26]

### Correlation between metformin exposure time and decreased vitamin $B_{12}$ concentration

#### Time

While the duration of the analysed studies varied, differences in $B_{12}$ concentration were found after a minimum of 6 weeks of metformin exposure, with ranges from 14.89 ($p < 0.119$) to 19.7 pmol/L ($p = 0.004$).[14, 18]

Some studies identified variances in $B_{12}$ concentrations after a 3-month period of metformin use

*Table 1: Summary of the information found in the systematic reviews and original studies*

| | Articles | N | Time (M) | Dose (mg) | % deficit | Δ $B_{12}$ (pmol/L) | Δ $B_{12}$ % | Risk | NNH | SORT | Observations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Systematic reviews | Niafar et al[7] | 7,611 | N/A | N/A | N/A | 65.80 p < 0.00001* | N/A | OR: 2.45 p < 0.00001* | N/A | C | |
| | Yang et al[8] | 5,500 | 36 | N/A | N/A | 63.70 p < 0.00001* | 14.70 % p < 0.00001* | RR: 2.09 p < 0.00001* | N/A | C | Annual monitoring of vitamin $B_{12}$ is recommended in patients receiving metformin. |
| | Chapman et al[9] | 14,945 | 48 | N/A | N/A | 57.10 p < 0.001* | 19 % p < 0.001* | N/A | N/A | C | It is prudent to monitor B12 in patients who are at increased risk of deficiency. |
| | Liu et al[6] | N/A | N/A | N/A | N/A | 53.93 p = 0.0001* | N/A | N/A | N/A | C | |
| | Li et al[10] | 218 | N/A | N/A | N/A | 24.70 p = 0.31 | N/A | N/A | N/A | C | |
| Original studies | Aroda et al[11] | 2,150 | 60.0<br>156.0 | 1,700 | 4.3 % vs 2.3 % p = 0.03*<br>7.4 % vs 5.4 % p = 0.13 | N/A<br>N/A | N/A<br>N/A | OR: 1.13 | N/A | 3 | |
| | Jager et al[12] | 390 | 48.0 | 2,500 | N/A | N/A | 19 % p < 0.001* | 1AR : 7.20 p = 0.004* | 13.8 | 3 | |
| | Lohmann et al[13] | 500 | 6.0 | 1,700 | N/A | 51 | 6.30 % | N/A | N/A | 3 | Monitoring vitamin $B_{12}$ on a regular basis may be prudent. |
| | Sahin et al[14] | 165 | 1.5 | 1,700 | N/A | 14.89 p < 0.119 | N/A | N/A | N/A | 3 | |
| | Mastroianni et al[15] | 165 | 36.0 | 1,700 | 32 % p < 0.02* | N/A | N/A | N/A | N/A | 3 | Monitor at baseline and during treatment routinely. |
| | Leung et al[16] | 20 | 3.0 | N/A | N/A | N/A | 6.30 % p = 0.04* | N/A | N/A | 3 | |
| | Griffin et al[17] | 249 | 6.0 | N/A | N/A | 7.70 | ND | N/A | N/A | 3 | |
| | Gatford et al[18] | 180 | 1.5 | ≤ 2,500 | N/A | 19.70 p = 0.004* | ND | N/A | N/A | 3 | |
| | Hassan et al[19] | 1,200 | 3.0 | 1,000 | N/A | ND | 35 % p < 0.01* | N/A | N/A | 3 | |
| | Hansen et al[20] | 412 | 18.0 | N/A | N/A | 19.90 p < 0.01* | N/A | N/A | N/A | 3 | |
| | Kancherla et al[21] | 16,945 | 6.0 | ≥ 500 | 7 % vs 3 % p < 0.0001* | N/A | N/A | N/A | N/A | 3 | Clinically based vitamin $B_{12}$ monitoring should be promoted. |

*AR - Absolute risk; M - months; N/A - Not applicable; NNH - Number needed to harm; OR - Odds ratio; RR - Relative risk; SORT - Strength of recommendations taxonomy;*

(6.3 %, p = 0.04, Leung et al) (35 %, p < 0.01, Hassan et al) and others found a similar variation after a 6-month period (6.3 %, Lohmann et al).[13, 16, 19] Furthermore, Hansen et al identified a 19.9 pmol/L variance (p < 0.01) after 18 months.[20]

In a longer approach (48 months), Hassan et al also found a 19 % (p < 0.01) variation in $B_{12}$ concentration, similar to the systematic reviews of Yang et al at 36 months (14.7 %, p < 0.0001) and Chapman (19 %, p < 0.001) at 48 months.[8, 9]

## $B_{12}$ concentration variation

Serum $B_{12}$ levels were assessed based on concentration or relative variation in the reviewed studies. Findings indicated a decrease in $B_{12}$ concentration between 7.7 pmol/L (Griffin et al, Sahin et al) and 65.8 pmol/L (p < 0.0001, Niafar et al).[7, 14, 17] Original studies reported a variation from 7.7 pmol/L to 51 pmol/L while systematic reviews showed a variation from 24.7 pmol/L (p = 0.31, Li et al) to 65.8 pmol/L (Niafar et al).[7, 10, 13, 14]

In terms of percentage, reductions in $B_{12}$ were noted from 35 % (p < 0.01, Hassan et al) to 6.3 % (Lohman et al and the Leung et al), with systematic reviews indicating reductions below 20 % (14.7, Yang et al and 19 %, Chapman et al).[8, 9]

## $B_{12}$ deficiency

More significant than changes in $B_{12}$ concentration is the detection of deficiency, due to its po-

tential health and quality of life implications. Kancherla et al found a statistically significant difference among groups, with a 7 % prevalence of $B_{12}$ deficiency in 16,945 patients treated with metformin for 6 months at doses as low as 500 mg, compared to 3 % in the non-metformin group.[21]

Another study reported a 4.3 % prevalence of $B_{12}$ deficiency after 60 months in patients treated with metformin at an average dose of 1700 mg per day, contrasting with 2.3 % in the non-metformin group ($p = 0.03$). After 156 months, the prevalence of $B_{12}$ deficiency was 7.4 % in the metformin group versus 5.4 % in the non-metformin group ($p = 0.13$).[11] Mastroianni et al identified the highest prevalence of $B_{12}$ deficiency (32 %, $p < 0.02$) in 165 patients receiving the same daily dose of metformin.[15]

## $B_{12}$ deficiency and its association with metformin dose

Metformin dose across studies ranged from 500 to 2500 mg per day. Kancherla et al found a 7 % prevalence of $B_{12}$ deficiency among patients using at least 500mg of metformin daily for 6 months.[21] Other studies showed that daily use of metformin at doses greater to or exceeding 1700 mg were linked to vitamin $B_{12}$ deficiency after 36 or 60 months (Mastroianni et al and Aroda et al, respectively).[11, 15]

## Risk measurements: odds ratio, relative risk and absolute risk

Niafar et al observed a greater prevalence of $B_{12}$ deficiency in the metformin group (OR = 2.45, $p < 0.0001$), while Aroda et al found a heightened risk (OR = 1.13).[7, 11]

Yang et al reported a significantly increased risk of vitamin $B_{12}$ deficiency among metformin users (RR 2.09, $p < 0.0001$).[8] Jager et al demonstrated a 7.2 percentage point higher absolute risk of vitamin $B_{12}$ deficiency ($p = 0.004$), with a number needed to harm of 13.8.[12]

# Discussion

In presented study, a prevalence of vitamin $B_{12}$ deficiency of 25.3 % among patients with type 2 diabetes receiving metformin therapy was identified. This high prevalence underscores the imperative need to promptly address this deficiency to alleviate potential symptoms and mitigate overall health repercussions. The observed prevalence aligns with findings from other studies, which report a range of $B_{12}$ deficiency between 6 % and 30 %.

Leung et al identified a prevalence of 22.2 % in a study involving 1111 patients, while Aroda et al, in a prospective study with 1073 participants, reported a prevalence of 19.1 % after 5 years and 20.3 % after 13 years of metformin usage.[11, 16] Additionally, the National Health and Nutrition Examination Survey demonstrated that 41 % of $B_{12}$ deficiency cases among individuals with diabetes were attributable to metformin use.[14] In a Korean study, the prevalence of vitamin $B_{12}$ deficit was lower (9.5 %), emphasising the influence of population differences as a potential bias.[25, 26]

Regarding the duration of metformin use, some studies suggest a cutoff of 4 years for detecting $B_{12}$ deficiency.[18] In presented study, patients with $B_{12}$ deficiency were identified after just 1 year of metformin use. The mean duration under metformin for the $B_{12}$ deficiency group was 5.33 years, consistent with previous data.

The dosage of metformin is also a significant consideration in various studies. For instance, Leung et al reported a decrease in vitamin $B_{12}$ levels by 0.142 pg/mL with a 1 mg increase in metformin, while Beulens et al found a decrease of 0.042 pg/mL.[16, 25] In presented study, doses as low as 500 mg per day were associated with $B_{12}$ deficiency and the majority of the deficiency group (55 %, n = 11) had prescribed doses exceeding 2000 mg/day, aligning with prior data.

In future studies, aim is to replicate these findings on a multicentre or national level to enhance the robustness of presented conclusions. Additional secondary outcomes, including folic acid levels, homocysteine levels, and methylmalonyl-CoA mutase, can also be explored to deepen understanding of $B_{12}$ deficiency.

$B_{12}$ deficiency presents with varied symptoms that may mislead doctors and patients, as neurologic symptoms (characterised by decreased position and vibratory sensation in the extremities accompanied by mild to moderate weakness and hyporeflexia, that may develop in a stocking-glove distribution). It can mimic the diabetic foot symptoms, leading to unnecessary therapy and investigation. Other symptoms such as irri-

tability, depression, weight loss and poorly localised abdominal pain may occur, leading to poor quality of life.[19]

Correcting this disorder is simple, as various $B_{12}$ supplement formulations are available and haematologic abnormalities are usually corrected within 6 weeks. However, doctors should be aware that neurologic symptoms may take much longer and may even become irreversible if they persist for months or years.[19]

## Conclusion

The significance of presented results, revealing a 25.3 % prevalence of $B_{12}$ deficiency in patients under metformin, emphasises the importance of physician awareness and proactive management of this side effect to minimise possible symptoms of the patients that may diminish their quality of life.

## Etics

The study was approved by the Ethic Committee of the *Administração Regional de Saúde do Norte* (Northern Regional Health Administration), decision No CE/2024/1, dated 4 January 2024.

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## Conflicts of interest

The authors declare that there is no conflict of interest.

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## Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request. Consent statement and permission obtained by the Technical Committee of USF Nova Estação.

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