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REVIEW ARTICLE

Vitamin B12 Deficiency in Dialysis Patients: Risk Factors, Diagnosis, Complications, and Treatment - A Comprehensive Review

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Abstract

Vitamin B12 deficiency is a significant concern among patients with end-stage kidney disease (ESKD) undergoing dialysis. However, there hasn't been extensive research conducted on this particular patient group. The reported incidence rates vary widely, ranging from 20% to 90%, reflecting the complexity of its diagnosis. Dialysis patients often face multiple nutritional deficiencies, including a lack of essential vitamins, due to factors such as dietary restrictions, impaired absorption, and nutrient loss during dialysis. Diagnosing vitamin B12 deficiency in these patients is challenging, and addressing it is crucial to prevent complications and improve their overall quality of life. This review paper delves into the available body of evidence on vitamin B12 deficiency in dialysis patients, examining the contributing risk factors, diagnostic challenges, potential complications, and available treatment options.

Keywords

Vitamin B12 deficiency, Dialysis, Risk factors, Diagnostic challenges, Complications, Treatment

Introduction

Vitamin B12 deficiency is a significant concern among patients with end-stage kidney disease (ESKD) undergoing dialysis, however, it has not been well studied. The incidence rates vary among studies, with estimates ranging from 20% to 90%, depending on the population studied, the diagnostic criteria utilized, and the duration of dialysis treatment. The prevalence tends to increase with the duration of dialysis therapy, making long-term dialysis patients more vulnerable to vitamin B12 deficiency [1-3]. This prevalence is significantly higher when compared to the general population with reported figures between 1.5% and 15% [4,5]. Although the major site of absorption of vitamin B12 is the terminal ileum, the kidneys also play a major role in vitamin B12 processing through excretion and tubular reabsorption. In the initial phases of chronic kidney disease (CKD), vitamin B12 deficiency is relatively infrequent. However as CKD progresses and noteworthy impairment of this function arises, the vulnerability to vitamin B12 deficiency increases [6,7]. Dialysis patients often experience multiple nutritional deficiencies, including vitamin deficiencies, due to a variety of factors, including restricted diets, poor nutrient absorption, and increased nutrient losses during dialysis [2,8,9]. Although it presents a diagnostic challenge in this population, identifying and addressing vitamin B12 deficiency in dialysis patients may play a role in preventing associated complications and improving their overall quality of life. This review paper explores the intricate aspects of vitamin B12 deficiency in dialysis patients, investigating the various risk factors that contribute to it, the challenges encountered in diagnosis, the potential complications associated with it, and the treatment options that are currently available.

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Search Strategy

To conduct a comprehensive review, articles were gathered from various resources including PubMed, Medline, Embase, and Google Scholar using the keywords "vitamin B12 deficiency" and "dialysis". Additionally, reference lists of identified articles were also screened for potentially relevant studies. The search was not limited by publication date, but rather focused on capturing a broad spectrum of literature to encompass the current understanding and gaps in knowledge regarding vitamin B12 deficiency in dialysis patients.

Risk Factors

A variety of factors predispose dialysis patients to nutritional deficiencies including vitamin b12 deficiency. First and foremost, dialysis patients are frequently advised to adhere to a restricted diet in order to manage other aspects of their disease, such as fluid and electrolyte balance. These dietary limitations could limit their intake of vitamin B12-rich foods including meat, fish, and dairy products, increasing their risk of deficiency [9,10]. Furthermore, many dialysis patients have gastrointestinal problems, commonly due to chronic gastritis, which can impede vitamin B12 absorption. Malabsorption in these patients is exacerbated by decreased production of stomach acid and intrinsic factor, both of which are required for B12 absorption. Some medications commonly prescribed to dialysis patients, such as proton pump inhibitors and histamine H2 receptor antagonists, can interfere with vitamin B12 absorption by increasing stomach pH and decreasing intrinsic factor release [11]. Additionally, erythropoiesis-stimulating agents used to treat anemia in dialysis patients might increase the need for vitamin B12, potentially aggravating deficiency if not well monitored [12]. Moreover, renal replacement therapies, whether hemodialysis or peritoneal dialysis, might result in the loss of water-soluble vitamins such as B12. This loss is exacerbated by the cumulative effect of repeated dialysis treatments and prolonged therapy [13,14]. Finally, dialysis patients frequently have concomitant comorbidities such as diabetes which can independently contribute to vitamin B12 deficiency. Metformin, a commonly prescribed medication for the management of type 2 diabetes, has been associated with vitamin B12 deficiency through several mechanisms, including altering stomach acidity and affecting small intestine motility [15]. Moreover, diabetic patients can develop gastrointestinal dysfunction which can impair absorption in the intestines and lead to vitamin deficiencies [16].

Diagnosis

Vitamin B12 deficiency presents a diagnostic dilemma in dialysis patients. Vitamin B12, homocysteine, and methylmalonic acid levels have not been examined in this population as markers of B12 insufficiency and have not been validated as gold standard diagnostic tools. Measuring serum vitamin B12 levels is often used as a first-line screening test, but the sensitivity and specificity vary widely across studies [17-19]. Serum B12 levels less than 100 pg/mL have been shown to have a specificity of 90% for identifying clinically evident deficiency [20]. However, It has been demonstrated that low vitamin B12 concentrations do not necessarily imply deficiency, and levels in the lower half of the reference interval do not rule out deficiency [21]. Moreover, vitamin B12 levels can be falsely normal or high in dialysis patients due to the presence of inactive analogues of vitamin B12 in the blood [22].

The diagnosis of macrocytic anemia frequently prompts a laboratory examination of possible vitamin B12 deficiency. When there is clinically obvious vitamin B12 insufficiency, macrocytosis (mean corpuscular volume [MCV] > 100 fL) usually precedes anemia; less commonly neurologic symptoms can occur when both values are normal. However, patients can develop vitamin B12 deficiency without hematologic changes of anemia and macrocytosis [17,23]. Moreover, other considerations should be taken into account in ESKD patients. There are several other factors that influence anemia and MCV in this population such as iron deficiency and erythropoietin deficiency. Studies have also showed that dialysis patients may have functional vitamin B12 deficiency even with normal serum levels which is manifested by high methylmalonic acid and homocysteine levels due to impaired metabolism [24]. Su, et al. [25] investigated the effect of intravenous vitamin B12 on dialysis patients with macrocytosis. These patients had higher methylmalonic acid levels at baseline compared to the controlled group with no macrocytosis although both of them had serum vitamin B12 levels within the normal range. The macrocytic group exhibited a higher and more sustained drop in methylmalonic acid after intravenous vitamin B12 but no improvement in hemoglobin, reticulocyte count, or MCV suggesting functional vitamin B12 deficiency in this group.

Neutrophil hypersegmentation is another feature of vitamin B12 deficiency that can be used for diagnosis and is an early manifestation of megaloblastosis [26]. However, it does not appear to be a sensitive indicator of mild B12 deficiency in the general population [27]. This feature has not been well studied as a diagnostic indicator of B12 deficiency in dialysis patients. Saifan, et al. [1] is the only study that defined dialysis patients with vitamin B12 deficiency as those with high methylmalonic acid levels > 800 nmol/L and peripheral smear showing characteristic findings of macrocytes or hypersegmented neutrophils. 58.25% of patients with high methylmalonic acid levels had positive smears. This percentage dropped to 31% after treatment with intravenous vitamin B12 and re-evaluation of the peripheral smears.

Other diagnostic markers commonly used are plasma homocysteine and methylmalonic acid which have a negative correlation to serum B12 levels. Studies have shown that serum homocysteine levels have superior sensitivity and specificity to serum B12, while high methylmalonic acid levels have been found to be the most sensitive and specific diagnostic tool in the general population [28-30]. However, it is not as straightforward in patients with renal insufficiency. Both homocysteine and methylmalonic acid are elevated in patients with renal insufficiency [31-33]. One study evaluated levels of both homocysteine and methylmalonic acid, in addition to levels of cystathionine in patients undergoing hemodialysis. They noted that renal dysfunction alone caused only a modest rise in methylmalonic acid, but patients undergoing hemodialysis had markedly elevated levels of homocysteine, methylmalonic acid, and cystathionine. They also noted that markedly elevated homocysteine level was mainly attributable to functional vitamin B12 deficiency indicated by high methylmalonic acid. They concluded that methylmalonic acid is a more sensitive indicator of intracellular vitamin B12 deficiency when compared to serum vitamin B12 levels [24]. Another study showed that plasma vitamin B12, not plasma folate or vitamin B6, was negatively linked with plasma homocysteine in hemodialysis patients before and after treatment, regardless of dose dialysis or taking B-vitamin supplementation. This significant association between vitamin B12 and homocysteine appeared to be attributable to poor vitamin metabolism and functional deficiency rather than insufficient intake or excessive loss in dialysate [34]. Similarly, in hemodialysis patients, B12 therapy has been shown to reverse low serum B12 levels as well as high homocysteine and methylmalonic acid levels [25,35]. On the contrary, other studies demonstrated that elevated methylmalonic acid levels is a general finding in uremic patients and is not related to vitamin B12 deficiency [36]. In conclusion, there is no consensus on the validity of these markers as a diagnostic tool in this population.

Another way of looking at vitamin B12 levels is through the lens of carrier proteins. Serum B12 is bound to two proteins: Haptocorrin (70-90%) and holotranscobalamin (10-20%). B12 bound to haptocorrin is unavailable for cellular delivery whereas B12 bound to holotranscobalamin is available ("active-B12"). One study looked at holotranscobalamin against plasma cobalamin, methylmalonic acid, and homocysteine and found it to have a sensitivity of 1.00 and a specificity of 0.89 [37]. Another study was done on 17 patients undergoing hemodialysis, whose methylmalonic acid, holotranscobalamin, and B12 levels were measured at the beginning of the study. They were then given B12 injections for 3 months and had their levels measured again. The study noted an appropriate and statistically significant response in all three markers. They concluded that holotranscobalamin can be used as a supplementary marker in addition to methylmalonic acid to assess the responsiveness of hemodialysis patients to vitamin B12 supplementation [38]. However, these study designs have been questioned, and there is currently no consensus that holotranscobalamin should be used instead of standard blood B12 testing [39,40].

Diagnosing vitamin B12 deficiency in dialysis patients is challenging and requires careful consideration of the clinical context and the use of multiple diagnostic methods (Table 1). Serum B12 levels, methylmalonic acid, homocysteine, and holotranscobalamin levels are useful tools, but their interpretation must be adjusted to account for the for the specific challenges presented by dialysis patients. More studies are needed to establish standardized diagnostic criteria and reference ranges adjusted to the challenges faced in dialysis patients.

Complications and Treatment

Anemia

Anemia in general and megaloblastic anemia in specific are important and preventable complications in ESKD patients and account for high morbidity and

Table 1: A summary of the different diagnostic methods for vitamin B12 deficiency in end-stage kidney disease patients, their utility, and cut-off criteria.

Diagnostic Method	Use in ESKD	Cut-off Criteria for Deficiency
Serum Vitamin B12 Level	Often used as a first-line screening test Limited use due to false normal and inactive analogues (functional deficiency)	< 200 pg/ml Levels < 100 pg/ml have 90% specificity for identifying clinically evident deficiency
Methylmalonic Acid	More sensitive in ESKD; elevated due to kidney dysfunction	> 0.4 µmol/L
Homocysteine	Elevated in ESKD; affected by B12 and folate status	> 15 µmol/L
Holotranscobalamin (Active-B12)	Promising but requires more research for ESKD specific cut-offs	< 50 µmol/L
Neutrophil Hypersegmentation	Rarely used; not sensitive for mild deficiency	Presence of > 5% neutrophils with ≥ 5 lobes
Macrocytosis (MCV)	May be present but not specific; affected by other factors in ESKD	MCV > 100 fL

mortality in this population [41-44]. The estimated prevalence of vitamin b12 deficiency is high in ESKD patients on hemodialysis [1,45]. Studies have shown that up to 20% of the patients on dialysis with anemia have macrocytic anemia [46,47]. Vitamin B12 is necessary for DNA synthesis and its deficiency leads to improper DNA maturation, S phase arrest with abnormally large nuclei, and other features of megaloblastic anemia [18,48]. Vitamin B12 deficiency along with the anemic effects from uremic toxins may worsen the anemia in hemodialysis patients leading to worse outcomes [49]. Su, et al. [25] investigated the effect of parenteral vitamin B12 administration in macrocytic hemodialysis patients. Vitamin B12 1,000g intravenous was administered once weekly for four weeks, with a 12-week follow-up. Methylmalonic acid level was used as an indicator of vitamin B12 status. The effect of B12 supplementation on MCV and hemoglobin was also investigated. Following intravenous vitamin B12, the macrocytic group had a greater and more sustained reduction in methylmalonic acid level, however, there was no improvement in hemoglobin, reticulocyte count or MCV. The decrease in methylmalonic acid level suggests functional vitamin B12 deficiency at baseline in macrocytic hemodialysis patients, despite no significant change in hemoglobin. Similarly, Saifan, et al. [1] found no effect of vitamin B12 supplementation on hemoglobin levels in deficient dialysis patients despite having lower erythropoietin stimulating agent requirements. Another study by Minar, et al. [50] showed no significant differences in folic acid and vitamin B12 serum levels between hemodialysis patients with MCV greater than 96 fl and those with MCV less than or equal to 96 fl. Further research is needed to establish the precise pathophysiology of vitamin B12 deficiency in hemodialysis patients, as well as its relationship with macrocytic anemia and the benefits of supplementation on anemia.

Neuropathy

Neuropathy in hemodialysis patients can be caused by a variety of factors, including uremia, vitamin deficiencies (B1, B12, etc.), edema, hyperkalemia, and others [51,52]. Up to 90% of hemodialysis patients suffer from neuropathy symptoms leading to pain, loss of sensation, weakness, and sometimes ulceration and amputation [53,54]. Studies have also shown improvement in uremic neuropathy in dialysis patients on treatment with vitamin B12 [55]. B12 deficiency leads to demyelination of sensory and motor peripheral nerves and central nervous system [56,57]. In B12 deficiency central nervous system hypomethylation, accumulation of methylmalonyl-coA, and impaired DNA synthesis with impaired oligodendrocyte growth together lead to abnormal myelin production and impaired nerve conduction of both sensory and motor nerves [57-60]. Although symptoms i.e symmetric paresthesia and numbness that is more in lower than upper extremities, may be overlapping with most other neuropathies and uremic neuropathy in ESKD patients, subacute combined degeneration is more specific to b12 deficiency [61]. Subacute combined degenration is characterized by ataxic gait, decreased proprioception, vibration, fine touch, spastic paraparesis, and may also include cognitive decline with MRI demonstrating hyperintense lesions of posterior columns [62]. Most studies have showed that B12 supplementation especially methylcobalamin, improves neuropathic symptoms in patients with ESKD [55,63]. Kuwabara, et al. [55] investigated the effects of intravenous methylcobalamin on neuropathy in patients on hemodialysis using neuropathic pain grading and nerve conduction study. After 6 months of treatment with 500 mcg intravenous methylcobalamin injection 3 times a week, patients reported reduced neuropathic pain and showed significant improvement in nerve conduction velocities. Similarly, another study found that parenteral vitamin B12 treatment improved nerve conduction velocities in dialysis patients with low serum vitamin B12 levels and slow nerve conduction velocities [63]. On the contrary, some studies suggest that elevated cyanide levels from cyanocobalamin supplementation and impaired renal clearance may worsen already existing uremic neuropathy [64-66].

Resistance to Erythropoiesis-Stimulating Drugs (ESA)

Since the US FDA approved recombinant human erythropoietin (epoetin alfa) in 1989, epoetin alfa and similar agents now known as erythropoietin stimulating agents (ESA) have become the standard of care for the treatment of erythropoietin-deficient anemia, which occurs in the majority of CKD patients especially dialysis patients [67,68]. Approximately 5-10% of patients with chronic renal disease are hyporesponsive to ESA, defined as a continuing need for more than 300 IU/kg erythropoietin or 1.5 mug/kg darbepoetin delivered subcutaneously. This type of hyporesponsiveness contributes significantly to morbidity, death, and the health-care economic burden in chronic renal disease, and it poses a serious diagnostic and therapeutic challenge. Noncompliance, absolute or functional iron shortage, and inflammation are the most common reasons of ESA resistance [69]. Furthermore, there have been reports of erythropoietin resistance caused by vitamin B12 deficiency that was reversed following supplementation [12,70]. Zachee, et al. [12] reported the first case of resistance to human recombinant erythropoietin treatment caused by vitamin B_{12} deficiency in a chronic hemodialysis patient. Despite having a normal B12 level before erythropoietin treatment, resistant anemia, a low B12 level, and megaloblastic bone marrow developed after only 8 months. Following B12 supplementation, there

was a rapid response with increase in reticulocyte count and decrease in transfusion requirements. They next analyzed measured B12 levels in 30 hemodialysis patients who were given human recombinant erythropoietin and discovered that the mean B12 levels were the same before and after treatment. Although the study showed that screening for B12 deficiency was ineffective, it still recommended that any patient with human recombinant erythropoietin resistance should have their B12 levels checked. Similarly, Saifan, et al. [1] investigated the effect of vitamin B12 supplementation in deficient hemodialysis patients on erythropoietin dosages and found a significant decrease in the mean erythropoietin dose post B12 treatment suggesting that maintaining serum vitamin B12 levels increases functionality and may allow for a reduction in erythropoietin stimulating agent use, avoiding their toxicities and expenses. Su, et al. [25], on the other hand, found no change in darbepoetin dosages in macrocytic hemodialysis patients after intravenous vitamin B12 supplementation.

Cardiovascular disease burden and mortality from increased homocysteine levels

Patients with CKD and ESKD are known to have elevated homocysteine levels likely from associated impaired renal metabolism i.e. trans-sulfuration or re-methylation pathways, clearance, and vitamin deficiency [71,72]. Homocysteine is known to induce atherogenesis and atherothrombosis from increased reactive oxygen species generation due to presence of thiol group and increased Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase activity. It is also believed to induce further endothelial dysfunction and stress from abnormal vascular smooth muscle proliferation, lipid peroxidation, impaired nitric oxide metabolism, and activation of metalloproteinases [73-77]. Several studies, including some meta-analyses, have demonstrated an elevated cardiovascular disease risk from high homocysteine levels and its subsequent reduction after vitamin B12 supplementation [78,79]. The HOST trial (Homocysteinemia in Kidney and End Stage Renal Disease), which included 2056 patients with advanced CKD and ESRD, found that vitamin supplementation (including B12) may lower homocysteine levels but did not show a cardiovascular or mortality benefit. However, the lack of adherence and the inclusion of CKD and ESRD patients in the same group are some of the trial's limitations [80]. Certain studies have also shown no or inverse relationship between homocysteine levels, cardiovascular risk, and the lowering effect of vitamin B12 supplementation [81-84]. There is conflicting data associating homocysteine to an increased risk of cardiovascular disease in patients with kidney disease. MTHFR gene variation may contribute to the mixed cardiovascular risk reported in ESRD patients with increased homocysteine and its reduction by B12, folate, and B6 therapy [85-87]. Moreover, there are very few studies that investigated the effect of vitamin B12 supplementation alone [35,88]. Further prospective and large scale clinical trials accounting for potential confounders, baseline levels, and focussed on dialysis patients and B12 supplementation will be needed to verify the effect of b12 supplementation on homocysteine lowering effect and cardiovascular risk reduction in this population.

As demonstrated above, vitamin B12 deficiency in dialysis patients is associated with a variety of serious complications, which emphasizes the importance of its prompt recognition and treatment. However, the existing body of literature provides limited insights into the effects of vitamin B12 supplementation in dialysis patients, particularly in terms of reducing the risks and treating associated complications such as anemia, neuropathy, and erythropoiesis-stimulating agent resistance.

Several studies have evaluated the efficacy of vitamin B12 supplementation alone and in combination with folic acid in dialysis patients. In most of these studies, the end goal was the reduction of total homocysteine levels in the blood. Homocysteine is metabolized in two ways: Remethylation and transsulfuration. Folate and vitamin B12 are both essential to homocysteine remethylation, whereas pyridoxal 5'-phosphate (PLP, the physiological coenzyme form of vitamin B6) works as a coenzyme during homocysteine transsulfuration. Because B vitamins (folate, vitamins B6 and B12) are required for homocysteine metabolism, the loss of B vitamins during hemodialysis treatment in these patients may raise homocysteine levels [24,89,90]. The effect of folic acid supplementation in lowering homocysteine levels is well established in the literature even in patients without underlying deficiency, however the effect of vitamin B12 supplementation alone is less clear [91-93]. Moreover, most of the studies investigated the effect of vitamin B12 on lowering homocysteine levels regardless of the presence of an underlying deficiency and included patients with normal baseline serum B12 levels, although as discussed previously, normal serum B12 levels cannot exclude deficiency.

Azadibakshsh, et al. [94] found a significant reduction in total homocysteine levels (by 30%) with high dose oral supplementation of folic acid (15 mg/day) combined with vitamin B12 (1 mg/day) in hemodialysis patients with a desirable effect on serum folic acid and vitamin B12 levels. Elian, et al. [95] compared the effect of oral folic acid, pyridoxine and vitamin B12 in dialysis patients to a regimen that includes 1 mg hydroxocobalamin administered subcutaneously once per week after dialysis and found that it reduces plasma total homocysteine and methylmalonic acid dramatically in vitamin B12-replete hemodialysis patients, suggesting that patients with considerable persisting hyperhomocysteinemia despite high-dose folic acid therapy are likely to respond to the addition of

hydroxocobalamin, irrespective of their serum vitamin B12 levels. Other studies showed similar effects of the addition of parenteral 1 mg hydroxocobalamin to oral folic acid supplementation on lowering homocysteine and methylmalonic acid levels and increasing serum B12 levels below the levels attainable by folic acid alone [96]. Vrentzos, et al. [97] investigated the effect of adding oral versus intravenous B12 to folic acid in dialysis patients. They found out that, patients receiving intravenous treatment had significantly lower total homocysteine levels compared to those on oral treatment and that the levels increased significantly when intravenous treatment was switched to oral treatment.

Chiu, et al. [98] demonstrated that an intravenous pharmacologic dose of Vitamin B12 alone is as effective as an intravenous low-dose folic acid in treating hyperhomocysteinemia in chronic hemodialysis patients, and that combining both drugs in low doses may have synergistic effects. Koyama, et al. [99] showed similar results with similar efficacy of oral folic acid and intravenous methylcobalamin post each dialysis in reducing homocysteine levels, and a greater effect of their combination. Kaplan, et al. [100] is another study that investigated the effect of parenteral vitamin B12 alone in dialysis patients and found it to be effective in lowering homocysteine levels and rising serum B12 levels even though all patients had a normal serum B12 at the beginning of the study. On the contrary, previous studies suggested that pharmacologic dose of vitamin B12 would work effectively only under folic acid supplementation [101-103], and other studies showed no effect of the addition of vitamin B12 supplementation to folic acid on homocysteine levels [3,104]. Similarly, Arnadottir, et al. [105] and Polkinghorne, et al. [88] found that oral and intramuscular vitamin B12 supplementation respectively had no effect on homocysteine levels in dialysis patients, despite increasing blood levels.

Hoffer, et al. [106] went further to try to investigate the optimal dosing interval of parenteral vitamin B12. They conducted a RCT to compare the plasma homocysteine lowering effects of three intravenous cyanocobalamin dosage regimens in patients on maintenance hemodialysis: 1 mg post-dialysis every 28, 14, and 7 days in addition to routine oral vitamin B supplementation. Results showed that intravenous cyanocobalamin at 7- or 14-day intervals had similar effect on the reduction of plasma total homocysteine concentrations of hemodialysis patients below the levels brought about by prior long-term administration every 4 weeks, with the 7-day regimen having the greatest effect on rising serum B12 levels. In another study, they also investigated the effect of different formulations of vitamin B12. They found that intravenous hydroxocobalamin caused a 30-fold higher increase in serum B12 levels when compared to an equivalent dose of intravenous cyanocobalamin, although both had a similar effect on reducing homocysteine levels [107].

Dierks, et al. [108] is the only study that investigated the effect of vitamin B12 supplementation in dialysis patients with low serum cobalamin levels (< 180 pmol/L). Prior to supplementation, all patients had high levels of plasma total homocysteine, methylmalonic acid, and cystathionine. Plasma total homocysteine and methylmalonic acid levels were reduced by 35% and 48%, respectively after supplementation with intravenous injection of cyanocobalamin (1 mg/wk for 4 weeks); however, cystathionine levels remained unaltered.

As seen above, the design, dosage of supplements, method of application, and status of other supplements and therapies varied among all studies, making the ultimate conclusion and recommendations unclear (Table 2). Furthermore, the vitamin B12 status of the patients studied has not been precisely determined. Despite the fact that almost all studies included patients with normal baseline serum B12 levels and high homocysteine and methylmalonic acid levels, it is unclear whether these patients had underlying vitamin B12 deficiency because, as previously discussed, there are no clear guidelines for diagnosing vitamin B12 deficiency in this population even with normal serum levels. What can be concluded from existing data is that the maximum effect of B12 supplementation in ESKD patients on dialysis is yielded by injection, rather than oral intake and it's evident by reducing homocysteine levels and increasing serum B12 levels. Furthermore, the administration of pharmacologic dosage of B12 in combination with folate makes it more efficient. Conducting future studies with randomized controlled design, sufficient sample size and on patients with underlying vitamin B12 deficiency defined based on specific criteria is highly recommended to clarify the effect of B12 supplementation in deficient patients.

An essential consideration in the administration of intravenous vitamin B12 supplementation, especially in high doses before dialysis, is its potential to trigger a false blood leak alarm during dialysis. Hemodialysis occurs through diffusion across a semi-permeable membrane, which separates the patient's blood from the dialysate. When this membrane is disrupted, blood can enter the dialysate resulting in significant blood loss. To avoid this complication, dialysis machines are equipped with a blood-leak sensor which shuts down the hemodialysis machine when activated. Intravenous vitamin B12 causes reddish discoloration of the dialysate leading to pseudo-activation of the blood leak alarm [109]. Several case reports show that patients who received intravenous vitamin B12 prior to dialysis sessions for different reasons encountered similar complications [109-112]. These occurrences highlight the importance of delivering intravenous vitamin B12 supplements after dialysis sessions to prevent false alarms and maintain patient safety.

Table 2: This table summarizes the studies on vitamin B12 supplementation in dialysis patients. It provides a comparison of the different treatment modalities and their effect on homocysteine, methylmalonic acid, and vitamin B12 levels.

Study	Endpoint	Treatment	Results
Azadibakshsh, et al. [94]	Effect of high dose oral folic acid and vitamin B12 on homocysteine levels	High dose oral folic acid (15 mg/day) + vitamin B12 (1 mg/day)	Significant reduction in total homocysteine levels by 30% with a desirable effect on serum folic acid and vitamin B12 levels
Elian, et al. [95]	Effect of hydroxocobalamin on plasma total homocysteine and methylmalonic acid levels	1 mg hydroxocobalamin subcutaneously per week after hemodialysis vs . standard treatment (oral folic acid + pyridoxine + vitamin B12)	32% reduction in plasma total homocysteine and 19% reduction in methylmalonic acid levels
Vrentzos, et al. [97]	Effect of oral vs. intravenous vitamin B12 with oral folic acid on homocysteine levels	Oral folic acid (1 mg/day) + oral vitamin B12 (600 mcg) vs. Oral folic acid (1 mg/day) + 1 mg intravenous vitamin B12	Significant reduction in total homocysteine levels with intravenous treatment compared to oral treatment
Chiu, et al. [98]	Effect of intravenous vitamin B12 alone vs. intravenous low-dose folic acid alone vs. combination of both on homocysteine levels	1 mg Intravenous vitamin B12 weekly after hemodialysis vs. 3mg intravenous folic acid weekly vs. combination of both	Intravenous vitamin B12 alone is as effective as intravenous low-dose folic acid in lowering homocysteine levels with the combination of both having a greater effect
Koyama, et al. [99]	Effect of high dose oral folic acid vs intravenous methylcobalamin vs combination of both on homocysteine levels	High dose oral folic acid (15 mg/day) vs. 500 mg intravenous methylcobalamin after each hemodialysis vs. Combination of both	Similar efficacy of both treatments in reducing homocysteine levels, with greater effect in combination
Kaplan, et al. [100]	Effect of parenteral vitamin B12 alone on homocysteine levels	Three parenteral injections of 1 mg vitamin B12 given at 4-week intervals	Significant reduction in homocysteine levels and increase in serum B12 levels
Arnadottir, et al. [105]	Effect of oral vitamin B12 on homocysteine levels and vitamin B12 levels	2 mg oral vitamin B12 3 times a week (after each dialysis session) for 6 weeks vs. No treatment	Significant increase in serum vitamin B12 levels in treated group with no significant reduction in homocysteine levels compared to control group
Polkinghorne, et al. [88]	Effect of intramuscular vitamin B12 on homocysteine levels and vitamin B12 levels	1 mg intramuscular vitamin B12 monthly for 3 months vs. 1 ml saline placebo injection	Significant increase in serum vitamin B12 levels in treated group with no significant reduction in homocysteine levels compared to placebo group
Hoffer, et al. [106]	Comparison of different intravenous cyanocobalamin dosage regimens on plasma homocysteine	1 mg Intravenous cyanocobalamin post-dialysis every 28, 14, and 7 days + routine oral vitamin B	7- or 14-day intervals had a similar effect on reducing homocysteine concentrations, with 7-day regimen increasing serum B12 the most
Hoffer, et al. [107]	Effect of different formulations of vitamin B12 on serum homocysteine and vitamin B12 levels	1 mg intravenous hydroxocobalamin weekly for 8 weeks followed by cyanocobalamin for 8 weeks vs. 1 mg intravenous cyanocobalamin weekly for 8 weeks followed by hydroxocobalamin for 8 weeks	Hydroxocobalamin increased serum vitamin B12 concentrations 40-fold compared to cyanocobalamin which increased them only 10-fold, but both treatments reduced plasma homocysteine concentrations similarly by 33%
Dierks, et al. [108]	Effect of vitamin B12 in patients with low baseline serum levels (< 180 pmol/L) on homocysteine and methylmalonic acid levels	1 mg intravenous cyanocobalamin weekly for 4 weeks	Reduction in plasma total homocysteine and methylmalonic acid levels by 35% and 48%, respectively

Conclusion

In conclusion, vitamin B12 deficiency in dialysis patients is a multifaceted challenge with wide-ranging implications for their health and quality of life. Diagnosis remains a diagnostic dilemma, with conventional markers showing limited sensitivity and specificity. Complications of vitamin B12 deficiency, such as anemia, neuropathy, and resistance to erythropoiesis-stimulating agents, highlight the importance of early recognition and treatment. Treatment options, particularly the use of parenteral supplementation, have shown promise in lowering homocysteine levels and improving B12 status. However, differences in study designs and dosages have raised concerns regarding the optimal approach. To address the unique challenges presented by dialysis patients, future research should focus on developing standardized diagnostic criteria and reference ranges and conducting well-designed randomized controlled trials to clarify the impact of B12 supplementation in deficient patients. Furthermore, it is worth noting that the majority of studies investigating vitamin B12 deficiency in dialysis patients have focused on those undergoing hemodialysis, emphasizing the need for additional research specifically targeting peritoneal dialysis patients. Overall, the complexity of vitamin B12 deficiency in dialysis patients highlight the importance of a tailored, multidisciplinary approach to prevention, diagnosis, and treatment to improve the well-being of this vulnerable patient population.

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Conflict of Interest Statement

Authors have no conflicts of interest to declare.

Disclosures

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Author's Contribution

All authors have contributed equally to this manuscript.

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