Vitamin B_{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_{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_{12} levels is crucial because a deficiency or deficiency has been linked to various health problems, from anemia to neurological disorders. This thesis explores the complex interactions between vitamin B_{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_{12} and health outcomes. A thorough description of the many methods by which vitamin B_{12} contributes to general health. It sheds insight into the complex pathways connecting a lack of vitamin B_{12} to anemia, neuropathy, and cognitive deficits, emphasizing the possible effects of low vitamin B_{12} levels.

One topic of particular concern is how vitamin B_{12} affects pregnancy-related issues. A review and refined analysis of empirical evidence by Van Welden et al. suggest that vitamin B_{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_{12} deficiency. This study explored the role of vitamin B_{12} in promoting and aiding metabolic health [1]. This study reveals the complex relationships between vitamin B_{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_{12} status [1, 2]. These studies emphasize the extensive effects of vitamin B_{12} deficiency on epigenetic changes and the possible ramifications for child health outcomes. Sobczyńska-Malefora et al. (2021) determined that vitamin B_{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_{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_{12} in preserving good health by exploring the complex web of relationships between vitamin B_{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_{12} affects human health.

2. Vitamin B_{12} Metabolism and Functions

Biochemical pathways and vitamin B_{12} 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 B_{12}, 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 B_{12} 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 B_{12}, 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 B_{12}. Malabsorption can result from any disturbance in this process.

For the two endogenous enzyme conversions of vitamin B_{12} in the body, methyl cobalamin and adenosyl cobalamin are active forms of vitamin B_{12} that help maintain enzyme function [3]. The CD320 receptor detects the vitamin B_{12} carrier protein holoTC on the cell surface. cblC enters the cell, and the mitochondrial version of cblD attaches to the cblC, where this protein drives vitamin B_{12} 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 B_{12} 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 B_{12} deficiency. Sobczysska-Malefora et al. further highlighted the impact of insufficient vitamin B_{12} levels [3]. Anemia, neurological abnormalities, and poor DNA synthesis are just a small subset of the health problems caused by inadequate levels of vitamin B_{12}. A case of vitamin deficiency in a 52-year-old British man who developed "pernicious anemia" after vitamin B_{12} deficiency but effectively recovered after treatment with the patient's liver [3]. This case can be very straightforward to show that after a vitamin B_{12} 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 B_{12} Deficiency

Note that symptoms of deficiency syndrome can be subtle and nonspecific, making accurate diagnosis challenging [3]. Common laboratory markers, such as serum vitamin B_{12} 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 B_{12} levels in younger people due to delayed cobalamin C (CblC) deficiency. Schiemsky and co-workers reported a case involving a woman aged 23 who showed normal vitamin B_{12} 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 B_{12} 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 B_{12} 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 [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. Sobczhyska-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 [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) [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 [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 [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 [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 [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 [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_{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_{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_{12} levels and MetS in women.

6. Childhood Acute Lymphoblastic Leukemia and Methylation

Studying the correlation mechanism between maternal folate content, infant vitamin B_{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_{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_{12} levels, respectively. By conducting statistical evaluations on genes linked with maternal folate and newborn vitamin B_{12} levels, they unequivocally demonstrated the impact of methylation on maternal folate and neonatal vitamin B_{12} statuses. Moreover, they noted the presence of negative correlations between the mean DNA methylation in the genes and maternal and infant vitamin B_{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_{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_{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_{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_{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_{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_{12} [1]. Therefore, it is recommended that maintaining optimal vitamin B_{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 KINAŞ (2020) elucidate how insufficient vitamin B_{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 transcriptor 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_{12} Status in Infancy and Interventions

After studying the health problems caused by maternal blood levels of folic acid and vitamin B_{12} during pregnancy, the newborn also depends on vitamin B_{12} during infant development. Infancy is a rapid growth and development period, and the need for vitamins and minerals is particularly critical. Vitamin B_{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_{12} as early as infancy [8]. They conducted a randomized controlled trial [8]. Through this trial, the investigators plan to administer vitamin B_{12} injections in infants to assess whether the injections positively affect infants with subclinical vitamin B_{12} deficiency. Meanwhile, the goal of this experiment is multifaceted [8]. Firstly, the research sought to ascertain the real condition of vitamin B_{12} levels during infancy, highlighting the disparities between healthy infants and those experiencing subclinical deficiencies. Secondly, the researchers assessed the impact of vitamin B_{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_{12} (cobalamin) deficiency in infants had a significant but small beneficial effect with a regimen of 1.8 μg of vitamin B_{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_{12} supplementation effects, as high doses of injections can rapidly increase vitamin B_{12} levels in the body. In contrast, the oral dosing regimens last longer and may be more beneficial for maintaining vitamin B_{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_{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_{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_{12} deficiency in infancy, vitamin B_{12} supplementation significantly affects the neurodevelopment and growth of infants, who improve their cognitive and motor skills after vitamin B_{12} supplementation [9]. Strand et al. described how vitamin B_{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_{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_{12} supplements quickly.

9. Conclusion

Cellular processes, maintenance of health, gestational diabetes, and metabolic syndrome are all significantly affected by vitamin B_{12}. Due to the complexity of its metabolic pathways, vitamin B_{12} absorption and metabolism may need to be controlled by internal variables. Vitamin B_{12} deficiency can lead to anemia, neurological problems, and problems with DNA synthesis. Vitamin B_{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_{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_{12} and folate levels is essential. In infancy, injecting high doses of vitamin B_{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_{12} and folic acid during gestation ensures that the maternal body maintains the ideal levels of vitamin B_{12} and folic acid, thereby averting a range of illnesses in infancy. In addition, when studying vitamin B_{12} function on infant deficiency symptoms in the future, we can try to find a way to maintain the stability of vitamin B_{12} during infant growth to replace the short board that high-dose vitamin B_{12} injection will gradually metabolize in the infant's body and avoid the inconvenience of frequent vitamin B_{12} consumption in infants.

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