Vitamin B-12 deficiency in type 2 diabetes patients on metformin therapy – A narrative review

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Abstract

Due to its increased incidence and related complications, T2DM (Type 2 diabetes mellitus) is becoming an issue of public health concern. This narrative review elucidates association between metformin therapy in T2DM and cobalamin (Vit. B12) deficiency. According to various studies, diabetic patients receiving metformin medication had a higher risk of Vit. B12 (vitamin B12) deficiency than those T2DM patients not receiving metformin therapy, ranging from 14% to 22.4% in those taking metformin and from 6% to 10% in those not taking metformin. Odds ratios for Vit. B12 deficiency associated with using metformin ranged from 2.2 to 2.7, indicating a moderate to high risk. The management of Vit. B12 deficiency in T2DM involves a combination of accurate diagnosis, appropriate supplementation strategies, patient education, and interdisciplinary collaboration. Consensus and guidelines recommend routine monitoring of serum vitamin B12 levels, high-dose oral supplementation, intramuscular injections for severe deficiency, and consideration of alternative routes of administration, along with lifestyle modifications.

Keywords: Diabetes mellitus type 2, Metformin therapy, Vitamin B12, Management, and treatment

Introduction

1. Type 2 diabetes mellitus:
T2DM (Type 2 Diabetes Mellitus), a metabolic condition, is caused by decreased insulin secretion and/or insulin resistance. Due to its increasing prevalence and related complications, it is becoming a serious public health issue.

Global Prevalence: T2DM has reached epidemic proportions globally, posing substantial challenges to healthcare systems worldwide. According to recent data from 2022-2023, the global prevalence of T2DM continues to increase. According to the International Diabetes Federation (IDF), T2DM accounts for about 90% to 95% of cases of diabetes and affects 463 million persons globally between the ages of 20 and 79. This indicates a substantial increase over earlier projections and emphasises the urgent requirement for efficient preventative and management solutions (1, 2).

Prevalence in Qatar: Qatar, a rapidly developing country in the Arabian Gulf region, has witnessed a dramatic rise in T2DM prevalence over the past years. Qatar's high socioeconomic status, sedentary lifestyles, and changing dietary habits might have contributed to the increased prevalence of T2DM. Recent data from 2022-2023 indicates that T2DM remains a pressing health concern in Qatar (3).

According to the Qatar National Diabetes Registry (QNDR), the diabetes prevalence in Qatar was estimated to be 16.7% among persons aged 20-79. Furthermore, most diabetes cases in Qatar were attributed to T2DM. The QNDR also highlights the increased risk of diabetes among Qatari nationals compared to expatriate residents, emphasizing the need for targeted interventions within the local population (4).

T2DM represents a global health challenge, with its prevalence continuing to rise worldwide, including in Qatar. The alarming rates of T2DM in Qatar require immediate action from healthcare policymakers, public health professionals, and researchers to implement comprehensive prevention and management strategies. Given the significant burden T2DM imposes on individuals, families, and healthcare systems, it is crucial to prioritize early detection, lifestyle interventions, and access to quality healthcare services to mitigate the impact of this chronic disease (5). Future research must focus on monitoring and evaluating the effectiveness of interventions to reduce T2DM prevalence and associated complications in both global and Qatar-specific contexts.

2. Recent Advances in the Management of Type 2 Diabetes Mellitus:
Significant improvements in T2DM management have been made over time, with an emphasis on glycaemic control, avoiding complications, and raising the general quality of life for those who have the condition. Precision medicine is now possible in managing T2DM due to recent developments in genomics and molecular biology. The identification of genetic variants associated with T2DM susceptibility and treatment response has enabled personalized approaches. Tailoring treatment plans based on an individual's genetic profile, metabolic characteristics, and lifestyle factors allows for more effective and targeted interventions (6).

There are now more choices for treating T2DM because of the emergence of novel types of glucose-lowering drugs. GLP-1 RA (Glucagon-like peptide-1 receptor agonist) and SGLT-2 (sodium-glucose cotransporter-2) inhibitors have demonstrated exceptional effectiveness in improving glycemic management and lowering cardiovascular and renal consequences. These substances not only lower blood glucose levels but also provide other advantages like enhanced cardiovascular outcomes, weight loss, and lowered blood pressure (7).

The integration of artificial intelligence (AI) and digital health technologies has the potential to revolutionize T2DM management (8). AI-based algorithms can analyse large datasets, including electronic health records and wearable device data, to generate personalized treatment recommendations and predict individual responses to therapies (9). Mobile applications and wearable devices provide facilities for monitoring the levels of glucose in the blood real-time. They also encourage increased physical activity, and to change dietary patterns, empowering patients to actively participate in self-management and enabling healthcare providers to deliver personalized care (10).

For obese people with T2DM, bariatric surgery can be a successful therapy option. Recent research has demonstrated that sleeve gastrectomy and the Roux-en-Y surgical procedures not only cause significant weight reduction but also create significant and long-lasting improvements in glycaemic control and diabetes remission (11). Bariatric surgery should be considered for carefully chosen T2DM patients who meet certain requirements (12).

However, more investigations are required to confirm the efficacy, safety, and affordability of these therapies. Accepting these developments in clinical practise has the potential to revolutionise T2DM management, resulting in improved outcomes and a higher quality and better life for people with this condition.

3. Metformin in the Management of Type 2 Diabetes Mellitus:
Metformin is an oral drug that is widely prescribed and is essential in the treatment of T2DM. Metformin has several advantages as a first-line medication, including its ability to decrease blood sugar, good safety profile, and potential cardiovascular advantages. The purpose of this summary is to clarify the mechanism of action, ideal dosage, and most recent consensus treatment recommendations for metformin monotherapy in T2DM (6).

Modalities of action: Multiple pathways are used by metformin to produce its therapeutic benefits. Gluconeogenesis and glycogenolysis are mostly inhibited,

which lowers hepatic glucose synthesis. Metformin also improves skeletal muscle glucose absorption and utilisation, which increases peripheral insulin sensitivity. Additionally, it prevents the absorption of intestinal glucose and, albeit little, encourages weight loss. These combined efforts help people with T2DM have better glycemic control (7).

Optimal Dosage: Based on the characteristics and tolerance of the patient, the dosage of metformin should be adjusted. Initially, 500 mg or 850 mg should be taken orally once or twice daily with meals. Up to a daily dose of 2,000–2,550 mg, the dose can be gradually increased every 1-2 weeks based on glycemic response and tolerability. It is possible to use once-daily dosage with extended-release formulations, which may increase gastrointestinal tolerability (7).

Latest consensus management recommendations: Guidelines for the management and treatment of hyperglycemia in T2DM were developed jointly by the ADA (American Diabetes Association) and the EASD (European Association for the Study of Diabetes). The 2022 ADA/EASD guidelines state that metformin monotherapy, excluding contraindications or intolerance, continues to be the front-line pharmaceutical treatment for most people with T2DM. The guidelines recommend initiating metformin at the time of diagnosis alongside lifestyle modifications and maintaining treatment unless contraindications or intolerance develop (13).

Furthermore, the guidelines emphasize the importance of individualizing treatment targets and incorporating shared decision-making with patients. They recommend considering metformin continuation even when additional glucose-lowering medications are required to achieve glycaemic control. In certain cases, such as when metformin is contraindicated or not tolerated, alternative therapies may be initiated as the initial pharmacological treatment.

4. Adverse effects of metformin:
Metformin is frequently used for the management and treatment of T2DM, and the drug has a generally positive safety profile and is well tolerated. However, metformin has certain drawbacks as well.

Effects on the Gastrointestinal Tract: The gastrointestinal tract is where metformin side effects are most frequently observed. Diarrhoea, nausea, vomiting, and abdominal discomfort are a few of them. According to clinical research, gastrointestinal side effects might occur somewhere between 5% and 30% of the time (14, 15). However, most of these side effects are minor and brief and go away on their own or after a dose modification.

Vitamin B12 Deficiency: Metformin use has been linked to a possible risk of Vit. B12 insufficiency. Metformin therapy for longer duration has been shown in investigations to potentially lower Vit. B12 and increase the prevalence of Vit. B12 insufficiency (15, 16). It is advised to regularly check vitamin B12 levels and think about prescribing supplements, most importantly in people who are at the risk of insufficiency, such as those in the geriatric age or those who have malabsorption problems (17).

Lactic Acidosis: This can be a rare but dangerous side effect while using metformin. It is important to remember that lactic acidosis associated with metformin-usage is extremely uncommon, with just 3 occurrences being documented per 100,000 patient years (18). People who have comorbidities or illnesses that predispose them to metabolic abnormalities, renal impairment, or acute sickness are more likely to develop lactic acidosis. When receiving the proper dosage, people with normal renal function run a very minimal risk of developing lactic acidosis (19).

Other Adverse Effects: Less commonly reported adverse effects of metformin include metallic taste, rash, reduced absorption of vitamin B12, and, rarely, hepatotoxicity. However, the occurrence of these adverse effects is infrequent, and the overall safety profile of metformin is favourable.

Overall, the benefits of metformin in achieving glycaemic control and in reducing the complications associated with T2DM far outweigh the potential adverse effects. The safety profile and metformin effectiveness in people with T2DM can be enhanced by regular monitoring, specific patient assessment, and appropriate dose adjustments.

5. Vitamin B12 – Biological functions and ADME:
Cobalamin, sometimes referred to as vitamin B-12, is important for several vital biological processes that occur in the human body. The production of DNA, RNA, and proteins, which are necessary for healthy cell division and growth, depends on Vit. B12. Furthermore, it also contributes in the development and maintenance of myelin sheaths, which safeguard nerve cells and support healthy brain activity. Additionally, it is involved in red blood cell formation, fatty acid metabolism, and amino acid metabolism (20).

The small intestine is where vitamin B-12 is largely absorbed. For effective absorption, an intrinsic factor released by the parietal cells in the gastric mucosa is needed. After being absorbed, Vit. B12 is carried to different tissues and organs via transcobalamin II, a transport protein that it interacts with. Vitamin B-12 is metabolised and transformed within the tissues into its active forms, methylcobalamin and adenosylcobalamin. A big part of storing vitamin B-12 for later use is the liver. Extra vitamin B-12 is removed through faeces and bile (20).

Role of Vitamin B12 in diabetic patients: In accordance with several studies, people living with diabetes have an increased risk of Vit. B12 insufficiency, than people without the disease (21, 22). Although the underlying causes of this connection are not entirely understood, they may include things like changed absorption, compromised transport proteins, and usage of the diabetes drug metformin. Diabetes patients with Vit. B12 deficiencies have an

increased probability of developing diabetic neuropathy, retinopathy, and cardiovascular problems.

Vitamin B12 insufficiency has been linked in clinical research to diabetic neuropathy, a common consequence of diabetes characterised by nerve damage. Due to the vitamin's significance in the production of myelin and the operation of the nervous system, Vit. B12 deficiency may contribute to the onset and progression of neuropathy. In a study involving diabetic patients with peripheral neuropathy, vitamin B12 supplementation improved nerve conduction velocity and neuropathic symptoms (21).

Diabetes-related vitamin B12 insufficiency has also been associated with increased risk of cardiovascular problems. In those with T2DM, Sato Y et al. showed that Vit. B12 treatment decreased cardiovascular risk factors such as homocysteine levels (22).

To effectively control diabetes and its consequences, Vit. B12 is essential. The incidence of Vit. B12 insufficiency in diabetic patients and its possible impact on diabetic neuropathy and cardiovascular consequences have been noted in clinical research. The consequences of Vit. B12 supplementation on neuropathic symptoms and risk markers of the cardiovascular system, have been encouraging. To better understand the mechanisms driving vitamin B12 insufficiency in diabetes and to identify the best preventative and care practises, more study is required.

Clinicians can optimise diabetes management and enhance patient outcomes by understanding of the importance of Vit. B12 in diabetes and its potential implications. Future research should concentrate on extensive clinical trials to determine the best vitamin B12 dosage, duration, and timing for diabetic patients and assess its long-term benefits on problems associated with diabetes.

6. General causes of Vitamin B12 deficiency in type 2 diabetes mellitus:

In comparison to the general population, Vit. B12 deficiency appears to be more prevalent in those with T2DM. The use of metformin, changed stomach physiology, and poor dietary practises are some of the many factors that contribute to vitamin B12 insufficiency in T2DM.

Utilisation of metformin: Vitamin B12 insufficiency has been linked to metformin, the first-line treatment for T2DM. Various research has found that taking metformin will decrease the absorption of Vit. B12 in the gut and hinders B12 transport through the intestinal epithelium. Long-term metformin medication, particularly at high doses, may cause a gradual drop in vitamin B12 levels (23).

Altered gastric physiology: Individuals with T2DM often exhibit changes in gastric physiology, such as delayed gastric emptying and reduced gastric acid secretion. These alterations can disrupt the normal release of vitamin B12 from food sources and impair its subsequent absorption. Additionally, reduced production of intrinsic factor, a protein necessary for B12 absorption in the ileum, can further contribute to vitamin B12 deficiency in T2DM (24).
Dietary factors: Poor dietary intake of vitamin B12-rich foods is another common cause of deficiency in both T2DM and the general population. The use of animal derived B12 sources, such as dairy products, fish, and meat, may be restricted for T2DM patients due to dietary limitations or food preferences (25).

To optimise their management and enhance clinical results, physicians should be made aware of these potential causes, and they may consider routine screening and Vit. B12 supplementation in T2DM patients at risk of deficiency.

7. Metformin induced vitamin B12 deficiency in T2DM:

Metformin, which is frequently recommended for T2DM (type 2 diabetic mellitus), was found to be associated with deficiency of Vit. B12. Vitamin B12 cannot be absorbed properly in the gut and cannot pass the intestinal epithelium when taken with metformin. Long-term metformin use, particularly at high doses, can cause a progressive drop in vitamin B12 levels. Clinically, vitamin B12 insufficiency can cause neurological and haematological problems, deteriorating the metabolic disorders already present in T2DM. For addressing this potential unwanted side effect of metformin, regular monitoring of Vit. B12 levels and consideration of supplemental solutions are essential (22).

Pathophysiology of Metformin-induced Vitamin B12 deficiency in T2DM:

New research has shed light on the pathophysiology of Vit. B12 insufficiency because of metformin in people with T2DM (type 2 diabetic mellitus). Ting et al. (25) in their research studied the fundamental mechanisms. They discovered metformin usage was linked to changes in gastrointestinal physiology, such as a reduction in stomach acid output and a delay in gastric emptying. These modifications may hinder Vit. B12 absorption and decrease its availability from dietary protein sources. Additionally, Ting et al. (25) recognised the influence of metformin on Vit. B12's intestinal transit. They found that metformin inhibited cubilin expression, which is a protein involved in the absorption of the intrinsic factor-Vit. B12 combination into enterocytes from the gut lumen. This decrease in cubilin expression can prevent vitamin B12 from being absorbed, which might result in a shortage.
In T2DM patients, Almatrafi et al. discovered a link between Vit. B12 levels and metformin usage. They discovered a highly significant negative connection, indicating that longer-term metformin medication was linked to decreased levels of Vit. B12. This finding backs up the idea that prolonged metformin usage can gradually worsen Vit. B12 insufficiency (26).

Impaired absorption: Metformin has been found to interfere with the gastrointestinal tract's ability to absorb vitamin B12, leading to impaired absorption. It is believed to disrupt the binding of Vit. B12 to the intrinsic factor in the stomach necessary for its absorption. Metformin's

interference with this binding process can result in a reduced availability of vitamin B12 for absorption, leading to deficiency (25).

Altered Intestinal Transport: The movement of vitamin B12 across the intestinal epithelium may also be impaired by metformin. According to studies, metformin inhibits the production and operations of proteins that are involved in the transportation of Vit. B12, such as cubilin and transcobalamin receptors. The intrinsic factor-Vit. B12 combination is taken up by cubilin from the gut lumen into enterocytes, and transcobalamin receptors help the vitamin B12 cross the enterocytes' basolateral membrane and enter the bloodstream. Metformin can affect these transport proteins' ability to function properly or downregulate them, which prevents the absorption and enterohepatic circulation of Vit. B12 and lead to insufficiency (23).

Gastric Physiology: Altered gastric physiology observed in T2DM, such as delayed gastric emptying and reduced gastric acid secretion, can also play a role in metformin-induced vitamin B12 deficiency. Delayed gastric emptying may prolong the contact time between metformin and the stomach, potentially increasing its interaction with the intrinsic factor and affecting its binding to Vit. B12. The release of Vit. B12 from food sources containing protein can be hampered by decreased stomach acid output, which is frequently seen in T2DM patients. Additionally, T2DM may result in decreased production of intrinsic factor in the gastric mucosa, further impairing Vit. B12 absorption (23).

Complex pathophysiological processes, such as reduced intestinal absorption, changed intestinal transport, and disturbed gastric physiology, contribute to metformin-induced Vit. B12 insufficiency in T2DM (Figure 1). To reduce the risk of consequences caused by Vit. B12 insufficiency, physicians should be made aware of this link, and consider routine monitoring of Vit. B12 levels and implement appropriate supplementing measures.

8. Metformin-induced Vitamin B12 deficiency – latest clinical evidence:

Metformin usage is associated with Vit. B12 deficit, according to many recent studies. According to Bell's 2010 research, 30% of individuals taking metformin on a chronic basis had vitamin B12 deficiencies, which might manifest as peripheral neuropathy (21). A favourable association of metformin use with Vit. B12 insufficiency was discovered by Khattab 2022 after conducting a systematic evaluation of 19 bodies of research, with higher metformin doses being closely linked to lower vitamin B12 levels (24). In individuals on metformin, Kang, 2014, discovered that sulfonylurea usage was a substantial independent risk factor for B12 insufficiency (27). The duration and dose of treatment with metformin were clinically significant risk factors for developing Vit. B12 deficiency, according to Ting's nested case-control study from 2006 (25). To avoid consequences from Vit. B12 deficiency, regular monitoring of Vit. B12 levels is advised during prolonged metformin administration.

Western Studies:

There is a wide variation in the incidence of Vit. B12 deficiency among metformin users that depends on the length and dosage of metformin therapy, and the population characteristics. As per recent meta-analysis, patients who used metformin had a prevalence of Vit. B12 deficiency that was 19.6% higher than that of non-users (9.5%) (28). However, studies from various nations and eras were included in this study, which could have had varied dietary customs and screening procedures.

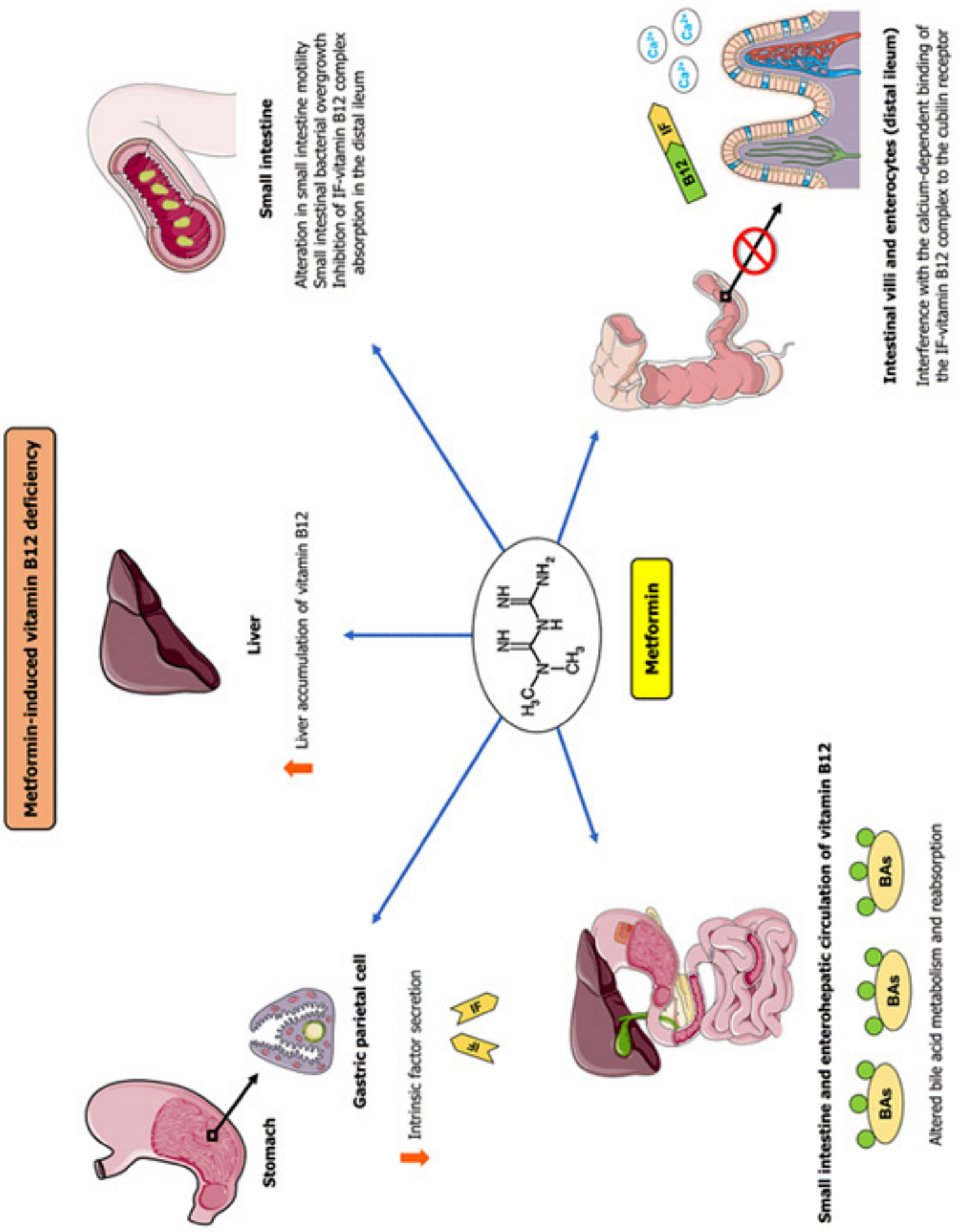
In a retrospective cohort analysis, Lee AK et al. (29) examined data from 14,623 type 2 diabetes patients who were recruited in a major Californian healthcare system between 2011 and 2017. According to the study, metformin users had a 6.3% prevalence of Vit. B12 insufficiency (200 pg/mL), while it was 2.4% in non-users. With higher dosages and longer treatment periods, the prevalence rose. Only 37% of metformin users checked their Vit. B12 levels during the study period, which points to a lower prevalence of screening for Vit. B12 deficiency.

Data from 1,621 T2DM patients who were a part of NHANES (National Health and Nutrition Examination Survey) between 2011 and 2016 were analysed by Kim JY et al. (30). According to this study, metformin users had Vit. B12 deficiency (200 pg/mL) higher than the non-users (5.8% vs. 2.4%). The frequency was higher in non-Hispanic females, older people (>60 years), , and those who had lower income and educational levels. Only 22% of metformin users checked their Vit. B12 levels in the previous year, according to the study's findings, which points to a lack of awareness of, and screening for, vitamin B12 deficiency.

Data from 4,368 type 2 diabetes patients who received care at a Texas Veterans Affairs Medical Centre between 2013 and 2018 were examined by Martin D et al. (31). The prevalence of Vit. B12 deficiency (200 pg/mL) was 7.4% among those using metformin, and 4.8% in non-users, according to the study. Higher metformin therapy doses led to an increase in prevalence, but no longer treatment times. Only 16% of metformin users had their vitamin B12 levels checked during the study period, according to the study's findings, indicating a low rate of vitamin B12 deficiency screening.

These three investigations demonstrate that metformin-induced vitamin B12 insufficiency is a prevalent and underreported condition among T2DM individuals in the United States. Depending on other characteristics and the dosage of metformin medication, the prevalence ranges from 5.8% to 7.4%. Despite recommendations from the American Diabetes Association and other organisations to frequently check vitamin B12 levels among metformin users, the screening rates for vitamin B12 deficiency are relatively low, ranging from 16% to 37%. This could result in missed opportunities for vitamin B12 deficient early detection and treatment, which can stop or reverse its effects.

Figure 1: Pathophysiology of Metformin induced Vitamin B12 deficiency in T2DM.



Note: Illustration obtained from Infante M et al. (23)

American individuals with type 2 diabetes frequently experience underdiagnosed metformin-induced vitamin B12 insufficiency. For these individuals' health and quality of life, it may have detrimental effects. Therefore, it is crucial to raise awareness of this issue, conduct more screenings, and offer suitable treatment and preventative measures.

Numerous studies have demonstrated that prolonged metformin treatment causes malabsorption of Vit. B12, with a drop in blood Vit. B12 content from 30% to 14%. It was discovered that patients who used higher dosages of metformin for longer periods of time had an increased chance of acquiring Vit. B12 insufficiency. Early identification of Vit. B12 deficiency in these patients is crucial to prevent further neurological and haematological symptoms (34).

In another cross-sectional study done in Spain, 312 people with T2DM who had used metformin for a period of six months were included. According to the study, 29.5% of the patients had borderline Vit. B12 deficiency (200-300 pg/mL) and 17.6% of the patients had severe deficiency (200 pg/mL). Patients who used greater metformin dosages (> 2000 mg/day) and for prolonged periods of time (> 5 years) had increased rates of vitamin B12 insufficiency. Additionally, the study discovered that lower levels of methylmalonic acid and homocysteine, indicators of poor Vit. B12 metabolism, were linked to vitamin B12 insufficiency (35).

There were 121 type 2 diabetics in an Italian prospective cohort research who had been on metformin for a period of one year. According to the study, 32.2% of the patients had borderline shortage of vitamin B12 (221–300 pmol/L), and 11.6% of the patients had severe deficiency (221 pmol/L). Patients who took metformin at larger doses (> 1500 mg/day) and for longer periods of time (> 10 years) had increased rates of vitamin B12 insufficiency. Additionally, the study discovered that low levels of haemoglobin and haematocrit, two markers of anaemia, were linked to Vit. B12 deficiency (36).

About 390 study participants with T2DM receiving metformin medication for a period of 4 months were enrolled in a randomised controlled trial from the Netherlands. In this experiment, blood vitamin B12 levels and clinical outcomes were examined after 52 weeks of oral vitamin B12 supplementation (850 mcg/day) against placebo. According to the research, vitamin B12 supplements significantly raised serum Vit. B12 levels by 55% as compared with placebo and stopped future Vit. B12 level reduction in individuals receiving metformin treatment. However, compared to placebo, vitamin B12 supplementation had no positive impact on homocysteine, haemoglobin, or quality of life scores (37).

These studies demonstrate that metformin medication in European patients with T2DM frequently results in Vit. B12 insufficiency, which may be a significant side effect. Additionally, they contend that lengthier use of metformin at higher doses and durations increases the chance of developing a vitamin B12 deficiency. These studies do, however, have several drawbacks, including small sample sizes, heterogeneity in the definition and measurement of Vit. B12 deficiency, a lack of confounding factor adjustment, and brief follow-up times.

Therefore, more investigation is required to establish the most effective screening frequency, cut-off values, and modes and dosages of Vit. B12 supplementation for individuals receiving metformin therapy. Furthermore, it's critical to examine the effects of Vit. B12 insufficiency and supplementation in metformin-treated patients, including anaemia, neuropathy, cognitive function, and cardiovascular risk.

Asian studies:

The association between metformin usage with Vit. B12 deficiency in various groups, including Asian individuals with T2DM has been examined in a number of systematic reviews and meta-analyses.

In a meta-analysis conducted by Khattab et al. (24), 19 studies that examined the impact of metformin on Vit. B12 levels in type 2 diabetes mellitus patients without Vit. B12 supplementation, were included (15 observational studies and 4 randomised controlled trials). The pooled odds ratio between metformin usage and Vit. B12 deficiency was found to be 2.23 (95% CI: 1.77 to 2.80), indicating a positive association between the two. Additionally, they noted that treatment duration was not highly correlated with Vit. B12 levels, although higher metformin doses were. The authors advised taking therapeutic Vit. B12 pills or injections together with a diet high in Vit. B12 to minimise consequences from Vit. B12 insufficiency. They also advised routine monitoring of Vit. B12 levels throughout long-term metformin use.

In another systematic review done by Infante et al. (23), 16 research (seven randomised controlled trials and nine observational) studies that examined the relationship of metformin medication with Vit. B12 deficiency in people with prediabetes or T2DM were included. In comparison to placebo or other antidiabetic medications, the authors discovered that treatment with metformin was related with a significant decrease in serum Vit. B12 levels, with a mean difference of -52.4 pmol/L (95% CI: -64.5 to -40.3). They added that elevated homocysteine and decreased folate levels were associated with metformin-induced vitamin B12 insufficiency, which may have detrimental effects on cardiovascular health. The authors recommended that people with prediabetes or T2DM who are using metformin for treatment should be evaluated for Vit. B12 deficiency, particularly if they had risk factors including advanced age, a vegetarian diet, or pernicious anaemia.

About 11 research (6 observational studies and 5 randomised controlled trials) that examined the impact of metformin on serum Vit. B12 levels in patients with prediabetes and T2DM in China were included in a meta-analysis done by Li et al. (38). When compared to those who did not take metformin, the researchers discovered a substantial drop in serum vitamin B12 levels, with a

mean difference of -55.6 pmol/L (95% CI: -74.9 to -36.4). They also noticed a link between lower serum levels of Vit. B12 and larger doses and longer periods of metformin treatment. The authors advised continuous monitoring of serum Vit. B12 levels in type 2 diabetes mellitus patients using metformin and, if necessary, Vit. B12 supplementation.

Studies from the Middle East region:
In several regions of the world, investigations have investigated the incidence of Vit. B12 insufficiency in diabetes patients and how it affects their response to metformin therapy. Additionally, metformin use has been linked to a 9%–52% drop in serum vitamin B12 levels, according to randomised control trials and cross-sectional investigations (39). However, there is a dearth of information on this subject throughout the Middle East, particularly in Qatar.

As shown in Table 1, the prevalence of Vit. B12 deficiency was found to be higher in diabetic patients receiving metformin therapy than in those not receiving it, ranging from 12.5% to 30.7% in individuals taking metformin and around 10% in individuals not using metformin, according to all five investigations. Metformin usage is found to have a moderate to high risk of Vit. B12 deficiency, according to odds ratios that ranged from 2.2 to 2.7.

The disparate approaches of the research and thresholds for identifying Vit. B12 deficiency, may make it difficult to interpret the findings. However, most of the research used a cut off value of < 150 pg/mL, which is consistent with the World Health Organization criteria for vitamin B12 deficiency. The studies also used different doses of metformin, but the mean doses were similar and within the recommended range of 1.5 to 2 g/day for T2DM patients. The length of metformin medication, another significant factor that may affect the likelihood of Vit. B12 deficiency, was not reported in the trials.

The clinical effects of Vit. B12 insufficiency in diabetic patients on metformin therapy, such as anaemia, neuropathy, or cognitive impairment, were not evaluated in the research. However, other studies found that individuals with Vit. B12 deficiency also had higher homocysteine and lower levels of haemoglobin and hematocrit, which may influence their hematopoietic and cardiovascular health.

9. Diagnosis of Vitamin B12 deficiency in T2DM:
Due to the potential consequences linked to a deficiency, the diagnosis of Vit. B12 deficiency in T2DM requires rigorous investigation. In the early assessment of Vit. B12 deficiency, clinical assessment is extremely important. It is important to look for signs and symptoms of deficiency in T2DM patients, such as fatigue, weakness, neuropathy, glossitis, and macrocytic anaemia. However, these clinical manifestations are non-specific and can overlap with other conditions, making a definitive diagnosis based on symptoms alone challenging.

Laboratory Testing:
Serum Vit. B12 Levels: The diagnosis of Vit. B12 deficiency is frequently made using serum vitamin B12 levels. The common reference range lies in the 200–900 pg/mL range. The ideal limit for identifying insufficiency in T2DM patients is still being debated, though. According to certain studies, concentrations below 300 pg/mL or even 350 pg/mL should be taken as a sign that this population is deficient (45).

Serum Folate and Homocysteine Levels: Since vitamin B12 deficiency can lead to elevated homocysteine and decreased serum folate levels, measuring these markers can provide supportive evidence. Elevated homocysteine levels (>15 µmol/L) and decreased serum folate levels can indicate impaired vitamin B12 metabolism (46).

Holotranscobalamin (holoTC): A portion of vitamin B12 that is biologically active and involved in cellular absorption is called holoTC. Assessing holoTC levels might offer a more precise evaluation of tissue B12 status. Even in the face of adequate total B12 levels, some studies contend that low holoTC levels (35 pmol/L) are a sign of functional vitamin B12 deficiency (47).

Methylmalonic Acid (MMA) and Homocysteine: MMA is a metabolite that accumulates in vitamin B12 deficiency. Elevated MMA levels (>0.37 µmol/L) can indicate impaired B12 metabolism. Combined measurement of MMA and homocysteine levels can improve diagnostic accuracy (48).

Table 1: Studies on metformin-induced vitamin B12 deficiency in the Middle East region

Study	Country	Sample size	Vit. B12 cutoff	Prevalence of Vit. B12 deficiency
Yousef Khan F et al. (40)	Qatar	3124	< 145 pg/ mL	30.7%
Alharbi TJ et al. (41)	Saudi Arabia	412	< 132.8 pg/ mL	Metformin group -9.4% Non-metformin group – 2.2%
Mohammed B et al. (42)	Saudi Arabia	347	< 145 pg/ mL	10.4%
Al Saeed RR et al. (43)	Saudi Arabia	307	< 150 pg/ mL	Deficiency -3.6% Borderline – 66.1%
Alshammari et al. (44)	Saudi Arabia	363	< 150 pg/ mL	12.5%

Intrinsic Factor Antibody (IFA) Testing: IFA testing is useful in detecting pernicious anaemia, an autoimmune condition found in vitamin B12 deficiencies. The presence of IFA is indicative of autoimmune-mediated destruction of intrinsic factors, impairing B12 absorption. However, it is important to note that IFA testing has limitations, including false-positive results and a lack of sensitivity in some cases (49).

The diagnosis and management of Vit. B12 deficiency in T2DM requires a comprehensive approach, considering clinical assessment and laboratory testing. Serum vitamin B12 levels, supplemented by measurements of folate, homocysteine, holoTC, MMA, and IFA, can aid in diagnosing deficiency and evaluating the functional status of vitamin B12. Additionally, considering the individual patient's clinical presentation, medical history, and response to supplementation is crucial for accurate diagnosis and appropriate management.

10. Management of Vitamin B12 deficiency in T2DM: To avoid potential problems and enhance patient outcomes, Vit. B12 deficiency in T2DM must be properly managed. It's critical to get an early and precise diagnosis of Vit. B12 insufficiency in T2DM. According to the most recent recommendations, serum levels of Vit. B12 should be measured along with other indicators such holotranscobalamin, methylmalonic acid (MMA), and homocysteine (50). In T2DM patients taking metformin or who have clinical signs of a vitamin B12 deficit, routine monitoring of Vit. B12 status is advised.

Oral Vit. B12 Supplementation: Oral Vit. B12 supplementation is a convenient and effective option for patients with T2DM. It is recommended to use high-dose oral B12 supplements (1,000 to 2,000 µg/day) due to the impaired absorption associated with T2DM. This high-dose approach compensates for the reduced absorption efficiency and ensures adequate vitamin B12 levels (51).
Intramuscular Vitamin B12 Injection: In cases of severe deficiency or malabsorption, intramuscular injection of vitamin B12 is the preferred route of administration. The initial treatment typically involves a series of injections (1,000 µg/day) for several days or weeks, followed by maintenance injections (1,000 µg/month) (52).

Subcutaneous or Intranasal Vitamin B12: Emerging evidence suggests that subcutaneous or intranasal administration of vitamin B12 may be a viable alternative to intramuscular injection. These approaches are more practical and might be preferred by patients. To determine their effectiveness and safety in T2DM, however, more research is required (51).

Patient education: Treatment of vitamin B12 insufficiency in T2DM includes patient education as a key component. Healthcare professionals should stress the value of consistent observation, adherence to supplementation plans, and knowledge of dietary sources of vitamin B12. It can also assist to promote a balanced diet that includes foods high in vitamin B12, such as dairy products, eggs, poultry, meat, and fish (52).

Interdisciplinary Collaboration: For the best therapy of vitamin B12 deficiency in T2DM, collaboration amongst healthcare professionals, including endocrinologists, primary care doctors, nutritionists, and pharmacists, is crucial. Comprehensive evaluation, appropriate supplements, routine monitoring, and continuous patient assistance are all made possible by an interdisciplinary approach (52).

Accurate diagnosis, sensible supplementation plans, patient education, and interdisciplinary cooperation all go into managing vitamin B12 deficiency in T2DM. Consensus and recommendations urge routine vitamin B12 level monitoring, high-dose oral supplementation, intramuscular injections for severe deficiency, and thought of alternate administration methods. Long-term management requires patient education and lifestyle changes. Healthcare providers can optimise the treatment of T2DM patients with vitamin B12 insufficiency and enhance their general health outcomes by putting these recommendations into practise.

Conclusion

One noticeable and potentially harmful adverse effect of metformin therapy in persons with T2DM is metformin-induced Vit. B12 deficiency. It may result in several clinical problems, including anaemia, neuropathy, memory loss, and cardiovascular disease. Therefore, to avoid the detrimental effects of this illness, regular screening and appropriate management are crucial. Measurement of serum Vit. B12 levels and other indicators, supplementation with oral or parenteral Vit. B12, and dietary changes are all part of the screening and management techniques for metformin-induced Vit. B12 insufficiency.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: International Diabetes Federation. (2019). Accessed: June 28, 2023: https://www.diabetesatlas.org.
2. American Diabetes Association; 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2020. Diabetes Care 1 January 2020; 43 (Supplement_1): S14–S31. 10.2337/dc20-S002.
3. Bener A, Zirie M, Janahi IM, et al. Prevalence of diagnosed and undiagnosed diabetes mellitus and its risk factors in a population-based study of Qatar. Diabetes Res Clin Pract. 2009;84(1):99-106. 10.1016/j.diabres.2009.02.003.
4. Alhyas L, McKay A, Balasanthiran A, et al. Prevalences of overweight, obesity, hyperglycaemia, hypertension and dyslipidaemia in the Gulf: systematic review. JRSM Short Rep. 2011 Jul;2(7):55. 10.1258/shorts.2011.011019.
5. Al-Kaabi J, Al-Maskari F, Saadi H, et al. Assessment of dietary practice among diabetic patients in the United arab emirates. Rev Diabet Stud. 2008 Summer;5(2):110-5. 10.1900/RDS.2008.5.110.

6. American Diabetes Association. Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45 (Supplement 1): S1-S232. 10.2337/dc22-SINT
7. American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45 (Supplement 1):S125-S143. 10.2337/dc22-S009.
8. Bonoto BC, de Araújo VE, Godói IP, et al. Efficacy of mobile apps to support the care of patients with diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. JMIR Mhealth Uhealth. 2017;5(3):e4. 10.2196/mhealth.6309.
9. Kitsiou S, Paré G, Jaana M, et al. Effectiveness of mHealth interventions for patients with diabetes: an overview of systematic reviews. PLoS One. 2017;12(3): e0173160. 10.1371/journal.pone.0173160.
10. Wang J, Cai C, Padhye N, et al. A behavioral lifestyle intervention enhanced with multiple-behavior self-monitoring using mobile and connected tools for underserved individuals with type 2 diabetes and comorbid overweight or obesity: pilot comparative effectiveness trial. JMIR Mhealth Uhealth. 2018;6(4):e92. 10.2196/ mhealth.4478.
11. Schauer PR, Bhatt DL, Kirwan JP. Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes. N Engl J Med. 2017;376(7):641-651. 10.1056/NEJMoa1600869.
12. Rubino F, Nathan DM, Eckel RH. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care. 2016;39(6):861-877. 10.2337/dc16-0236.
13. Buse JB, Wexler DJ, Tsapas A, et al. 2022 update to: Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022;45(1):4-36. 10.2337/dci19-0066.
14. Bailey CJ, Turner RC. Metformin. N Engl J Med. 1996;334(9):574-579. 10.1056/NEJM199602293340906.
15. 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. 10.1136/bmj. c2181.
16. Wulffelé MG, Kooy A, Lehert P, et al. Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial. J Intern Med. 2003;254(5):455-463. 10.1046/j.1365-2796.2003.01213.x.
17. Pflipsen MC, Oh RC, Saguil A, et al. The prevalence of vitamin B(12) deficiency in patients with type 2 diabetes: a cross-sectional study. J Am Board Fam Med. 2009;22(5):528-534. 10.3122/jabfm.2009.05.090044.
18. Misbin RI. The phantom of lactic acidosis due to metformin in patients with diabetes. Diabetes Care. 2004 Jul;27(7):1791-3. 10.2337/diacare.27.7.1791.
19. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients: prognostic value of arterial lactate levels and plasma metformin concentrations. Drug Saf. 1999 Mar;20(3):377-84. 10.2165/00002018-199920040-00006.
20. Reynolds E. Vitamin B12, folic acid, and the nervous system. Lancet Neurol. 2006;5(11):949-60. 10.1016/S1474-4422(06)70598-1.
21. Bell DS. Metformin-induced vitamin B12 deficiency presenting as a peripheral neuropathy. South Med J. 2010 Mar;103(3):265-7. 10.1097/SMJ.0b013e3181ce0e4d.
22. Sato Y, Ouchi K, Funase Y, et al. Relationship between metformin use, vitamin B12 deficiency, hyperhomocysteinemia and vascular complications in patients with type 2 diabetes. Endocr J. 2013;60(12):1275-80. 10.1507/endocrj.ej13-0332.
23. 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; 12(7): 916-931. 10.4239/wjd.v12.i7.916.
24. Khattab R, Albannawi M, Alhajjmohammed D, et al. Metformin-Induced Vitamin B12 Deficiency among Type 2 Diabetes Mellitus' Patients: A Systematic Review. Curr Diabetes Rev. 2023;19(4):1-10. 10.2174/157339981 8666220418080959.
25. Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM. Risk factors of vitamin B12 deficiency in patients receiving metformin. Arch Intern Med. 2006;166(18):1975-1979. 10.1001/archinte.166.18.1975.
26. Almatrafi SB, Bakr EH, Almatrafi AA, et al. Prevalence of vitamin B12 deficiency and its association with metformin-treated type 2 diabetic patients: A cross sectional study. Human Nutrition & Metabolism, 2022;27, 200138. 10.1016/j.hnm.2022.200138.
27. Kang D, Yun JS, Ko SH, et al. Higher prevalence of metformin-induced vitamin B12 deficiency in sulfonylurea combination compared with insulin combination in patients with type 2 diabetes: a cross-sectional study. PLoS One. 2014 Oct 9;9(10):e109878. 10.1371/journal. pone.0109878.
28. 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. 10.1016/j.diabres.2012.06.001.
29. Lee AK, Lee CJ, Huang ES, et al. Risk of hypoglycemia following intensification of metformin treatment with insulin versus sulfonylurea. CMAJ. 2016;188(4):E98-E106. 10.2337/dc17-0819.
30. Kim J, Ahn CW, Fang S, et al. Association between metformin dose and vitamin B12 deficiency in patients with type 2 diabetes. Medicine (Baltimore). 2019 Nov;98(46): e17918. 10.1097/MD.0000000000017918.
31. Martin D, Thaker J, Shreve M, et al. Assessment of vitamin B12 deficiency and B12 screening trends for patients on metformin: a retrospective cohort case review. BMJ Nutr Prev Health. 2021 Jan 4;4(1):30-35. 10.1136/ bmjnph-2020-000193.
32. American Diabetes Association. Standards of medical care in diabetes-2020 abridged for primary care providers. Clin Diabetes. 2020;38(1):10-38. 10.2337/cd20-as01.
33. Qaseem A, Barry MJ, Humphrey LL, et al. Clinical Guidelines Committee of the American College of Physicians; Fitterman N, Horwitch C, Kansagara D, McLean RM, Wilt TJ. Oral Pharmacologic Treatment of

Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med. 2017 Feb 21;166(4):279-290. 10.7326/M16-1860.
34. Al-Hamdi A, Al-Gahhafi M, Al-Roshdi S, et al. Vitamin B12 Deficiency in Diabetic Patients on Metformin Therapy: A cross-sectional study from Oman. Sultan Qaboos Univ Med J. 2020 Feb;20(1):e90-e94. 10.18295/squmj.2020.20.01.013.
35. Calvo Romero JM, Ramiro Lozano JM. Vitamin B (12) in type 2 diabetic patients treated with metformin. Endocrinol Nutr. 2012 Oct;59(8):487-90. 10.1016/j.endonu.2012.06.005.
36. Sayedali E, Yalin AE, Yalin S. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes. World J Diabetes. 2023 May 15;14(5):585-593. 10.4239/wjd.v14.i5.585.
37. van Wijngaarden JP, Swart KM, Enneman AW, et al. Effect of daily vitamin B-12 and folic acid supplementation on fracture incidence in elderly individuals with an elevated plasma homocysteine concentration: B-PROOF, a randomized controlled trial. Am J Clin Nutr. 2014 Dec;100(6):1578-86. 10.3945/ajcn.114.090043.
38. Yang W, Cai X, Wu H, et al. Associations between metformin use and vitamin B12 levels, anemia, and neuropathy in patients with diabetes: a meta-analysis. J Diabetes. 2019 Sep;11(9):729-743. 10.1111/1753-0407.12900.
39. 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 Nov;42(5):316-327. 10.1016/j.diabet.2016.03.008.
40. Yousef Khan F, Yousif AB, Suliman A, et al. Association of vitamin B12 deficiency with metformin use in patients with type 2 diabetes treated in the largest tertiary care hospital in Qatar. Qatar Med J. 2021 Sep 9;2021(2):39. 10.5339/qmj.2021.39.
41. Alharbi TJ, Tourkmani AM, Abdelhay O, et al. The association between metformin therapy and vitamin B12 deficiency: a cross-sectional study. J Family Community Med. 2019;26(3):206-211. 10.1371/journal.pone.0204420.
42. Mohammad B. Jajah, Amjad A. Althagafi, Norah M, et al. Prevalence of vitamin B12 deficiency in type 2 diabetes patient treated with metformin. World Family Medicine. 2020; 18(1): 54-59. 10.5742MEWFM.2020.
43. Al Saeed RR, Baraja MA. Vitamin B12 deficiency in patients with type 2 diabetes mellitus using metformin and the associated factors in Saudi Arabia. Saudi Med J. 2021 Feb;42(2):161-165. 10.15537/smj.2021.2.25693.
44. Alshammari AN, Iqbal R, Baksh IP. Vitamin B12 deficiency and the knowledge and practice of physicians regarding screening for vitamin B12 deficiency among type 2 diabetic patients on metformin in selected hospitals in Riyadh, Saudi Arabia. J. Fam. Med. Prim. Care. 2019;8:2306–2311. 10.4103/jfmpc.jfmpc_416_19.
45. Carmel R. How I treat cobalamin (vitamin B12) deficiency. Blood. 2008 Sep 15;112(6):2214-21. 10.1182/blood-2008-03-040253.
46. Allen LH. Vitamin B-12. Adv Nutr 2012;3:54-55. 10.3945/an.111.001370.
47. Nexo E, Hoffmann-Lücke E. Holotranscobalamin, a marker of vitamin B-12 status: analytical aspects and clinical utility. Am J Clin Nutr. 2011 Jul;94(1):359S-365S. 10.3945/ajcn.111.013458.
48. Langan RC, Goodbred AJ. Vitamin B12 deficiency: Recognition and management. Am Fam Physician 2017;96:384-9. Accessed: June 29, 2023: https://www.aafp.org/pubs/afp/issues/2017/0915/p384.html
49. Mineva EM, Sternberg MR, Zhang M, Aoki Y, Storandt R, Bailey RL, et al. Age-specific reference ranges are needed to interpret serum methylmalonic acid concentrations in the US population. Am J Clin Nutr 2019;110:158-68. 10.1093/ajcn/nqz045.
50. Hannibal L, Lysne V, Bjørke-Monsen A-L, Behringer S, Grünert SC, Spiekerkoetter U, et al. Biomarkers and algorithms for the diagnosis of vitamin B12 deficiency. Front Mol Biosci 2016;3:27. 10.3389/fmolb.2016.00027.
51. Devalia V, Hamilton MS, Molloy AM British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014;166:496–513. 10.1111/bjh.12959.
52. Andrès E, Noel E, Goichot B. Metformin-associated vitamin B12 deficiency. Arch Intern Med. 2002;162:2251–2252. 10.1001/archinte.162.19.2251-a.