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Short Communication

Metformin And Vitamin B12 Deficiency: A Concise Exploration

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Abstract

Type 2 diabetes mellitus (T2DM) management with metformin, a first-line oral antidiabetic, is associated with emerging concerns about potential vitamin B12 deficiency. Approximately 6% to 30% of metformin users may experience this deficiency. Recent studies suggest interference in absorption and metabolism processes, prompting exploration of underlying mechanisms.

Proposed mechanisms include disruption of calcium-dependent binding, alteration in small intestine motility, changes in bile acid metabolism, enhanced liver accumulation, and decreased intrinsic factor secretion. Inhibition of calcium-dependent absorption at the terminal ileum, reversible with calcium supplementation, is increasingly recognized as a key mechanism.

Studies report varying prevalence rates of vitamin B12 deficiency with metformin use, emphasizing the need for careful monitoring. Daily dose appears more strongly associated with deficiency than duration. In conclusion, this mini-review underscores the intricate relationship between metformin and vitamin B12 deficiency, emphasizing the importance of vigilant monitoring and tailored interventions for comprehensive patient care.

Key words: metformin; vitamin b12; deficiency; type 2 diabetes mellitus; mechanisms

Introduction

Type 2 diabetes mellitus (T2DM) is a prevalent chronic metabolic disorder characterized by insulin resistance and impaired glucose metabolism. Metformin, a first-line oral antidiabetic medication, plays a pivotal role in managing T2DM by improving insulin sensitivity and reducing hepatic glucose production (American Diabetes Association, 2021; Inzucchi et al., 2015). While metformin is widely acclaimed for its efficacy and safety profile, emerging evidence suggests a potential association between its long-term use and vitamin B12 deficiency. According to reports, an estimated 6% to 30% of individuals using metformin may exhibit vitamin B12 deficiency (Kos E et al., 2012). Vitamin B12, an essential water-soluble vitamin, plays a critical role in various physiological processes, including DNA synthesis, erythropoiesis, and neurological function (Stabler, 2013). Berchtold and colleagues initially disclosed in 1969 that metformin might induce vitamin B12 deficiency by diminishing vitamin B12 absorption in the gastrointestinal tract. (Berchtold P et al., 1969).

Recent studies have raised concerns about the impact of metformin on vitamin B12 levels, with some evidence suggesting interference in absorption and metabolism processes (de Jager et al., 2010; Niafar et al., 2015). This burgeoning area of research prompts a comprehensive exploration of the mechanisms underlying metformin-induced vitamin B12 deficiency and its potential clinical ramifications.

The precise mechanisms responsible for metformin-induced vitamin B12 deficiency remain incompletely understood. Proposed mechanisms contributing to metformin-induced vitamin B12 deficiency by influencing vitamin B12 absorption and metabolism encompass:

- Disruption of the calcium-dependent binding of the IF-vitamin B12 complex to the cubilin receptor on enterocytes at the ileum level and/or interaction with the cubilin endocytic receptor; Modification of small intestine motility, resulting in bacterial overgrowth in the small intestine and subsequent inhibition of IF-vitamin B12 complex absorption in the distal ileum;
- Changes in bile acid metabolism and reabsorption, leading to impaired enterohepatic circulation of vitamin B12;
- Enhanced liver accumulation of vitamin B12, causing alterations in tissue distribution and metabolism of vitamin B12; and
- Decreased secretion of IF by gastric parietal cells. Importantly, the inhibition of calcium-dependent absorption of the IF-vitamin

B12 complex at the terminal ileum has been increasingly acknowledged as the most plausible mechanism responsible for metformin-induced vitamin B12 deficiency. Notably, this inhibitory effect can be reversed by calcium supplementation (Bauman WA et al., 2000).

A prospective study reported a prevalence of 20.3% for vitamin B12 deficiency after 9.5 years of metformin usage (Aroda VR et al., 2016), and an extensive dataset from the National Health and Nutrition Examination Survey indicated a 22% prevalence when defining vitamin B12 deficiency as levels below 300pg/mL (Reinstatler L et al., 2012). Another recent investigation from Korea documented a lower prevalence of vitamin B12 deficiency at 9.5% and higher mean B12 levels at 662.5±246.7 pg/mL (Ko SH et al., 2014). Discrepancies in testing methods, alcohol consumption, and metformin doses may contribute to these variations. Several studies have explored the influence of metformin duration and dosage on vitamin B12 deficiency. In the aforementioned research, both the duration and daily metformin dose exhibited significant associations with vitamin B12 deficiency, with cut-off values set at 4 years and 1100mg/d, respectively (Ko SH et al., 2014). Another study found a negative correlation between metformin dose and vitamin B12 levels, revealing that an increase of 1mg in the daily metformin dose corresponded to a 0.042pg/mL decrease in vitamin B12 levels. However, the duration of metformin use did not demonstrate significant effects (Beulens JW, et al., 2015). Similarly, multiple studies have emphasized that daily dose holds a stronger association with vitamin B12 deficiency than duration, as reported in several subsequent studies de Groot-Kamphuis DM et al., 2013;71:386–90).

A recent retrospective study conducted in a substantial cohort of adult patients (n = 13,489) who had been prescribed metformin for over 1 year aimed to evaluate the appropriateness and advantages of screening recommendations for vitamin B12 deficiency (Martin D et al.,. 2021). The average duration between the initiation of metformin and the onset of vitamin B12 deficiency was 5.3 years. Within the older patient subgroup (> 65 years of age), there was a notably higher rate of vitamin B12 deficiency compared to younger patients (4.2% vs 2.5%). In multivariable logistic regression models, older age emerged as the sole factor associated with vitamin B12 deficiency, while African-American ethnicity almost reached statistical significance as a protective factor. These findings imply that individuals using metformin for more than 5 years and those aged over 65 are at an elevated risk of vitamin B12 deficiency. Consequently, the authors concluded that screening for vitamin B12 deficiency might be advisable in such populations, even if they exhibit no symptoms of the deficiency. ((Martin D et al., 2021).

In conclusion, this mini-review has shed light on the intricate relationship between metformin and vitamin B12 deficiency. The existing body of evidence underscores the need for vigilance in monitoring vitamin B12 levels, particularly in individuals who have been on metformin for an extended duration or are above the age of 65. The proposed mechanisms contributing to metformin-induced vitamin B12 deficiency, including interference with absorption and metabolism, altered small intestine motility, and changes in bile acid metabolism, provide valuable insights into potential preventive measures. The acknowledgment of calcium-dependent absorption as a key mechanism, reversible with calcium supplementation, emphasizes the significance of tailored interventions. As our understanding of this relationship continues to evolve, healthcare providers should consider proactive screening for vitamin B12 deficiency in at-risk populations, even in the absence of apparent symptoms, to ensure comprehensive and personalized patient care.

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