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Assessment of vitamin B12 value with end stage renal disease patients on hemodialysis

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Abstract

Background: Chronic kidney disease (CKD) is a progressive disorder characterised by kidney abnormalities, often shown by an eGFR below 60 ml/min/1.73m² or kidney damage indicators for at least 3 months. ESRD, characterised by a GFR below 15 mL/min/1.73 m², generally requires RRT, with haemodialysis (HD) being the most prevalent method. HD patients may lack water-soluble vitamins such Vitamin B12 (cobalamin), which is essential for cell function and metabolism. These deficiencies can come from HD-related losses, decreased nutrition, gastrointestinal malabsorption, and altered metabolism. The aim of this study was to investigate the relationship between Vitamin B12 status and ESRD in patients undergoing hemodialysis.

Methods: This case-control study included 100 participants from Baquaba Teaching Hospital, conducted from April 1, 2023, to July 1, 2023. The participants were divided into three groups: 32 adults on HD for more than 3 years with a mean age of 49.5 years, 38 adults on HD for less than 3 years with a mean age of 48.0 years, and 30 healthy adults with no history of CKD as a control group with a mean age of 44.7 years. Serum B12, blood urea, serum creatinine, and serum albumin levels were measured in all participants.

Results: The study found a significant difference in serum Vitamin B12 levels between the ESRD and control groups, with the ESRD group exhibiting lower levels (220.8±110.7 ρg/mL) compared to the control group (340.7±89.4 ρg/mL) with a p-value of < 0.001. Additionally, there was a moderate negative correlation between dialysis duration and Vitamin B12 levels (rho = -0.259, P=0.029), indicating that longer dialysis duration is associated with lower Vitamin B12 levels.

Conclusion: This study highlights a significant correlation between Vitamin B12 deficiency and chronic renal failure. ESRD patients had lower Vitamin B12 levels than the control group, and longer durations of dialysis were associated with greater deficiencies. These findings underscore the importance of monitoring and addressing Vitamin B12 deficiency in individuals with ESRD to improve clinical outcomes.

Keywords: Assessment, vitamin B12, end stage, renal disease, hemodialysis

Introduction

Chronic kidney disease (CKD) is a progressive condition characterized by structural and functional changes in the kidneys, typically defined by an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73m² or markers of kidney damage present for at least 3 months [1]. Reports from the Global Burden of Disease study indicate a rising CKD burden over the past 20 years, with diabetes being a significant contributor [2]. CKD necessitates aggressive monitoring and early specialist referral for dialysis or renal transplant. End-stage renal disease (ESRD) is defined by a GFR of less than 15 mL/min/1.73 m² [3]. Numerous chronic diseases can cause ESRD, with diabetes mellitus (DM) being the leading cause globally [4]. Other causes include hypertension, vascular disease, glomerular disease, cystic kidney diseases, urinary tract obstruction, congenital defects, and unrecovered acute kidney injury [5]. Kidney function loss can result from infections, autoimmune diseases, cancer, and toxic chemicals [6]. Studies have associated tobacco use and alcohol consumption with CKD [7]. In many Arab countries, obstructive uropathy, primarily due to renal calculi and schistosomiasis, constitutes a major cause of ESRD [8]. In CKD, nephron destruction leads to compensatory hyperfiltration and hypertrophy in the remaining nephrons, maintaining GFR initially and allowing the disease to go undetected due to normal creatinine values [9]. However, reduced eGFR, increased urinary protein and albumin excretion, and greater tubule-interstitial atrophy and fibrosis predict poorer CKD outcomes [10].

Pathological changes are driven by inflammatory cell infiltration, fibroblast activation, extracellular matrix deposition, and peritubular capillary rarefaction [10]. Compensatory changes in healthy nephrons eventually lead to nephron injury and death, reducing functional nephrons to about 25% of normal [11]. Decreased GFR leads to waste accumulation in the blood, causing metabolic disturbances and organ intoxication [12]. CKD is often asymptomatic until advanced stages (eGFR <30 mL/min/1.73 m²). Disease progression varies by etiology, exposures, and interventions. Symptoms result from progressive uremia, anemia, volume overload, electrolyte abnormalities, mineral and bone disorders, and acidosis, leading to death if untreated (13). Up to 90% of renal patients exhibit oral symptoms of uremia, such as altered taste and smell, stomatitis, gingivitis, xerostomia, and parotitis [6]. Uremic toxicity, an indication for renal replacement therapy (RRT), manifests as anorexia, nausea, vomiting, bleeding, pericarditis, neuropathy, encephalopathy, seizures, coma, and death [14]. High-risk groups for CKD include those with a family history of the disease, DM, hypertension, recurrent UTIs, urinary obstruction, or systemic illnesses affecting the kidneys [15]. CKD prevalence increases with age, affecting approximately 17% of those over 60 with an eGFR <60 mL/min/1.73m² [16]. Additional risk factors include advanced age, smoking, obesity, unhealthy lifestyles, and genetic susceptibility [17]. Early detection and treatment of CKD can prevent or delay adverse outcomes. Routine laboratory tests can identify early disease stages [18]. CKD diagnosis relies on increased levels of urea and creatinine, which are crucial for monitoring to delay ESRD onset and associated morbidity and mortality [19]. CKD treatments aim to prevent development, slow progression, reduce complications, and improve survival and quality of life [20]. Hemodialysis (HD) is a common RRT, requiring monitoring of urea levels to evaluate efficacy and nutritional status. HD involves the diffusion of solutes through a semipermeable membrane, performed two to three times a week [21]. HD patients are at risk of vitamin B12 deficiencies due to losses during dialysis, reduced dietary intake, malabsorption, and altered metabolism. Vitamin B12 is crucial for neurologic function, RBC production, and DNA synthesis. It is obtained from diet and supplements, and its deficiency can lead to adverse outcomes [22]. The aim of the current study was to investigate the relationship between Vit B12 status and end stage renal disease on hemodialysis in patients of Diyala Province.

Methods

The case-control study was conducted at Baquaba Teaching Hospital from April 1, 2023, to July 1, 2023, involving 100 participants divided into three groups. The first group (N=32) comprised adult patients undergoing hemodialysis for more than 3 years, with a mean age of 49.5 years, clinically diagnosed with CKD by a nephrologist. The second group (N=38) included patients undergoing hemodialysis for less than 3 years with a mean age of 48.0 years. The third group (N=30) consisted of healthy adults with no prior medical or family history of CKD, serving as controls with a mean age of 44.7 years. Serum Vitamin B12, blood urea, serum creatinine, and serum albumin were measured in all participants.

Inclusion Criteria

1. Adults with ESRD on hemodialysis.
2. Patients with negative viral screens for Hepatitis B, C, and HIV.
3. Patients not taking any vitamin supplements.

Exclusion Criteria: Patients with other chronic diseases (hypertension, DM, systemic lupus erythematosus), nutritional malabsorption, anorexia, gastroparesis, sluggish intestinal transit or diarrhea, heightened gut permeability, and disruptions in gut microbiota were excluded.

Clinical and Laboratory Information: CKD diagnosis was based on history, clinical examination, laboratory investigations, and imaging studies.

Anthropometric Measurements: Height and body weight were measured, and BMI was calculated as weight (kg) divided by the square of height (m²).

Ethical Approval: Approval was granted by the University of Baghdad, the Iraqi Board for Medical Specializations, and Baquaba Teaching Hospital. Informed oral consent was obtained from all participants.

Sample Collection: About 5ml of blood was collected from each participant. The blood samples were transferred into gel tubes, allowed to clot, and then centrifuged to obtain serum. Serum was divided into two aliquots: One for measuring urea, creatinine, and serum albumin using the Neochem100 automated clinical chemistry analyzer, and the other stored at -20 °C for Vitamin B12 measurement using the Cobas e 411 analyzer.

Analytical Methods

1. **Vitamin B12:** Measured using the Cobas e 411 analyzer following a competition principle assay.
2. **Blood Urea:** Measured using urease to produce ammonia and carbon dioxide, with the resulting absorbance decrease directly proportional to the urea concentration.
3. **Serum Creatinine:** Measured using enzymatic hydrolysis with creatininase and sarcosine oxidase, with hydrogen peroxide detected in a coupled reaction.
4. **Serum Albumin:** Measured using Bromocresol Green (BCG) dye binding.

Statistical Analysis: Continuous variables were expressed as means and standard deviations or medians with ranges, depending on distribution. Categorical variables were expressed as frequencies and percentages. Differences in means were tested using Welch's t-test, while differences between categorical variables were tested using the $\chi 2$ test or Fisher's exact test. Spearman's rank correlation was used to study correlations between parameters. The Youden method calculated the optimal cut-off point for Vitamin B12's diagnostic performance. A p-value less than 0.05 was considered statistically significant. Data processing, visualization, and statistical analysis were performed using R software packages.

Results

ESRD subjects had a slightly higher mean age (48.7±14.1 years) compared to the control group (44.7±7.5 years), but the difference was not statistically significant (P-Value = 0.146). Gender distribution was similar in the ESRD and control groups. ESRD patients were 61.4% male and 38.6% female. In the control group, 60% were men and 40% women. Weight, height, and BMI were similar in the ESRD and control groups. Parameters analyzed were weight (68.1±13.6 kg vs. 69.4±11.4 kg), height (163.5±7.2 cm vs.

162.8±8.0 cm), and BMI (24.2±4.1 kg/m² vs. 26.2±4.8 kg/m²) with p values of 0.3, 0.7, and 0.061. As in Table 1.

Table 1: Description of patient's demographics and anthropometrics

Characteristic	ESRD, N = 70[1]	Control, N = 30[1]	P-Value[2]
Age (years)	48.7±14.1	44.7±7.5	0.146
Sex			0.9
Male	43 (61.4%)	18 (60.0%)	
Female	27 (38.6%)	12 (40.0%)	
Weight (kg)	68.1±13.6	69.4±11.4	0.3
Height (cm)	163.5±7.2	162.8±8.0	0.7
BMI (kg/m^2)	24.2±4.1	26.2±4.8	0.061

[1]Mean±SD; n (%)
[2]Two Sample t-test, Pearson's Chi-squared test

The ESRD group had substantially higher urea (129.6±30.0 mg/dL) and creatinine (8.0±2.2 mg/dL) levels than the control group (Urea: 29.3±7.3 mg/dL; Creatinine: 0.9±0.2 mg/dL), with p-values <0.001. Additionally, the ESRD group showed significantly lower albumin levels (3.7±0.4 g/dL) compared to the control group (4.4±0.6 g/dL), (p-value <0.001). The median dialysis duration for ESRD patients was 3.0 years (range: 0.6-17.0 years). The mean vitamin B12 level in the ESRD group was 220.8 pg/mL, ranging from 45 to 731.1. In comparison, the control group had a significantly higher vitamin B12 level (mean 340.7±89.4 pg/mL, range 234.4 to 580 pg/mL, P-Value < 0.001). As in Table 2.

Table 2: Renal function test, serum albumin, vitamin B12, and duration of dialysis in ESRD and control groups

Characteristic	ESRD, N = 70[1]	Control, N = 30[1]	P-Value[2]
Urea (mg/dL)	129.6±30.0	29.3±7.3	<0.001
Creatinine (mg/dL)	8.0±2.2	0.9±0.2	<0.001
Albumin (g/dL)	3.7±0.4	4.4±0.6	<0.001
Vitamin B-12 (pg/mL)	220.8±110.7	340.7±89.4	<0.001
Normal	19 (27.1%)	30 (100.0%)	
Low	51 (72.9%)	0 (0.0%)	
Median duration of dialysis (years)	3.0 (0.6-17.0)		

[1]Mean±SD
[2]Welch Two Sample t-test.

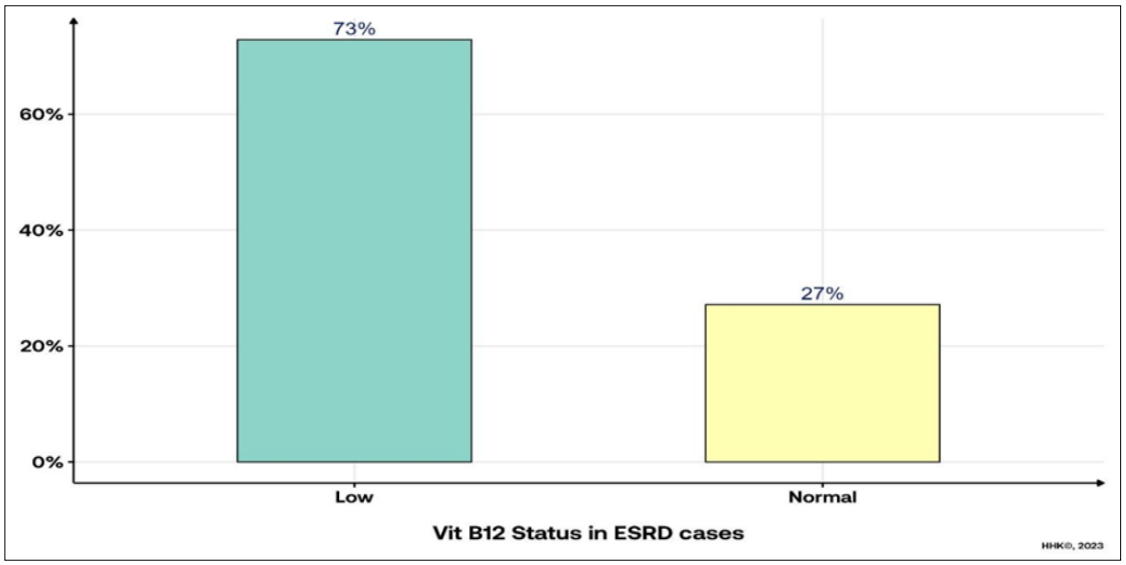

Fig 1: Prevalence of low vitamin B12 levels in ESRD cases.

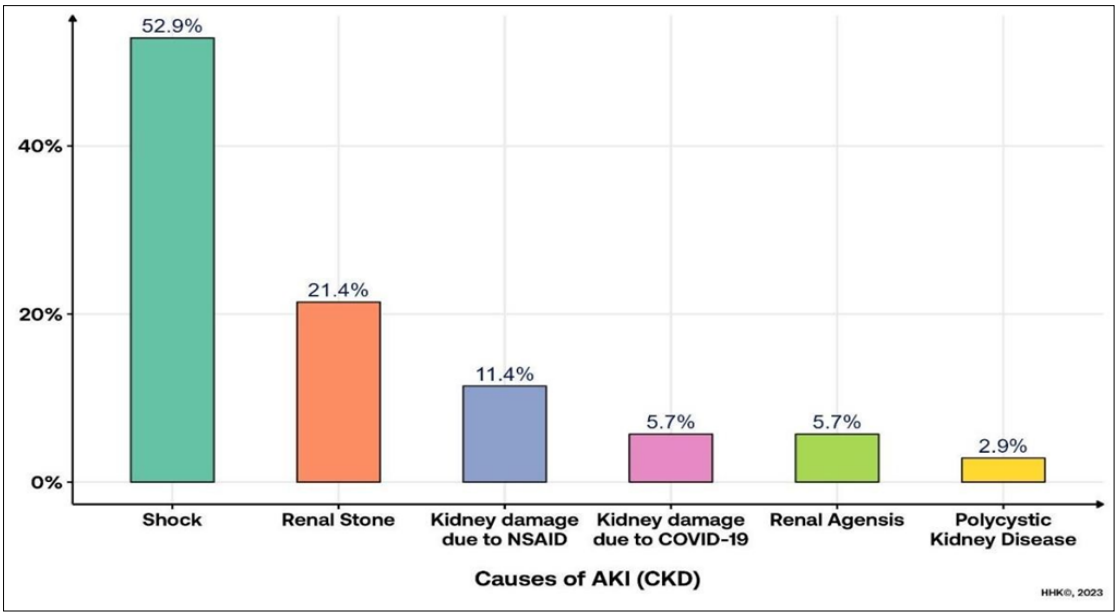

Fig 2: Causes of chronic kidney disease in the cases group.

Trauma led to the majority of cases, followed by renal stones, NSAID use, and COVID-19. Survivors of COVID-19 have a higher risk of worse kidney outcomes in the post-acute phase and may be predisposed to chronic kidney disease. Chronic renal disease was caused by renal agenesis and polycystic kidney disease, according to our findings. Importantly, 72.9% of participants had low vitamin B12 levels, whereas 27.1% had normal levels. As in Fig 1, 2.

In a comparison between cases with ≤ 3 years and >3 years of dialysis, age and gender were similar between the groups. BMI showed no significant difference. However, those with >3 years of dialysis had significantly higher urea levels. Other parameters like creatinine and albumin did not differ significantly between the groups. Vitamin B12 levels differed significantly between the two groups, with those in the >3 years of dialysis group having lower vitamin B12 levels (161.7 pg/mL) compared to the ≤ 3 years of dialysis group (251.1 pg/mL) with a p-value of 0.002. As in Table 3.

Table 3: Study parameters stratified by the duration of dialysis

Characteristic	≤ 3 years, N = 38[1]	>3 years, N = 32[1]	P-Value[2]
Age (years)	48.0±15.4	49.5±12.6	0.7
Sex			0.7
Male	24 (63.2%)	19 (59.4%)	
Female	14 (36.8%)	13 (40.6%)	
BMI (kg/m^2)	27.2±8.0	27.3±7.8	>0.9
Urea (mg/dL)	121.6±28.4	139.2±29.5	0.014
Creatinine (mg/dL)	7.7±2.0	8.3±2.4	0.3
Albumin (g/dL)	3.7±0.3	3.8±0.4	0.3
Vitamin B-12 (pg/mL)	251.1±120.8	161.7±81.7	0.002

[1]n (%); Mean ± SD

[2]Pearson's Chi-squared test, welch two sample t-test

To evaluate the correlation between vitamin B12 levels and various biomarkers, Spearman rank correlation coefficients were calculated. Age showed a very weak positive correlation with vitamin B12 (rho = 0.029, P=0.76), indicating that age did not significantly affect vitamin B12 levels in this study. Similarly, BMI showed a weak negative correlation (rho = -0.104, P=0.3), indicating that there was no significant relationship between BMI and vitamin B12 levels. Urea and creatinine had no correlation with vitamin B12 (urea: rho = 0.097, P=0.3; creatinine: rho = 0.14, P=0.16). Similarly, albumin levels showed a weak positive correlation with vitamin B12 (rho = 0.11, P=0.25). In particular, dialysis duration showed a moderate negative correlation with vitamin B12 levels (rho = -0.259, P=0.029), indicating that vitamin B12 levels tend to decrease with increasing dialysis duration. This correlation was statistically significant, suggesting a possible link between dialysis duration and vitamin B12 status in the studied population. As in Table 4.

Table 4: Correlation between vit B12 and other study parameters

Characteristics	Correlation Coefficient (rho)	P-Value
Age	0.029	0.76
BMI	-0.104	0.3
Urea	0.097	0.3
Creatinine Albumin	0.14, 0.11	0.16, 0.25
Duration of dialysis	-0.259	0.029
Spearman's rank correlation		

Discussion

Chronic Kidney Disease (CKD) presents a significant global health challenge, contributing to both mortality and morbidity. Anemia is common in CKD, driven by factors such as insufficient erythropoietin, iron deficiency, shortened red blood cell lifespan, nutritional deficiencies, and altered vitamin metabolism, which collectively promote cardiovascular disease, the leading cause of death in CKD [23]. CKD patients often exhibit megaloblastosis, indicating potential Vitamin B12 and folic acid deficiencies. These deficiencies are exacerbated by medication interactions, dietary restrictions, malnutrition, and the dialysis procedure itself, which can lead to nutrient loss [24, 25]. In this study, significant differences in serum Vitamin B12 levels were observed between ESRD and control groups, with ESRD patients showing lower levels (220.8±110.7 ρg/mL) compared to controls (340.7±89.4 ρg/mL) (p<0.001). Additionally, 72.9% of individuals with ESRD had low Vitamin B12 levels, highlighting the prevalence of this deficiency in ESRD patients and the need for clinicians to monitor and address it. Dandge *et al*. [26] found that 60% of CKD patients in India had inadequate Vitamin B12 levels. Similarly, Nahas *et al*. [27] reported that 32.7% of hemodialysis patients in Palestine had low Vitamin B12 levels (average: 362.62±166.40 ρg/mL) compared to controls (average: 483.36±115.07 ρg/mL). Heinz *et al*. [28] in Germany observed an average baseline serum Vitamin B12 level of 350 ρg/mL in dialysis patients, noting no correlation between B12 intake and reduced mortality risk in ESRD. These studies indicate a high risk of Vitamin B12 deficiency among dialysis patients [29]. Hemodialysis patients often experience Vitamin B12 depletion due to poor nutritional intake and the need to avoid high-electrolyte foods, limiting B12 sources [30, 31]. Chronic uremia also contributes to muscle wasting and toxicity. Vitamin B12, being a water-soluble vitamin with a molecular weight of 1,355.38 g/mol, is cleared effectively with modern high-flux dialyzers, potentially exceeding normal urinary excretion rates and leading to deficiency [32]. Malnutrition in CKD and ESRD patients, compounded by metabolic changes such as acidosis, systemic inflammation, and hormonal imbalances, further elevates the risk of Vitamin B12 deficiency. Additional factors include anorexia, gastro paresis, sluggish intestinal transit, diarrhea, heightened gut permeability, and disruptions in gut microbiota, worsening nutritional status (33). The study found that ESRD patients had a median dialysis duration of 3.0 years, compared to 6 years in Dandge *et al*. [26] and 7 years in Nahas *et al*. (34). Acute cases of AKI progressing to CKD likely explain this variance. Vitamin B12 levels were higher in patients with ≤3 years of dialysis (251.1±120.8 pg/mL) compared to those with >3 years (161.7±81.7 pg/mL) (P=0.002). A moderate negative correlation (rho = -0.259) between Vitamin B12 levels and dialysis duration was observed. Dandge *et al*. also reported a significant inverse correlation between dialysis duration and Vitamin B12 levels (P=0.02). Prolonged dialysis duration contributes to Vitamin B12 depletion through nutrient loss, gastrointestinal absorption issues, anemia, dietary restrictions, medication interactions, and increased metabolic demands [34].

Conclusion

In this case-control study, the results showed a significant association between vitamin B12 levels and chronic renal failure. Specifically, patients with end-stage renal failure had lower vitamin B12 levels than controls. In addition, dialysis duration was significantly inversely correlated with

vitamin B12 levels. These results suggest that monitoring and treating vitamin B12 deficiency in patients with end-stage renal failure has important clinical implications.

Conflict of Interest
Not available

Financial Support
Not available

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