Vitamin B\textsubscript{12}: Insights into Health Implications and Diagnostic Challenges

Aoxuan Li*
Department of Chemistry, University of Toronto, Toronto, M5S 3H6, Canada
* Corresponding author: aoxuan.li@mail.utoronto.ca

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1. Introduction

A water-soluble element essential to various physiological processes is vitamin B\textsubscript{12}, sometimes referred to as cobalamin. Its roles include producing DNA, building red blood cells, balancing the nervous system, and promoting amino and fatty acid metabolism. Maintaining proper vitamin B\textsubscript{12} levels is crucial because a deficiency has been linked to various health problems, from anemia to neurological disorders. This thesis explores the complex interactions between vitamin B\textsubscript{12} status, health effects, and the difficulties in diagnosing the vitamin's levels. In recent years, an increasing corpus of studies has shed light on the complex connection between vitamin B\textsubscript{12} and health outcomes. A thorough description of the many methods by which vitamin B\textsubscript{12} contributes to general health. It sheds insight into the complex pathways connecting a lack of vitamin B\textsubscript{12} to anemia, neuropathy, and cognitive deficits, emphasizing the possible effects of low vitamin B\textsubscript{12} levels.

One topic of particular concern is how vitamin B\textsubscript{12} affects pregnancy-related issues. A review and refined analysis of empirical evidence by Van Welden et al. suggest that vitamin B\textsubscript{12} and folic acid potentially reduce the incidence of gestational diabetes [1]. The results of this study highlight the importance of understanding the mother and fetus and their susceptibility to vitamin B\textsubscript{12} deficiency. This study explored the role of vitamin B\textsubscript{12} in promoting and aiding metabolic health [1]. This study reveals the complex relationships between vitamin B\textsubscript{12} status and metabolic dysregulation, shedding important light on prospective treatment approaches for treating metabolic problems linked to obesity. Furthermore, studies shed light on the intergenerational effects of vitamin B\textsubscript{12} status [1, 2]. These studies emphasize the extensive effects of vitamin B\textsubscript{12} deficiency on epigenetic changes and the possible ramifications for child health outcomes. Sobczyńska-Malefora et al. (2021) determined that vitamin B\textsubscript{12} deficiency poses special difficulties [3]. Clinical and laboratory indicators must be considered for an accurate evaluation outcome, including serum levels, functional markers, and patient-specific characteristics.

To fully address the state of vitamin B\textsubscript{12} in the human body, this thesis intends to consolidate the results from various investigations. This research endeavor advances knowledge of the vital function of vitamin B\textsubscript{12} in preserving good health by exploring the complex web of relationships between vitamin B\textsubscript{12} levels and various health consequences and illuminating diagnostic complexities. This article will examine the details covered by this research in more detail in the following sections, highlighting how vitamin B\textsubscript{12} affects human health.
2. Vitamin B₁₂ Metabolism and Functions

Biochemical pathways and vitamin B₁₂ absorption are complex regulatory processes essential for maintaining optimal cell function and overall health. First, it is important to understand the biochemical pathways of vitamin B₁₂, released from dietary proteins in our lives through a series of chemical reactions. It leads to the mediated absorption of endogenous factors and allows vitamin B₁₂ to function successfully after the steps associated with cellular uptake and conversion of the two enzymes through haptocorrin or transcobalamin-mediated transport [3]. At the same time, the significance of these pathways was disclosed [3]. Only foods containing animal products, such as meat, may provide vitamin B₁₂, and its absorption involves several intricate procedures. A glycoprotein, an intrinsic factor secreted by the stomach, is necessary for the small intestine ileum to absorb vitamin B₁₂. Malabsorption can result from any disturbance in this process.

For the two endogenous enzyme conversions of vitamin B₁₂ in the body, methyl cobalamin and adenosyl cobalamin are active forms of vitamin B₁₂ that help maintain enzyme function [3]. The CD320 receptor detects the vitamin B₁₂ carrier protein holoTC on the cell surface. cbIC enters the cell, and the mitochondrial version of cbID attaches to the cbIC, where this protein drives vitamin B₁₂ to the mitochondria and deacidifies methyl cobalamin, adenosyl cobalamin, and cyanocobalamin to cobalamin, among other functions. Methionine synthetase, an enzyme that methylates homocysteine to methionine, catalyzes the cofactor of methyl alanine’s methylmalonyl-CoA altering enzyme, supporting its conversion to adenosyl cobalamin (Ado-Cbl). Succinyl-CoA, utilized in propionic acid's metabolism and oxidation, is created from the conversion of diacyl-coa [3].

In addition, vitamin B₁₂ can participate in synthesizing important chemicals in the body as a coenzyme in key reactions, including DNA synthesis, methionine synthesis, and myelin maintenance. Negative health effects of vitamin B₁₂ deficiency. Sobczyńska-Malefora et al. further highlighted the impact of insufficient vitamin B₁₂ levels [3]. Anemia, neurological abnormalities, and poor DNA synthesis are just a small subset of the health problems caused by inadequate levels of vitamin B₁₂. A case of vitamin deficiency in a 52-year-old British man who developed "pernicious anemia" after vitamin B₁₂ deficiency but effectively recovered after treatment with the patient's liver [3]. This case can be very straightforward to show that after a vitamin B₁₂ deficiency, the body cannot autonomously synthesize the chemicals needed to maintain the body's red blood cells, so the symptoms of so-called anemia are produced.

3. Diagnosis of Vitamin B₁₂ Deficiency

Note that symptoms of deficiency syndrome can be subtle and nonspecific, making accurate diagnosis challenging [3]. Common laboratory markers, such as serum vitamin B₁₂ levels, can be misleading due to their limitations in reflecting tissue availability. This emphasizes the need for an integrated diagnostic approach, considering clinical symptoms and other biomarkers such as methylmalonic acid and transcobalamin levels. Sobczyńska-Malefora et al. also highlights the complexity of diagnosing functional insufficiency, which may exist despite normal serum levels [3].

A typical example is the neurological symptoms of low vitamin B₁₂ levels in younger people due to delayed cobalamin C (CbIC) deficiency. Schiemsky and co-workers reported a case involving a woman aged 23 who showed normal vitamin B₁₂ and folate levels on routine laboratory tests but developed a cobalamin C deficiency the following time [4]. Therefore, these patients must identify Hcys and/or methylmalonic acid to rule out this neurological disorder [4]. Identifying and medically managing conditions resulting from inadequate vitamin B₁₂ levels presents considerable challenges. Carmel (2008) states that the clinical treatment of cobalamin deficiency has become more complex over time, while the inference that biochemical expression is related to the pathophysiological determinants of cobalamin deficiency seems to be less effective now that biochemical and molecular techniques have made significant advances [5].

When diagnosing vitamin B₁₂ deficiency, clinical and laboratory methods are necessary. Clinical manifestations, including fatigue, anemia, and neurological symptoms, often guide the diagnosis.
However, these symptoms are not specific and may overlap with other health problems, so further tests are needed to confirm the diagnosis. Laboratory testing of vitamin B$_{12}$ levels is a common method and is typically evaluated by determining the level of vitamin B$_{12}$ in the blood serum. In the early days, Minot used a reticulocytic counting method, which can take advantage of the conjugated double bond system contained in vitamin B$_{12}$, which gives vitamin B$_{12}$ a red state at high concentrations \cite{3}. However, a single test result may not accurately reflect the bioavailability and intracellular storage of vitamin B$_{12}$, so it is necessary to consider multiple indicators, such as serum methionine, homocysteine and methylmalonate monoacyl-coA.

Despite multiple diagnostic methods, there are still many challenges and potential pitfalls in diagnosing vitamin B$_{12}$ deficiency. Sobczyska-Malefora et al. pointed out that common disease states, such as liver disease, thyroid problems, and bone marrow abnormalities, may affect vitamin B$_{12}$ metabolism and absorption, leading to misdiagnosis or missed diagnosis \cite{3}. In addition, certain populations, such as older people and vegetarians, are more prone to vitamin B$_{12}$ deficiency, but its symptoms may not be obvious, adding to the difficulty of diagnosis.

4. Gestational Diabetes Mellitus and Vitamin B$_{12}$

Gestational diabetes mellitus (GDM) is a significant health problem during pregnancy because of its potential adverse consequences for maternal and newborn health. Recent investigations have highlighted a complicated link between the levels of vitamin B$_{12}$ and the potential to develop gestational diabetes. A disparity in vitamin B$_{12}$ levels during pregnancy can increase the likelihood of developing gestational diabetes mellitus (GDM) \cite{1}. The study found that the risk of GDM was still higher even when folic acid was sufficient, but vitamin B$_{12}$ was insufficient. Research has also unveiled a connection between decreased levels of vitamin B$_{12}$ and GDM. This relationship was scrutinized extensively, offering vital perspectives on the functionality of vitamin B$_{12}$ and its influence on GDM susceptibility \cite{1}. The researchers employed a comprehensive approach and deductive analysis techniques to thoroughly examine numerous observational studies, thereby achieving a more intricate comprehension of the role played by vitamin B$_{12}$ in GDM \cite{1}. The results underscore the significance of maintaining appropriate vitamin B$_{12}$ levels in mitigating the risk of gestational diabetes. Various studies have documented that a deficiency in vitamin B$_{12}$ could escalate the probability of contracting GDM \cite{1}. By amalgamating data from diverse sources, the research establishes a robust groundwork for deciphering the intricacies of this association.

Van Weelden et al. claimed they took blood samples from women at 23-30 weeks’ gestation and stored them at -80 °C \cite{1}. They collected umbilical cord blood immediately after birth, checked the purity of the DNA, and used chemiluminescent particle immunoassay to measure the concentrations of various substances in the serum, and they found a causal relationship between maternal levels of folic acid and vitamin B$_{12}$ and DNA methylation in infants. Additionally, they discovered that pregnant obese women with low micronutrient status had higher BMI \cite{1}. Overall, the study highlights the importance of vitamin B$_{12}$ in gestational diabetes. They emphasize the need for comprehensive maternal nutrition assessments during pregnancy, especially for high-risk groups such as obese women. The findings highlight the potential of vitamin B$_{12}$ status as a modifiable factor affecting the risk of GDM. In addition, complex interactions between vitamin B$_{12}$ and other nutrients, such as folic acid, influence maternal blood sugar levels and neonatal DNA methylation patterns, suggesting that GDM prevention and management should take a multifaceted approach.

5. Vitamin B$_{12}$, Folate, and Metabolic Syndrome

Obesity, insulin resistance, high blood pressure, and dyslipidemia are four interconnected risk factors that comprise the metabolic syndrome and pose a significant threat to public health due to its association with cardiovascular disease and type 2 diabetes. Woo et al. shed light on the complex relationship between vitamin B$_{12}$, folate, and metabolic syndrome, revealing potential pathways for
prevention and management [6]. They examined the correlation between blood homocysteine, folic acid, and vitamin B\textsubscript{12} and the prevalence of MetS in Korean people over 40 [6]. Higher levels of homocysteine (Hcy) are positively correlated with the risk of metabolic syndrome (MetS); however, greater blood vitamin B\textsubscript{12} levels were only statistically connected with MetS in men, and folic acid concentration in serum is not correlated with the condition [6]. This study advances understanding of the complex biochemical interactions that lead to the development of metabolic syndrome, highlights the potential of these nutrients as modifiable factors in its pathogenesis, and states that there is no direct link between higher serum vitamin B\textsubscript{12} levels and MetS in women.

6. **Childhood Acute Lymphoblastic Leukemia and Methylation**

Studying the correlation mechanism between maternal folate content, infant vitamin B\textsubscript{12} reserve and gene methylation and discussing their effects on childhood acute lymphoblastic leukemia (ALL) has become an important study and discovery in the study of vitamin B\textsubscript{12} status. First, concerning maternal folic acid levels, Potter et al. claimed that the genetic epigenetic landscape that may affect a child's propensity to develop acute lymphoblastic leukemia (ALL) is significantly shaped by the maternal consumption of folic acid [2]. Based on the study data, they reported that 73.5 \% of people showed methylation changes in the relevant direction due to folic acid consumption, and maternal folic acid consumption may contribute to the pathogenic pathway by altering DNA methylation of ALL related genes [2]. Through the analysis and scrutiny of DNA methylation patterns linked with leukemia, coupled with the integration of their experimental data with the subjects of their study, they suggest that the abnormal process of DNA methylation, which is a risk factor for ALL in children, might be linked to the mother's absorption of folic acid. Specifically, they indicate that the methylation of the SH3GL3 and ASCL2 correlates with maternal folate and infantile vitamin B\textsubscript{12} levels, respectively. By conducting statistical evaluations on genes linked with maternal folate and newborn vitamin B\textsubscript{12} levels, they unequivocally demonstrated the impact of methylation on maternal folate and neonatal vitamin B\textsubscript{12} statuses. Moreover, they noted the presence of negative correlations between the mean DNA methylation in the genes and maternal and infant vitamin B\textsubscript{12} concentrations, along with folate levels [2]. Drawing from the statistical correlations observed, it can be deduced that sustaining appropriate levels of maternal folic acid and infant vitamin B\textsubscript{12} can act as a potent strategy to lessen the probability of disease manifestation in the progeny. The likelihood of DNA methylation occurrences is heightened when maternal folate and infant vitamin B\textsubscript{12} concentrations swing to extremes - exceedingly high or low.

7. **Dysglycaemia, DNA Methylation, and Pregnancy**

Nutritional balance during pregnancy is thought to reduce metabolic problems in the newborn, thereby minimizing obesity and health problems in childhood and later. ÜNSÜR and KINAŞ (2020) indicated that the concentrations of vitamin B\textsubscript{12} and folic acid in expectant mothers have a significant correlation with the growth markers of neonates, and maintaining optimal levels of these nutrients is linked with favorable newborn metrics such as weight, length, and head circumference among others [7]. This implies that adequate intake of vitamin B\textsubscript{12} and folic acid during the gestational period is pivotal for the regular development of the fetus. Furthermore, the glucose levels in mothers during the gestational period are linked with the metabolic state of the neonate. One investigation found that 3.7\% of females grappling with GDM exhibited a deficiency in folate [1]. Therefore, high glucose levels in pregnant women may lead to an imbalance of folate in the blood of these pregnant women, which can lead to metabolic abnormalities in the newborn, as already mentioned. At the same time, higher maternal BMI is associated with lower vitamin B\textsubscript{12} levels, which may have related health consequences, including maternal and infant diseases, fatigue, anemia, and neurological defects due to deficiency and poor vitamin B\textsubscript{12} [1]. Therefore, it is recommended that maintaining optimal vitamin B\textsubscript{12} and folic acid levels while controlling blood glucose levels and controlling maternal BMI during
pregnancy play an important role in the health of the newborn (to reduce metabolic, obesity and other problems in the newborn). At the same time, findings from ÜNSÜR and KINAYAŞ (2020) elucidate how insufficient vitamin B\textsubscript{12} and folate levels during pregnancy could influence the DNA methylation patterns in embryos [7]. DNA methylation serves a crucial function in the modulation of gene expression and can influence fetal growth, metabolism and developmental programming. The study examined the correlation between folate status and infant DNA methylation in mothers over 28 weeks gestation. They measured DNA methylation of genes in the cord blood of 23 newborns and found different methylated CPGS in various regions of the genome [1]. Their results also revealed a hypomethylated region upstream of the ZFP57 transcription that regulates DNA methylation in early pregnancy. The findings strongly suggest that maternal folic acid status affects DNA methylation genes in newborns, so it is important to maintain maternal folic acid and vitamin levels.

8. Vitamin B\textsubscript{12} Status in Infancy and Interventions

After studying the health problems caused by maternal blood levels of folic acid and vitamin B\textsubscript{12} during pregnancy, the newborn also depends on vitamin B\textsubscript{12} during infant development. Infancy is a rapid growth and development period, and the need for vitamins and minerals is particularly critical. Vitamin B\textsubscript{12} is key in protein synthesis, DNA repair, nervous system development and more. However, Bakken et al. reported that some newborns may have a subclinical deficiency of vitamin B\textsubscript{12} as early as infancy [8]. They conducted a randomized controlled trial [8]. Through this trial, the investigators plan to administer vitamin B\textsubscript{12} injections in infants to assess whether the injections positively affect infants with subclinical vitamin B\textsubscript{12} deficiency. Meanwhile, the goal of this experiment is multifaceted [8]. Firstly, the research sought to ascertain the real condition of vitamin B\textsubscript{12} levels during infancy, highlighting the disparities between healthy infants and those experiencing subclinical deficiencies. Secondly, the researchers assessed the impact of vitamin B\textsubscript{12} injections on infants grappling with subclinical deficiencies (focusing on improvements in growth and development, nervous system function, and other relevant measures). They conducted an intervention on the subjects and samples. They took blood samples from all infants in the study before randomization, analyzed plasma cobalamin concentrations, evaluated them, and used statistical methods to analyze the results and verify the accuracy of the experimental results [8]. Symptoms of slow neurodevelopment and growth following vitamin B\textsubscript{12} (cobalamin) deficiency in infants had a significant but small beneficial effect with a regimen of 1.8 µg of vitamin B\textsubscript{12} daily for 6 months. Moreover, randomized controlled trials on infants exhibiting low body weight or developmental lag have demonstrated that a solitary intramuscular injection containing 400 µg of ox cobalamin markedly influences short-term motor development [8].

By comparison, firstly, a single intramuscular injection dosing regimen may provide faster vitamin B\textsubscript{12} supplementation effects, as high doses of injections can rapidly increase vitamin B\textsubscript{12} levels in the body. In contrast, the oral dosing regimens last longer and may be more beneficial for maintaining vitamin B\textsubscript{12} levels over the long term. Second, although the single injection dose is high, more frequent supplementation may be required because of the metabolic role of vitamin B\textsubscript{12} in the body. The oral dosing regimens, taken daily, may be more suitable for individuals who cannot receive frequent injections while also helping to maintain stable vitamin B\textsubscript{12} levels. Therefore, intramuscular injection of 400 µg hydroxycobalamin may have better effects and side effects on infant development for newly emerging and developing infants. In addition, small randomized controlled trials can show significant beneficial effects of high doses of ox cobalamin in clinical populations [8].

While other studies have shown that later supplementation can effectively improve vitamin B\textsubscript{12} deficiency in infancy, vitamin B\textsubscript{12} supplementation significantly affects the neurodevelopment and growth of infants, who improve their cognitive and motor skills after vitamin B\textsubscript{12} supplementation [9]. Strand et al. described how vitamin B\textsubscript{12} intake affects the vitamin status of vulnerable populations, discussing vegetarians, older adults, and pregnant women who are found to be more susceptible to vitamin B\textsubscript{12} deficiency due to dietary restrictions, age-related factors, and during pregnancy [10].
Therefore, these people should monitor their health more closely and take vitamin B\textsubscript{12} supplements quickly.

9. Conclusion

Cellular processes, maintenance of health, gestational diabetes, and metabolic syndrome are all significantly affected by vitamin B\textsubscript{12}. Due to the complexity of its metabolic pathways, vitamin B\textsubscript{12} absorption and metabolism may need to be controlled by internal variables. Vitamin B\textsubscript{12} deficiency can lead to anemia, neurological problems, and problems with DNA synthesis. Vitamin B\textsubscript{12} deficiency is difficult to identify and requires a combination of clinical symptoms and laboratory test results. In particular, delayed CblC deficiency causes neurological symptoms, vitamin B\textsubscript{12} and folate levels are strongly associated with good development in pregnant women and babies, and DNA methylation is also associated with these vitamin states. To prevent and treat various health problems, maintaining proper vitamin B\textsubscript{12} and folate levels is essential. In infancy, injecting high doses of vitamin B\textsubscript{12} may positively affect subclinical deficiency, but the choice of intervention should be based on individual circumstances. Therefore, it is emphasized that the maternal monitoring of nutrients such as vitamin B\textsubscript{12} and folic acid during gestation ensures that the maternal body maintains the ideal levels of vitamin B\textsubscript{12} and folic acid, thereby averting a range of illnesses in infancy. In addition, when studying vitamin B\textsubscript{12} function on infant deficiency symptoms in the future, we can try to find a way to maintain the stability of vitamin B\textsubscript{12} during infant growth to replace the short board that high-dose vitamin B\textsubscript{12} injection will gradually metabolize in the infant's body and avoid the inconvenience of frequent vitamin B\textsubscript{12} consumption in infants.

References