

Systematic Review

Diet-Related Anemias: A Comprehensive Review on Types, Causes, Diagnosis, and Treatment

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ABSTRACT

Background: Anemia, a prevalent blood disorder characterized by reduced red blood cells or hemoglobin, has diverse etiologies related to nutritional deficiencies, notably iron, vitamin B12, and B9. Its impact on quality of life is especially significant in elderly individuals and those with chronic conditions.

Objective: This systematic review aims to collate and synthesize the current literature on nutrient-related anemias, focusing on types, pathophysiology, diagnosis, and treatment.

Methods: A thorough search was conducted in databases including Google Scholar, PubMed, and Research Gate using keywords such as "anemia," "types," "pathophysiology," "diagnosis," and "treatment." The review encompasses studies that detail the prevalence, causes, symptoms, risk factors, diagnostic methods, and treatment options for anemias related to iron, vitamin B12, and B9 deficiencies.

Results: The review found that anemia affects approximately 24.8% of the global population, with higher prevalence rates in vulnerable groups such as infants, children, and pregnant women. Iron deficiency anemia, the primary form globally, is prevalent in various populations due to factors like poverty, malnutrition, and gastrointestinal conditions. Diagnostic approaches include both traditional laboratory tests and newer metabolite tests like homocysteine and methylmalonic acid. Treatment strategies vary based on the type of deficiency and include oral and intramuscular supplements, with intravenous iron for malabsorption cases and folic acid for folate deficiency.

Conclusion: Early detection and effective treatment of diet-related anemias are crucial to prevent serious complications and mitigate their impact on quality of life. The review highlights the importance of tailored treatment approaches, including dietary changes, supplements, and medications, to address the specific needs of individuals with different types of anemia.

Keywords: Anemia, Diet-Related Anemias, Iron Deficiency, Treatment, Vitamin B12 Deficiency, Vitamin B9 Deficiency.

INTRODUCTION

Anemia, encompassing a spectrum of conditions marked by diminished hemoglobin levels, presents a complex medical challenge due to its multifaceted causes and the possibility of concurrent occurrence in patients (1). This condition, particularly detrimental to the elderly, has been linked to deteriorating quality of life and adverse prognoses in chronic diseases such as heart failure, chronic renal failure, and cerebrovascular disorders, especially in individuals who are frail or weakened (2, 3). Despite its increased prevalence with age, anemia should not be misconstrued as an inevitable consequence of aging, as it significantly elevates mortality rates (4). The role of iron extends beyond oxygen transport in hemoglobin; it is integral in various cellular proteins like myoglobin and cytochromes, highlighting the broader implications of iron deficiency (5, 6).

Iron deficiency anemia (IDA), the primary anemia type stemming from nutritional deficits, is globally prevalent (7). Even with efficient iron conservation mechanisms, deficiencies can arise from inadequate intake or depleted reserves. Populations at heightened risk include premenopausal women, the elderly, hospitalized patients, infants, children, and those with gastrointestinal disorders or histories of gastric surgeries (8-10). IDA not only diminishes adult work capacity (7) but also adversely impacts the cognitive and motor development of infants and children. Notably, iron deficiency, even in the absence of anemia, has been linked to cognitive

and mental development issues in adolescent girls and is a major contributor to fatigue in adult women (5, 11). Furthermore, it affects auditory and visual functions and is associated with impaired cognitive development in children (5, 11).

Vitamin B12, or cobalamin, is vital for DNA production and neurological function, with deficiencies leading to a spectrum of hematologic and neuropsychiatric disorders (12). Produced by microorganisms, cobalamin is primarily found in animal-based foods. The absorption of cobalamin necessitates intrinsic factors from stomach parietal cells and the cubam receptor in the small intestine (13). Autoimmune atrophic gastritis, leading to intrinsic factor loss, is a common cause of severe pernicious anemia, often resulting in pancytopenia and macrocytic anemia (14).

Malnutrition and poor dietary habits are the main contributors to vitamin B9 deficiency, frequently observed in the elderly with malabsorption syndromes like celiac disease. This deficiency is often characterized by symptoms like weakness, poor weight gain, and weight loss, and is prevalent in patients with advanced dementia or Alzheimer's disease (4). This review delves into the etiology, symptoms, and risk factors of various diet-related anemias, exploring diagnostic methods and treatment options in a comprehensive manner.

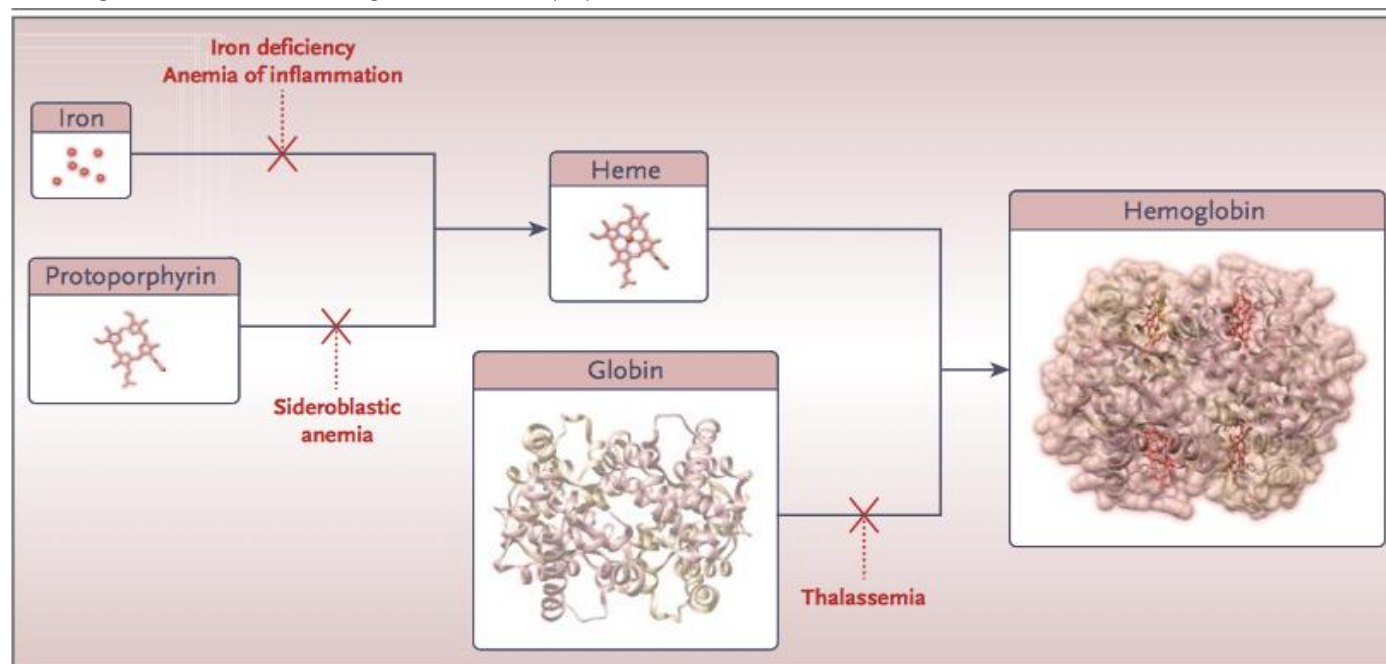
MATERIAL AND METHODS

The present systematic review aimed to identify and summarize the current literature on anemia, which is caused by any nutrient, its types, pathophysiology, diagnosis, and treatment. A comprehensive searching was performed from the following databases: Google Scholar, PubMed, and Research Gate. The search strategy included the following keywords: anemia, it's types, pathophysiology, diagnosis, and treatment.

REVIEW OF LITERATURE

The global landscape of anemia presents a challenging picture, primarily due to varied definitions and diverse population segments such as infants, children, and pregnant women. World Health Organization data from 1993 to 2005 suggests that approximately 24.8% of the global population is affected by anemia, with the highest prevalence seen in preschool children, pregnant women, and the elderly (15). In contrast, the United States shows a lower prevalence, under 5%, yet the same demographic groups remain disproportionately affected. Notably, the incidence in individuals over 65 years of age stands at 11%, escalating to over 30% in those above 85 years (16, 17). Despite its frequency in older adults, anemia is not a normal part of aging, and its risk factors include gender, aging, nutritional deficiencies, and chronic illnesses (18-22).

Pregnancy emerges as a critical period for anemia, especially in developing countries where over half of pregnant women may be affected. This rate is significantly lower in developed nations, falling below 20% (23). In the United States, low socioeconomic status, along with nutritional deficiencies and chronic diseases, are primary risk factors for anemia during pregnancy. It is also observed that hemoglobin levels are generally lower in women than in men, and African Americans tend to have lower hemoglobin levels due to the higher occurrence of hemoglobin variations (24).



(25)

Iron deficiency is a global health concern, affecting more than 2 billion people worldwide (15). Studies spanning 187 countries between 1990 and 2010 identified iron-deficiency anemia as the predominant cause of anemia, particularly among young children and preschool-aged women (26, 27). Although there has been a global reduction in the prevalence of iron deficiency anemia, it remains most prevalent in Central and West Africa, and South Asia (26, 27). Iron deficiency is estimated to be twice as prevalent as iron deficiency anemia (28).

The nutritional requirements for iron vary significantly across different sexes and life stages. Estimates indicate that 38% of pregnant women, 40% of menstruating girls and women, and 30% of preschool children are iron deficient (26, 27, 29). Adolescence, particularly for girls, is another critical period due to increased iron demands, menstrual blood loss, and often inadequate dietary iron intake (30). Addressing adolescent nutrition is vital for their healthy development, and school health nurses play a crucial role in educating teenage girls about healthy diets to prevent and manage iron deficiency anemia (31-33).

Iron deficiency and anemia in less developed countries are often caused by poor dietary intake and blood loss from intestinal worm infections. In contrast, high-income countries frequently attribute these conditions to specific dietary choices and pathological conditions like chronic blood loss or malabsorption. Intriguingly, higher-income countries face greater challenges in reducing the prevalence of iron deficiency anemia compared to their lower-income counterparts, partly due to the high incidence of iron deficiency in their aging populations (26).

Iron deficiency, a prevalent global health issue, manifests in two distinct forms: true iron deficiency and functional iron deficiency. True iron deficiency is characterized by significantly reduced or absent iron stores in the bone marrow, liver, and spleen. In contrast, functional iron deficiency denotes a condition where normal or elevated total body iron reserves are present but cannot be effectively utilized for erythropoiesis in erythroid precursors (34). Functional iron deficiency often arises from elevated hepcidin levels, which impede the mobilization of iron reserves from reticuloendothelial cells and hepatocytes for red blood cell production. Iron metabolism is uniquely regulated through absorption rather than excretion, with losses primarily occurring through blood loss or cell shedding. In men and non-menstruating women, daily iron loss averages around 1 mg, while menstruating women may lose an additional 0.6 to 2.5 mg daily. During menstruation, a woman weighing approximately 132 lbs (60 kg) may lose an additional 10 mg of iron per cycle, potentially reaching up to 42 mg depending on the menstrual flow's intensity (35).

In developing countries, poverty, malnutrition, and hunger are straightforward causes of anemia, particularly in children and pregnant women. Diets rich in cereals can further exacerbate this issue, as phytates in grains bind iron in an indigestible complex. Chronic blood loss from conditions such as schistosomiasis and hookworm infections also contributes significantly to anemia in these regions (26). In affluent countries, iron deficiency anemia is often linked to dietary choices such as veganism or vegetarianism, malabsorption issues, and chronic blood loss due to heavy menstrual bleeding or gastrointestinal issues. Gastrointestinal blood loss, particularly in older adults and men, might indicate underlying conditions like malignancy or benign lesions. When iron-deficiency anemia tests yield inconclusive results, video-capsule endoscopy, particularly for the small bowel, becomes a valuable diagnostic tool (36, 37).

Regular blood donors, endurance athletes, and individuals using certain medications like anticoagulants and NSAIDs are also at risk for iron deficiency (28, 38). In adolescents, poor dietary habits, particularly in developing countries like Egypt, contribute significantly to anemia. A notable proportion of anemic adolescent girls in these regions do not consume a balanced diet, often skipping meals and consuming tea, which inhibits iron absorption (47-51). In the elderly, chronic gastrointestinal blood loss from conditions such as esophagitis, gastritis, ulcers, or *Helicobacter pylori* infections, often leads to iron deficiency anemia (52).

This intricate web of causes and risk factors for iron deficiency demonstrates the need for a multifaceted approach to prevention and treatment. Addressing dietary habits, managing chronic conditions, and raising awareness about the importance of balanced nutrition are crucial steps in mitigating the impact of this widespread health issue.

Vitamin B12, essential for the functioning of enzymes like methionine synthase and l-methylmalonyl-coenzyme mutase, plays a critical role in human health (53). Deficiencies in both folate and B12 can lead to megaloblastic anemia, highlighting the interdependence of these vitamins. Beyond its hematological effects, vitamin B12 is crucial for the development and maintenance of the central nervous system, particularly in myelination processes. A deficiency in B12 can cause demyelination in the spinal cord, peripheral nerves, brain, and brain white matter, a condition known as combined-systems disease or subacute combined degeneration. Pathologically, this is characterized by spongy degeneration due to the loss and swelling of myelin sheaths, which is observable through magnetic resonance imaging (54, 55). Interestingly, there seems to be an inverse relationship between the severity of megaloblastic anemia and the extent of neurological dysfunction (54, 56).

Pernicious anemia, a form of B12 deficiency, shows considerable variation in prevalence, with estimates ranging from 50 to 4000 cases per 100,000 individuals, depending on diagnostic criteria (12). This condition is more commonly diagnosed in older adults, typically between the ages of 70 and 80 (57, 58), and is more prevalent among individuals of African or European descent compared

to those of Asian ancestry (10, 58). Up to 20% of older adults may experience milder forms of atrophic gastritis with hypochlorhydria, affecting the release of dietary protein-bound vitamin B12 (59, 60). The causes of vitamin B12 deficiency can be categorized into nutritional deficiency, malabsorption syndromes, and other gastrointestinal issues (61). Pernicious anemia is a notable malabsorption disorder caused by an autoimmune response against gastric parietal cells, leading to a decrease in intrinsic factor production and subsequent impairment in B12 absorption. Food-bound malabsorption, where B12 bound to proteins in food cannot be adequately released, often results from conditions that affect gastric acid production (62).

Vitamin B9 deficiency primarily stems from inadequate dietary intake and malnutrition, especially prevalent in elderly patients and those with malabsorption disorders like coeliac disease. The average diet contains 500-700 µg of vitamin B9, with body stores lasting only about 4-6 months. Symptoms such as weight loss, poor weight gain, and weakness are common in individuals with B9 deficiency, particularly in those with Alzheimer's disease or advanced dementia (4). Certain medications like methotrexate, cotrimoxazole, sulfasalazine, anticonvulsants, and alcohol consumption can also induce a deficiency in folic acid.

DIAGNOSIS

Diagnosing iron status and related conditions, such as iron-deficiency anemia and anemia associated with chronic diseases, relies on established standard laboratory tests. Serum ferritin levels serve as the most accurate and sensitive indicator of iron deficiency. In iron-deficiency anemia, transferrin saturation levels of 16% or less signify insufficient iron for healthy erythropoiesis. Guidelines for differential diagnosis of microcytic anemias have been extensively reviewed (63). Diagnosing iron deficiency anemia is challenging in the presence of inflammation, as it cannot be based on a single test result. In cases of anemia linked with inflammation, higher ferritin cutoff levels are indicative, with levels below 100 µg per liter being a key marker (64).

RESULTS

The Recommended Dietary Intake (RDI) for vitamin B12, as established by the Institute of Medicine Food and Nutrition Board, is set at 2.4 mg daily for adults. Specifically, it is advised that individuals aged 51 and older should primarily obtain this vitamin through foods fortified with B12 or supplements, in order to prevent B12 deficiency (65). Traditionally, intramuscular (IM) injections have been the preferred method for treating B12 deficiency, largely due to a lack of awareness among practitioners about the efficacy of oral B12 supplements. However, studies dating back to 1968 have demonstrated that oral vitamin B12 is equally effective as injections in treating pernicious anemia and other B12 deficiency disorders (66, 67).

Oral iron supplementation offers a practical, cost-effective, and efficient treatment for individuals with stable iron deficiency anemia. Iron sulfate is the most commonly used preparation, although other iron salts like gluconate and fumarate are also effective. The recommended daily dose for children with iron deficiency is 3-6 mg per kilogram of body weight in a liquid form. For adults, the advised dosage is 100-200 mg of elemental iron, preferably taken in divided doses and on an empty stomach. The addition of vitamin C can enhance iron absorption. Low hepcidin levels in patients with iron-deficiency anemia ensure effective iron absorption and facilitate rapid recovery of hemoglobin levels. However, treatment typically requires 3 to 6 months to replenish iron stores and normalize serum ferritin levels. Side effects of oral iron, such as constipation, nausea, vomiting, and a metallic taste, can limit its long-term use, although these are generally mild and cause concern more often due to their frequency rather than severity (41).

Intravenous iron is necessary for patients with malabsorption issues. One emerging indication for intravenous iron administration is active inflammatory bowel disease, where oral iron may be ineffective and even exacerbate local inflammation (68). Folic acid supplementation is essential for treating folate deficiency anemia, with 1 to 5 mg of oral folic acid daily typically sufficing to correct the deficiency (69). In cases where oral administration is not possible, folic acid can be administered intravenously, subcutaneously, or intramuscularly. Folinic acid, or leucovorin, a reduced form of folate, is primarily used to prevent methotrexate toxicity. The duration of treatment depends on whether the underlying cause of the initial deficiency persists. Patients with conditions like small gut syndrome or malabsorption often require long-term care. It is crucial to address vitamin B12 deficiency in patients with concurrent folate deficiency, as B12 deficiency can cause neurological symptoms and signs that are not alleviated by folate treatment alone. If left untreated, this can lead to permanent neurological damage. A diet rich in fruits and vegetables is recommended for all patients to promote overall health (70).

Table 1. Procedure of Therapy of Vitamin B12 Deficiency Anemia

| Route | Initial Dose | Maintenance Dose |
|--------------------|--|-----------------------------------|
| Oral dose | 1,000 to 2,000 mcg / day for 1-2 weeks | 1,000 mcg / day for life |
| Intramuscular dose | 100 to 1,000 mcg / day for 1-2 weeks | 100 to 1,000 mcg every 1-2 months |

CONCLUSION

This comprehensive review underscores the complexity of anemia, primarily caused by deficiencies in iron, vitamin B12, and folate, with a notable global impact, especially on vulnerable groups like infants, children, and pregnant women. Iron deficiency, influenced by factors such as poverty, malnutrition, and gastrointestinal issues, remains a leading cause. Megaloblastic anemia, stemming from vitamin B12 and folate deficiencies, can impair neurological functions. Diagnostics employ a range of laboratory tests and clinical observations, including newer metabolite tests like homocysteine and methylmalonic acid. Treatment involves oral and intramuscular supplements, with intravenous iron for malabsorption cases and folic acid for folate deficiency, highlighting the tailored approach to addressing these deficiencies.

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