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Effect of B12 supplementation on renal anemia among hemodialysis patients at El-Najar hospital, Gaza strip

Abdul Rahman Mahmoud F. Nahas[1*], Raghdaa Hamdan Al Zarzour[2], Asmaa Salama M. Abu Laila[3], Ahmed Mahmoud Tabash[4], Ayman Mustafa Abu Mustafa[5], Faten Mohamad Allyan[6], Abdrabbou Mohammed Elregeb[7], Eyad Elabed Abou Teior[8], Abdulkareem Mohammed Al-Shami[9], Mohamed Hassan Elnaem[1]

[1]Department of Pharmacy Practice, Faculty of Pharmacy, International Islamic University Malaysia, Pahang, Malaysia
[2]Discipline of Pharmacology, School of Pharmaceutical Sciences, University Sains Malaysia; Penang, Malaysia
[3]Department of Pharmacy, El-Najar Hospital, Gaza Strip, Palestine
[4]Department of Laboratory Medicine, El-Najar Hospital, Gaza Strip, Palestine
[5]Continuing Education Department, Palestine College of Nursing, Gaza Strip, Palestine
[6]Department of Biomedical Science, College of Medical Science, Israa University, Gaza Strip, Palestine
[7]Department of Laboratory Medicine, European Hospital, Gaza Strip, Palestine
[8]Nephrology Department, El-Najar Hospital, Gaza Strip, Palestine
[9]Department of Pharmacy Practice and Clinical Pharmacy, PICOMS International University College, Kula Lumpur, Malaysia

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ABSTRACT

Introduction: Patients with end-stage renal disease (ESRD) are predisposed to nutritional deficiencies, resulting in vitamin B12 deficiency with negative hematologic consequences.
Objective: This study aimed to investigate the impact of intramuscular B12 on renal anemia among ESRD patients receiving hemodialysis (HD) at El-Najar hospital, Gaza Strip.
Patients and Methods: A case-control study conducted, which included 110 healthy controls and 110 HD patients who received B12 on a daily, weekly, and monthly basis over two months. Sociodemographics and current diseases were reported. Serum levels of serum B12, white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), mean corpuscular volume (MCV), and platelet (PLT) were recorded before and after treatment. Data analysis was conducted using SPSS.
Results: Baseline serum B12 level was significantly lower in HD patients compared to controls (362.62 ± 166.40 versus 483.36 ± 115.07 ρg/mL, $P<0.001$), which significantly improved after vitamin B12 treatment (639.08 ± 362.99 ρg/mL, $P<0.001$). Additionally, mean WBCs, RBCs, Hb, and PLT levels were significantly increased after treatment ($P<0.001$). Serum B12 level was positively and significantly ($P<0.001$) correlated with levels of WBC (r = 0.45), RBC (r = 0.43), Hb (r = 0.39) and PLT (r = 0.51), and negatively correlated with MCV (r = -0.46, $P<0.001$).
Conclusion: Administration of vitamin B12 improves serum B12 levels in HD patients, which was associated with increased WBCs, RBCs, Hb, and PLT levels and decreased MCV levels. Treatment by vitamin B12 can improve HD patients' renal anemia. Future studies with larger sample sizes and prolonged follow-up are advocated.

Implication for health policy/practice/research/medical education:
In 110 ESRD patients who were on hemodialysis, we reported a significantly lower serum B12 levels, compared to 110 healthy individuals. The administration of vitamin B12 significantly improves serum B12 levels in our patients. Additionally, mean WBCs, RBCs, Hb and PLT counts were significantly increased. As such, vitamin B12 administration can improve renal anemia in ESRD patients receiving hemodialysis. Future research with a larger sample size and extended follow-up is encouraged.

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***Corresponding author**: Abdul Rahman Mahmoud F. Nahas, Email: abd_mfn@hotmail.com

Original

Introduction

Anemia has long been recognized as a hallmark of chronic kidney disease (CKD), having a detrimental effect on hematopoiesis as a result of the imbalance between the later and expanded obliteration (1). Consequently, anemia affects end-stage renal disease (ESRD) patients, with a substantial impact on morbidity, mortality and a significant economic burden (2,3).

End-stage renal disease patients on dialysis are also more prone to nutritional deficiencies as a result of medication interactions, dietary restrictions, and malnutrition (4). Therefore, these patients are at increased risk of vitamin B12 deficiency (5), a coenzyme involved in the catabolism of methylmalonic acid and homocysteine (6). Around 20% of vitamin B12 in the blood is bound to transcobalamin, forming the natural dynamic structure that cells can take up. While CKD patients have increased transcobalamin levels, they have a reduced ability to absorb vitamin B12 from food sources. In fact, the expanded trans-cobalamin loss in the urine and its reduced absorption in the proximal tubule results in lower plasma vitamin B12 in uremic patients (7).

Vitamin B12 deficiency has been linked to megaloblastic anemia and neurologic and cognitive consequences. Additionally, disruption of vitamin B12 homeostasis may be directly associated with cardiovascular risk and CKD progression (8). Moreover, ESRD patients on hemodialysis (HD) have also to face many symptoms such as tired-ness, muscle weakness, numbness, headache, joint-muscle pain and arrhythmia that might be linked to vitamin B12 deficiency (9,10). Consequently, it is crucial to address the demand for vitamin B12 among CKD patients. Unfortunately, food sources of vitamin B12 contain high concentration of electrolytes, which are detrimental to dialysis patients, and then, relying on other vitamin B12 supplements is essential (2).

Therefore, vitamin B12 supplementation is recommended for dialysis-dependent patients considering the crucial role of methylcobalamin, the active form of vitamin B12, in the metabolic pathways of homocysteine and the underlying risk of vitamin B12 deficiency among these patients (10).

Objectives

We aimed in this study to determine serum vitamin B12 level in HD patients and investigate the impact of vitamin B12 supplementation on improving renal anemia among these patients. We also aimed to assess the presence of common neurological symptoms; i.e., numbness, muscle weakness, tiredness in our sample.

Patients and Methods

This was a case-control study in which 110 healthy adult controls and the same number of ESRD adult patients on HD were included. HD patients were given intra-muscular vitamin B12 over two months. One milligram daily doses were given in the first seven days, followed by 1 mg once weekly for the next 4 weeks, and 1 mg at the end of the second month. Both groups were matched in age and gender. Patients diagnosed with ESRD on HD were recruited from the HD unit at Martyr Mohammed Youssef El-Najar in Gaza strip. The study was conducted between January 2020 and June 2020. Pregnant women, patients with hepatitis and those who had been taking vitamins were excluded from the study.

Data collection and specimens processing

Demographic data and medical history were obtained with an interview-based questionnaire. Blood pressure was measured, and blood samples were collected before HD sessions. About 6 ml of blood was obtained from each subject and divided into EDTA tubes (2 mL), and processed by an automatic counter for hemoglobin (Hb) concentration and other whole blood component concentrations (CELL-DYN Emerald). The other 4 ml was left in vacutainer plain tube to allow blood clotting. To ensure consistency of results, specimens were transferred to centrifuge tubes and centrifuged for 10 minutes at >10 000 relative centrifugal force before being tested for the presence of fibrin, red blood cells (RBCs), or other particulate matter. Alternatively, specimens were frozen and thawed and centrifuged specimens with a lipid layer on top were transferred to a sample cup or secondary tube. Precautions are taken to ensure that only the clarified specimen is transferred and not the lipemic material. The clarified specimens were then transferred to a sample cup or secondary tube for serum vitamin B12 testing, determined by the ARCHITECT i System.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 22.0 was conducted for data entry and analysis. All numeric variables were expressed as a mean and standard deviation. Results were analyzed by the paired T-test, followed by a chi-square test. $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics of the study sample

Study sample (N = 220) equally encompassed case [males; n = 54 (48.6%), females; n = 56 (51.4%)] and control [males: n = 57 (51.4%); females: n = 53 (48.6%)] groups, with no significant difference ($\chi^2 = 0.16$, $P = 0.69$). Similarly, there was no significant difference ($\chi^2 = 0.09$, P=0.96) between the two studied groups in age, which ranged from the early 20s to 94 years.

Disease characteristics of the study sample

No known comorbidities were reported in the control group. On the contrary, hypertension was the most common reported disease in the case group (n = 81,74%), with just 10% of the group (n = 11) being disease-free.

Assessment of serum vitamin B12 levels among cases and controls

One-third of case group (32.7%) had low-vitamin B12 serum level (M = 362.62 ± 166.40 ρg/mL), which was significantly lower ($P < 0.001$) compared to the control group (M = 483.36 ± 115.07 ρg/mL), whose vitamin B12 levels was normal.

Vitamin B12 levels before and after treatment

We revealed a statistically significant difference ($P < 0.001$) in serum levels of vitamin B12 before treatment (M = 362.62 ± 166.40 ρg/mL) and after treatment (M = 639.08 ± 362.99 ρg/mL), indicating a significant improvement in serum levels of vitamin B12 following treatment.

Change in values of WBCs, RBCs, hemoglobin, MCV, and PLT following vitamins B12 supplementation

As shown in Table 1, we reported statistically significant differences in white blood cells (WBCs), RBCs, Hb, mean corpuscular volume (MCV), and platelet (PLT) mean levels following treatment with vitamin B12.

We also reported significant positive correlations ($P<0.001$) between mean serum vitamin B12 level and each of WBCs (r = 0.45), RBCs (r = 0.43), Hb level (r = 0.39), and PLT counts (r = 0.51) in case group. Conversely, there was a significant negative correlation between serum vitamin B12 levels with MCV (r = -0.46, $P<0.001$).

Assessment of numbness, muscle weakness and tiredness among case group

Unsurprisingly, we reported the presence of numbness, muscle weakness and tiredness in 36 patients in our case group whose vitamin B12 serum levels were low. However, all these symptoms disappear following treatment with vitamin B12 supplementation.

Discussion

Clinical data of HD patients in this study showed that the mean duration of HD was about seven years, which was consistent with earlier findings in HD patients in the Gaza Strip (11,12). The most common self-reported disorders among HD patients were hypertension and diabetes, corresponding to other previously published research (12,13). In fact, it is well-established that hypertension and diabetes contribute significantly to the advancement of renal failure (13,14).

Compared to our study controls, we found a significant decreased baseline mean serum vitamin B12 level (362.62 ρg/mL) in cases. This was similar to Heinz and colleagues' trial among 650 dialysis patients (15), which reported a baseline mean serum vitamin B12 level of 350 ρg/mL. This finding, in fact, would indicate an increased risk of vitamin B12 insufficiency in dialysis patients as shown in a previous study by Rees and Shaw (16). Malnutrition with subsequent folic acid and vitamin B12 deficiency among CKD and ESRD patients is aggravated by several metabolic alterations, including acidosis, systemic inflammation and hormonal dysregulation, together with comorbidities and multidrug therapies. In addition, anorexia, gastroparesis, slow intestinal transit or diarrhea, increased gut mucosal permeability, and gut microbiota impairment may represent worsening factors (17).

Patil and associates reported a high percentage (56%) of vitamin B12 deficiency among CKD patients (1). In our study; however, only 32.7% of case group had vitamin B12 deficiency, which was similar to the study by Stabler (9). Patients with ESRD are at higher risk for nutritional deficiencies due to medication interactions, dietary restrictions and malnutrition (18), that would precipitate vitamin B12 deficiency. Several studies revealed that vitamin B12 serum concentrations in HD patients were equivalent to or higher than the normal range in healthy people. (19-21). This finding was attributed to vitamin B12 larger molecular size and subsequent difficulty in being cleared during HD. It is noteworthy to state here that absence of vitamin B12 deficiency in ESRD patients does not translate into normal functioning of this vitamin, as functional vitamin B12 deficiency can be detected in uremic patients due to the increased loss of transcobalamin in the urine (22).

Furthermore, our treatment with vitamin B12 supplementation improved mean serum level (639.08 ρg/mL), which is similar to the study by Iqbal et al (23), who reported an improvement from 402 ρg/mL to 739 mg/mL in mean serum vitamin B12 level following treatment with vitamin B12 in 17 ESRD patients. Treatment with vitamin B12 also increased the mean levels of hematologic parameters; i.e., Hb, RBCs, WBCs, and PLT however it

Table 1. Parameters changes before and after vitamin B12 treatment

Parameter	Before	After	t-value	*P* value
WBCs (thousand/mm^3)	6.25 ± 1.38	6.73 ± 0.877	5.74	0.001
RBCs (million/mm^3)	4.04 ± 0.62	4.29 ± 0.36	6.55	0.001
Hb (g/dL)	12.23 ± 1.96	12.39 ± 1.41	2.73	0.001
MCV (fL)	89.95 ± 5.28	87.82 ± 2.12	-6.26	0.001
PLT (thousand/mm^3)	316.95 ± 88.66	331.71 ± 63.11	5.289	0.001

Hb; haemoglobin, MCV; mean corpuscular volume, PLT; platelets, RBC; Red blood cell, WBC; white blood cell.
Differences analysis was conducted using paired T-test, significant at $P \leq 0.05$

is accompanied by diminution of MCV mean values. A previous study established that vitamin B12 administration increased the mean level of Hb and improved anemia as well (24).

In the present study, neurological symptoms, i.e., numbness, muscle weakness and tiredness, were associated with vitamin B12 deficiency in the case group. Similar findings were observed in a study by Patil and colleagues among 50 CKD patients (1), since all these symptoms disappeared following our treatment with vitamin B12. Vitamin B12 is required for optimal nervous system function and acting as a cofactor in the formation of methionine from homocysteine. Methionine is vital for myelin sheath phospholipids methylation, in addition, methylcobalamin is required for synthesizing and maintaining myelin sheath; therefore, vitamin B12 deficiency accounts for retarded myelination (25).

Conclusion

While further research is needed with probably larger sample sizes and extended time frame and follow-up, our study showed that baseline mean serum vitamin B12 level was significantly lower in HD patients compared to controls, and vitamin B12 supplementation improved it. This resulted in elevation in WBCs, RBCs, Hb and PLT levels, as well as MCV level reduction. Notably, we believe that our study signifies that vitamin B12 deficiency should be addressed in ESRD patients receiving HD, while vitamin B12 supplementation may provide promising positive outcomes in the management of renal anemia among this group of population.

Limitations of the study

Despite the fact that our intervention resulted in a significant improvement in the case group's mean serum vitamin B12 level, our findings must be interpreted in light of the study's limitations. First, this study lacks ferritin, transferrin saturation, erythropoietin, and folate measurements, which were not feasible due to financial constraints and laboratory limitations. Second, it has been shown that people with less education are less inclined to participate in studies, regardless of the study design. Both of these limitations would make it difficult to generalize our findings.

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Authors' contribution

Conceptualization, methodology, validation and data curation: ASMAL, AMT and EEAT; software, formal analysis and project administration: ASMAL and AMT; investigation, resources and writing—original draft preparation: ASMAL, AMT, AMAM, FMA, AME and EEAT; writing—review and editing: ARMFN, RHAZ, MHE and AMAS; supervision: ARMFN and EEAT; funding acquisition: ARMFN. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Ethical issues

The study conducted in accordance with the tents of the Declaration of Helsinki. The study and its protocol were approved by the Palestinian Health Research Council (ethical approval number# PHRC/HC/822/20). Accordingly, each participant signed an informed consent form after being fully informed about the purpose of the study and assured for the confidentiality of the information obtained through the questionnaire and blood analysis.

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