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VITAMIN B12 DEFICIENCY AS A CAUSE OF HEMATOLOGICAL ABNORMALITIES: DIAGNOSTIC AND THERAPEUTIC INSIGHTS

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Abstract

Vitamin B12 is also called cobalamin and it is necessary for the synthesis of DNA, nuclear maturation, and hematopoiesis. Deficiency of this essential nutrient has been a global health concern in people with low dietary intake, malabsorption, and increased physiological requirements. This review aims to bring together the current information regarding the chemistry, dietary intake, absorption, metabolism, and etiology of vitamin B12 deficiency, particularly its impact on the hematological system. Deficiency of this nutrient affects DNA synthesis in proliferating hematopoietic precursor cells, leading to ineffective erythropoiesis, as manifested as hematological abnormalities. These abnormalities are macrocytic anemia, leucopenia, thrombocytopenia, and pancytopenia. Alterations in red cell parameters, white blood cell morphology, platelet counts, and peripheral blood smear results are critically discussed. The diagnostic approach by different parameters such as hematological parameters, levels of vitamin B12, and operating parameters such as methyl malonic acid and homocysteine is reviewed. The therapeutic approach by supplements of vitamin B12, which are administered in oral and parenteral forms, and their impact on hematological parameters are discussed. The public health implications and preventive measures are highlighted with the gaps in the research in vitamin B12 deficiency and associated hematological disorders, which emphasize the need for detection and prevention of the condition.

INTRODUCTION

Vitamin B12 is a water soluble vitamin responsible for normal brain function, DNA synthesis and cellular metabolism. Food derived from animals is a source of cobalamin and it is absorbed by a complex process which includes terminal ileum and intrinsic factor (Ankar & Kumar, 2025). Vitamin B12 is used as cofactor along with methionine synthase and methylmalonyl-CoA mutase enzymes during cellular energy metabolism and nucleotide synthesis (R. Green, 2017). Although deficiency of vitamin B12 is global, it is more prevalent in underdeveloped nations. Vitamin B12 insufficiency is caused by malabsorption syndromes, pernicious anemia, gastrointestinal disorders, or prolonged use of certain medications (Sobczyńska-Malefora et al., 2021).

The main function of vitamin B12 in DNA synthesis and nuclear maturation of hematopoietic precursor cells makes it important for erythropoiesis. Deficiency of vitamin B12 disrupts DNA replication which results in intramedullary red blood cell

destruction precursor and ineffective erythropoiesis (R. Green, 2017). The usual symptom of vitamin B12 deficiency is megaloblastic anemia which is characterized by macrocytosis, decreased hemoglobin levels, increased mean corpuscular volume, and hyper segmented neutrophils (E. Andrès et al., 2006). Vitamin B12 insufficiency appears as a number of hematological anomalies such as normocytic or microcytic anemia when there are nutritional deficiencies or chronic inflammatory disorders (Aditya R Agrawal et al., 2024).

Besides affecting red blood cells, deficiency of vitamin B12 also affects various blood lineages resulting in severe leukopenia, thrombocytopenia, or pancytopenia (A. R. Agrawal et al., 2024). Vitamin B12 insufficiency affects both qualitative and quantitative blood cell indices, manifested by alteration in red cell distribution width (RDW), platelet indices, and reticulocyte counts (Aditya R Agrawal et al., 2024; E. Andrès et al., 2006). These non-specific symptoms make diagnosis complex, especially when MCV is used as sole indicator (Sobczyńska-Malefora et al., 2021).

Although vitamin B12 deficiency is a curable condition if treated timely, it is often overlooked or diagnosed late because of the variability of symptoms. Hence, a clear understanding of its influence on hematological values is necessary for early detection and effective management. The main aim of this review is to examine the existing information on the influence of vitamin B12 deficiency on hematological values such as leukocyte and platelet counts, and red blood cell parameters, and to emphasize the importance of early management.

Chemistry, Sources, and Metabolism

The only vitamin that incorporates a metal ion in its structure is vitamin B12. It is water soluble complex in nature and can be detected by the presence of a corrin ring that contains a cobalt (Kräutler, 2005). There are several biologically active vitamin B12, including methyl cobalamin and adenosylcobalamin, which act as coenzymes in the human body, while hydroxocobalamin and cyanocobalamin are commonly used in medications (O'Leary & Samman, 2010). Vitamin B12 is important in synthesis of DNA, one carbon metabolism, and the mitochondrial energy metabolism system because of its unique chemical structure (Moravcová et al., 2025).

Since humans are not capable of producing sufficient vitamin B12 on their own, they need to obtain it from their diet. Since vitamin B12 is only formed by bacteria and accumulates in animal tissues through the food chain, it is found in foods derived from animals like meat, liver, fish, eggs, and dairy products (Moravcová et al., 2025; Temova Rakuša et al., 2023). Since biologically active vitamin B12 is absent in plant foods, vegetarians and vegans are more susceptible to vitamin B12 deficiency unless they consume vitamin B12 supplements or vitamin B12 fortified meals (O'Leary & Samman, 2010). Food processing and gastrointestinal factors may have a potential effect on the availability of vitamin B12 from the diet (Temova Rakuša et al., 2023).

Vitamin B12 absorption is a sophisticated and finely tuned process. Gastric acid and pepsin in the stomach release dietary cobalamin from food proteins, which then binds to haptocorrin (R-protein), secreted in saliva and gastric fluids (Kozyraki & Cases, 2013). Vitamin B12 can bind intrinsic factor, a glycoprotein produced by gastric parietal cells, after pancreatic enzymes degrade haptocorrin in the duodenum. The cubilin amnionless receptor complex is part of the receptor mediated endocytosis responsible for absorption of vitamin B12 intrinsic factor complex in the terminal ileum (Kozyraki & Cases, 2013; Moravcová et al., 2025). After absorbing, more vitamin B12 is transported in the bloodstream in a bound form with haptocorrin as a storage and transport form, while the majority is transported in a bound form with trans cobalamin II, which facilitates cellular uptake (E. Andrès et al., 2006). Approximately 50-60% of the total of vitamin B12 is in the liver, which is the main storage site. Under normal conditions, the liver has adequate storage to meet the physiological requirements for several years (Moravcová et al., 2025). Due to the reabsorption of biliary excreted cobalamin in the colon, the enterohepatic circulation also helps conserve vitamin B12 (Kräutler, 2005). Any disruption in the process of absorption, transport, and storage of vitamin B12 can result in a deficiency of vitamin B12, which may have hematological and metabolic consequences.

Etiology and Risk Factors of Vitamin B12 Deficiency

Nutritional deficiency, particularly in communities that do not consume many foods of animal origin, is primary reasons for vitamin B12 deficiency (Figure 01). Vegetarians and vegans are particularly vulnerable unless they consume supplements or enriched food because vitamin B12 is produced by microbes and is found in foods of animal (L. H. Allen, 2008; O'Leary & Samman, 2010). Nutritional deficiencies are also common in underdeveloped countries due to poor consumption of animal proteins, food insecurity, and lack of finances (L. H. Allen, 2008). Vitamin B12 deficiency in infants can also happen if the mother is a vitamin B12 deficient individual and the infant is breastfed without any supplements (S. P. Stabler, 2013).

The most common underlying cause of vitamin B12 insufficiency of a medical severity is malabsorption. Intrinsic factor deficiency is the characteristic feature of pernicious anemia, an inflammatory condition that remains a leading cause in adults, particularly in the elderly (R. Green, 2017). Helicobacter pylori infection, Crohn's disease, chronic atrophic gastritis, and celiac disease involving the terminal ileum, and post gastrectomy or bariatric surgery are other gastrointestinal disorders that impair absorption (E. Andrès et al., 2006; Quadros, 2010). The frequency of vitamin B12 deficiency in older people is also raised by age related gastric hypochlorhydria, which also inhibits the liberation of vitamin B12 from dietary proteins (S. P. Stabler, 2013).

Vitamin B12 insufficiency has been strongly related to the long term use of certain medications. The calcium dependent mechanism of the ileum in absorbing the vitamin B12 intrinsic factor complex is also affected by metformin, which is commonly prescribed for type 2 diabetes mellitus. The high dose and longer duration of treatment increases the risk of deficiency (de Jager et al., 2010). H2 receptor antagonists and Proton pump are examples of acid suppressive medications that reduce gastric acid secretion, which in turn affects the secretion of vitamin B12 from dietary proteins (Langan & Zawistoski, 2011). Such drug induced side effects are particularly dangerous in older patients and in individuals who possess pre-existing risk factors.

Vitamin B12 deficiency also affects certain people. Older people are at risk due to low nutritional intake, poor absorption, multiple medications, and age related gastrointestinal disorders (R. Green, 2017). Pregnant and lactating women require higher amounts of vitamin B12, and deficiency during pregnancy can cause adverse outcomes for both the mother and the baby (S. P. Stabler, 2013). People with genetic disorders related to cobalamin transport and metabolism, as well as those with chronic conditions like diabetes mellitus, autoimmune disorders, and gastrointestinal diseases, are also at risk (Sobczyńska-Malefora et al., 2021).Taken together, these risk factors indicate the heterogeneity of vitamin B12 deficiency and the need for targeted screening strategies in high-risk populations (Figure 01).

Pathophysiology of Vitamin B12 Deficiency

Methionine synthase, an enzyme that catalyzes the conversion of homocysteine to methionine, requires vitamin B12 as a co-factor, simultaneously converting 5-methyltetrahydrofolate to tetrahydrofolate (Figure 02). Without vitamin B12, folate is locked in its form as 5-methyltetrahydrofolate, a process referred to as the methyl-folate trap. This causes defective DNA synthesis, as it affects thymidine and purine synthesis, leading to defective DNA replication (Ralph Green, 2017). Defective DNA synthesis causes nuclear/cytoplasmic asynchrony in developing erythroid precursor cells (Figure 02). The cytoplasm of these precursor cells normally matures, but nuclear maturation is delayed due to defective DNA replication (Figure 02). This causes these precursor cells to become enlarged with immature nuclei, a characteristic referred to as megaloblastic change. Most of these abnormal precursor cells undergo apoptosis in the bone marrow, resulting in ineffective erythropoiesis, intramedullary destruction of these precursor cells, and consequently, decreased mature circulating red blood cells (O'Leary & Samman, 2010). In vitamin B12 deficiency, bone marrow examination usually reveals hyper cellular marrow with megaloblastic changes in hematopoiesis (Figure 02). Large erythroid precursors, giant metamyelocytes, and abnormal megakaryocytes are frequently seen. This is due to defective DNA synthesis, as it affects all rapidly dividing cell lines, including those of hematopoietic cells, which may

lead to pancytopenia in severe cases (Ralph Green, 2017). Vitamin B12 deficiency causes a variety of characteristic hematological changes, which can be easily detected by routine investigations.

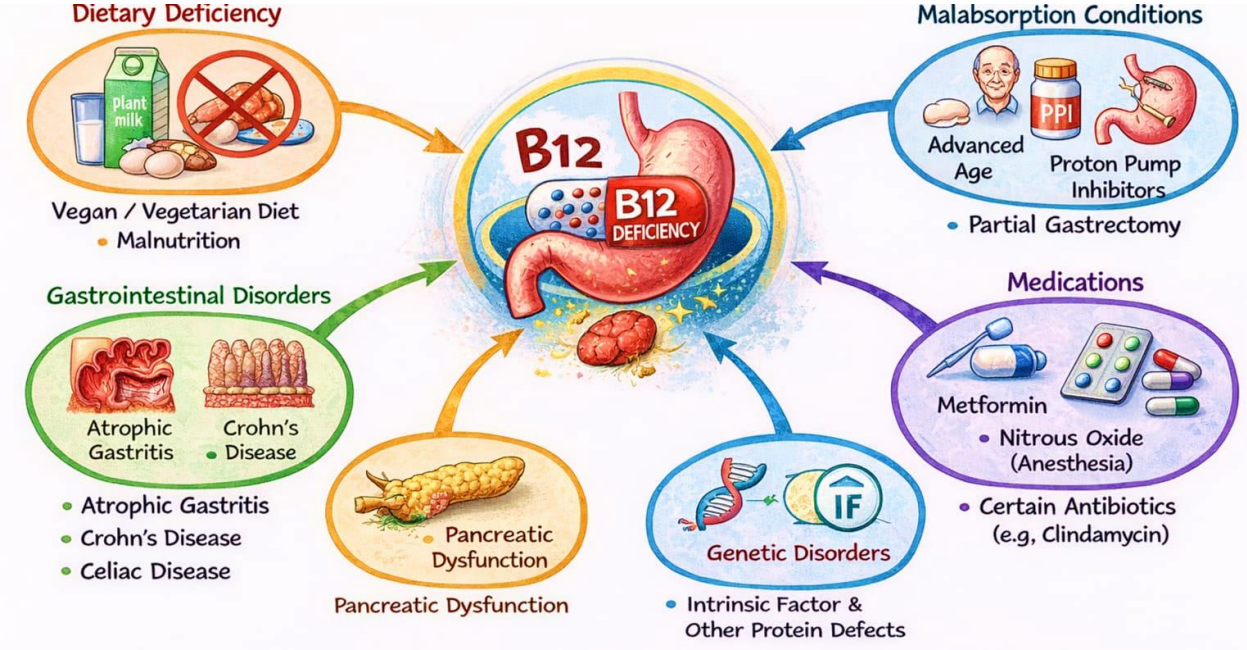

Fig 01. Etiology of Vitamin B12 deficiency (insufficient intake, impaired absorption, or increased demand.

The ineffective erythropoiesis causes macrocytic anemia, as evidenced by an increase in mean corpuscular volume (MCV) and decreased levels of hemoglobin. The peripheral blood smear reveals macro ovalocytes and hypersegmented neutrophils, which are considered hallmarks of megaloblastic anemias (Figure 02). Hypersegmented neutrophils develop as a secondary phenomenon of defective DNA synthesis in granulocyte precursors, resulting in abnormal nuclear development. The presence of neutrophils with more than five nuclear segments is associated with vitamin B12 insufficiency (Hoffbrand et al., 2016). Other than the hematological effects, vitamin B12 deficiency has significant neurological effects as well. The metabolism of methylmalonyl-CoA to succinyl-CoA needs vitamin B12 in the action of the enzyme methylmalonyl-CoA mutase. Vitamin B12 insufficiency leads to the buildup of the methyl malonic acid thus disrupting the metabolism of fatty acids in the production of myelin, leading to demyelination of peripheral nerves and the spinal cord thus leading to neurological symptoms like paresthesia, gait disturbance and impaired thinking (Sally P Stabler, 2013). From the biochemical point of view, vitamin B12 insufficiency is associated with high levels of homocysteine and methyl malonic acid in the serum. These compounds are produced due to the failure of the enzymatic processes in the body, which are dependent on vitamin B12. The level of methyl malonic acid is said to be a sensitive indicator of vitamin B12 insufficiency, especially in conditions where the level of vitamin B12 is borderline (Figure 02). The presence of these compounds is said to be responsible for the blood and neurological abnormalities observed in the body of the affected persons (Langan & Goodbred, 2017). Rapidly dividing epithelial cells in the gastrointestinal tract are also affected by impaired DNA synthesis. As such, patients suffering from vitamin B12 deficiency may experience glossitis, atrophy of the mucosa, anorexia, gastrointestinal symptoms, etc., contributing to worsening nutritional status (Langan & Goodbred, 2017).

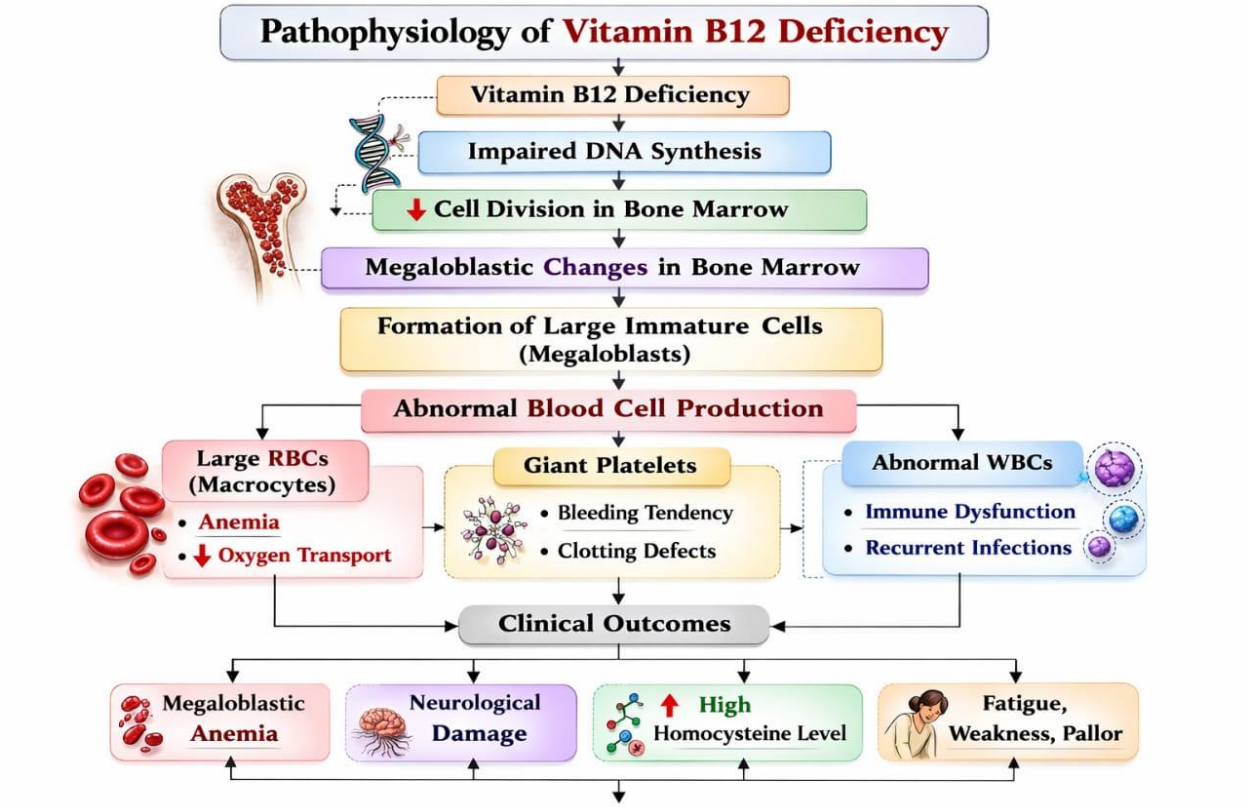

Fig 02. Vitamin B12 deficiency disrupts DNA synthesis and myelin formation, leading to megaloblastic anemia and neurological dysfunction

Effect of Vitamin B12 Deficiency on Hematological Parameters

Vitamin B12 deficiency results in a distinctive set of hematological abnormalities that indicate ineffective hematopoiesis. Among these abnormalities, macrocytic anemia is the most frequently observed. Clinical studies have established that patients with a deficiency in cobalamin exhibit elevated mean corpuscular volume (MCV) greater than 100 fL, low hemoglobin levels, and high red cell distribution width (RDW), which indicates anisocytosis. These hematological abnormalities result from defective nuclear maturation and impaired erythroid precursor cell growth in the bone marrow (Emmanuel Andrès et al., 2006).

In vitamin B12 deficiency, ineffective erythropoiesis causes quantitative and qualitative abnormalities in the former red cells. This results in a substantial increase in the mean corpuscular volume (MCV) and sometimes in the mean corpuscular hemoglobin (MCH) values. However, the mean corpuscular hemoglobin concentration (MCHC) is usually normal because the synthesis of hemoglobin is less affected than DNA synthesis. An increased red cell distribution width (RDW) is commonly observed because of the presence of red cells of varying sizes in the peripheral blood (Snow, 1999).

Leukopenia in vitamin B12 insufficiency is caused by the failure of myeloid precursor cell proliferation in the bone marrow. Abnormal nuclear maturation in these cells results in the formation of giant forms of both metamyelocytes and neutrophils. Giant forms of both these cells are considered to be the hallmark of megaloblastic anemia. Hypersegmented neutrophils, i.e., neutrophils with more than five nuclear segments, can be present in the peripheral circulation before the onset of anemia (D. Savage et al., 1994).

Thrombocytopenia in vitamin B12 insufficiency is caused by an inability to properly mature megakaryocytes, resulting in defective DNA synthesis. This leads to abnormal nuclear

development in megakaryocytic cells in the bone marrow, resulting in thrombocytopenia. Severe or prolonged insufficiency of vitamin B12 can lead to the suppression of all cell lines, resulting in pancytopenia, which is characterized by anemia, leukopenia, and thrombocytopenia (Ralph Green, 2017).

In vitamin B12 deficiency, the peripheral blood smear typically shows the presence of macro ovalocytes, indicative of defective erythrocyte maturation. Hypersegmented neutrophils are often present and are indicative of megaloblastic anemia. The peripheral blood smear findings often occur before the development of abnormalities in the red cell parameters and are thus helpful in the early detection of vitamin B12 insufficiency (O'Leary & Samman, 2010).

Clinical Manifestations Related to Hematological Changes

Vitamin B12 insufficiency has a broad range of manifestations. The manifestations are mostly due to the impairment of hematopoiesis, defective DNA synthesis, and neurological abnormalities. The manifestations are insidious in onset and may differ depending on the duration and intensity of the vitamin B12 insufficiency. The hematological abnormalities are an important cause of the manifestations observed in vitamin B12 deficiency. The anemia that occurs due to ineffective erythropoiesis leads to reduced oxygen carrying capacity of the blood. The manifestations are fatigue, generalized weakness, pallor, breathlessness on exertion, and palpitations. Severe vitamin B12 deficiency may result in the suppression of various cellular lines in the bone marrow and may result in pancytopenia. Leukopenia increases the risk of recurrent infections. Thrombocytopenia also can be characterized by easy bruising and bleeding. They are associated with the level of anemia and bone marrow failure (Hunt et al., 2014). The neurological symptoms are a significant characteristic of vitamin B12 deficiency, which may be present without hemologic alterations. Paresthesia, numbness, gait problems, proprioceptive abnormalities, and weakness are observed in the absence of vitamin B12 and this is caused by the demyelination of peripheral nerves and the spinal cord. The vitamin B12 deficiency is also seen in cognitive disturbances, memory, mood changes, and neuropsychiatric disturbances and this is attributed to the interference in the normal production of the myelin due to the accumulation of the methyl malonic acid which is irreversible when it is not addressed in a timely manner (O'Leary & Samman, 2010). The impaired regeneration of the gastrointestinal mucosal rapid cell division populations leads to gastrointestinal manifestations. The patients who are affected by the lack of vitamin B12 develop symptoms such as glossitis, angular stomatitis, mucosal atrophy, anorexia, weight loss, diarrhea, and other gastrointestinal defects. The patients that develop a vitamin B12 deficiency have symptoms that cause complications, which worsen the state of the condition in case it is not addressed promptly (Langan & Goodbred, 2017). The diverse presentations of vitamin B12 insufficiency emphasize the importance of the timely detection and management. Through early treatment, the hematologic abnormalities are not only controlled, but also avoid neurological injury. This is yet another reason why the clinical significance of early diagnosis and treatment of the deficiency can be made (Ralph Green, 2017).

Diagnostic Approaches

A set of biochemical tests, clinical correlation, and hematological tests is employed to diagnose vitamin B12 insufficiency. In suspected cases, the complete blood count test is the first test that is carried out on the blood sample. The reduced level of hemoglobin is an indication of anemia, which is the most frequent clinical presentation of vitamin B12 insufficiency. A clinical study showed that the level of hemoglobin in vitamin B12 deficient individuals is significantly low, i.e., about 9.7 g/dL on average, which improves dramatically with the administration of vitamin B12 supplements. The data presented in Table 01 clearly indicate that the hematological disorders that occur due to deficiency of vitamin B12 can be reversed (Aditya R Agrawal et al., 2024). The clinical manifestations of megaloblastic anemia include macrocytosis, which is due to the reduced synthesis of DNA and increased values of mean corpuscular volume (MCV). Vitamin B12 deficient individuals have reported increased values of MCV,

which ranges from 104 to 115 fL and normalizes with treatment (Table 01).

Hematological Investigations

The red cell distribution width, as well as other auxiliary red cell measurements are usually elevated, indicating anisocytosis as a result of inefficient erythropoiesis (Table 01). Some changes in platelets are also reported, including a reduction in mean platelet volume, and this could point to vitamin B12 insufficiency interfering with the maturation of megakaryocytes. In severe cases of vitamin B12 deficiency, bone marrow suppression can cause leukopenia, neutropenia, thrombocytopenia, or, in some cases, pancytopenia, so the impact of vitamin B12 insufficiency on the organism may be underscored. An essential supplement to CBC results is peripheral blood smear testing. Macro ovalocytes and hyper segmented neutrophils are distinctive physical traits that are thought to be sensitive and early markers of megaloblastic hematopoiesis (Table 01). These characteristics may exist even prior to the detection of noticeable macrocytosis and are caused by faulty nuclear maturation in hematopoietic precursor cells (O'Leary & Samman, 2010).

Table: 01 Hematological and Biochemical Markers for Vitamin B12 Deficiency

Investigation	Expected Finding	Pathophysiological Basis	References
Serum Vitamin B12	Decreased level	Reflects reduced circulating cobalamin	(Aditya R Agrawal et al., 2024; S. P. Stabler, 2013)
Methyl malonic Acid (MMA)	Increased	Impaired conversion of methylmalonyl-CoA due to B12 deficiency	(Carmel, 2011);(O'Leary & Samman, 2010)
Homocysteine	Increased	Impaired methionine synthase activity	(Savage et al., 1994; O'Leary & Samman, 2010)
Hemoglobin	Decreased	Ineffective erythropoiesis	(E. Andrès et al., 2006; R. Green, 2017)
Mean Corpuscular Volume (MCV)	Increased (>100 fL)	Defective DNA synthesis leading to macrocytosis	(R. Green, 2017)
Red Cell Distribution Width	Increased	Anisocytosis due to abnormal erythrocyte maturation	(E. Andrès et al., 2006)
Leukocyte Count	Decreased (Leukopenia)	Bone marrow suppression	(Andrès et al., 2004)
Platelet Count	Decreased (Thrombocytopenia)	Impaired megakaryocyte maturation	(Antony, 2017)
Peripheral Blood Smear	Macro-ovalocytes and hypersegmented neutrophils	Abnormal nuclear maturation	(Hoffbrand & Weir, 2001);(D. G. Savage et al., 1994)
Bone Marrow Examination	Hypercellular marrow with megaloblastic changes	Ineffective hematopoiesis	(Hoffbrand & Weir, 2001)

Serum Vitamin B 12 levels

For the diagnosis to be confirmed, serum vitamin B12 levels must be measured. Although blood vitamin B12 estimate alone has limited sensitivity because normal levels may be seen in functional insufficiency conditions, Table 01 shows readings below established laboratory reference ranges typically support the diagnosis (Aditya R Agrawal et

al., 2024). As a result, metabolic indicators like homocysteine and methyl malonic acid (MMA) are being used more frequently, especially when vitamin B12 levels are borderline or hematological results are unclear (Table 01). While homocysteine levels may also rise but are controlled by folate status, data presented in Table 01 demonstrates that elevated MMA is thought to be a more specific sign of cellular vitamin B12 insufficiency (O'Leary & Samman, 2010).

Numerous investigations have shown a correlation between hematological markers and the severity of vitamin B12 insufficiency. Serum vitamin B12 blood level is reduced in relation to increased RDW, high MCV values and extent of anemia. Nonetheless, the difference in hematological manifestation once again explains the necessity to approach the diagnosis with a proper strategy that would consider both laboratory values and clinical manifestation, including neurological signs, pallor, and exhaustion. Although this is not usually necessary in everyday clinical practice, as implied by reports in Table 01, bone marrow examination can indicate megaloblastic changes in certain cases where the diagnosis remains unclear (Khanduri & Sharma, 2007).

Management and Therapeutic Implications

The objectives of treatment of vitamin B12 insufficiency are to avoid permanent neurological damage, to treat hematological abnormalities, and to treat the deficiency itself. The treatment of vitamin B12 insufficiency is essentially vitamin B12 replacement therapy, which may be achieved by either oral or parenteral routes depending on the severity of deficiency and underlying causes of deficiency. Parenteral Intramuscular injections for vitamin B12 replacement therapy of cyanocobalamin or hydroxocobalamin is recommended for those with severe deficiency, malabsorption, and marked hematological and neurological abnormalities. It has been proven that with routine treatment, there is rapid hematological response, with reticulocytosis occurring within three to five days and subsequent increases in hemoglobin concentrations in the following weeks (O'Leary & Samman, 2010).

Hematological markers significantly improve with therapeutic intervention. Following vitamin B12 supplementation, studies have shown normalization of mean corpuscular volume (MCV), red cell distribution width (RDW), and hemoglobin concentration, suggesting that inefficient erythropoiesis is highly reversible if treated promptly (Aditya R Agrawal et al., 2024).

Since high dose oral supplementation can achieve adequate absorption by passive diffusion, oral vitamin B12 therapy has gained support as an effective alternative in patients without severe malabsorption. Oral medication is a more affordable and patient friendly approach for long term maintenance because several clinical trials have demonstrated similar hematological recovery with oral and intramuscular therapy (Kuzminski et al., 1998).

Monitoring hematological markers is crucial from a therapeutic perspective in order to evaluate therapy response. Objective markers of successful treatment include normalizing leukocyte and platelet counts, rising hemoglobin levels, and declining MCV. Reevaluating the diagnosis, treatment compliance, or the existence of concurrent deficiencies such iron or folate deficit, which may impede hematological recovery, should be prompted by treatment failure (Khanduri & Sharma, 2007).

Beyond treating anemia, vitamin B12 shortage has therapeutic ramifications. In addition to restoring normal hematopoiesis, early correction of the deficiency lowers the likelihood of neurological consequences, some of which may become irreversible if treatment is postponed. In the case of patients suffering from hematological problems as a result of this deficiency, early treatment has great prognostic value and emphasizes the need for the supplementation of vitamin B12 as a preventative and curative measure (O'Leary & Samman, 2010).

Public health and preventive aspects

The high incidence and variety of symptoms and the preventable nature of vitamin B12 insufficiency make it a public health problem. The elderly population, vegans and vegetarians, pregnant women, and individuals suffering from malabsorption problems and having limited access to animal products are at risk (Figure 03). According to epidemiological research, subclinical vitamin B12 deficiency is prevalent in underdeveloped nations, where low socioeconomic status and dietary

deficiencies lead to insufficient intake (L.H. Allen, 2008).

Early detection by population level screening in high risk groups is crucial from a preventive standpoint. In addition to measuring serum vitamin B12, routine evaluation of hematological markers such hemoglobin, red cell distribution width, and mean corpuscular volume might help diagnose severe anemia or neurological damage early (Figure 03). To lower the burden of disease and enhance long term results, public health methods that integrate vitamin B12 testing into prenatal care and geriatric health programs have been proposed (O'Leary & Samman, 2010).

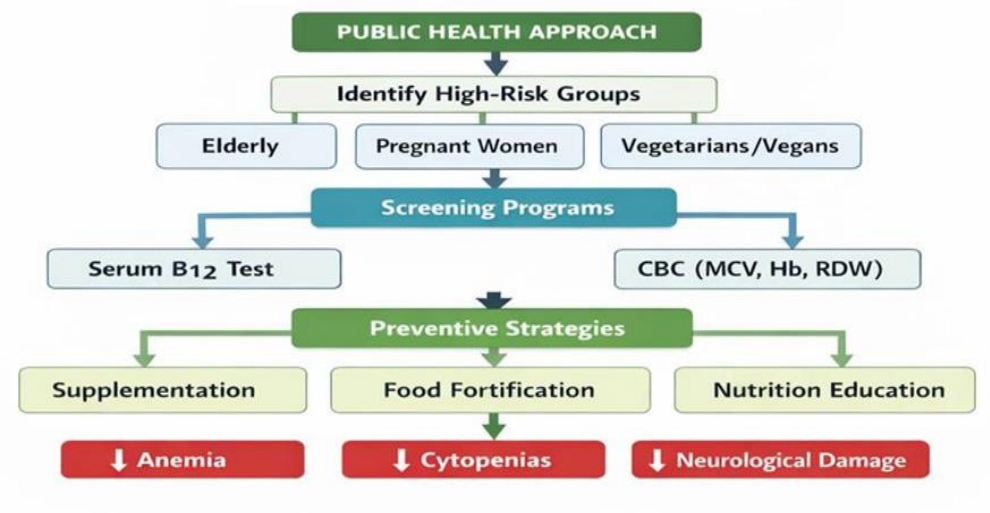

Fig 03. Public health approaches and preventive strategies for the deficiency of Vitamin B12 levels.

Programs for supplements are another successful preventive strategy. Preventive vitamin B12 supplementation is related to better hematological indices and a lower incidence of anemia in high risk groups, including older adults and pregnant women (Figure 03). The prevalence of deficiency related hematological illnesses can be significantly reduced by public health measures that facilitate inexpensive access to supplements (Green et al., 2017). Additionally, in order to guarantee prompt identification and treatment of vitamin B12 insufficiency, especially in patients who arrive with unexplained anemia or cytopenias, awareness programs aimed at healthcare professionals are crucial (Figure 03).

Animal products are a natural source of vitamin B12 such as meat, dairy, eggs, and fish, individuals who consume vegetarian or vegan diets are at great risk for vitamin B12 deficiency (Figure 03). Especially in countries where vegetarian or vegan diets are part of the traditional diet, dietetic interventions are also important (L.H. Allen, 2008). In some countries, food fortification programs, such as vitamin B12 enriched breakfast cereals and dairy drinks, have also been shown to be effective in raising vitamin B12 levels in the population and reducing hematological abnormalities (Ralph Green, 2017).

In conclusion, vitamin B12 insufficiency can be prevented by using a multifaceted strategy that includes dietetic interventions, supplementation, and education (Figure 03). These tactics can greatly lessen the neurological and hematological effects of deficiency, improving population health outcomes and lowering the long term cost of healthcare (L.H. Allen, 2008).

Future Perspectives and Research Gaps

Many studies have been carried out to confirm that even though changes in the hematological state become apparent in the latter stages, it has been confirmed that it is not possible to identify a deficiency of vitamin B12 simply on the basis of its level in the serum. Emphasis has been given to the fact that in order to more accurately relate the level

of vitamin B12 with hematological disorders, it is necessary to include the functional levels of homocysteine and methyl malonic acid as well. Research studies have identified that a large number of patients suffer from normocytic or even microcytic anemia, although it is a known fact that macrocytic anemia is a presenting symptom for a vitamin B12 deficiency (Ralph Green, 2017).

Recent literature indicates that a substantial proportion of patients present with normocytic or even microcytic anemia, despite the fact that macrocytic anemia is considered a characteristic and hallmark symptom of vitamin B12 deficiency. This atypical presentation, often precipitated by a co-existing iron deficiency or inflammation, has not yet received the attention it deserves and could lead to an underestimation (Aditya R Agrawal et al., 2024).

The bulk of recent studies is centered on short term hematological responses following vitamin B12 supplementation and is cross sectional. Longitudinal studies examining long term hematological responses, rates of recurrence, and optimal treatment duration in different populations are remarkably absent (Langan & Goodbred, 2017).

There is not enough information available on the deficiency of vitamin B12 and its impact on hematology. Moreover, it is also a fact that there is inadequacy of data available on the effect of vitamin B12 deficiency in underdeveloped countries (L. H. Allen, 2008; S. P. Stabler, 2013).

Moreover, it is also unclear that how the deficiency of vitamin B12 impacts the red cell indices and erythropoiesis. Future studies may help in shedding light on the differences in the presentation of the disease in different people (S. P. Stabler, 2013).

Serum vitamin B12 levels by themselves might not be adequate in the assessment of early or subclinical deficiency states, as has been evident in a number of studies. As has been stated by Carmel (2011), functional deficiency may also occur in the presence of normal serum vitamin B12 levels, and hematological disturbances do not become apparent till a much later date. The identification of more sensitive functional biomarkers that are more closely related to hematological changes is a major research need (Carmel, 2011).

Vitamin B12 alone in the serum is not enough to diagnose early or functional deficiency; however, future studies should focus on harmonizing combined biomarkers such as holotranscobalamin and methyl malonic acid for accurate diagnostic results (Nexo & Parkner, 2024). New studies on metabolomics indicate that vitamin B12 deficiency may affect several metabolic pathways, and future research should concentrate on the role of metabolomics based biomarkers in early and accurate diagnosis. Further research is required to evaluate the long term metabolic and hematological response to vitamin B12 supplementation (Devi et al., 2025).

Conclusion

Vitamin B12 insufficiency is a critical cause of various hematological abnormalities in the world, particularly in populations where animal products are not consumed frequently or with gastrointestinal diseases that impact vitamin B12 absorption. Vitamin B12 is crucial for the synthesis of DNA, and its insufficiency is associated with ineffective hematopoiesis. This results in various hematological abnormalities that include macrocytic anemia, leukopenia, thrombocytopenia, and abnormalities in the morphology of peripheral blood cells. Biochemical tests that include the measurement of serum vitamin B12, methyl malonic acid, and homocysteine levels are useful in diagnosing a vitamin B12 deficit. It is very important that the public is aware of the effects of vitamin B12 insufficiency, as a vitamin B12 therapy supplements is effective in rapidly correcting most of the associated hematological abnormalities.

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