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REVIEW ARTICLE

A pandemic within a pandemic: Diabetes, gestational diabetes, and vitamin B12 deficiency in pregnant women during the COVID-19 era

Huseyin Karakaya[1], Meral Ekim[2], Hasan Ekim[3], and Gokhan Dogukan Akarsu[4]*

[1]Department of Gynecology and Obstetrics, Faculty of Medicine, Yozgat Bozok University, Yozgat, Türkiye

[2]Department of Biochemistry, Faculty of Medicine, Yozgat Bozok University, Yozgat, Türkiye

[3]Department of Cardiovascular Surgery, Faculty of Medicine, Yozgat Bozok University, Yozgat, Türkiye

[4]Department of Pharmacy Services, Vocational School of Health Services, Yozgat Bozok University, Yozgat, Türkiye

***Corresponding author:**
Gokhan Dogukan Akarsu
(gokhan_dogukan_akarsu@hotmail.com)

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic has significantly worsened health outcomes in pregnant women, a population already vulnerable due to physiological immune suppression and increased insulin resistance. Gestational diabetes mellitus (GDM) and vitamin B12 deficiency further compound these risks, creating a complex and potentially dangerous clinical picture. **Aim:** This review examines the interrelationships between COVID-19, GDM, and vitamin B12 deficiency in pregnancy, and evaluates the clinical implications for maternal and fetal health. **Methods:** A narrative review of the current literature was conducted, focusing on the mechanisms linking severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, GDM, vitamin B12 metabolism, metformin use, and nutritional status during pregnancy. **Results:** SARS-CoV-2 directly damages pancreatic beta cells and triggers hyperinflammation, disrupting glycemic control in pregnant women. Vitamin B12 deficiency elevates homocysteine levels, impairing insulin signaling and promoting thrombosis, thereby increasing risks of GDM, preeclampsia, and adverse fetal neurodevelopmental outcomes. Metformin, widely used in GDM and polycystic ovary syndrome (PCOS) management, further reduces B12 absorption. Pandemic-related disruptions to antenatal care, food access, and psychosocial stress accelerated B12 depletion in this population. The Mediterranean diet offers partial mitigation, though targeted supplementation remains necessary in high-risk individuals. **Conclusion:** Routine B12 screening should be integrated into standard antenatal care, particularly for women with GDM, PCOS, or long-term metformin use. **Relevance for patients:** Pregnant women with GDM or PCOS using metformin are at heightened risk of vitamin B12 deficiency, which can silently harm both mother and baby. Regular B12 monitoring and timely supplementation are simple, safe, and potentially life-changing interventions.

Keywords: COVID-19; Gestational diabetes; Vitamin B12 deficiency; Pregnancy; Metformin; Mediterranean diet; Homocysteine; SARS-CoV-2

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a multisystem disease that can affect multiple organs. The global spread of SARS-CoV-2 resulted in a pandemic with substantial adverse effects, especially among the elderly and diabetic patients.[1,2] At the onset of the pandemic, diabetes mellitus was identified as one of the factors predisposing patients to severe COVID-19, along with advanced age, hypertension, tobacco use, and obesity.[3] Some researchers have also reported that COVID-19 increased the likelihood of being diagnosed with new-onset type 2 diabetes mellitus (T2DM).[1,4] For example, a decrease in the number of insulin-secreting granules in the beta cells of the pancreas was detected after COVID-19 disease [4]. In this review, the term “diabetes” refers to diabetes mellitus.

Diabetes has become one of the main threats to human health in the current century.[5] According to the American Diabetes Association (ADA), diabetes is a complex, chronic metabolic disease that requires ongoing medical care with multifactorial risk reduction strategies beyond glycemic control.[6] During the pandemic, diabetes patients using metformin avoided coming to the hospital to protect themselves from COVID-19, causing many problems. Diabetes management methods have undoubtedly been adversely affected due to the pandemic. The frequency of vitamin B12, vitamin D, and magnesium deficiencies has increased due to restrictions on outdoor activities and diets dominated by processed foods. The deficiencies of these micronutrients also affected diabetic patients more adversely during the pandemic period.

Since vitamin B12 and folic acid have an important role in one-carbon metabolism, deficiency of these vitamins can increase homocysteine levels, resulting in hyperhomocysteinemia, an important risk factor for T2DM.[7] During the COVID-19 pandemic, diabetes-related analyses could not be performed due to diabetes patients’ fear of infection and warnings by health authorities, so control of the disease became difficult and caused patients to experience new complications. Low B12 levels, especially in patients using metformin, also cause B12-related health problems.[8–12]

Therefore, targeting the homocysteine level with vitamin B12 and folate may be a potential strategy to alleviate the adverse consequences.[13] Vitamin B12 deficiency has also been associated with an increased risk of gestational diabetes mellitus (GDM).[14,15]

One of the important problems in the treatment of type 1 diabetes mellitus (T1DM) is pernicious anemia, and therefore the risk of vitamin B12 deficiency is 3 times higher in T1DM patients.[16]

According to a recent study, vitamin B12 supplementation had a positive effect on glycemic control and insulin resistance in T2DM patients.[13] Indeed, glycemic control and insulin resistance improved with vitamin B12 supplementation in these patients.[13] Additionally, vitamin B12 therapy was found to be associated with a reduction in serum triglyceride levels independent of other factors.[17]

It was reported that measures such as long-term lockdown applied due to COVID-19 worsened glucose regulation and increased triglyceride levels in patients with diabetes.[18]

Vitamin B12, taken at adequate levels through a balanced diet, can be effective in reducing the effects of diabetes. When balanced nutrition is mentioned, the first type of diet that comes to mind is the Mediterranean-style diet. The Mediterranean diet, which has antioxidant and anti-inflammatory properties, improves glucose control and reduces cardiovascular risk in patients with diabetes.[19] This review examines the interrelationships among COVID-19, diabete and GDM, vitamin B12 deficiency, metformin use, and nutrition during pregnancy, with emphasis on maternal and fetal implications.

2. SARS-CoV-2 infection and vitamin B12 status: Possible indirect mechanism

The mechanism by which SARS-CoV-2 causes infection in the human body begins with the spike (S) protein on the surface of the virus. The spike protein binds to receptors called angiotensin-converting enzyme 2 (ACE2), which are found on the surface of human cells. ACE2 receptors are particularly abundant in the lung, heart, kidney, and intestinal cells. This binding enables the virus to attach to the cell. Subsequently, an enzyme in the body called furin cleaves the spike protein into two subunits. One of these subunits (S1) binds tightly to ACE2, while the other (S2) facilitates the fusion of the virus with the cell membrane. Another enzyme, transmembrane serine protease 2, also supports this process.[20,21]

Following its attachment to the cell membrane, the virus introduces its genetic material (RNA) into the host cell. This viral RNA utilizes the host cell’s protein synthesis machinery to produce proteins essential for viral replication. Key enzymes, such as the main protease and RNA-dependent RNA polymerase, facilitate this process. The viral genome is then replicated, and new virions are assembled and subsequently released from the host cell, enabling the spread of infection to neighboring cells. While vitamin B12 has no established direct role in inhibiting this replication cycle, its deficiency may indirectly compromise the host’s capacity to mount an effective antiviral response.

Impaired immune cell function, reduced natural killer cell activity, and dysregulated cytokine signaling, all associated with B12 deficiency, may facilitate viral propagation by weakening the cellular immune environment in which replication occurs. Current evidence supports an immunomodulatory rather than a directly antiviral role for vitamin B12, and ongoing research continues to explore the broader contribution of micronutrients to host-virus interactions.[22]

SARS-CoV-2 infection triggers the immune system, leading to inflammation. However, the virus has the ability to evade the immune response by suppressing one of the key defense mechanisms of the immune system, the interferon response. This immune evasion facilitates the spread of the infection and can result in severe damage, particularly in the lungs. In severe cases, this pathological process may progress to multi-organ failure.[23]

The relationship between SARS-CoV-2 infection and vitamin B12 status can be explained indirectly through its effects on the immune system and inflammation processes. Vitamin B12 plays a critical role in the proper functioning of the immune system, DNA synthesis, red blood cell production, and neurological functions. In cases of deficiency, the immune system is weakened, and the capacity to combat infections is reduced. The increased metabolic demand during SARS-CoV-2 infection may lead to a more rapid depletion of B12 levels. Additionally, the virus's binding to ACE2 receptors in intestinal cells can damage the intestinal epithelium, impairing B12 absorption. This intestinal epithelial injury may increase the risk of B12 deficiency, particularly during the course of infection.[24]

Vitamin B12 also plays a crucial role in regulating homocysteine levels. Elevated homocysteine levels can lead to increased inflammation and a higher risk of thrombosis. The intense inflammatory response and thrombotic complications observed in COVID-19 patients may be further exacerbated by B12 deficiency.[25]

Monitoring vitamin B12 levels during SARS-CoV-2 infection and providing supplementation when necessary may enhance the immune system's capacity to combat the infection, mitigate inflammation-induced damage, and support the recovery process in COVID-19 patients.[26,27]

3. Relationship between COVID-19 and diabetes mellitus

In Türkiye, the Ministry of Health has stated that adults over the age of 45 should have regular diabetes tests.[27,28] The restrictions imposed during the pandemic and avoidance of hospital visits by members of the public due to the risk of infection caused people who needed to be diagnosed with diabetes to receive these diagnoses and treatments late. Diabetes is a dangerous disease, and uncontrolled diabetes can be fatal.[29,30] For this reason, patients with undiagnosed diabetes during the COVID-19 pandemic may have been particularly affected by disruptions to healthcare access. Various medications were used or investigated for the treatment of COVID-19.[31–33] However, therapeutic options were often limited in patients with chronic diseases because of comorbidities, contraindications, and potential drug interactions.[34,35] In addition, some studies have reported adverse effects after COVID-19 vaccination in certain individuals and patient groups, although the relevance of these findings to diabetes should be clearly specified.[36–39] The effects of COVID-19 infection and its treatment on glucocorticoid and catecholamine responses remain under discussion.[40–42] Excessive glucocorticoid and catecholamine release during or after COVID-19 may aggravate diabetic complications by worsening insulin resistance and glycemic control.[41,43–46]

Therefore, regular glycemic monitoring should be maintained during and after viral infections, especially in diabetic patients.[47–48]

A study conducted in Türkiye reported that the clinical course of COVID-19 patients with vitamin B12 deficiency showed more severe progression than those without vitamin B12 deficiency.[49] COVID-19-specific symptoms, such as fever, loss of taste/smell, and cough, were found to be more common in patients with vitamin B12 deficiency.[50,51] In addition, inflammation markers were found to be higher in patients with vitamin B12 deficiency.[49,52,53] Therefore, vitamin B12 is likely to have positive effects on prognosis and symptoms in patients with COVID-19.[49,53] Considering the potential diabetogenic effects of SARS-CoV-2, attention should be paid to the presence of new-onset hyperglycemia and diabetes, especially in those receiving corticosteroid therapies.[54–56] Additionally, preliminary studies suggest that diabetes may be associated with long COVID.[57–61]

4. Importance of vitamin B12 in diabetes mellitus

Vitamin B12 deficiency should be managed, especially in diabetic patients. Preventing nutritional deficiencies, identifying high-risk individuals with suboptimal nutritional status, and implementing safe and effective dietary guidelines can help strengthen individuals' ability to fight against COVID-19.[62]

Vitamin B12 deficiency is a common denominator among the elderly and diabetic patients.[63] Vitamin B12 deficiency is increasingly recognized as a potentially modifiable risk factor in the context of COVID-19. While current evidence does not support a direct antiviral effect of vitamin B12 on SARS-CoV-2 replication, its deficiency is associated with impaired immune cell function, reduced natural killer cell activity, and dysregulated inflammatory responses, all of which may worsen the clinical course of infection. Ongoing research continues to explore the broader role of micronutrients, including vitamin B12, in immune modulation and host-virus interactions. Addressing B12 deficiency in high-risk groups such as the elderly and diabetic patients therefore remains a clinically meaningful and preventable concern.[63] In a prospective study of 30 patients with B12 deficiency and pernicious anemia, improvements in lymphocyte counts, natural killer cell activity, and $CD4^+$:$CD8^+$ ratios were observed after parenteral vitamin B12 therapy.[64] Thus, adequate vitamin B12 status may be beneficial in the prevention of diabetes mellitus.

Vitamin B12, also called cobalamin, is an important micronutrient derived predominantly from foods of animal origin.[65,66]

Diabetic patients, particularly those treated with metformin, are more prone to vitamin B12 deficiency because long-term metformin use may impair B12 absorption; inadequate dietary intake may further increase this risk.[47] Hyperhomocysteinemia and vitamin B12 deficiency are strongly correlated in individuals with diabetes taking metformin at levels equivalent to or greater than 1,500 mg daily.[2] Since long-term metformin therapy in diabetic patients may be associated with vitamin B12 deficiency, vitamin B12 levels should be evaluated periodically in individuals with diabetes receiving metformin treatment, especially if they also have anemia and peripheral neuropathy.[6,67] Some previous studies have shown that the decrease in serum B12 levels occurs within 3–4 months after switching to metformin therapy.[68–72]

However, according to most studies, vitamin B12 deficiency occurs only 5–10 years after the use of metformin.[73–77] This delay in the occurrence of B12 deficiency may be due to the significant storage of this vitamin in the liver.[78]

Diabetes and aging are associated with B12 deficiencies worldwide.[5] There are also data that B12 alone can add a potential therapeutic dimension by interfering with SARS-CoV-2 replication. Therefore, vitamin B12 deficiency should be avoided in the elderly and diabetic patients. Considering the COVID-19 pandemic, this review recommends addressing this issue more urgently and regularly screening elderly individuals and diabetic patients for vitamin B12 levels.[63]

A potential health problem resulting from vitamin B12 deficiency is neuropathy, and approximately 30% of diabetic patients over the age of 40 have a sensory impairment in the feet.[79] Diabetic polyneuropathy is a primarily symmetrical sensory polyneuropathy that initially affects the distal lower limb.[80] Mild or severe nervous system damage may occur in 60% to 70% of diabetic patients.[79] Studies in European T2DM patients using metformin reported that the prevalence of vitamin B12 deficiency ranged from 5.8% to 22%.[81,82] In the British population, B12 deficiency was 27% in all T2DM cases, compared to 32.1% in those using metformin.[83] In a study conducted in India, vitamin B12 deficiency (<200 pg/dL) was detected in 7.5% of dementia patients.[84] In the same study, vitamin B12 level was found to be at the borderline (between 200–300 pg/dL) in 22.5% of the patients. Elsayed *et al.*[85] found vitamin B12 deficiency in 10% of T2DM patients and 6.7% of T1DM patients. They also confirmed that metformin therapy is associated with vitamin B12 deficiency in patients with T2DM and therefore supported the need to follow the ADA's recommendations for periodic monitoring of vitamin B12 levels in patients with T2DM who are taking metformin to avoid the risk of neuropathy or anemia. Baig *et al.*[86] found a significant association between metformin use and vitamin B12 deficiency in diabetic patients. Therefore, they considered B12 deficiency as a potential side effect of long-term metformin use. In such patients, periodic B12 screening followed by vitamin B12 supplementation may be an effective and safe way to prevent the development or worsening of peripheral nerve damage and other clinical manifestations.

5. Factors influencing vitamin B12 status

Although vitamin B12 levels are directly influenced by factors such as acute or chronic illnesses, dietary habits, alcohol consumption, medication use, pregnancy, and breastfeeding, studies have shown that B12 levels also vary based on gender and age.[87–92] Studies conducted on the basis of gender have determined that healthy male participants tend to have lower B12 levels compared to female participants.[93,94]

In males, the higher muscle mass increases the need for creatine synthesis. Two key amino acids, glycine and L-arginine, play a role in creatine biosynthesis. In the first step of the process, these amino acids combine through the action of the arginine-glycine amidinotransferase enzyme to form guanidinoacetate. Subsequently, guanidinoacetate is methylated by the enzyme guanidinoacetate methyltransferase, transforming it into creatine. During this methylation process, S-adenosylmethionine serves as the methyl group donor, and as a result, S-adenosylhomocysteine is formed. S-adenosylhomocysteine is also a precursor to homocysteine. The higher homocysteine levels in males are a significant factor that increases the need for vitamin B12.[94,95]

With aging, vitamin B12 absorption decreases due to structural and functional changes in the gastrointestinal tract. A decrease in gastric acid production (hypochlorhydria) makes it more difficult to release B12 from food, while a reduction in intrinsic factor production negatively affects the absorption process. Additionally, low stomach acid can lead to bacterial overgrowth in the intestines, causing these bacteria to consume B12. Damage or inflammation in the small intestine, particularly in the terminal ileum, can further impair B12 absorption. Medication use is also a significant factor; drugs such as proton pump inhibitors, H2-receptor antagonists, and metformin can negatively impact absorption. Furthermore, individuals who have undergone stomach or intestinal surgery may experience a marked reduction in B12 absorption. All these factors increase the risk of B12 deficiency in older individuals, and regular monitoring and supplementation when necessary are recommended.[96,97]

6. Importance of glycemic control

Hemoglobin A1c (HbA1c) is an important laboratory parameter both in the diagnosis of diabetes and in the follow-up of diabetic patients. When HbA1c alone is used for diabetes diagnosis, approximately 35% of patients may be misclassified as having prediabetes.[98] As a matter of fact, when vitamin B12 deficiency was corrected in prediabetes patients, HbA1c level decreased significantly.[98] Thus, it was recommended to rule out vitamin B12 deficiency anemia before making a diagnosis of diabetes based on HbA1c level.[98]

Weight gain, hyperglycemia, and increased HbA1c and blood lipids seen in diabetic patients as a result of the measures taken to prevent COVID-19 may also be a triggering factor, especially for cardiovascular diseases.[18] It is well established that optimal control of glycemia level is important for reducing the incidence of diabetic complications, and excessive glycemia fluctuation is an independent risk factor for the development of atherosclerosis in diabetic patients.[66] Keeping the HbA1c level below 48 mmol/mol (6.5%) is recommended by the ADA's guidelines, claiming that it can prevent diabetes complications.[6] Vitamin B12 supplementation over an eight-week period has been demonstrated to lead to significant improvement in glycemic control in patients with T2DM.[13] However, long-term vitamin B12 administration should also be avoided in patients with T2DM, as it may adversely affect cellular glucose metabolism and homeostasis.[66] Therefore, routine supplementation is not recommended for patients with normal vitamin B12 levels unless clinically indicated.

7. Benefits of nutrition and Mediterranean diet

Malnutrition can adversely affect the course and pathogenicity of viral infections.[47] Nutritional status is likely not only to impact the immune functions of the body but also to have some direct effects on viral genomes and virulence.[99] Diabetic patients should maintain adequate nutritional status during the pandemic to support immune function and reduce susceptibility to severe viral infections, including SARS-CoV-2 infection. Deficiencies in protein, essential fatty acids, and certain micronutrients are associated with decreased immune function and increased susceptibility to viral infections, including SARS-CoV-2, which can exacerbate the severity of infections, particularly in vulnerable patients such as those with T2DM. Therefore, it is crucial to consider patients' nutritional status and ensure adequate intake of both macronutrients and micronutrients in the management of COVID-19.[47]

The consumption of fresh and unprocessed plant-based foods, such as vegetables, fruits, olive oil, fish, and whole grain products, is encouraged based on existing evidence supporting the Mediterranean diet, one of the healthiest diets worldwide.[100] Additionally, foods included in the Mediterranean diet are low in advanced glycation end products.[101] Higher adherence to the Mediterranean diet has been suggested to be associated with a lower risk of COVID-19 or a less severe disease course.[102]

The Mediterranean diet, known for its preventive effects on cardiovascular diseases and T2DM, appears promising in reducing the severity of COVID-19 due to its high antioxidant, anti-inflammatory, and potential antimicrobial and immunomodulatory properties.[100] The replacement of organic agricultural products with processed industrial foods during quarantine has adversely affected diabetic patients.[103] Preferring the Mediterranean diet during the pandemic offers an opportunity to protect diabetic patients from worse outcomes in the context of COVID-19.[19] The high consumption of cabbage and fermented dairy products has contributed to lower COVID-19-related mortality in Türkiye compared to European countries.[104] Homemade cabbage pickles, due to their vitamin B12 content, provide a significant contribution to the Mediterranean diet. It is suggested that diabetic patients using metformin during the pandemic would benefit from adopting the Mediterranean diet, including homemade cabbage pickles. Mediterranean diet polyphenols and metabolites, including microbial phenolic metabolites synthesized by the gut microbiota, have been reported to have beneficial effects on health and insulin resistance.[105] The metabolites of the Mediterranean diet are thought to positively influence gut microbiota, which is associated with cardiovascular health. When evaluating health benefits, it has been reported that the effects of microbial phenolic metabolites should be assessed in combination rather than individually.[9,105,106] Moreover, the synergistic benefits of physical activity on immune functions and psychological health should be considered alongside the Mediterranean diet. It is highlighted that individuals following the Mediterranean diet, combined with regular physical activity, can enhance immune functions and reduce the risk of COVID-19.

Finally, the changes in dietary habits at a societal level during the pandemic and their impacts on diabetic patients should be addressed. The shift toward unhealthy dietary preferences in society has increased the consumption of processed foods, worsening the health status of individuals with chronic diseases such as diabetes. The Mediterranean diet is considered to have the potential to reduce societal health costs.

8. Pregnancy, COVID-19, diabetes, and vitamin B12: An assessment from the perspective of women's health

While the COVID-19 pandemic affected the entire world, pregnancy emerged as a particularly vulnerable period. Pregnant women may be more susceptible to viral infections due to physiological changes in the immune system. When GDM and vitamin B12 deficiency coexist, the risk takes on a far more complex dimension. The metabolic changes that occur during pregnancy increase insulin resistance, laying the groundwork for GDM. This condition carries serious risks for both maternal and fetal health. During the pandemic, these risks were further compounded by delayed diagnosis, problems with access to treatment, and altered dietary habits.

Pregnancy itself is fundamentally a process of immunological transformation. The immune system is reorganized to ensure fetal tolerance. During this process, type 1 helper T (Th1) responses are suppressed while type 2 helper T (Th2) responses become more prominent. This weakens cellular immunity against viruses, which may cause COVID-19 infection to follow a more severe course. Indeed, the World Health Organization and many national guidelines have defined pregnant women as a high-risk group with respect to COVID-19. Studies have demonstrated significant increases in the rates of preeclampsia, preterm birth, intrauterine growth restriction, and cesarean delivery among pregnant women who contracted SARS-CoV-2 infection. Underlying these complications are systemic inflammation and coagulation disorders. Both mechanisms are directly related to vitamin B12 metabolism.[107–110]

8.1. Gestational diabetes mellitus and vitamin B12 deficiency

Gestational diabetes mellitus is defined as glucose intolerance that first appears or is recognized during pregnancy. Its global prevalence ranges from 1% to 28% and has been increasing in recent years due to obesity and advanced maternal age. GDM increases the mother's risk of developing T2DM in later years by approximately seven-fold, while is also associated with macrosomia, neonatal hypoglycemia, and long-term obesity and insulin resistance in the infant. The indirect effects of the COVID-19 pandemic on GDM must also be taken into account. During the pandemic, a more sedentary lifestyle, carbohydrate-heavy dietary habits, and stress-related cortisol elevation have markedly increased the risk of GDM development.[110–113]

The relationship between vitamin B12 deficiency and GDM has been increasingly investigated in recent years. The requirement for vitamin B12 increases during pregnancy. This vitamin must be consumed at adequate levels to meet the needs of both the mother and the fetus. However, particularly in pregnant women following vegetarian or vegan diets, B12 deficiency may be overlooked while attention is focused on iron supplementation due to iron deficiency anemia. B12 deficiency raises homocysteine levels. Elevated homocysteine adversely affects insulin signaling pathways and contributes to increased insulin resistance. It has been proposed that B12 deficiency increases GDM risk through this mechanism. Systematic reviews and meta-analyses have shown that inadequate vitamin B12 levels are associated with a significant increase in GDM risk. These findings point to the importance of assessing B12 levels in the preconception and early pregnancy periods.[114,115]

Studies conducted in South Asian countries, particularly India, present noteworthy data. In these populations, the co-occurrence of high B12 deficiency rates and high GDM prevalence strengthens the possible association between the two conditions. Similarly, studies conducted in Türkiye have reported that multiple micronutrient deficiencies co-occur, especially during winter months when exposure to sunlight is limited, and that GDM prevalence increases alongside this pattern. During the COVID-19 pandemic, restrictions on going outdoors reduced sun exposure time, further worsening this trend.[114–116]

8.2. The diabetogenic potential of COVID-19 in pregnancy

The direct cytotoxic effect of SARS-CoV-2 on pancreatic beta cells may increase the risk of new-onset hyperglycemia and diabetes in pregnant women. The ACE2 is expressed in several organs, including the pancreas, small intestine, liver, and placenta. The damage initiated through this receptor during the course of infection may impair insulin secretion. ACE2 expression has also been demonstrated in the placenta during pregnancy, which raises the possibility of the virus reaching the fetus.[107,109]

The hyperinflammatory state that develops following COVID-19 infection creates substantial risk when it coincides with GDM. Both conditions give rise to a pro-inflammatory and prothrombotic environment. Elevation of inflammatory markers such as tumor necrosis factor alpha, interleukin-6, and C-reactive protein adversely affects insulin receptor signaling pathways, disrupting glycemic control. For this reason, COVID-19 infection in pregnant women who have been diagnosed with GDM or who carry GDM risk may lead to far more severe metabolic consequences.

Corticosteroid therapy has been widely used in severe cases of COVID-19. However, these medications can have significant adverse effects on glucose metabolism, particularly during pregnancy. Synthetic glucocorticoids such as dexamethasone and betamethasone cause hyperglycemia by stimulating hepatic glucose production and reducing peripheral insulin sensitivity. It is therefore emphasized that glycemic monitoring of pregnant women diagnosed with COVID-19 should be performed at more frequent intervals throughout the duration of corticosteroid therapy. Additionally, studies examining the long-term effects of COVID-19 ("long COVID") report that in some pregnant women who have recovered from the disease, insulin resistance remains persistently elevated and the risk of postpartum diabetes is increased.[108–110]

8.3. The role of vitamin B12 in pregnancy: Fetal and maternal health

Vitamin B12 is critically important during pregnancy for neural tube development, DNA synthesis, and erythropoiesis. Working in conjunction with folate, this vitamin plays a decisive role in the prevention of neural tube defects. Inadequate B12 intake triggers homocysteine accumulation, which may lead to endothelial damage and a tendency toward thrombosis in the placenta. Since placental endothelial dysfunction plays a central role in the pathophysiology of preeclampsia, the connection between B12 and preeclampsia is attracting increasing attention. Studies have shown that low serum B12 levels are associated with an increased risk of preeclampsia.

From the fetal perspective, B12 deficiency is known to adversely affect neurological development during the intrauterine period. It has been proposed that inadequate B12 exposure in the womb may, through epigenetic modifications, predispose the child to developing obesity and T2DM in later years. This concept aligns with the Developmental Origins of Health and Disease hypothesis, drawing attention to the impact of maternal nutritional quality across generations.

The breastfeeding period also constitutes a critical phase with respect to B12. The concentration of B12 in breast milk is directly dependent on the mother's serum B12 level. An infant of a mother with B12 deficiency may face neurological developmental risks due to receiving inadequate B12 through breast milk. During the pandemic period, rising food prices, reduced access to animal-source foods, and psychosocial stress may have caused B12 levels to decline further in lactating women.[115,117]

8.4. Metformin use in pregnancy and the risk of B12 deficiency

Metformin is increasingly used as an alternative or adjunct to insulin in the pharmacological treatment of GDM. Several guidelines find metformin acceptable in terms of its safety and efficacy profile. However, prolonged metformin use is known to reduce vitamin B12 absorption. This risk cannot be overlooked in pregnant women who are started on metformin following a GDM diagnosis. Pregnancy is already a period that places physiological demands on B12. Metformin-associated impairment of B12 absorption may therefore create a combined risk for both mother and fetus.

Polycystic ovary syndrome (PCOS) is one of the gynecological conditions most frequently treated with metformin and is commonly associated with insulin resistance. A large proportion of women with PCOS are using metformin prior to conception; this may bring already low B12 levels during pregnancy to an even more critical point. Pregnant women with PCOS constitute a particularly high-risk group for both GDM and B12 deficiency, owing to both insulin resistance and prolonged metformin use. In clinical practice, adding B12 screening to the antenatal follow-up of these patients is of great importance.[118,119]

9. Conclusion

Pregnancy is not just a period of increased nutritional needs; it is a period of profound immunoprogramming. The deliberate suppression of Th1-mediated cellular immunity, while necessary for fetal tolerance, also reduces the mother's capacity to fight viral pathogens. SARS-

CoV-2 exploited this weakness. Emerging infections were more likely to be more severe, and complications such as preeclampsia, premature birth, intrauterine growth retardation, and cesarean delivery occurred at significantly higher rates in infected pregnant women. These constitute real and lasting harms for mothers and children.

Gestational diabetes mellitus added another layer of risk. The prevalence of GDM was already increasing globally before the pandemic due to rising obesity rates and advanced maternal age. The pandemic accelerated this trend. Sedentary lifestyles, carbohydrate-heavy diets, disrupted sleep, and chronic psychosocial stress increase insulin resistance. Routine GDM screening was delayed or completely skipped in many settings because women avoided hospitals for fear of infection. Many cases went undetected and unmanaged during critical periods of pregnancy. The long-term consequences of this (both in terms of the risk of T2DM in expectant mothers and the metabolic health of offspring) are only just beginning to be understood.

Vitamin B12 deficiency elevates homocysteine, which damages endothelial cells, promotes thrombosis, and disrupts insulin receptor signaling. It compromises the immune response at a time when immune capacity is already diminished. It disrupts fetal neurological development through mechanisms that can leave epigenetic imprints that may persist into adulthood. Yet, B12 deficiency remains one of the least screened nutritional issues in prenatal care. B12 deficiency is often invisible until it causes damage.

The relationship between metformin and B12 depletion deserves particular emphasis. Metformin is now widely accepted as a safe and effective option in the management of GDM, and its use in pre-pregnancy PCOS is extremely common. However, its interference with ileal B12 absorption is well documented, meaning that many pregnant women enter and progress into pregnancy with progressively depleted B12 stores. Women with PCOS who use metformin long-term face double the risk. They bear both the metabolic burden of insulin resistance and the nutritional consequences of impaired B12 absorption. This group requires proactive, not reactive, clinical management. The SARS-CoV-2 virus itself contributed to B12 depletion through additional mechanisms. Viral damage to intestinal epithelial cells (particularly in the terminal ileum, where B12 absorption occurs) directly disrupted absorption. The intense metabolic demands of acute infection accelerated B12 depletion. And the virus-induced hyperinflammatory state further elevated homocysteine levels, increasing the cardiovascular and thrombotic risks already present in GDM. In severe cases, corticosteroid treatment added another layer to glycemic imbalance, requiring more intensive monitoring, which is often unavailable in overloaded healthcare systems. The Developmental Origins of Health and Disease hypothesis adds a multigenerational dimension to this issue. Insufficient B12 availability during intrauterine life may affect the fetus in the short term and, through epigenetic modifications, may increase susceptibility to obesity, insulin resistance, and T2DM later in life. This means that nutritional deficiencies during the pandemic could have consequences stretching into decades to come, including a generation not yet born when the virus first emerged. In this context, diet is both a problem and a solution. Disruptions in food supply chains, increased costs of animal-derived foods, and behavioral shifts toward processed and industrial foods during lockdown periods worsened the nutritional status of pregnant women worldwide. The Mediterranean diet, emphasizing whole grains, legumes, olive oil, vegetables, fruits, and fatty fish, offers an evidence-based dietary framework that can reduce inflammation, support glycemic control, and partially meet B12 requirements through regular fish consumption. However, it must be acknowledged that the Mediterranean diet alone cannot guarantee B12 sufficiency in all pregnant women, especially those who are vegetarian, vegan, or unable to consume sufficient amounts of fish due to mercury concerns. Targeted supplementation remains a crucial component of care. In conclusion, this review presents a simple but urgent clinical argument. Vitamin B12 screening should become a standard, routine component of prenatal care, rather than an optional supplement reserved for symptomatic patients or marked cases. The evidence linking B12 deficiency to GDM risk, preeclampsia, impaired fetal neurodevelopment, and worsened COVID-19 outcomes is now substantial enough to justify this recommendation without reservation. High-risk groups (including women with GDM, PCOS, long-term metformin use, vegetarian or vegan diets, and limited access to animal-source foods) should be prioritized for early and repeated screening. When deficiency is identified, supplementation is safe, inexpensive, and effective.

The pandemic revealed how fragile the infrastructure of maternal nutritional care truly is. It is time to rebuild that infrastructure with vitamin B12 firmly included. The health of mothers, and the long-term health of the children they carry, depends on it.

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Further disclosure

The authors declare that artificial intelligence (AI)-based translation tools were used in the preparation of the English version of this article. The authors are fully responsible for the accuracy, completeness, and originality of the final article.

References

1. Sharma A, Misra-Hebert AD, Mariam A, *et al*. Impacts of COVID-19 on glycemia and risk of diabetic ketoacidosis. *Diabetes*. 2023;72(5):627-637.

   doi: 10.2337/db22-0264

2. Abbas RH, Thaker AA, Ali HH. Relationship between vitamin B12, homocysteine, and immunological parameters in patients with type 2 diabetes. *J Pharm Negative Results*. 2022;13(S01):689-693.

   doi: 10.47750/pnr.2022.13.s01.85

3. Bouhanick B, Cracowski JL, Faillie JL; French Society of Pharmacology, Therapeutics (SFPT). Diabetes and COVID-19. Therapie. 2020;75(4):327-333.

   doi: 10.1016/j.therap.2020.05.006

4. Rathmann W, Kuss O, Kostev K. Incidence of newly diagnosed diabetes after Covid-19. *Diabetologia*. 2022;65(6):949-954.

   doi: 10.1007/s00125-022-05670-0

5. Georgoulis M, Kontogianni MD, Yiannakouris N. Mediterranean diet and diabetes: prevention and treatment. *Nutrients*. 2014;6(4):1406-1423.

   doi: 10.3390/nu6041406

6. American Diabetes Association. *Standards of medical care in diabetes*—2017. *Diabetes Care*. 2017;40(suppl 1):S1-S2.

   doi: 10.2337/dc17-S001

7. Finer S, Saravanan P, Hitman G, Yajnik C. The role of the one-carbon cycle in the developmental origins of type 2 diabetes and obesity. *Diabet Med*. 2014;31(3):263-272.

   doi: 10.1111/dme.12390

8. Zalaket J, Wehbe T, Abou Jaoude E. Vitamin B12 deficiency in diabetic subjects taking metformin: a cross sectional study in a Lebanese cohort. *J Nutr Intermed Metab*. 2018;11:9-13.

   doi: 10.1016/j.jnim.2017.12.001

9. 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):e160922209008.

   doi: 10.2174/1573399818666220418080959

10. Gul A, Siddiqi FA, Amir M, Arshad AR, Qayyum S, Shakireen N. Vitamin B12 deficiency in relation to metformin use in adults with type-2 diabetes mellitus. *Life Sci*. 2023;4(2):4.

    doi: 10.37185/lns.1.1.271

11. Sayedali E, Yalin AE, Yalin S. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes. *World J Diabetes*. 2023;14(5):585-593.

    doi: 10.4239/wjd.v14.i5.585

12. Eskin F, Tutan D. Is there a relationship between metformin-related gastrointestinal symptoms and vitamin B12 deficiency in patients with type 2 diabetes mellitus? *Med Sci*. 2023;12(1):324.

    doi: 10.5455/medscience.2022.11.338

13. Satapathy S, Bandyopadhyay D, Patro BK, Khan S, Naik S. Folic acid and vitamin B12 supplementation in subjects with type 2 diabetes mellitus: a multi-arm randomized controlled clinical trial. *Complement Ther Med*. 2020;53:102526.

    doi: 10.1016/j.ctim.2020.102526

14. Kouroglou E, Anagnostis P, Daponte A, Bargiota A. Vitamin B12 insufficiency is associated with increased risk of gestational diabetes mellitus: a systematic review and meta-analysis. *Endocrine*. 2019;66(2):149-156.

    doi: 10.1007/s12020-019-02053-1

15. Sukumar N, Venkataraman H, Wilson S, *et al*. Vitamin B12 status among pregnant women in the UK and its association with obesity and gestational diabetes. *Nutrients*. 2016;8(12):768.

    doi: 10.3390/nu8120768

16. Ashiq S, Shabana. Vitamin B12 deficiency in type I diabetes. *J Microbiol Mol Genet*. 2020;1(2):44-49.

doi: 10.52700/jmmg.v1i2.19

17. Sezgin Y, Becel S. Evaluation of lipid parameters in patients receiving vitamin B12 therapy. *Istanbul Med J*. 2019;20(3):214-217.

doi: 10.4274/imj.galenos.2019.37974

18. Karatas S, Yesim T, Beysel S. Impact of lockdown COVID-19 on metabolic control in type 2 diabetes mellitus and healthy people. *Prim Care Diabetes*. 2021;15(3):424-427.

doi: 10.1016/j.pcd.2021.01.003

19. Maiorino MI, Bellastella G, Longo M, Caruso P, Esposito K. Mediterranean diet and COVID-19: hypothesizing potential benefits in people with diabetes. *Front Endocrinol*. 2020;11:574315.

doi: 10.3389/fendo.2020.574315

20. Wu C, Zheng M, Yang Y, *et al*. Furin: a potential therapeutic target for COVID-19. *iScience*. 2020;23(10):101642.

doi: 10.1016/j.isci.2020.101642

21. Ou X, Liu Y, Lei X, *et al*. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat Commun*. 2020;11(1):1620.

doi: 10.1038/s41467-020-15562-9

22. Alsaadi EAJ, Jones IM. Membrane binding proteins of coronaviruses. *Future Virol*. 2019;14(4):275-286.

doi: 10.2217/fvl-2018-0144

23. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol*. 2020;20(6):355-362.

doi: 10.1038/s41577-020-0331-4

24. dos Santos LMJ. Can vitamin B12 be an adjuvant to COVID-19 treatment? *GSC Biol Pharm Sci*. 2020;11(3):001-005.

doi: 10.30574/gscbps.2020.11.3.0155

25. Pandya M, Shah S, Dhanalakshmi M, *et al*. Unravelling vitamin B12 as a potential inhibitor against SARS-CoV-2: a computational approach. *Inform Med Unlocked*. 2022;30:100951.

doi: 10.1016/j.imu.2022.100951

26. Troen AM. Folate and vitamin B12: function and importance in cognitive development. In: *Nestle Nutr Inst Workshop Ser*. *S. Karger AG;* 2012;70:161-171.

doi: 10.1159/000337684

27. Kennedy DO. B vitamins and the brain: mechanisms, dose and efficacy—a review. *Nutrients*. 2016;8(2):68.

doi: 10.3390/nu8020068

28. Ulusal Diyabet Konsensus Grubu. *Diyabet Tanı ve Tedavi Rehberi 2021* [in Turkish]. Türkiye Diyabet Vakfı; 2021. Available from: https://www.turkdiab.org/admin/PICS/webfiles/Diyabet_Tani_ve_Tedavi_Rehberi_2021.pdf [Last accessed on April 30, 2026].

29. Roglic G, Unwin N. Mortality attributable to diabetes: estimates for the year 2010. *Diabetes Res Clin Pract*. 2010;87(1):15-19.

doi: 10.1016/j.diabres.2009.10.006

30. Emerging Risk Factors Collaboration; Seshasai SR, Kaptoge S, Thompson A, *et al*. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med*. 2011;364(9):829-841.

doi: 10.1056/NEJMoa1008862

31. Stasi C, Fallani S, Voller F, Silvestri C. Treatment for COVID-19: an overview. *Eur J Pharmacol*. 2020;889:173644.

doi: 10.1016/j.ejphar.2020.173644

32. Rezaee H, Pourkarim F, Pourtaghi-Anvarian S, *et al*. Drug-drug interactions with candidate medications used for COVID-19 treatment: an overview. *Pharmacol Res Perspect*. 2021;9(1):e00705.

doi: 10.1002/prp2.705

33. Gil C, Ginex T, Maestro I, *et al*. COVID-19: drug targets and potential treatments. *J Med Chem*. 2020;63(21):12359-12386.

doi: 10.1021/acs.jmedchem.0c00606

34. Ramakrishnan M, Poojari PG, Rashid M, *et al*. Impact of COVID-19 pandemic on medicine supply chain for patients with chronic diseases: experiences of the community pharmacists. *Clin Epidemiol Glob Health*. 2023;20:101243.

doi: 10.1016/j.cegh.2023.101243

35. Clement J, Jacobi M, Greenwood BN. Patient access to chronic medications during the Covid-19 pandemic: evidence from a comprehensive dataset of US insurance claims. *PLoS ONE*. 2021;16(4):e0249453.

doi: 10.1371/journal.pone.0249453

36. Meo SA, Bukhari IA, Akram J, Meo AS, Klonoff DC. COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna vaccines. *Eur Rev Med Pharmacol Sci*. 2021;25(3):1663-1669.

doi: 10.26355/eurrev_202102_24877

37. Freise NF, Kivel M, Grebe O, *et al*. Acute cardiac side effects after COVID-19 mRNA vaccination: a case series. *Eur J Med Res*. 2022;27(1):80.

doi: 10.1186/s40001-022-00695-y

38. Badell ML, Dude CM, Rasmussen SA, Jamieson DJ. Covid-19 vaccination in pregnancy. *BMJ*. 2022;378:e069741.

doi: 10.1136/bmj-2021-069741

39. Khan F, Khan MT, Zaman S, *et al*. Side effects of COVID-19 vaccines among diabetic subjects and healthy individuals. *Cureus*. 2023;15(3):e36005.

doi: 10.7759/cureus.36005

40. Gubbi S, Nazari MA, Taieb D, Klubo-Gwiezdzinska J, Pacak K. Catecholamine physiology and its implications in patients with COVID-19. *Lancet Diabetes Endocrinol*. 2020;8(12):978-986.

doi: 10.1016/s2213-8587(20)30342-9

41. Guarnotta V, Ferrigno R, Martino M, *et al*. Glucocorticoid excess and COVID-19 disease. *Rev Endocr Metab Disord*. 2020;22(4):703-714.

doi: 10.1007/s11154-020-09598-x

42. Specktor P, Hadar D, Cohen H. Glucocorticoid treatment during COVID-19 infection: does it affect the incidence of long COVID? *Inflammopharmacology*. 2024;32(6):3707-3715.

doi: 10.1007/s10787-024-01576-y

43. Wang A, Zhao W, Xu Z, Gu J. *Timely blood glucose management for the outbreak of* 2019 novel coronavirus disease (COVID-19) is urgently needed. *Diabetes Res Clin Pract*. 2020;162:108118.

doi: 10.1016/j.diabres.2020.108118

44. Mahrooz A, Muscogiuri G, Buzzetti R, Maddaloni E. The complex combination of COVID-19 and diabetes: pleiotropic changes in glucose metabolism. *Endocrine*. 2021;72(2):317-325.

doi: 10.1007/s12020-021-02729-7

45. Hasan SS, Kow CS, Bain A, Kavanagh S, Merchant HA, Hadi MA. Pharmacotherapeutic considerations for the management of diabetes mellitus among hospitalized COVID-19 patients. *Expert Opin Pharmacother*. 2020;22(2):229-240.

doi: 10.1080/14656566.2020.1837114

46. Xie L, Zhang Z, Wang Q, Chen Y, Lu D, Wu W. COVID-19 and diabetes: a comprehensive review of angiotensin converting enzyme 2, mutual effects and pharmacotherapy. *Front Endocrinol*. 2021;12:772865.

doi: 10.3389/fendo.2021.772865

47. Mahluji S, Jalili M, Ostadrahimi A, Hallajzadeh J, Ebrahimzadeh-Attari V, Saghafi-Asl M. Nutritional management of diabetes mellitus during the pandemic of COVID-19: a comprehensive narrative review. *J Diabetes Metab Disord*. 2021;20(1):963-972.

doi: 10.1007/s40200-021-00784-5

48. Pettus J, Skolnik N. Importance of diabetes management during the COVID-19 pandemic. *Postgrad Med*. 2021;133(8):912-919.

doi: 10.1080/00325481.2021.1978704

49. Aslaner H, İnanç N, Gökçek MB, *et al*. The effect of vitamin B12 levels on prognosis in COVID-19 patients. *J Contemp Med*. 2022;12(2):359-363.

doi: 10.16899/jcm.1035078

50. Nalbandian A, Sehgal K, Gupta A, *et al*. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4):601-615.

doi: 10.1038/s41591-021-01283-z

51. Halpin SJ, McIvor C, Whyatt G, *et al*. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J Med Virol*. 2021;93(2):1013-1022.

doi: 10.1002/jmv.26368

52. Manzanares W, Hardy G. Farmaconutrición de la vitamina B12 para COVID-19 [in Spanish]. *Rev Nutr Clínica y Metab*. 2020;4(1):65-69..

doi: 10.35454/rncm.v4n1.187

53. Lymperaki E, Kazeli K, Variti G, *et al*. Potential role of certain biomarkers such as vitamin B12, ROS, albumin, as early predictors for prognosis of COVID-19 outcomes. *Medicines*. 2022;9(6):36.

doi: 10.3390/medicines9060036

54. Rayman G, Lumb A, Kennon B, *et al*. Dexamethasone therapy in COVID-19 patients: implications and guidance for the management of blood glucose in people with and without diabetes. *Diabet Med*. 2021;38(1):e14378.

doi: 10.1111/dme.14378

55. Younes YR, Stockley S, Keegan L, *et al*. COVID-19 and dexamethasone-induced hyperglycaemia: workload implications for diabetes inpatient teams. *Diabet Med*. 2022;39(2):e14716.

doi: 10.1111/dme.14716

56. Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of COVID-19: a systemic review and a clinician's perspective. *Diabetes Metab Syndr*. 2020;14(5):971-978.

doi: 10.1016/j.dsx.2020.06.054

57. Unnikrishnan R, Misra A. Diabetes and COVID-19: a bidirectional relationship. *Nutr Diabetes*. 2021;11(1):21.

doi: 10.1038/s41387-021-00163-2

58. Harding JL, Oviedo SA, Ali MK, *et al*. The bidirectional association between diabetes and long-COVID-19: a systematic review. *Diabetes Res Clin Pract*. 2023;195:110202.

doi: 10.1016/j.diabres.2022.110202

59. Hayden MR. An immediate and long-term complication of COVID-19 may be type 2 diabetes mellitus: the central role

of β-cell dysfunction, apoptosis and exploration of possible mechanisms. *Cells*. 2020;9(11):2475.

doi: 10.3390/cells9112475

60. Kanzy A, Madkhali M, Imam S, Jaume J. Development of latent autoimmune diabetes of adults post SARS-CoV-2 mRNA vaccination. *Diabetes Res Clin Pract*. 2022;186:109369.

doi: 10.1016/j.diabres.2022.109369

61. Lu JY, Wilson J, Hou W, *et al*. Incidence of new-onset in-hospital and persistent diabetes in COVID-19 patients: comparison with influenza. *eBioMedicine*. 2023;90:487.

doi: 10.1016/j.ebiom.2023.104487

62. Rai S, Rai BS, Pakkala PR. The potential role of vitamin B12 in the prevention of COVID-19 complications: a narrative review. *J Pure Appl Microbiol*. 2021;15(4):1735-1744.

doi: 10.22207/jpam.15.4.04

63. Wee AKH. COVID-19's toll on the elderly and those with diabetes mellitus—is vitamin B12 deficiency an accomplice? *Med Hypotheses*. 2021;146:110374.

doi: 10.1016/j.mehy.2020.110374

64. Erkurt MA, Aydogdu I, Dikilitaş M, *et al*. Effects of cyanocobalamin on immunity in patients with pernicious anemia. *Med Princ Pract*. 2008;17(2):131-135.

doi: 10.1159/000112967

65. Jayawardena R, Jeyakumar DT, Francis TV, Misra A. Impact of the vitamin D deficiency on COVID-19 infection and mortality in Asian countries. *Diabetes Metab Syndr*. 2021;15(3):757-764.

doi: 10.1016/j.dsx.2021.03.006

66. Li W, Zhao J, Zhu LL, Peng YF. Serum vitamin B12 levels and glycemic fluctuation in patients with type 2 diabetes mellitus. *Ther Adv Endocrinol Metab*. 2022;13:20420188221102800.

doi: 10.1177/20420188221102800

67. 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;2021(2):39.

doi: 10.5339/qmj.2021.39

68. Wulffele 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.

doi: 10.1046/j.1365-2796.2003.01213.x

69. 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(may19 4):c2181.

doi: 10.1136/bmj.c2181

70. Yang W, Cai X, Wu H, Ji L. Associations between metformin use and vitamin B12 levels, anemia, and neuropathy in patients with diabetes: a meta-analysis. *J Diabetes*. 2019;11(9):729-743.

doi: 10.1111/1753-0407.12900

71. Kos E, Liszek MJ, Emanuele MA, Durazo-Arvizu R, Camacho P. Effect of metformin therapy on vitamin D and vitamin B12 levels in patients with type 2 diabetes mellitus. *Endocr Pract*. 2012;18(2):179-184.

doi: 10.4158/EP11009.OR

72. Chapman LE, Darling AL, Brown JE. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Metab*. 2016;42(5):316-327.

doi: 10.1016/j.diabet.2016.03.008

73. Wile DJ, Toth C. Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. *Diabetes Care*. 2010;33(1):156-161.

doi: 10.2337/dc09-0606

74. Aroda VR, Edelstein SL, Goldberg RB, *et al*. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. *J Clin Endocrinol Metab*. 2016;101(4):1754-1761.

doi: 10.1210/jc.2015-3754

75. Ko SH, Ko SH, Ahn YB, *et al*. Association of vitamin B12 deficiency and metformin use in patients with type 2 diabetes. *J Korean Med Sci*. 2014;29(7):965.

doi: 10.3346/jkms.2014.29.7.965

76. Ahmed MA, Muntingh G, Rheeder P. Vitamin B12 deficiency in metformin-treated type-2 diabetes patients, prevalence and association with peripheral neuropathy. *BMC Pharmacol Toxicol*. 2016;17(1):44.

doi: 10.1186/s40360-016-0088-3

77. Bell DS. Metformin-induced vitamin B12 deficiency can cause or worsen distal symmetrical, autonomic and cardiac neuropathy in the patient with diabetes. *Diabetes Obes Metab*. 2022;24(8):1423-1428.

doi: 10.1111/dom.14734

78. Ruscin JM, Page RL 2nd, Valuck RJ. Vitamin B12 deficiency associated with histamine2-receptor antagonists and a proton-pump inhibitor. *Ann Pharmacother*. 2002;36(5):812-816.

doi: 10.1345/aph.10325

79. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United

States, 2011. US Department of Health and Human Services; 2011. Accessed on April 30, 2026. https://stacks.cdc.gov/view/cdc/13329

80. Khalaf KM, Khudhair MS, Ashor AW. Vitamin B12 status and peripheral neuropathy in patients with type 2 diabetes mellitus. *JPMA J Pak Med Assoc*. 2019;69(suppl 3)(8):S40-S44.

81. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley GP Jr. Association of biochemical B12 deficiency with metformin therapy and vitamin B12 supplements. *Diabetes Care*. 2012;35(2):327-333.

doi: 10.2337/dc11-1582

82. Pflipsen MC, Oh RC, Saguil A, Seehusen DA, Seaquist D, Topolski R. The prevalence of vitamin B12 deficiency in patients with type 2 diabetes: a cross-sectional study. *J Am Board Fam Med*. 2009;22(5):528-534.

doi: 10.3122/jabfm.2009.05.090044

83. Adaikalakoteswari A, Jayashri R, Sukumar N, *et al*. Vitamin B12 deficiency is associated with adverse lipid profile in Europeans and Indians with type 2 diabetes. *Cardiovasc Diabetol*. 2014;13(1):129.

doi: 10.1186/s12933-014-0129-4

84. Sashindran VK, Aggarwal V, Khera A. Prevalence of vitamin B12 deficiency in elderly population (>60 years) presenting with dementia to outpatient department. *Med J Armed Forces India*. 2022;78(1):94-98.

doi: 10.1016/j.mjafi.2020.11.003

85. Elsayed AM, Ibrahim WM, Magdi MA, Elbadawy A. Prevalence of vitamin B12 deficiency among diabetic patients in Benha City, Egypt, a hospital based: a cross-section study. *Benha Med J*. 2022;39(2):334-345.

doi: 10.21608/bmfj.2021.94243.1475

86. Baig FA, Khan S, Rizwan A. Frequency of vitamin B12 deficiency in type 2 diabetic patients taking metformin. *Cureus*. 2022;14(3):e22924.

doi: 10.7759/cureus.22924

87. Dror DK, Allen LH. Interventions with vitamins B6, B12 and C in pregnancy. *Paediatr Perinat Epidemiol*. 2012;26(suppl 1):55-74.

doi: 10.1111/j.1365-3016.2012.01277.x

88. Kırat S. The importance of micronutrient deficiency in the etiology of anemia in the first trimester of pregnancy: a cross-sectional study. *Kafkas J Med Sci*. 2024;14(3):304-310.

doi: 10.5505/kjms.2024.73478

89. Myilsamy S, Kandasamy S, Vijayakumar P, Periaswamy P. A cross-sectional study of serum B12 and folate level in alcoholics and nonalcoholics. *Muller J Med Sci Res*. 2022;13(1):18-21.

doi: 10.4103/mjmsr.mjmsr_10_22

90. Vogiatzoglou A, Smith AD, Nurk E, *et al*. Dietary sources of vitamin B-12 and their association with plasma vitamin B-12 concentrations in the general population: the Hordaland Homocysteine Study. *Am J Clin Nutr*. 2009;89(4):1078-1087.

doi: 10.3945/ajcn.2008.26598

91. Jung SB, Nagaraja V, Kapur A, Eslick GD. Association between vitamin B12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis. *Intern Med J*. 2015;45(4):409-416.

doi: 10.1111/imj.12697

92. Linnebank M, Moskau S, Semmler A, *et al*. Antiepileptic drugs interact with folate and vitamin B12 serum levels. *Ann Neurol*. 2011;69(2):352-359.

doi: 10.1002/ana.22229

93. Margalit I, Cohen E, Goldberg E, Krause I. Vitamin B12 deficiency and the role of gender: a cross-sectional study of a large cohort. *Ann Nutr Metab*. 2018;72(4):265-271.

doi: 10.1159/000488326

94. Cohen E, Margalit I, Shochat T, Goldberg E, Krause I. Gender differences in homocysteine concentrations, a population-based cross-sectional study. *Nutr Metab Cardiovasc Dis*. 2019;29(1):9-14.

doi: 10.1016/j.numecd.2018.09.003

95. Schwahn BC, Chen Z, Laryea MD, *et al*. Homocysteine-betaine interactions in a murine model of 5,10-methylenetetrahydrofolate reductase deficiency. *FASEB J*. 2003;17(3):1-25.

doi: 10.1096/fj.02-0456fje

96. Carmel R, Green R, Rosenblatt DS, Watkins D. Update on cobalamin, folate, and homocysteine. *Hematology*. 2003;2003(1):62-81.

doi: 10.1182/asheducation-2003.1.62

97. Fried M, Siegrist H, Frei R, *et al*. Duodenal bacterial overgrowth during treatment in outpatients with omeprazole. *Gut*. 1994;35(1):23-26.

doi: 10.1136/gut.35.1.23

98. Aydin B, Cansu GB, Ozlu C. Relationship between glycosylated hemoglobin and vitamin B12 deficiency anemia. *North Clin Istanb*. 2022;9(5):459-463.

doi: 10.14744/nci.2022.76259

99. Beck MA, Handy J, Levander OA. Host nutritional status: the neglected virulence factor. *Trends Microbiol*. 2004;12(9):417-423.

doi: 10.1016/j.tim.2004.07.007

100. Angelidi AM, Kokkinos A, Katechaki E, Ros E, Mantzoros CS. Mediterranean diet as a nutritional approach for COVID-19. *Metabolism*. 2021;114:154407.

doi: 10.1016/j.metabol.2020.154407

101. Demirer B, Yardımcı H, Basmaz SE. Inflammation level in type 2 diabetes is associated with dietary advanced glycation end products, Mediterranean diet adherence and oxidative balance score: a pathway analysis. *J Diabetes Complications*. 2023;37(1):108354.

doi: 10.1016/j.jdiacomp.2022.108354

102. Perez-Araluce R, Martinez-Gonzalez MA, Fernández-Lázaro CI, Bes-Rastrollo M, Gea A, Carlos S. Mediterranean diet and the risk of COVID-19 in the 'Seguimiento Universidad de Navarra' cohort. *Clin Nutr*. 2022;41(12):3061-3068.

doi: 10.1016/j.clnu.2021.04.001

103. Hirabara SM, Gorjao R, Curi R, Leandro CG, Marzuca-Nassr GN. Nutritional modulation of inflammation and insulin resistance. *Front Nutr*. 2023;10:1181809.

doi: 10.3389/fnut.2023.1181809

104. Bousquet J, Anto JM, Iaccarino G, *et al*. Is diet partly responsible for differences in COVID-19 death rates between and within countries? *Clin Transl Allergy*. 2020;10(1).

doi: 10.1186/s13601-020-00323-0

105. Domínguez-López I, Arancibia-Riveros C, Marhuenda-Muñoz M, *et al*. Association of microbiota polyphenols with cardiovascular health in the context of a Mediterranean diet. *Food Res Int*. 2023;165:112499.

doi: 10.1016/j.foodres.2023.112499

106. Iddir M, Brito A, Dingeo G, *et al*. Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: considerations during the COVID-19 crisis. *Nutrients*. 2020;12(6):1562.

doi: 10.3390/nu12061562

107. Dashraath P, Wong JLJ, Lim MXK, *et al*. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *Am J Obstet Gynecol*. 2020;222(6):521-531.

doi: 10.1016/j.ajog.2020.03.021

108. Allotey J, Fernandez S, Bonet M, *et al*. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2020;370:m3320.

doi: 10.1136/bmj.m3320

109. Metz TD, Clifton RG, Hughes BL, *et al*. Association of SARS-CoV-2 infection with serious maternal morbidity and mortality from obstetric complications. *JAMA*. 2022;327(8):748.

doi: 10.1001/jama.2022.1190

110. Sweeting A, Wong J, Murphy HR, Ross GP. A clinical update on gestational diabetes mellitus. *Endocr Rev*. 2022;43(5):763-793.

doi: 10.1210/endrev/bnac003

111. Khalil EM, Madney YM, Hassan M, *et al*. Maternal and fetal outcome of COVID-19 infection among pregnant women. *Medicina*. 2024;60(10):1676.

doi: 10.3390/medicina60101676

112. Kashif A, Chekera M, Malakasis A, Sarli V, Machairiotis N. Mediterranean diet as a management strategy for gestational diabetes mellitus: a narrative review of the literature. *Cureus*. 2025;17(1):e76906.

doi: 10.7759/cureus.76906

113. Rasmussen L, Knorr S, Antoniussen CS, *et al*. The impact of lifestyle, diet and physical activity on epigenetic changes in the offspring—a systematic review. *Nutrients*. 2021;13(8):2821.

doi: 10.3390/nu13082821

114. Krishnaveni GV, Hill JC, Veena SR, *et al*. Low plasma vitamin B12 in pregnancy is associated with gestational 'diabesity' and later diabetes. *Diabetologia*. 2009;52(11):2350-2358.

doi: 10.1007/s00125-009-1499-0

115. Sukumar N, Rafnsson SB, Kandala NB, Bhopal R, Yajnik CS, Saravanan P. Prevalence of vitamin B-12 insufficiency during pregnancy and its effect on offspring birth weight: a systematic review and meta-analysis. *Am J Clin Nutr*. 2016;103(5):1232-1251.

doi: 10.3945/ajcn.115.123083

116. Gernand AD, Schulze KJ, Stewart CP, West KP Jr, Christian P. Micronutrient deficiencies in pregnancy worldwide: health effects and prevention. *Nat Rev Endocrinol*. 2016;12(5):274-289.

doi: 10.1038/nrendo.2016.37

117. Rogne T, Tielemans MJ, Chong MFF, *et al*. Associations of maternal vitamin B12 concentration in pregnancy with the risks of preterm birth and low birth weight: a systematic review and meta-analysis of individual participant data. *Am J Epidemiol*. 2017;185(3):212-223.

doi: 10.1093/aje/kww212

118. Kalra B, Kalra S, Sharma JB. The inositols and polycystic ovary syndrome. *Indian J Endocrinol Metab*. 2016;20(5):720-724.

doi: 10.4103/2230-8210.189231

119. Palomba S, Falbo A, La Sala GB. Clomiphene citrate, metformin or aromatase inhibitors for anovulatory infertility in women with polycystic ovary syndrome (PCOS): a systematic review of meta-analyses and randomized controlled trials. *Clin Immunol Endocr Metab Drugs*. 2014;1(1):2-10.

doi: 10.2174/22127070114019990001