

# The Role of Supplements in Managing Complications Due to Long-Term Metformin Therapy

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## ABSTRACT

Metformin, a common medication prescribed and used in the management of T2DM. While metformin is considered safe and effective, its long-term usage has been associated with potential risks: lactic acidosis, vitamin B12 deficiency, muscle-related symptoms like myalgia, anaemia, mouth ulcers, weight loss, peripheral neuropathy, and renal impairment. This review article intends to provide an overview of the utility of supplements in dealing with these complications. We discuss the evidence for the use of vitamin B12, probiotics, antioxidants, omega-3 fatty acids, and magnesium and potassium supplements in mitigating the adverse effects of long-term metformin therapy.

**KEYWORDS:** Metformin, long-term therapy, complications, supplements, type 2 diabetes mellitus (T2DM), vitamin B12 deficiency, lactic acidosis, gastrointestinal issues, Peripheral neuropathy

## I. INTRODUCTION

Metformin is a biguanide, an antidiabetic agent, and a widely prescribed medication for managing type 2 diabetes mellitus (T2DM). [1] While it is effective for controlling blood glucose levels, its long-term use is associated with certain complications, particularly vitamin B12 deficiency and anaemia.

This review article aims to provide a comprehensive overview of the role of supplements in managing complications associated with long-term metformin therapy [1]. Metformin is a widely prescribed medication for type 2 diabetes mellitus (T2DM) that can lead to various complications, including vitamin B12 deficiency, lactic acidosis, and gastrointestinal issues [2, 3]. The article will focus on the specific complications that arise from prolonged metformin use and the types of supplements that can help mitigate these complications.

## COMPLICATIONS OF LONG-TERM METFORMIN THERAPY

Long-term use of metformin can result in various complications, including:

- ❖ **Vitamin B12 Deficiency:** The exact way metformin affects the absorption of vitamin B12 is not completely clear, but it is thought to interfere with the process in the digestive system. Over time, this can lead to a deficiency in vitamin B12. This deficiency may cause issues such as blood-related disorders, nerve damage, and other neurological problems. Research has shown a strong link between long-term metformin use and higher rates of vitamin B12 deficiency. For instance, a cross-sectional study found a high rate of vitamin B12 deficiency in people with type 2 diabetes taking metformin [8][9]. Evidence from the Diabetes Prevention Program Outcomes Study [4] and data from the National Health and Nutrition Examination Survey (1999–2006) [5] also show an association between metformin use and a lack of sufficient vitamin B12. People with type 2 diabetes who use metformin for an extended period of time are more likely to develop a vitamin B12 deficit, according to a randomised placebo-controlled experiment [6]. Recent studies have emphasized the importance of checking vitamin B12 levels in patients who are on long-term metformin treatment due to the possibility of deficiency [7][29].
- ❖ **Lactic Acidosis:** This is a rare but very serious condition in which too much lactic acid accumulates in the blood. Risk factors include problems with the kidneys or liver, heavy alcohol use, and severe heart failure. Symptoms of this condition require urgent medical care. A serious side effect that requires immediate detection and treatment is metformin-associated lactic acidosis (MALA)

[2]. Understanding the body's response to MALA is important for treating critically ill patients [3].

- ❖ **Gastrointestinal Problems:** Bloating, nausea, diarrhoea, and abdominal pain are typical adverse effects. When beginning a drug or raising the dosage, these symptoms frequently appear.
- ❖ **Peripheral Neuropathy:** Long-term metformin use has been linked to an increased risk of peripheral neuropathy, particularly in older adults. Duration of metformin therapy is a risk factor, with a rate of approximately 1% per month and slightly over 10% per year of treatment. [15]

To manage the complications associated with long-term metformin therapy, healthcare providers employ several strategies. Monitoring vitamin B12 levels in long-term metformin users is crucial, as deficiency can lead to serious health issues. Healthcare providers may recommend dietary supplementation or B12 injections to mitigate this risk. Healthcare providers on the use of supplements in patients on long-term metformin therapy [13]. Regular monitoring of kidney and liver function is also essential to prevent lactic acidosis, a rare but potentially life-threatening complication.

The role of supplements in managing complications due to long-term metformin therapy is a crucial topic. Research has shown that metformin can lead to vitamin B12 deficiency, which can cause neurological symptoms, megaloblastic anaemia, and peripheral neuropathy. By incorporating supplements, such as vitamin B12, into treatment plans, healthcare providers can help alleviate these complications and ensure the safe and effective use of metformin. Ultimately, a comprehensive approach to managing metformin-related complications can improve patient outcomes and quality of life. [8] [9]

Vital Supplements for Managing Complications:

- ✓ Vitamin B12 supplements: Essential for preventing and treating vitamin B12 deficiency, which can be caused by long-term metformin use.
- ✓ Calcium supplements: Can help reverse metformin-induced B12 malabsorption, as it is calcium-dependent.
- ✓ Omega-3 fatty acids: May help reduce inflammation and promote cardiovascular health in patients with diabetes.

- ✓ Probiotics: Can help maintain gut health and prevent gastrointestinal side effects associated with metformin use. [11] [12]

#### ROLE OF SUPPLEMENTS

1. **Vitamin B12:** Vitamin B12 supplementation is crucial for patients on long-term metformin therapy to prevent deficiency and associated complications like anaemia and neuropathy, related complications in patients on long-term metformin therapy [6]. It supports red blood cell formation, nerve cell function, and overall metabolic health. Foods rich in vitamin B12, such as meat, fish, and dairy products, can also help maintain adequate levels. [16] Healthcare providers should consider monitoring vitamin B12 levels in patients on long-term metformin therapy and recommending supplementation as needed [14] [36].
2. **Vitamin D:** Vitamin D supplementation may play a role in preventing type 2 diabetes and is an important aspect of comprehensive diabetes management. By improving insulin sensitivity and reducing cardiovascular risks, vitamin D can be beneficial for individuals with type 2 diabetes. Despite metformin not directly causing vitamin D deficiency, supplementation is often recommended due to the high prevalence of deficiency in this population. Research suggests that vitamin D supplementation may only benefit those with very low vitamin D levels (<12 ng/ml) or poor glycemic control (HbA1c >8%), highlighting the need for personalized approaches to supplementation. [10]
3. **Chromium:** Chromium supplementation offers several benefits for diabetes patients, including improved glycemic control, lipid metabolism, and reduced oxidative stress and inflammation. It also enhances insulin sensitivity and supports weight management. However, it's essential to follow recommended dosages, as excessive intake can be harmful. Research suggests that higher doses (1,000 mcg daily) may be more effective than lower doses (200 mcg daily) in producing significant benefits. Further studies are needed to determine the optimal form and amount of chromium supplementation for diabetes management and prevention. [18]
4. **Magnesium:** Magnesium plays a vital role in glucose metabolism and insulin sensitivity.

Supplementing with magnesium can improve glycemic control and reduce cardiovascular complication risks in diabetes patients. It also controls blood sugar levels and improves the efficiency of insulin. Research studies show that higher dietary magnesium intake is associated with a lower risk of developing type 2 diabetes. However, the benefits of magnesium supplementation for individuals with type 2 diabetes are less clear and require further study. In contrast, studies in non-diabetic individuals have consistently shown that magnesium supplementation improves insulin sensitivity and glucose levels. [19]

5. **Calcium:** Can help reverse metformin-induced B12 malabsorption, as it's calcium-dependent. Respectable calcium input may help in mollifying the trouble of vitamin B12 insufficiency associated with long-term metformin treatment, and thus there is an increase in vitamin B12 situations seen with oral calcium supplementation, just as there is in elderly individuals given oral vitamin B12 supplementation. [12] [26] Individuals with type 2 diabetes entering metformin develop low bioavailable B12 (holoTCII), which, if allowed to progress, would be anticipated to be followed by low serum total vitamin B12 situations and, presumably, eventual clinical insufficiency. Since metformin and calcium compete for the mucosal cell membrane, ionic calcium is necessary for the B12-IF complex to connect to ileal cell face receptors. This form of vitamin B12 malabsorption was reversible with an oral calcium supplement. Cases with type 2 diabetes treated with metformin, especially those who don't consume milk or milk products on a quotidian basis or don't take supplemental calcium, should be encouraged to increase their input of calcium as well as be nearly covered for vitamin B12 insufficiency. [12]

6. **Probiotics:** Can help maintain gut health and prevent gastrointestinal side effects associated with metformin use, such as diarrhoea and bloating.

- Lactobacillus and Bifidobacterium species: These probiotics maintain intestinal health and bolster the gut barrier, supporting beneficial shifts induced by metformin.
- Lactobacillus rhamnosus: Reduces gut inflammation and improves intestinal

permeability, potentially enhancing systemic well-being.

- Saccharomyces boulardii: A beneficial yeast that modulates gut immune responses, enhancing metformin's effects by fostering an environment less prone to inflammatory responses.
- OMNi-BiOTiC HETOX light: A probiotic supplement shown to improve insulin resistance, reduce belly fat, and lower lipopolysaccharide levels, indicating a reduced risk of endotoxemia. [20] [21]

Probiotics are beneficial because:

- ✓ Improved gut health: Probiotics maintain gut homeostasis, reduce pro-inflammatory markers, and promote beneficial gut microbiota.
- ✓ Decreased risk of gastrointestinal adverse events: Probiotics may help reduce the likelihood of gastrointestinal adverse events when taken with metformin medication.
- ✓ Improved glycaemic control: Probiotics may help reduce fasting glucose and HbA1c levels in patients with type 2 diabetes mellitus treated with metformin. [22]

7. **Biotin:** In individuals with type 2 diabetes, biotin along with chromium can help improve glucose metabolism and reduce coronary risk factors. Further study is required to completely comprehend the advantages of biotin in the treatment of diabetes. [23] Taking biotin as a supplement may assist in managing long-term side effects of metformin, especially for those with type 2 diabetes.

Benefits of Biotin Supplementation:

- ✓ Improved Glycaemic Control: Studies show that taking biotin supplements can lower fasting blood glucose (FBG) levels, particularly when consumed in doses greater than 9 mg per day.
- ✓ Improved Lipid Profile: Biotin supplements can help reduce triglycerides (TG) and total cholesterol (TC) levels.
- ✓ Potential Benefits: Although more research is needed to confirm this, biotin may also have positive effects on insulin levels.[30]

8. **Coenzyme Q10 (CoQ10):** Taking CoQ10 as a supplement supports energy production, heart

health, and offers antioxidant protection. Medications that lower CoQ10 levels can cause tiredness and muscle weakness, making CoQ10 especially beneficial for those on metformin. While the impact of CoQ10 on lipid profiles is not fully understood, research indicates it may help people with diabetes manage their blood glucose levels. [24] As a strong antioxidant, CoQ10 helps reduce inflammation and oxidative stress, offering protection against several diseases, including diabetes and heart conditions. However, due to its low bioavailability and inconsistent research methods, the clinical use of CoQ10 has been limited. To better understand its effects and potential benefits, more studies are needed. Additionally, extensive clinical trials are required to evaluate the therapeutic potential of CoQ10. [35]

**9. Omega-3 Fatty Acids:** Taking omega-3 fatty acids can improve overall health and enhance the effects of metformin. These fats support the reduction of inflammation, improve cognitive function, and promote heart health. It is important to take omega-3 supplements because metformin may lower omega-3 levels. [25] Although the benefits of omega-3 fatty acids on cardiovascular health in individuals with type 2 diabetes have been studied before, our study highlights the need for longer-term and more comprehensive trials. We found that omega-3 supplementation slightly increased LDL cholesterol, which is a concern. Larger, well-designed trials with standardised measurements are needed to better understand the risks and benefits of omega-3s in managing diabetes. These studies should also assess both established and emerging cardiovascular risk factors to provide more conclusive evidence on the role of omega-3s in reducing cardiovascular disease risk in type 2 diabetes.

**10. Berberine:** This natural extract has shown potential as a supplement or alternative to metformin. Because of its antibacterial, anti-inflammatory, and antioxidant qualities, it promotes metabolic health and glucose management. Berberines are potent oral hypoglycemics with no effect on lipid metabolism. Berberine treatment is both inexpensive and secure. For the management of type 2 diabetes, it could offer a unique treatment option. However, this is a pilot study, and it is important to evaluate berberine's

effectiveness across a broader population and compare it with the duration of diabetes. [26]

**11. Vitamin E:** It is important to consider vitamin E levels when taking metformin for type 2 diabetes, as metformin may affect its absorption or use. Vitamin E is a crucial nutrient that supports overall health, with antioxidant properties that protect cells from damage, promote cardiovascular health, and maintain healthy skin and tissues. To maintain adequate vitamin E levels, include vitamin E-rich foods in your diet, such as dark leafy greens like kale and spinach, nuts and seeds like almonds and sunflower seeds, and avocados. If necessary, vitamin E supplements may be recommended, especially for those with confirmed deficiencies or at risk of deficiency. Consult with a healthcare professional to determine the best approach for your individual needs. [33]

## II. CASE REPORT

Case Report on Managing Complications Due to Long-Term Metformin Therapy with Supplements

A major complication of prolonged metformin use is vitamin B12 deficiency, which can lead to neurological symptoms such as fatigue, weakness, muscle pain, and other neurological issues. To manage this issue, supplements like vitamin B12 can play a vital role.

An 84-year-old man with type 2 diabetes was on long-term metformin therapy (1700 mg/day for over 25 years) and presented with dizziness, fatigue, and reduced vibratory sensation and proprioception in both feet. A vitamin B12 deficiency and elevated plasma homocysteine levels were found during laboratory testing. Treatment with intramuscular cyanocobalamin injections (1000 µg daily for one week, followed by weekly injections) resulted in improved gait and reduced dizziness. This case illustrates the importance of monitoring vitamin B12 levels in patients on long-term metformin and the role of vitamin B12 supplements in treating deficiency and related neurological symptoms. Regular monitoring and timely intervention can help prevent long-term complications. [28]

## III. CONCLUSION

Long-term use of metformin can lead to complications such as vitamin B12 deficiency, lactic acidosis, and gastrointestinal issues. Supplementing with vitamins and minerals

such as vitamin B12, vitamin D, vitamin E, chromium, magnesium, and biotin can help manage these complications and improve overall health outcomes for diabetic patients. Further research is needed to determine the best dosages and long-term safety of these supplements. Routine monitoring and tailored treatment plans can improve patient outcomes. By integrating supplements and monitoring into care, healthcare providers can ensure safer and more effective management for patients with type 2 diabetes mellitus. Patients on long-term metformin therapy should work closely with their healthcare professionals to detect side effects early and develop a customised management plan that may involve lifestyle changes and supplements.

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